CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213388Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Division of Urology, Obstetrics and Gynecology (DUOG)

Addendum to Summary Unireview

NDA 213388 Oriahnn

Applicant: AbbVie

Date of Review: May 29, 2020

This is an addendum to the summary review dated May 29, 2020 for NDA 213388 Oriahnn, proposed to treat heavy menstrual bleeding (HMB) associated with uterine fibroids. Oriahnn contains elagolix 300 mg, estradiol (E2), and norethindrone acetate (NETA) capsule and elagolix 300 mg capsule. The capsule containing the triple combination is to be taken orally in the morning and the elagolix alone capsule is to be taken orally in the evening.

Based on amended information provided by the Applicant and continued discussion with the Applicant, this addendum corrects or supplements the summary unireview in the following sections:

1. Extent of safety exposure:

Per the Applicant's Clinical Summary of Safety (Table 2, on page 21) submitted on July 31, 2019, the total number of subjects exposed to Oriahnn for ≥6 months was 391. In revised labeling submitted on May 21, 2020, the Applicant clarified that the total number of phase 3 subjects exposed to Oriahnn for ≥6 months was 341. This number includes subject who were exposed to Oriahnn in two randomized, double-blind, placebo-controlled trials of 6-month (Studies 815, 817) and the 6-month extension (Study 816) but excluded subjects from a phase 2 study (study 813). The clinical review team and I concur with this correction for labeling purposes.

2. Labeling; final agreement was reached on May 27, 2020:

2.1 Prescribing Information:

a. Regarding assessment of bone mineral density (BMD), the Division initially recommended assessing DXA "prior to starting treatment and annually." To allow prescribers more flexibility to individualize management, the Division and the Applicant agreed to not explicitly state the frequency of DXA; instead, the recommendation in Highlights, Section 5 (Warnings and Precautions), and Section 6 (Adverse Reactions) would be to obtain DXA to assess BMD "at baseline and periodically thereafter".
b. Regarding events of alopecia, the Division did not agree to the Applicant's proposal to delete alopecia from Section 5. Agreement was reached on inclusion of alopecia in both Sections 5 and 6, with clarifications regarding women who discontinued therapy due to alopecia and reversibility. The final language in Section 6.1 states: "In almost one-third (4/14) of affected ORIAHNN-treated women, alopecia was a reason for study drug discontinuation; no placebo-treated women discontinued because of alopecia. In ORIAHNN-treated women, 79% of the cases were mild and 21% were moderate in severity. Hair loss was ongoing at the end of the study for 4 out of 14 women (29%). Of these 4 women, one discontinued treatment due to hair loss, two had ongoing hair loss

12 months after discontinuing ORIAHNN, and one was lost to follow-up. In the remaining 10 women (71%), hair loss either resolved while on treatment or resolved within 24 days to approximately 9 months after discontinuing ORIAHNN."

c. Regarding changes in lipid parameters, the Division and the Applicant agreed to more detailed description of the shift changes in cholesterol in Section 6.
d. Regarding the proportion of responders who met the primary efficacy endpoint, the Division initially rounded the results for each treatment arm in Table 8 to remove decimal points. After further consideration, the Division and the Applicant agreed on keeping one decimal place for all percentages in Table 8 to avoid under-reporting the efficacy.
e. The Division requested deletion of a paragraph on proportion of women who experienced [redacted (b) (4)]. This endpoint was not a pre-specified, ranked secondary endpoint. The Applicant agreed.

Agreement on labeling was reached on May 27, 2020. The final, agreed-upon labeling, including Medication Guide, was submitted on May 28, 2020.

2.2 Carton and container labeling:

f. The Division and the Applicant agreed on the presenting the established name of the product without slashes between each ingredient, per recommendations outlined in the 2018 Draft Guidance: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format.[1] The agreed-upon established name of the product displayed on the carton labeling is thus: "elagolix, estradiol and norethindrone acetate capsules; elagolix capsules."
g. The Applicant [redacted (b) (4)] agreed to direct the user to the PI for details on all of the contraindications ("Contraindications: see Prescribing Information").

The final, agreed-upon carton and container labeling was submitted on May 27, 2020.

