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Hormone Suppression by Elagolix

**Dose-Dependent Suppression of Gonadotropins and Ovarian Hormones by Elagolix in Healthy Premenopausal Women**

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**Context:** Elagolix is a nonpeptide, oral gonadotropin-releasing hormone (GnRH) antagonist being developed for sex-hormone dependent diseases in women.

**Objective:** To evaluate the pharmacokinetics and pharmacodynamics of elagolix.

**Design, Setting, and Participants:** Randomized, double-blind, placebo-controlled, multiple-ascending dose study in 45 healthy premenopausal women at a research unit.

**Interventions:** Elagolix 150 mg once daily or 100, 200, 300 or 400 mg twice daily or placebo for 21 days.

**Main Outcome Measures:** Elagolix pharmacokinetics; suppression of gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]), and ovarian hormones (estradiol [E2], progesterone [P]); adverse events.

**Results:** Elagolix was rapidly absorbed after oral dosing, reaching maximum concentrations (Cmax) at 1.0 to 1.5 hours, with a half-life of 4 to 6 hours. FSH, LH, and E2 were suppressed within hours of elagolix administration on Day 1. Dose-dependent suppression of E2 was observed, with maximum suppression achieved with elagolix 200 mg twice daily. Dose-dependent suppression of FSH and LH was also observed, with maximal or near maximal suppression achieved at 300 mg twice daily and 200 mg twice daily, respectively. At elagolix doses ≥ 100 mg twice daily, P concentrations remained at anovulatory levels throughout 21 days of dosing. The most frequently reported adverse events were headache and hot flush.

**Conclusions:** Elagolix administration allows for modulation of gonadotropin and ovarian hormone concentrations, from partial suppression at lower doses to nearly full suppression at higher doses. The results of this study provide a rationale for elagolix dose selection for treatment of sex hormone-dependent diseases in women.

We studied the effects of elagolix on gonadotropins and ovarian sex hormones in healthy premenopausal women and found that elagolix rapidly suppressed these hormones in a dose-dependent manner.

**Introduction**

Gonadotropin releasing hormone (GnRH) is a pivotal central regulator of the human reproductive axis that regulates both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion from the anterior pituitary gland after binding to GnRH receptors (1, 2). It is secreted in pulsatile manner from the hypothalamus and changes in the frequency of GnRH pulses are responsible for the differential regulation of LH and FSH secretion in women and consequently for gonadal production of sex hormones (3, 4).
Synthetic peptide GnRH analogues (GnRH agonists and antagonists) have been widely used for sex hormone-dependent diseases in women and men, including endometriosis, uterine fibroids, prostate and breast cancer, central precocious puberty, and prevention of ovarian hyper-stimulation during assisted reproductive technology (ART) procedures (5, 6). Continuous administration of GnRH agonists at high doses suppresses the activity of the pituitary-gonadal axis through down-regulation of GnRH receptors in the anterior pituitary gland after an initial stimulation of gonadotropic and gonadal hormones (hormonal flare effect) that may last 1 to 2 weeks, and subsequently leads to a profound suppression of gonadal hormones (7, 8). Currently, the GnRH agonists are mostly used as long-acting depot formulations, subcutaneous implants, or daily nasal solutions. In contrast, peptide GnRH antagonists have a rapid onset of action and do not produce a flare effect, but they are usually delivered as daily subcutaneous injections (ART procedures) or long-acting depot formulations (prostate cancer).

GnRH agonists are highly effective in the management of pain in women with endometriosis. However, this treatment is associated with severe hypoestrogenic side effects, including vasomotor symptoms and progressive bone loss that limit the duration of treatment. Moreover, management of women with endometriosis may not require full estrogen (E2) suppression for symptom relief, as previously proposed (9).

More recently, several nonpeptide, orally active GnRH antagonists have been synthetized in order to overcome a number of these disadvantages and expand current therapeutic options, including achievement of partial suppression of gonadal steroids and the convenience of oral dosing (10). Elagolix is a nonpeptide, oral GnRH antagonist (11) that is currently being developed for management of pain associated with endometriosis and heavy menstrual bleeding associated with uterine fibroids. Elagolix may offer advantages over GnRH agonists or peptide GnRH antagonists in these diseases because it does not produce a flare effect, has a rapid onset of action, is orally bioavailable, and can be readily discontinued if necessary (12, 13). In addition, elagolix has the ability to reduce gonadotropins and ovarian hormones in a dose-dependent manner raising the possibility of tailoring the dose in order to achieve an acceptable balance between therapeutic efficacy and unwanted side effects (13).

