

## **Suppression of Gonadotropins and Estradiol in Premenopausal Women by Oral Administration of the Nonpeptide GnRH Antagonist Elagolix**

Abbreviated Title: HPG Suppression by an Oral Nonpeptide GnRH Antagonist

R. Scott Struthers, Andrew J. Nicholls, John Grundy, Takung Chen, Roland Jimenez, Samuel S.C. Yen\*, Haig P. Bozigian

Neurocrine Biosciences Inc.(R.S.S., A.N., J.G., T.C., R.J., H.P.B), 12790 El Camino Real, San Diego, California 92130 and Department of Reproductive Medicine (S.C.C.Y.), University of California, San Diego

Corresponding Author & to whom reprint requests should be addressed:

R. Scott Struthers: Neurocrine Biosciences Inc., 12780 El Camino Real, San Diego, CA 92130. Tel: 858-617-7740; Fax 858-617-7696; E-mail: [sstruthers@neurocrine.com](mailto:sstruthers@neurocrine.com)

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Précis: Oral administration of the nonpeptide GnRH antagonist, elagolix, to premenopausal women results in transient suppression of gonadotropins, and more sustained suppression of estradiol.

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## **ABSTRACT**

**Context:** Parenteral administration of peptide GnRH analogs is widely employed for treatment of endometriosis, fibroids and in assisted-reproductive therapy protocols. Elagolix is a novel, orally available nonpeptide GnRH antagonist.

**Objective:** To evaluate the safety, pharmacokinetics and inhibitory effects on gonadotropins and estradiol of single dose and 7-day elagolix administration to healthy premenopausal women.

**Design:** This was a first-in-human, double-blind, placebo-controlled, single- and multiple dose study with sequential dose-escalation.

**Participants:** Fifty-five healthy, regularly cycling pre-menopausal women.

**Interventions:** Subjects were administered a single oral dose of 25 to 400 mg or placebo. In a second arm of the study, subjects received placebo or 50, 100, or 200 mg q.d. or 100 mg b.i.d. for seven days. Treatment was initiated on Day 7 ( $\pm 1$ ) following onset of menses.

**Main Outcome Measures:** Safety, tolerability, pharmacokinetics and serum LH, FSH and estradiol concentrations.

**Results:** Elagolix was well-tolerated and rapidly bioavailable following oral administration. Serum gonadotropins declined rapidly. Estradiol was suppressed by 24 hours in subjects receiving  $\geq 50$  mg/day. Daily (50 to 200 mg) or twice daily (100 mg) administration for 7 days maintained low estradiol levels ( $17 \pm 3$  pg/mL to  $68 \pm 46$  pg/mL) in most subjects during late follicular phase. Effects of the compound were rapidly reversed following discontinuation.

**Conclusions:** Oral administration of a nonpeptide GnRH antagonist, elagolix, suppressed the reproductive endocrine axis in healthy premenopausal women. These results suggest that elagolix may enable dose-related pituitary and gonadal suppression in premenopausal women as part of treatment strategies for reproductive hormone-dependent disease states.

### Introduction

Peptide analogs of GnRH are now widely used in a variety of clinical applications for suppression of the reproductive endocrine axis (1-3). Continuous administration of peptide agonists (typically as depot formulations) cause the down regulation of pituitary gonadotropin secretion, and profound suppression of gonadal function following a stimulatory phase of one to two weeks (4, 5). While complete gonadal suppression is desirable for treatment of sex steroid dependent cancers of the prostate or breast, non-malignant conditions (such as endometriosis or uterine fibroids) can be treated by maintaining estrogen at low, but not necessarily menopausal, levels(6). Accordingly, various “add-back” strategies have been successfully employed where GnRH agonist gonadal suppression is accompanied by co-administration of estrogens, progestins or combinations to relieve menopausal symptoms (such as hot flashes) and prevent bone-loss (7, 8). However, while add-back hormonal levels can be controlled, agonist induced down regulation offers limited opportunity to control the degree of HPG suppression, although some range of suppression has been achieved with “draw-back” approaches (9).

Peptide GnRH antagonists immediately reduce gonadal steroid levels (10) and avoid the initial stimulatory phase of the agonists, eliminating the flare in symptoms (11, 12) and resulting in

more rapid onset of therapeutic effect (13, 14). When utilized as part of *in vitro* fertilization protocols, frequency of injection and duration of treatment is reduced compared to peptide agonists (2). Varying the dose of an antagonist may also enable a degree of control over the extent of pituitary suppression and hence control over circulating levels of estrogens(15, 16).