3. Postmarketing requirements (PMR) related to alopecia:

During the safety review, the clinical review team identified an imbalance of alopecia, hair thinning and hair loss. A higher rates in events were reported by subjects receiving Oriahnn (3.5%) compared to placebo (1.0%). Onset of alopecia was within 6 months of treatment but no specific pattern/distribution could be discerned. Approximately 29% of subjects had ongoing alopecia at the end of the study.

The Division initially requested that the Applicant conduct a prospective, observational study in premenopausal women receiving treatment with Oriahnn to assess the incidence, time to onset,

[1] https://www.fda.gov/media/110453/download

pattern, extent, and reversibility of alopecia as well as any racial/ethnic differences in developing alopecia. This study will also compare the risk of alopecia among new users of Oriahnn to a suitable comparator cohort of women not treated with Oriahnn.

On May 22, 2020, the Applicant submitted a revised proposal to conduct two separate PMR studies, an observational study with primary data collection and a cohort study to compare the rate of alopecia in Oriahnn-treated women and a comparator population, to address the safety concern regarding alopecia.

On May 28, 2020, DUOG and the Division of Epidemiology II (DEPI) reached agreement with the Applicant on the content and the timelines of the two new PMR studies. Brief synopses of these agreed to PMRs are outlined below:

a. A prospective observational study in premenopausal women receiving treatment with Oriahnn to assess the incidence rate, time to onset, pattern, extent, and reversibility of alopecia as well as any racial/ethnic differences in developing alopecia. Physician/observer-reported outcome and/or patient survey should be developed and included in the PMR study to capture timing, pattern, extent and reversibility of alopecia cases. The study shall evaluate 50 cases of alopecia.

   PMR schedule milestones:

Draft Protocol Submission:	02 / 2021
Final Protocol Submission:	08 / 2021
Interim Study Report :	08 / 2024
Study/Trial Completion:	08 / 2026
Final Report Submission:	08 / 2027

b. A cohort study to compare the incidence rate of alopecia in premenopausal women who initiate Oriahnn and an appropriate comparator population of women not treated with Oriahnn. The study should be powered to detect a 2-fold increase in the risk for alopecia with Oriahnn use. The study should also be powered for a subgroup analysis among African Americans who are treated with Oriahnn. If an electronic healthcare database is selected for the study, then conduct a validation study in the selected database to develop and validate an algorithm with a sufficient positive predictive value (PPV) to identify alopecia, prior to initiating the comparative safety study. If a sufficient PPV cannot be obtained, conduct a prospective cohort study with primary data collection with case adjudication.

PMR schedule milestones:

Draft Protocol Submission:	02 / 2021
Final Protocol Submission:	08 / 2021
Validation/feasibility Report:	08 / 2023
Interim Report/Other:	08 / 2025
Study/Trial Completion:	08 / 2026
Final Report Submission:	12 / 2027

Summary Comment and Recommendation: The CDTL and the Signatory (Deputy Director) have reviewed the submitted labeling and PMR synopses with the Applicant's proposed timelines. We agree with the review team that the Application can now be Approved.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINA Y CHANG
05/29/2020 09:07:16 AM

AUDREY L GASSMAN
05/29/2020 09:16:36 AM
I concur that this application is acceptable for Approval

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213388
Priority or Standard	Standard
Submit Date(s)	July 31, 2019
Received Date(s)	July 31, 2019
PDUFA Goal Date	May 31, 2020
Division/Office	Division of Urology, Obstetrics and Gynecology (DUOG)/ Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine (ORPURM)
Review Completion Date	
Established/Proper Name	Elagolix, estradiol and norethindrone acetate; elagolix
(Proposed) Trade Name	Oriahnn
Pharmacologic Classes	Gonadotropin releasing-hormone receptor antagonist, estrogen and progestin
Applicant	AbbVie Inc.
Dosage Form	Orall Capsules
Applicant Proposed Dosing Regimen	Morning: elagolix 300 mg, estradiol (E2) 1 mg, and norethindrone acetate (NETA) 0.5 mg Evening: elagolix 300 mg Treatment duration is limited to (b) (4) months
Applicant Proposed Indication(s)/Population(s)	Management of heavy menstrual bleeding associated with uterine fibroids
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	95315005 |Uterine leiomyoma (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Management of heavy menstrual bleeding associated in uterine fibroids in premenopausal women
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	95315005 |Uterine leiomyoma (disorder)|
Recommended Dosing Regimen	Morning: elagolix 300 mg, E2 1 mg, and NETA 0.5 mg Evening: elagolix 300 mg Treatment duration is limited to 24 months