The pharmacokinetics and hormone suppressive effects of elagolix have been previously evaluated in a limited number of healthy premenopausal women during treatment for up to 7 days for doses up to 200 mg per day (13). The aim of the present study was to characterize the pharmacokinetics, hormone responses, and safety profile of multiple ascending doses of elagolix in a larger number of healthy premenopausal women during 21 days of continuous dosing at doses up to 400 mg twice a day to evaluate ovarian suppression at higher doses. The results of the present study are being used to inform dosing selection in elagolix Phase 3 studies.

Materials and Methods

Participants and Study Design
This was a Phase 1, randomized, double-blind, placebo-controlled, sequential dose-escalation study conducted at the AbbVie Clinical Pharmacology Research Unit (Grayslake, IL). The study was conducted 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 an institutional review board (Vista Medical Center East Institutional Review Board, Waukegan, IL) and written informed consent was obtained from each participant before study-related procedures were performed.

Adult premenopausal women aged between 18 and 49 years, inclusive, who were in general good health based on their medical history, a physical examination, vital signs and 12-lead electrocardiogram assessments, and laboratory tests were eligible to enroll in the study. Women were required to have a body mass index of 18 to 35 kg/m², a history of regular menstrual cycles (24 to 32 days) with 3 to 7 days of bleeding per month for at least 3 months before study drug administration, and an FSH level < 35 mIU/mL at screening. Women must have been at least 6 months postpartum, postabortion, or postlactation at the start of study drug dosing, must not have received a GnRH agonist or antagonist in the previous 6 months or Depo-Provera® in the previous 12 months, and must have agreed to use 2 forms of nonhormonal contraception throughout the study, including screening and follow-up. Women must not have used or consumed any of the following before study drug administration or throughout the study: known inhibitors or inducers of cytochrome P450 3A or inhibitors of P-glycoprotein within 1 month; a drug by injection within 30 days; over-the-counter and/or prescription medications, vitamins, or herbal supplements within 2 weeks; or alcohol, caffeine, grapefruit or grapefruit products, star fruit, Seville oranges, or quinine/tonic water within 72 hours of receiving the first eligolix dose on Day 1.

Participants were assigned to eligolix (150 mg once daily or 100, 200, 300 or 400 mg twice daily) or matching placebo for 21 consecutive days under fasting conditions (approximately a 10-hour fast for the morning dose and approximately a 2-hour fast for the evening dose). Within each group, participants were randomized to receive eligolix or placebo in a 3:1 ratio. The 300 mg and 400 mg twice daily groups were dosed after the safety and available pharmacokinetic data from the preceding lower dose groups had been evaluated; the lower dose groups (150 mg once daily and 100 mg twice daily) enrolled concurrently with other dose groups, as safety had been previously established at these lower doses. Dosing for each participant began within 2 days after the onset of menstruation and participants who prematurely discontinued from the study were replaced. Confinement began on Day –1 and ended after the collection of the 48-hour pharmacokinetic sample on Day 23.

Sample Collection and Bioanalytical Methods
Blood samples for assay of eligolix were collected by venipuncture prior to dosing (0 hour) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing on Days 1 and 21 and 36 and 48 hours after dosing on Day 21. Trough samples were collected prior to the morning dose on Days 5, 7, 9, 15, 17, and 19. Eligolix plasma concentrations were measured using a validated salt-assisted protein precipitation extraction, high performance liquid chromatography tandem mass spectrometric (LC-MS/MS) method. The lowest limit of quantitation (LLOQ) for eligolix was 0.126 ng/mL. Samples quantified below the lowest standard were reported as zero. The precision (coefficient of variation) for
elagolix was $\leq 11.4\%$ and mean accuracy (expressed as percent bias) for elagolix ranged between -6.6% and 7.2%.