However, because of their peptide structure existing GnRH antagonists require frequent injections or implantation of long acting depots. Drawbacks include injection site reactions and inability to discontinue therapy should tolerability or safety concerns arise. In order to develop orally active GnRH antagonists, several groups have explored nonpeptide, small molecule structures with high affinity for the GnRH receptor (for a recent review see reference (17)). We have previously described gonadotropin suppression in postmenopausal women by oral administration of a first generation nonpeptide GnRH antagonist, NBI-42902 (18). However, in subsequent studies this compound showed inhibition of the liver P450 enzymes CYP3A4 and CYP2C19 leading to discontinuation of its clinical development. This liability was overcome with a second generation nonpeptide GnRH antagonist, elagolix, R-(+)-4-{2-[5-(2-Fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino}-butyrate (19). It is a highly potent ( $K_D = 54$  pM) antagonist of the human GnRH

receptor and suppresses LH in castrate macaques following oral administration. In the present study, we evaluate the safety, tolerability, pharmacokinetics and effect on gonadotropins and estrogen of this compound following oral administration to premenopausal women in mid-follicular phase of the menstrual cycle.

## Materials and Methods

### *SUBJECTS*

All subjects participating in the study gave written informed consent prior to screening for eligibility. The study was approved by the local Ethics Committee and clinical procedures were performed at MDS Pharma Services (Phoenix, AZ). Subjects were required to have a history of regular menstrual cycles ( $28 \pm 2$  days) for  $\geq 2$  years and a positive ovulation test between days 11 and 16 of the menstrual cycle immediately preceding dosing. Each participant underwent a physical examination, including a pelvic examination.

A summary of subject demographics is provided in Table 1. 30 healthy premenopausal female subjects participated in and completed the single dose escalation phase of this study. Subject ages and weights ranged from 18–37 years [mean ( $\pm$ SD) =  $27.8 \pm 6.1$  years] and 50.4–76.0 kg [mean ( $\pm$ SD) =  $61.6 \pm 6.2$  kg], respectively. Body mass index ranged from 19.5 to 27.4  $\text{kg}/\text{m}^2$  [mean ( $\pm$ SD) =  $23.6 \pm 2.1$   $\text{kg}/\text{m}^2$ ].

25 healthy premenopausal female subjects participated in, and 24 of these subjects completed, the multiple dose-escalation phase of this study. Subject ages and weights ranged from 19–39 years [mean ( $\pm$ SD) =  $25.6 \pm 4.7$  years] and 44.7–76.2 kg [mean ( $\pm$ SD) =  $58.8 \pm 7.7$  kg], respectively. Body mass index ranged from 18.0 to 26.2  $\text{kg}/\text{m}^2$  [mean ( $\pm$ SD) =  $22.3 \pm 2.2$   $\text{kg}/\text{m}^2$ ].

### *STUDY DESIGN*

This was a Phase I, randomized, double-blind, placebo-controlled, sequential dose escalation study. Five cohorts of six subjects each received a single dose of elagolix (25, 50, 100, 200 or 400 mg) or placebo (elagolix:placebo = 5:1). An additional three cohorts, each comprising six subjects, received once daily doses of elagolix (50, 100 or 200 mg) or placebo (elagolix:placebo = 5:1) for seven days. The final cohort of seven subjects received elagolix (100 mg) or placebo twice daily (elagolix:placebo = 5:2) for seven days. The first multiple dose cohort was enrolled after satisfactory safety results were observed for the first three single dose cohorts. Initial administration was 7 ( $\pm 1$ ) days following the onset of menstruation. Antagonist (or placebo) was administered at 0800 following an overnight fast. Blood samples were collected at the indicated timepoints for serum hormone or plasma antagonists measurements.

Adverse events, including hot flashes, were characterized as mild, moderate, or severe. Mild: causing no limitation of usual activities; the patient may experience slight discomfort. Moderate: causing some limitation of usual activities; the patient may experience annoying discomfort. Severe: causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.

#### ASSAYS

Plasma concentrations of elagolix and metabolite NBI-61962 (R-(+)-4-{2-[5-(2-Fluoro-3-hydroxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenylethylamino}-butyrate) were determined by a validated method (Neurocrine Biosciences, Inc., San Diego, CA) based on liquid chromatography with tandem mass spectroscopy. The lower and upper limits of quantification were 0.50 and 250.0 ng/mL, respectively. The precision (coefficient of variation, %CV) for elagolix ranged from 3.0% to 5.6% and for NBI-61962 ranged from 4.7% to 6.7% across concentrations and analytical batches. Mean accuracy (expressed as % bias) for elagolix ranged from 0.8% to 0.9% and for NBI-61962 ranged from 0.5% to 0.7% across concentrations and analytical batches. Concentrations of elagolix are typically expressed as ng/mL of the free acid and can be converted to nM by multiplying by 1.58.

Serum concentrations of LH and FSH were determined by validated immunoassay methods using chemluminescence (MDS Pharma Services, Lincoln, NE). The lower and upper limits of quantification for LH were 1.01 and 50.5 mIU/mL, respectively. The lower and upper limits of quantification for FSH were 2 and 49 mIU/mL, respectively.