Blood samples for assay of gonadotropin (FSH and LH) and ovarian hormone (E2 and P) concentrations were obtained by venipuncture at Screening, prior to dosing (0 hour), and 2, 4, 6, 8, 10, 12, 16, and 24 hours after dosing on Days 1 and 21 and 30, 36, and 48 hours after dosing on Day 21. In addition, a blood sample was collected prior to the morning dose (0 hour) on Study Days 3, 5, 7, 9, 11, 13, 15, 17, and 19. Serum hormone concentrations were measured using validated chemiluminescent immunoassay methods at a commercial laboratory (Chicago Clinical Labs, Northbrook, IL). The LLOQ values were 0.3 mIU/mL for FSH, 0.070 mIU/mL for LH, 11.8 pg/mL for E2, and 0.477 nmol/L for P.

**Pharmacokinetic and Statistical Analyses**

Elagolix pharmacokinetic parameters were estimated using noncompartmental methods in Phoenix WinNonlin, Version 6.3 (Pharsight, A Certara Company, Princeton, NJ). The maximum concentration ($C_{\text{max}}$), time to maximum concentration ($T_{\text{max}}$), and trough concentration at 12 or 24 hours after dosing ($C_{\text{trough}}$) were determined directly from the plasma concentration-time data. Calculated pharmacokinetic parameters included the terminal phase elimination rate constant ($\beta$), the terminal phase elimination half-life ($t_{1/2}$), the area under the concentration-time curve (AUC) over a 12- or 24-hour dosing interval (AUC$_{12}$; AUC$_{12}$ or AUC$_{24}$), dose-normalized $C_{\text{max}}$ and AUC, and the accumulation ratio based on AUC ($R_{ac}$).

FSH, LH, E2, and P concentrations were determined at multiple time points throughout the study and were summarized using descriptive statistics. For LH, E2, and P, concentrations below the LLOQ were set to one-half the LLOQ (LLOQ/2). Hormone suppression was defined as a hormone concentration that was lower than the baseline value. All participants who received placebo were pooled for comparison to the elagolix groups.

Statistical analyses were conducted using SAS®, Version 9.2 (SAS Institute, Inc., Cary, NC). Pharmacokinetic parameters were tabulated by group using summary statistics. Elagolix linear kinetics and dose proportionality were analyzed using ANCOVA for natural log transformed, dose-normalized values for $C_{\text{max}}$ and AUC$_{12}$ for the twice daily dosing regimens.

**Safety and Tolerability**

Safety and tolerability were assessed throughout the study based on adverse event monitoring, physical examinations, laboratory tests, vital signs measurements, and electrocardiogram assessments. Study participants maintained a daily diary of uterine bleeding beginning at Screening and ending at the follow-up visit, which took place upon the return of menses or at 60 days after the end of dosing, whichever was sooner. Menstrual and nonmenstrual bleeding was recorded. If menses had not returned by the 60-day follow-up visit, an adverse event of amenorrhea was to be reported.

**Results**

**Participants**
Forty-five healthy, premenopausal women ranging in age from 20 to 47 years at the time of screening were enrolled in the study and 40 completed the study. The 5 women who did not complete the study discontinued due to adverse events, as described in the Safety section. The groups were well balanced with regard to demographic characteristics (Table 1). Data from all participants who received at least 1 dose of study drug (elagolix or placebo) were included in the analyses of hormone concentrations and safety data. All available pharmacokinetic data were used in the statistical analyses and calculations of pharmacokinetic parameters.

**Elagolix Pharmacokinetics**
Mean + SD elagolix plasma concentration-time profiles by group on Day 1 and 21 are shown in Figure 1 and the pharmacokinetic parameters for elagolix are provided in Table 2. Elagolix was rapidly absorbed after oral dosing, with median $T_{\text{max}}$ values of 1.0 to 1.5 hours across groups. After reaching $C_{\text{max}}$, elagolix concentrations declined in a biphasic manner, with an estimated mean terminal phase elimination half-life of 4 to 6 hours. Little to no accumulation was observed, including with twice daily dosing, as elagolix predose concentrations were 1% to 2% of the $C_{\text{max}}$ values and the mean $R_{\text{ac}}$ value based on AUC accumulation was less than 1 in all groups. On the basis of ANCOVA and pairwise comparisons of steady-state pharmacokinetic data obtained on Day 21, no statistically significant trend was observed for dose-normalized $C_{\text{max}}$, $AUC_{\tau}$, or $C_{\text{trough}}$ ($P \geq 0.05$) in the dose range of 100 to 400 mg, indicating that pharmacokinetic exposures were dose proportional.