Serum concentrations of E2 were determined by a validated method (MDS Pharma Services, Montreal, Quebec, Canada) based on liquid chromatography with tandem mass spectroscopy. The lower and upper limits of quantification were 2.50 and 500 pg/mL, respectively.

#### DATA ANALYSIS

Derived plasma and urine PK parameters were determined using standard non-compartmental methods from the available plasma and urine data of parent drug (elagolix) and metabolite (NBI-61962) from each individual subject. Parameter calculations were performed using WinNonlin<sup>®</sup> Professional Version 4.1 (Pharsight Corporation, Mountain View, CA), with any values below the limit of quantitation set to zero prior to calculation.

This was a Phase I safety and tolerability study without pre-specified statistical tests or formal hypothesis testing. Post hoc analysis of serum hormone concentrations was carried out by ANOVA-based comparisons of mean values and Wilcoxon rank-sum tests for comparisons of

median values. Differences between elagolix dose groups and placebo at selected timepoints were tested for significance using a two-tailed t-test. All statistical analyses were performed using SAS Release 8.2 (SAS Institute, Cary NC). Differences were considered significant if  $p < 0.05$ .

## Results

### *SIDE EFFECT AND SAFETY PROFILE*

A total of 55 healthy, regularly-cycling women ranging in age from 18 to 39 years were enrolled in the study. There were no relevant differences in the mean age, height, weight or BMI among cohorts (Table I).

Elagolix was well tolerated both during the single dose escalation up to 400 mg and the multiple dose escalation up to 200 mg q.d. and 100 mg b.i.d. for 7 days. There were no clinically significant safety findings across dose groups, between single- and multiple dose cohorts, or between elagolix and placebo treatments. One subject experienced a serious adverse event (AE) following a single dose of elagolix 25 mg (pelvic abscess, which was surgically drained at a hospital and not considered drug-related). All subjects completed the study protocol with the exception of one who terminated prior to collection of day 9 samples due to family relocation.

Among the single dose cohorts, the most frequently experienced adverse events were

headache (4/25 elagolix and 1/5 placebo) and nausea (2/25 elagolix and 2/5 placebo). Among the multiple-dose cohorts of the study, the most frequently experienced AEs overall were headache (15/20 elagolix and 3/5 placebo), abdominal pain (6/20 elagolix and 0/5 placebo) and hot flashes. The majority of AEs were reported as mild in intensity and a few as moderate; none was reported as severe. Because of the prior history of histamine related adverse events associated with peptide antagonists, it is interesting to note that the nonpeptide, elagolix, showed little evidence of similar problems. The only adverse event that could remotely be attributed to a “histamine effect” was one subject reporting a “small rash on left arm” shortly after oral administration of a single dose of elagolix (100 mg). Other nonpeptide GnRH antagonists do not exhibit histamine releasing activity using *in vitro* rat mast cell assays (17, 20), and elagolix is inactive in this assay as well (unpublished observation).

Hot flashes were reported by subjects as adverse events as described above. Six subjects receiving elagolix experienced hot flashes (all mild, except one moderate) during the treatment period. These appeared to be dose related (100 mg, 1 subject; 200 mg, 2 subjects; 100 mg b.i.d., 3 subjects) and more prevalent in subjects with the lowest estrogen levels. Two subjects (both in the 100 mg b.i.d. group) experienced hot flashes on more than one treatment day (subject 61, 6 events on 5 days; subject 62, 4 events on 3

days). Elagolix was not associated with the high-intensity hot flashes that commonly occur with profound E2 suppression such as is achieved with GnRH agonist depots (21).

#### *ELAGOLIX PLASMA CONCENTRATIONS AND PHARMACOKINETIC PARAMETERS*

Mean elagolix plasma concentration-time profiles by dose group for the single dose cohort are shown in Figure 1. Summary statistics of plasma pharmacokinetic parameters by dose group for the single dose cohort are provided in Table 2.

Elagolix was rapidly absorbed after oral administration, with median  $T_{max}$  values ranging from 0.5 to 1 hour and reaching peak plasma concentrations from  $55.5 \pm 23.8$  to  $1504 \pm 492$  ng/mL (88 nM to 2.4  $\mu$ M) in the 25 and 400 mg groups, respectively. Dose-dependent increases in both mean peak ( $C_{max}$ ) and total (AUC) exposure measures were observed.

Summary statistics of elagolix plasma pharmacokinetic parameters by dose group for the multiple dose cohort are provided in Table 3. The exposure of the 50 and 200 mg groups were comparable to those obtained in the corresponding single dose cohorts. The 100 mg group showed lower exposure ( $AUC_{0-\infty}=466 \pm 150$  ng·h/mL) compared to the corresponding 100 mg group in the single dose cohort ( $AUC_{0-\infty}=1069 \pm 603$  ng·h/mL). Little or no plasma accumulation and apparent time-invariant PK

were observed over the 7 days of dosing for both the q.d. and b.i.d. regimens.