**Hormone Concentrations**
Changes in gonadotropin and ovarian hormone concentrations over 21 days for placebo participants and each elagolix group are presented in Figure 2. Administration of elagolix resulted in suppression of gonadotropins and ovarian hormones in a dose-dependent manner. In the placebo group, physiological cycle-dependent changes in FSH, LH, E2, and P were observed. Because treatment was initiated during the first 2 days of the menstrual cycle, all hormone levels were relatively low at baseline.

Mean FSH concentrations in elagolix participants decreased in a dose-dependent manner compared to those in placebo participants, with maximum suppression occurring in the elagolix 300 and 400 mg twice daily groups (Figure 2A). In the 150 mg once daily group, the initial decline in mean FSH concentrations on Day 1 was followed by a rebound in FSH concentrations, which became slightly higher than those observed in the placebo group, with an apparent loss of cyclicity. FSH was suppressed below baseline in all but one participant at an elagolix dose of 200 mg twice daily. The largest reduction in FSH concentrations was observed when the elagolix dose was increased from 200 mg twice daily to 300 mg twice daily. Further reduction in FSH concentrations was small when the elagolix dose was increased from 300 mg twice daily to 400 mg twice daily. At all elagolix dose levels, FSH concentrations rebounded to baseline concentrations or
above within 24 to 48 hours after the last dose on Day 21 (150 mg once daily and 200 mg twice daily groups shown in right panel of Figure 3A).

Mean LH concentrations also decreased in an elagolix dose-dependent manner compared to placebo, with maximum inhibition occurring in the elagolix 200 mg twice daily group and above (Figure 2B). Examination of LH concentrations on Day 1 (Figure 3B) showed that the initial decline in mean LH concentrations after the first 150 mg dose was followed by a rebound to baseline at the time of the next 150 mg once daily dose. In the 150 mg group, an LH increase was observed on Day 15 in 2 participants, one of whom had a subsequent increase in progesterone to above 5 nmol/L. At all elagolix dose levels, LH concentrations rebounded to baseline levels or above within approximately 24 to 48 hours after the last dose (the 150 mg once daily and 200 mg twice daily groups are shown in Figure 3B).

A dose-dependent suppression of E2 concentrations was observed in all elagolix groups relative to placebo (Figure 2C). Suppression of E2 occurred quickly, within hours after the first dose (the 150 mg once daily and 200 mg twice daily groups are shown in Figure 3C), and the concentrations were lower than those observed in participants who received placebo. Maximum E2 suppression (to concentrations near the LLOQ of 11.8 pg/mL) was achieved in all participants at elagolix doses of 200 mg twice daily and higher. Partial suppression of E2 was observed in the 150 mg once daily group (E2: 56.5 ± 43.0 pg/mL, Day 21 pre-dose mean value, SD) and the 100 mg twice daily group (E2: 27.1 ± 14.6 pg/mL, Day 21 pre-dose mean value, SD). Following the last dose of elagolix on Day 21, nearly full suppression of E2 was maintained for the dosing interval (12 hours) in the 200 mg twice daily group, but appeared to rebound within 24 to 48 hours after the last 150 mg once daily dose was administered (Figure 3C).

Anovulatory P concentrations (i.e., < 5 nmol/mL) were observed throughout the 21 days of dosing in all participants who received elagolix doses of 100 mg twice daily or higher (Figure 2D). Anovulatory concentrations were also observed in 5 of the 6 participants who received an elagolix dose of 150 mg once daily. In one participant, P concentrations increased beginning on Day 17 following an LH increase on Day 15. In all other participants across groups, P concentrations continued to be below 5 nmol/mL 24 hours after the last dose of elagolix. P concentrations rose above 5 nmol/mL in 7 of the 10 placebo participants through Day 21 (data not shown).