Overall, exposure to high concentrations of elagolix in plasma was relatively brief. In the single dose arm, mean plasma  $t_{1/2}$  ranged from 2.4 to 6.3 hours. Generally comparable concentration-time profiles were observed across all q.d. dose levels tested on either day 1 or 7. Relatively low mean renal clearance ( $CL_r$ ) of NBI-56418 was observed (range: 2.1–3.0 L/h), with less than 3% of the administered doses excreted intact in urine.

The primary metabolite identified by *in vitro* microsomal studies was NBI-61962. This compound appeared in the systemic circulation rapidly following elagolix administration. However, relatively low plasma exposure to NBI-61962 was observed, with mean peak ( $C_{max}$ ) and total (AUC) exposure measures being  $\leq 3\%$  of the corresponding values for the parent drug. Because of its reduced potency ( $K_i = 3.5$  nM) and relatively low plasma exposure, this metabolite is unlikely to contribute significantly to the biological activity of elagolix in this study.

#### *HPG SUPPRESSION IN SINGLE DOSE COHORTS*

Responses of LH, FSH and estradiol to oral administration of elagolix in the single dose cohorts are shown in Figure 1. At the lowest dose evaluated (25 mg), plasma concentrations of elagolix rapidly reach  $55.5 \pm 23.8$  ng/ml (mean  $\pm$  SEM or 89 nM) which are >1000-fold

excess of the affinity of the antagonist for the GnRH receptor ( $K_D = 54 \text{ pM}$ ). Accordingly, LH concentrations begin to decline almost immediately. The rate of decline of all elagolix dose groups are similar and consistent with the rate of clearance of LH from the circulation (22). These data suggest that all dose groups achieve immediate blockade of the GnRH receptor. By 4 hours following antagonist administration, LH levels of 22% to 35% of predose baseline are achieved in all groups receiving antagonist ( $p < <0.0001$  vs placebo). In contrast, LH levels of subjects receiving placebo are relatively unchanged. After 4 to 6 hours serum LH levels begin to recover with higher doses of antagonist resulting in more prolonged suppression. However, all groups return to approximately baseline levels by 24 hours consistent with reduced plasma levels of the antagonist. Thus, a transient suppression of LH is achieved and varying the dose of antagonist controls the duration of suppression throughout the day.

FSH levels follow a similar pattern to LH, although suppressed to a lesser extent and declining more slowly. All groups receiving antagonist show reduced FSH (62% - 71% of baseline) between 8 and 12 hours, ( $p < 0.02$  vs placebo). This is consistent with slower removal of FSH from the circulation and has been observed repeatedly with peptide GnRH antagonists(23).

In contrast to gonadotropins, estradiol in the elagolix treated subjects receiving 50, 200 or

400 mg remains partially suppressed (42% to 65% of baseline) at 24 hours ( $p < 0.02$  vs placebo). Suppression of estradiol in the 100 mg group does not quite reach statistical significance ( $p = 0.057$  vs placebo). Differences from placebo in these groups were no longer apparent by 48 hours (data not shown). Mean estradiol concentrations of the 25 mg group appeared similar to placebo. Although it appears that LH may begin to break through antagonist blockade at the 6-hour timepoint in this dose-group, and has returned to normal by 18 hours, the basis for the difference in estradiol suppression between these subjects and those receiving higher doses of elagolix remains unclear. Likely additional studies involving larger numbers of subjects, and possibly more frequent blood sampling will be required to characterize the PK/PD relationships between antagonist and gonadotropin concentrations and the resulting suppression of estradiol.

#### *HPG SUPPRESSION IN MULTIPLE DOSE COHORTS*

Data from the single dose cohorts suggested that transient suppression of gonadotropins by oral administration of  $\geq 50$  mg elagolix could result in more prolonged suppression of estradiol synthesis. Accordingly, as safety data from the single dose escalation became available, subjects were initiated in the multiple dose cohorts.

Median gonadotropin and estradiol levels on the day before and during the 7-day treatment, and subsequent follow-up periods are shown in

Figure 2. Similar to the single dose cohorts LH is rapidly suppressed reaching a nadir between 4 and 6 hours following administration of the compound (Figure 2, right). At these times, LH levels frequently approached the limit of detection of the assay (1 mIU/mL) in the treated groups. However, LH levels return to predose levels (or above) by the next morning in the q.d. cohorts as illustrated by mean individual LH values of  $103 \pm 12\%$  to  $149 \pm 23\%$  in these cohorts compared to  $98 \pm 4\%$  in placebo. The 100 mg b.i.d. cohort continued to show some level of suppression at this timepoint ( $77 \pm 13\%$ ). FSH levels following initial antagonist administration are similarly suppressed and recover, with the exception of the 100 mg b.i.d. cohort where subjects continued to show suppression of FSH ( $74 \pm 7\%$  of individual baselines) compared to placebo ( $105 \pm 9\%$ ) in the pre-dose serum sample the following morning. All cohorts and all individuals receiving elagolix (with the exception of one subject receiving 200 mg q.d. who will be discussed below) showed a reduction from baseline estradiol concentrations on the first day following administration of elagolix.

Less frequent sampling data is available for days 2 through 7 of treatment. While samples at 6 hrs ( $E_2$ ) and 12 hrs (LH & FSH) were obtained on day 2, sampling frequency for hormones was reduced to once daily (immediately prior to treatment) for the remaining treatment and follow-up period. Hence daily hormone values

during this period were obtained at a time when antagonist concentrations are at a minimum and the transient daily excursion to reduced gonadotropin levels would not be observed based on the more frequent sampling data from day 1. Thus, while day 1 suppression of LH and FSH is apparent in all cohorts, further suppression in days 2-7 of treatment is not observed (Figure 2). Rather, the 50 and 100 mg cohorts may show some apparent elevation of predose LH and FSH levels, respectively.

In contrast, estradiol levels appear suppressed in the 50 and 200 mg q.d. and 100 mg b.i.d. cohorts while estradiol levels in the placebo cohort continue to rise consistent with follicular development. However, only the 100 mg b.i.d. group showed consistent statistically significant suppression compared to placebo for most of the treatment period ( $p < 0.05$  for days 2-7). Despite an initial decline in estradiol levels of subjects in the 100 mg q.d. cohort, median levels tended to rise in parallel with the placebo group, albeit perhaps somewhat delayed. Following elagolix discontinuation, serum  $E_2$  levels rose in all dose groups over the course of days 8 through 10. All evaluable subjects menstruated within 35 days of initial elagolix (or placebo) administration.

Figure 3 shows pre- and during treatment mean ( $\pm$  range) estradiol levels for all individuals in the multiple-dose arm of this study. Individuals receiving placebo started with plasma  $E_2$  concentrations between 24 and 75 pg/mL and all reach higher concentrations over the next 7 days

consistent with normal progression of the menstrual cycle. However, in all four elagolix treated groups, most women maintained or lowered mean E<sub>2</sub> levels during the 7 days of treatment. Further, variability in E<sub>2</sub> was greatly diminished by elagolix treatment and high plasma concentrations consistent with a mid cycle estrogen surge were not observed in most subjects. In the 100 mg b.i.d. cohort, mean morning E<sub>2</sub> levels for days 1 through 7 reached 17 ± 3 pg/mL indicating a high degree of gonadal suppression. In the q.d. cohorts mean E<sub>2</sub> levels during the treatment period ranged from 34 ± 4 pg/mL to 68 ± 46 pg/mL although the higher end of this range is skewed by two subjects who “escaped” suppression (one each in the 100 mg q.d. and 200 mg q.d. groups). The “escape” subject in the 100 mg q.d. cohort (subject 051) entered with relatively high plasma E<sub>2</sub> (83 pg/mL at 24 hr prior to dosing) and after a decrease upon initial administration of elagolix, continued to progress to even higher levels reaching 342 pg/mL on the morning of day 7 (14 days following onset of menstruation). This was followed by LH/FSH surge on day 8. The “escape” subject in the 200 mg q.d. cohort (subject 055) also showed high E<sub>2</sub> (102 pg/mL) and FSH (12.1 mIU/mL) immediately prior to administration of elagolix. Despite initial decreases in LH, FSH and E<sub>2</sub>, she also progressed to increasingly higher E<sub>2</sub> concentrations followed by a LH/FSH surge on day 8 (15 days following onset of menstruation). Plasma elagolix concentrations of both these

subjects were consistent with other subjects receiving the same dosage.

## Discussion

These results provide the first demonstration of the suppression of the reproductive endocrine axis in premenopausal women by an oral GnRH antagonist. Oral administration of a second generation nonpeptide GnRH antagonist, elagolix, to healthy premenopausal women results in its rapid absorption and immediate suppression of LH and FSH, followed by a somewhat delayed dose-related suppression of estradiol. Because of its relatively rapid clearance and short plasma residence time (2.5 to 4.1 hours) pituitary suppression is only maintained for a portion of the day (25 to 400 mg), and baseline gonadotropin levels return by 24 hours. However, suppression of estradiol is more prolonged at doses of 50 mg and higher. Daily (50 to 200 mg) or twice-daily (100 mg) administration for 7 days during mid-follicular phase results in a prevention of high mid-cycle estradiol levels in most subjects. Overall, the compound was safe and well tolerated.

Previous reports of daily subcutaneous administration of the peptide GnRH antagonists cetrorelix and ganirelix to cycling premenopausal women showed results similar to those presented here including a more pronounced suppression of circulating LH than FSH (16, 24). This is also consistent with our previous report of another nonpeptide GnRH

antagonist (NBI-42902) in postmenopausal women (18). The daily excursions to reduced gonadotropin levels and partial suppression of estradiol observed with once daily elagolix administration is in marked contrast to the continuous and profound suppression observed with peptide agonist depots (3).