Safety
All adverse events were mild or moderate in severity and no serious adverse events were reported. Hot flush and headache were the most frequently reported adverse events. In placebo participants and in the 100 mg twice daily, 150 mg once daily, 200 mg twice daily, 300 mg twice daily, and 400 mg twice daily elagolix groups, headache occurred in 54.5%, 71.4%, 50%, 57.1%, 37.5%, and 50% of participants, respectively, and hot flush occurred in 18.2%, 28.6%, 16.7%, 57.1%, 37.5%, and 33.3% of participants, respectively (Table 3). Despite the small number of participants in each group, the hot-flush rate was overall higher for the elagolix doses that were at or above 200 mg twice daily. The onset of the event of hot flush was recorded as early as Day 2. Most of these events were mild
in severity and none led to discontinuation from the study. Laboratory tests, electrocardiogram assessments, and vital signs values were clinically unremarkable.

Nine participants who received elagolix and 1 participant who received placebo reported spotting in the daily bleeding diary. In the elagolix participants, spotting occurred as early as Day 6 and lasted from 1 to 7 days. Four of these participants (1 each in the 150 mg and 400 mg groups and 2 in the 100 mg group) had vaginal hemorrhage reported as an adverse event and all events were characterized as mild in severity.

Five participants discontinued from the study due to an adverse event: one in the placebo group (gingivitis), one in the 100 mg twice daily group (allergic dermatitis following an arthropod bite), one in the 200 mg twice daily group (hypersensitivity), and 2 in the 300 mg twice daily group (alopecia and otitis media). The participant in the 200 mg twice daily group who experienced hypersensitivity had a skin reaction at the blood sampling needle insertion site approximately 8 hours after the first dose of elagolix on Day 1. On Day 6, a rash was present in several areas of the body and the elagolix dose was not administered. The participant was treated with antihistamines and systemic corticosteroids and the rash improved. The participant in the 300 mg twice daily group who experienced alopecia noted hair loss on Day 7 and elagolix dosing was discontinued on Day 9. The event was considered resolved on Day 23.

One participant in the 200 mg twice daily group reported an adverse event of amenorrhea on Day 21 that ended on Day 166. Moderate bleeding was noted on Day 60 in the diary for this participant.

Discussion

This study showed that in premenopausal women elagolix was rapidly absorbed and its pharmacokinetics was approximately dose-proportional from 100 to 400 mg twice daily, with minimal accumulation. These changes were accompanied by a rapid, dose-dependent suppression of FSH, LH, E2 and P. The maximal suppression of FSH and LH occurred at an elagolix dose of 300 mg twice daily and 200 mg twice daily or higher, respectively. The E2 suppression reached a maximum effect at doses of 200 mg twice daily or higher, and P remained at anovulatory concentrations (< 5 nmol/L) over the 21-day dosing period at doses of 100 mg twice daily or higher. Overall, the 400 mg twice daily dose of elagolix did not appear to result in additional hormone suppression beyond that observed with the 300 mg twice daily dose.

The pharmacokinetics and hormone suppressive effects of lower doses (up to 100 mg twice daily) of elagolix was first evaluated in a small, 7-day study in premenopausal women (13). In that study, administration of elagolix beginning on approximately day 7 of the menstrual cycle resulted in immediate suppression of FSH and LH, followed by suppression of E2. These initial observations were extended in the current study by evaluating the pharmacokinetics and hormone suppressive effects of higher doses (up to 400 mg twice daily) of elagolix for 21 days. In addition, in the present study, elagolix was administered within 2 days of the start of the menstrual cycle, rather than at the midpoint of follicular development as in the previous study, to achieve a more consistent hormone response to elagolix administration.
As in the previous study (13), administration of elagolix led to more pronounced suppression of LH than FSH as evidenced by sustained suppression of LH in all but the 150 mg group, but a rebound of FSH concentrations above those observed in the placebo group in the 100 and 150 mg groups. Similar results have been observed for peptide GnRH antagonists and a nonpeptide GnRH antagonist that was a precursor to elagolix (12, 14, 15).

Elagolix at doses up to 400 mg twice daily for 21 days demonstrated an acceptable safety profile in the healthy premenopausal women in this study. In all but 1 woman, menses resumed within 60 days or less upon cessation of elagolix dosing. The incidence of hot flush was slightly higher in the higher elagolix dose groups; however, the events of hot flush were mild in severity and did not lead to discontinuation from the study. These observations suggest that E2 suppression at elagolix doses of 200 mg twice daily and higher may be less profound than that observed with GnRH agonists, which lead to profound inhibition of the pituitary-ovarian axis (16, 17).