As illustrated by the two “escape” subjects, the timing of onset of antagonist exposure during the menstrual cycle may contribute the subsequent estradiol response. The developing ovarian follicle varies in its tolerance to gonadotropin withdrawal and the dominant follicle becomes increasingly controlled by local factors during late follicular phase and more resistant to short-term gonadotropin deprivation (25, 26). This variability in follicular response to gonadotropin suppression may explain the two “escape” subjects (one in the 100 mg q.d. group and one in the 200 mg q.d. group) who showed progression to high estradiol levels despite gonadotropin suppression by elagolix. Although ultrasound observation of follicular status was not made, both subjects started treatment with somewhat higher estradiol levels than others in the cohort consistent with a more advanced stage of follicular development. Thus a more consistent response might be expected with onset of treatment earlier in the menstrual cycle.

Overall, these data indicate that oral administration of a nonpeptide GnRH antagonist can produce dose-related suppression of the reproductive endocrine axis. Studies in larger

numbers of subjects are required to determine the reliability of gonadal suppression by this compound. In addition, at the once daily doses studied, gonadotropins undergo excursions to reduced serum levels for a portion of the day resulting in a partial suppression of ovarian estradiol secretion. The effect of this regimen on progression of the overall menstrual cycle is unknown and requires longer term studies. The overall safety profile and endocrine responses in this first-in-human phase I study supports additional clinical studies to characterize these longer term responses in larger groups of women. These studies, as well as exploratory studies of efficacy for pain relief in patients with endometriosis have been completed and will be described in detail elsewhere.

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## Figure Legends

**Figure 1.** Time course of plasma elagolix and serum gonadotropin and estrogen levels in the single dose cohorts. Subjects were administered 25 mg (●), 50 mg (△), 100 mg (▲), 200 mg (▽) or 400 mg (◆) of elagolix or placebo (○) at t=0. Data shown are mean ( $\pm$  SEM). Changes in LH, FSH and E<sub>2</sub> are shown as the mean percentage of each individual's average predose serum concentration measured 24 hours prior to and immediately prior to administration of antagonist.

**Figure 2.** Effect of elagolix on serum gonadotropin and estrogen levels over 7 days of treatment. Subjects were administered 50 mg (△), 100 mg (▲), 200 mg (▽) of elagolix once daily, 100 mg (▼) twice daily or placebo (○) for 7 days beginning at ~08:00 on day 0. Subjects were scheduled such that day 0 was  $7 \pm 1$  days following onset of spontaneous menstruation. Median hormone levels of each dose group are shown (error bars indicate interquartile range). Right panels show the same data as left panels, but with an expanded x-axis to see dynamics of hormonal responses on day one and two. Some points are slightly offset along the x-axis for clarity.

**Figure 3.** Individual serum E<sub>2</sub> concentrations before and after elagolix administration. Data shown are mean  $\pm$  range for each individual subject. Pre-dose mean concentrations were calculated from the serum samples taken 24 hrs and immediately prior to initial administration of elagolix or placebo. Post-dose concentrations are the mean of samples taken at 24 hour intervals for 7 days following initial administration of elagolix or placebo (corresponding to days 1 through 7 in Figure 2).

## TABLES

Table 1. Selected demographic characteristics of subjects.

	Study Cohorts	
	Single Dose N = 30	Multiple Dose N = 25
Age (yr)	27.8 ± 6.1 [18.0 – 37.0]	25.6 ± 4.7 [19.0 – 39.0]
Height (cm)	162 ± 7 [146 – 177]	162 ± 7 [150 – 181]
Weight (kg)	61.6 ± 6.2 [50.4 – 76.0]	58.8 ± 7.7 [44.7 – 76.2]
BMI (kg/m <sup>2</sup> )	23.6 ± 2.1 [19.5 – 27.4]	22.3 ± 2.2 [18.0 – 26.2]

Data are presented as mean ± SD [range].

Table 2. Pharmacokinetic parameters in single dose cohorts

Parameter	25 mg N = 5	50 mg N = 5	100 mg N = 5	200 mg N = 5	400 mg N = 5
AUC <sub>0-t</sub> (ng·h/mL)	142 ± 65	242 ± 80	1062 ± 601	1793 ± 408	3770 ± 1502
AUC <sub>0-∞</sub> (ng·h/mL)	146 ± 67	249 ± 81	1069 ± 603	1798 ± 407	3778 ± 1505
C <sub>max</sub> (ng/mL)	55.5 ± 23.8	86.3 ± 42.9	397 ± 241	707 ± 211	1504 ± 492
T <sub>max</sub> (h)	0.5 [0.5 – 1.0]	0.5 [0.5 – 1.0]	0.5 [0.3 – 1.0]	0.5 [0.5 – 1.5]	1.0 [0.5 – 1.1]
t <sub>1/2</sub> (h)	2.4 ± 0.7	2.6 ± 1.1	6.1 ± 2.1	5.4 ± 1.4	6.3 ± 2.3
MRT (h)	2.7 ± 0.3	3.0 ± 0.4	3.2 ± 0.3	2.9 ± 0.2	2.9 ± 0.5

Data are presented as mean ± SD, except for T<sub>max</sub> which is presented as median [range].

Table 3. Pharmacokinetic parameters in multiple-dose cohorts

Parameter	50 mg N = 5	100 mg N = 5	200 mg N = 5	100 mg (bid)* N = 5
Day 1				
AUC <sub>0-t</sub> (ng·h/mL)	276 ± 102	458 ± 152	1554 ± 284	675 ± 131
AUC <sub>0-∞</sub> (ng·h/mL)	283 ± 104	466 ± 150	1560 ± 285	685 ± 128
C <sub>max</sub> (ng/mL)	103 ± 52	205 ± 90	721 ± 121	281 ± 93
T <sub>max</sub> (h)	0.5 [0.5 – 2.0]	0.5 [0.4 – 1.0]	0.5 [0.3 – 0.5]	0.7 [0.5 – 1.0]
t <sub>1/2</sub> (h)	5.7 ± 3.1	4.8 ± 2.6	4.2 ± 0.6	2.4 ± 0.6
MRT (h)	3.9 ± 1.1	3.2 ± 0.3	2.7 ± 0.3	2.5 ± 0.5
Day 7				
AUC <sub>0-t</sub> (ng·h/mL)	305 ± 154	497 ± 115	1513 ± 199	690 ± 168
AUC <sub>0-∞</sub> (ng·h/mL)	314 ± 162	507 ± 113	1530 ± 201	704 ± 169
C <sub>max</sub> (ng/mL)	112 ± 59	228 ± 96	626 ± 195	250 ± 72
T <sub>max</sub> (h)	0.6 [0.5 – 1.0]	0.5 [0.5 – 0.5]	0.5 [0.5 – 1.1]	0.5 [0.5 – 1.0]
t <sub>1/2</sub> (h)	8.2 ± 6.9	7.0 ± 4.3	10.8 ± 14.0	2.2 ± 0.5
MRT (h)	4.1 ± 0.9	3.1 ± 0.8	3.3 ± 1.0	2.9 ± 0.3

Data are presented as mean ± SD, except for T<sub>max</sub> which is presented as median [range].

\*PK parameter values for 100 mg b.i.d. dose group were determined from data in the first 12 hours following administration of compound and reflect the morning dose (100 mg) only. Most of the AUC from the afternoon dose would not have been measured due to the lack of blood samples between 12 & 24 hrs.

Figure 1.