Collectively, the results of the current study and the study by Struthers et al. (13) demonstrate that elagolix can provide dose-dependent, sustained suppression of E2 concentrations, from partial suppression at 150 mg once daily to nearly full suppression at 200 and 300 mg twice daily. The ability to partially or almost fully suppress ovarian E2 production may provide new therapeutic options for management of symptoms associated with sex hormone-dependent diseases in women such as endometriosis and uterine fibroids.

The results of the current and the study by Struthers et al. (13) provided the rationale for elagolix dose selection for Phase 2 and ongoing Phase 3 clinical trials in endometriosis and uterine fibroids. The 3-month Phase 2 studies in women with endometriosis-associated pain showed promising efficacy at elagolix doses that provided partial suppression of E2 (18-20), and a 6-month study with elagolix and subcutaneous medroxyprogesterone acetate showed that both treatments had minimal impact on bone mineral density while demonstrating similar efficacy on endometriosis-associated pain (21).

Conclusions

Elagolix administration in premenopausal women allows for modulation of gonadotropin and ovarian sex hormone concentrations from partial suppression at lower doses to nearly full suppression at higher doses. The effects of elagolix on hormone suppression were rapid and readily reversible when therapy was discontinued. Elagolix has the potential to increase and expand therapeutic options for the treatment of sex hormone-dependent diseases in women.

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References


**Figure 1.** Mean + SD Elagolix Plasma Concentration-Time Profiles for a 12- or 24-Hour Dosing Interval on Day 1 and 21. QD, once daily; BID, twice daily

**Figure 2.** Mean (+ SD) Concentrations of FSH (A), LH (B), E2 (C) and P (D) During 21 Days of Dosing with Placebo or Elagolix. FSH, follicle-stimulating hormone; LH,
luteinizing hormone; E2, estradiol; P, progesterone; QD, once daily; BID, twice daily. For the placebo group, the error bars for some time points have been truncated.

**Figure 3. Mean (+SD) Concentrations of FSH, LH, and E2 after the First Dose (Day 1, Left) and Last Dose (Day 21, Right) of Elagolix.** FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; QD, once daily; BID, twice daily. On Day 21, the last dose of elagolix was administered at 0 hr for the 150 mg QD dose and 12 hr for the 200 mg BID dose.

**Table 1. Participant Demographics and Disposition**

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<th>100 mg BID N = 7</th>
<th>150 mg QD N = 6</th>
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<th>300 mg BID N = 8</th>
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<td>3 (50.0)</td>
<td>3 (42.9)</td>
<td>6 (75.0)</td>
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**Table 2. Elagolix Pharmacokinetic Parameters**

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<th>200 mg BID N = 7</th>
<th>300 mg BID N = 8</th>
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<td>1.3 (1.0 - 1.5)</td>
<td>1.0 (0.5 - 1.5)</td>
<td>1.3 (0.5 - 1.5)</td>
<td>1.3 (0.5 - 2.0)</td>
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<td>(C_{\text{max}}), ng/mL</td>
<td>285 ± 89.2</td>
<td>507 ± 207</td>
<td>712 ± 362</td>
<td>1479 ± 740</td>
<td>1928 ± 783</td>
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<td>AUCₜ, ng·hr/mL</td>
<td>787 ± 288</td>
<td>1331 ± 487</td>
<td>1813 ± 876</td>
<td>3509 ± 1556</td>
<td>4918 ± 2070</td>
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<td>(C_{\text{max}}/\text{Dose}), ng/mL/mg</td>
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<td>3.38 ± 1.38</td>
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<tr>
<td>(T_{\text{max}}), hr (a)</td>
<td>1.0 (0.5 - 1.5)</td>
<td>1.0 (0.5 - 1.0)</td>
<td>1.0 (0.5 - 1.5)</td>
<td>1.3 (0.5 - 1.5)</td>
<td>1.3 (0.5 - 1.5)</td>
</tr>
<tr>
<td>(C_{\text{max}}), ng/mL</td>
<td>278 ± 131</td>
<td>574 ± 164</td>
<td>774 ± 530</td>
<td>1200 ± 544</td>
<td>1758 ± 308</td>
</tr>
<tr>
<td>AUCₜ, ng·hr/mL</td>
<td>779 ± 373</td>
<td>1292 ± 403</td>
<td>1725 ± 990</td>
<td>2826 ± 1231</td>
<td>3716 ± 592</td>
</tr>
<tr>
<td>(t_{1/2}), hr (^c)</td>
<td>4.05 ± 2.54</td>
<td>6.62 ± 3.20</td>
<td>4.29 ± 0.47</td>
<td>5.32 ± 1.52</td>
<td>5.62 ± 1.82</td>
</tr>
<tr>
<td>(R_{\text{AUC}})</td>
<td>0.98 ± 0.15</td>
<td>0.98 ± 0.07</td>
<td>0.89 ± 0.17</td>
<td>0.78 ± 0.09</td>
<td>0.84 ± 0.29</td>
</tr>
<tr>
<td>(C_{\text{trough}}), ng/mL (^e)</td>
<td>5.06 ± 4.25</td>
<td>0.84 ± 0.38</td>
<td>5.92 ± 4.05</td>
<td>9.78 ± 4.68</td>
<td>11.9 ± 5.52</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Cmax/Dose, ng/mL/mg</th>
<th>2.78 ± 1.32</th>
<th>3.83 ± 1.09</th>
<th>3.87 ± 2.65</th>
<th>4.00 ± 1.81</th>
<th>4.40 ± 0.77</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC/Dose, ng•hr/mL/mg</td>
<td>7.79 ± 3.73</td>
<td>8.61 ± 2.68</td>
<td>8.62 ± 4.95</td>
<td>9.42 ± 4.10</td>
<td>9.29 ± 1.48</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD unless noted otherwise.

T<sub>max</sub>, time to maximum plasma concentration; C<sub>max</sub>, maximum plasma concentration; AUC, area under the plasma concentration-time curve, where τ (tau) is the dosing interval (i.e., 12 hours for twice daily and 24 hours for once daily dosing); t<sub>1/2</sub>, terminal phase elimination half-life; R<sub>ac</sub>, accumulation ratio based on AUC; C<sub>trough</sub>, trough concentration 12 or 24 hours after dosing; C<sub>max</sub>/Dose, dose-normalized C<sub>max</sub>; AUC<sub>τ</sub>/Dose, dose-normalized AUC<sub>τ</sub>.

a. Median (range)
b. N = 6 on Study Day 21 for each of the groups.
c. Harmonic mean, pseudo-standard deviation.
d. Accumulation ratio calculated as the ratio of Study Day 21 AUC<sub>τ</sub> to Study Day 1 AUC<sub>τ</sub>.
e. C<sub>trough</sub> is C<sub>12</sub> for twice daily groups and C<sub>24</sub> for the once daily group.

Table 3. Treatment-Emergent Adverse Events Reported by Two or More Participants in any Treatment Group

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Preferred Term</th>
<th>Placebo N = 11</th>
<th>100 mg BID N = 7</th>
<th>150 mg QD N = 6</th>
<th>200 mg BID N = 7</th>
<th>300 mg BID N = 8</th>
<th>400 mg BID N = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>10 (90.9)</td>
<td>7 (100)</td>
<td>4 (66.7)</td>
<td>7 (100)</td>
<td>4 (50.0)</td>
<td>5 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2 (18.2)</td>
<td>2 (28.6)</td>
<td>1 (16.7)</td>
<td>3 (42.9)</td>
<td>1 (12.5)</td>
<td>3 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (18.2)</td>
<td>0</td>
<td>0</td>
<td>2 (33.3)</td>
<td>1 (14.3)</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1 (14.3)</td>
<td>2 (33.3)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (27.3)</td>
<td>0</td>
<td>2 (33.3)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (18.2)</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Infections &amp; Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (9.1)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>3 (42.9)</td>
<td>0</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6 (54.5)</td>
<td>5 (71.4)</td>
<td>3 (50.0)</td>
<td>4 (57.1)</td>
<td>3 (37.5)</td>
<td>3 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Altered</td>
<td>1 (9.1)</td>
<td>0</td>
<td>1 (16.7)</td>
<td>2 (28.6)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Hemorrhage</td>
<td>0</td>
<td>2 (28.6)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>2 (18.2)</td>
<td>2 (28.6)</td>
<td>1 (16.7)</td>
<td>4 (57.1)</td>
<td>3 (37.5)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%). BID, twice daily; QD, once daily