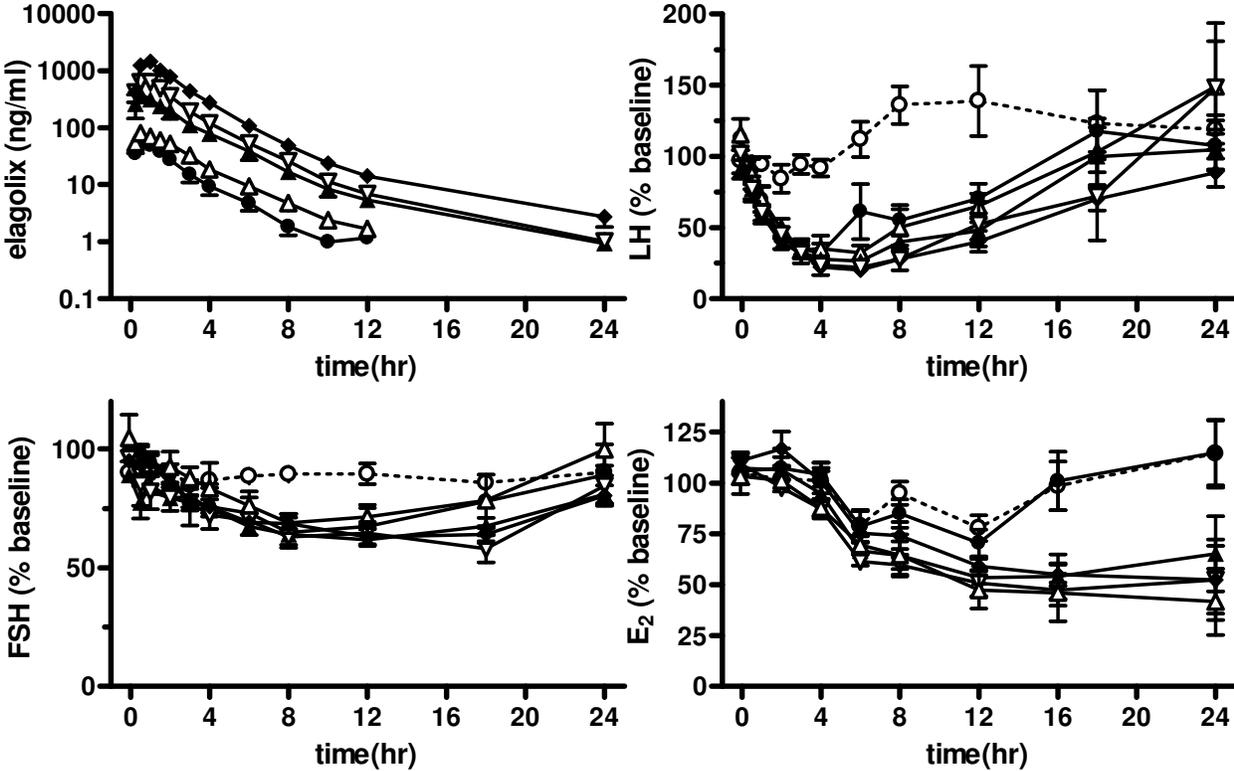


Figure 2.

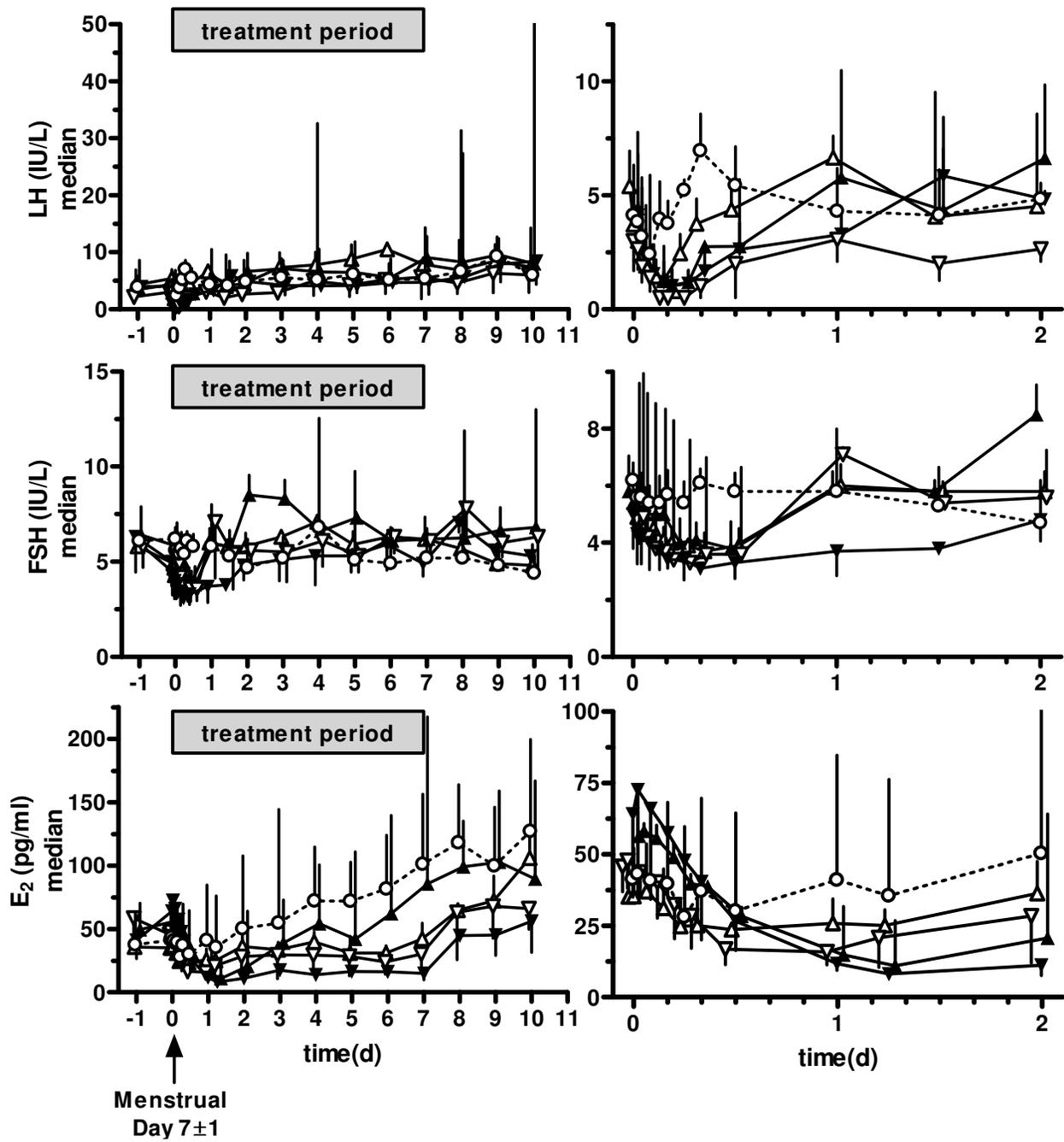


Figure 3.