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRM = Division of Risk Management
DMPP = Division of Medical Policy Programs
COA = Division of Clinical Outcome Assessment
OCP = Office of Clinical Pharmacology
OB = Office of Biometrics
DUOG = Division of Urology, Obstetrics and Gynecology

Signatures

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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	Signature: IN DARRTS			
Signatory, Deputy Division Director (DUOG)	Audrey Gassman	ORPURM/DUOG	Sections: all	**Select one:** ___ Authored _x_ Approved
	Signature: IN DARRTS			

Glossary

AE	adverse event
ALT	alanine amino transferase
AST	aspartate amino transferase
AUC	area under the curve
$AUC_{0\text{-inf}}$	area under the curve from zero to infinity
BA	bioavailability
BE	bioequivalence
BF	black female
BID	twice daily
BLA	biologics license application
BMD	bone mineral density
BMI	body mass index
COA	Clinical Outcome Assessment
CSR	clinical study report
DHOT	Division of Hematology Oncology Toxicology
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
CYP	cytochrome P450
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DB	double-blind
DBP	diastolic blood pressure
DDI	drug-drug interaction
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
ET	extensive transporter
FDA	Food and Drug Administration
FDC	fixed-dose combination
FN	femoral neck
FSD	Fibroid Symptom Diary
HMB	heavy menstrual bleeding
ICH	International Conference on Harmonisation
IND	investigational new drug
IP	investigational product
iPSP	Initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	Integrated Summary of Safety
IT	intermediate transporter
LD	low dose
LS	lumbar spine
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

NDA	new drug application
OPQ	Office of Pharmaceutical Quality
NETA	norethindrone acetate
OATP	organic anion-transporting peptide
OSI	Office of Scientific Investigation
PBO	placebo
PBPK	physiologically-based pharmacokinetic
PGIC-MB	Patient Global Impression of Change on Menstrual Bleeding
PI	Prescribing Information
PD	pharmacodynamics
PK	pharmacokinetic
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PT	poor transporter
PTFU	post-treatment follow-up
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard dose
± SD	plus or minus standard deviation
SIS	Saline Infusion Sonohysterography
TBM	to-be-marketed
TDD	total daily dose
SOC	standard of care
TEAE	treatment emergent adverse event
TH	total hip
TQT	thorough QT
UBQ	Uterine Bleeding Questionnaire
UFS-QoL	Uterine Fibroid Quality of Life
ULN	upper limit of normal
US	ultrasound
WPAI:UF	Work Productivity and Activity Impairment Questionnaire: Uterine Fibroids
WRO	written response only

1. Executive Summary

1.1. Product Introduction

Oriahnn is a fixed-dose combination (FDC), copackaged, oral capsule product containing three active ingredients—elagolix sodium 300 mg (Ela), estradiol (E2) 1 mg, and norethindrone acetate (NETA) 0.5 mg. The Applicant seeks to market Oriahnn for the management of heavy menstrual bleeding associated with uterine fibroids. The recommended dosage of Oriahnn is one capsule (containing elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg) in the morning (a.m.) and one capsule (containing elagolix 300 mg) in the evening (p.m.). The dosing regimen will be elagolix 300 mg twice daily (BID) and E2 1 mg/NETA 0.5 mg once daily (QD).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Two replicative, randomized, double-blind, placebo-controlled Phase 3 clinical trials of six months duration were conducted to support the effectiveness of Ela + E2/NETA to reduce heavy menstrual bleeding (HMB) associated with uterine fibroids. Adhering to Division request, in these trials, menstrual blood loss (MBL) was assessed using the alkaline hematin method for the collection of sanitary products. HMB was defined as menstrual blood loss (MBL) greater than 80 mL.

The primary endpoint in both trials was the proportion of responders, defined as women who achieved (1) MBL volume less than 80 mL at the Final Month, and (2) 50% or greater reduction in MBL volume from Baseline to the Final Month. Final month was defined as the last 28 days before and including the last treatment visit date or the last dose date. After six months of treatment with Ela + E2/NETA, approximately two-thirds of subjects met the responder definition when compared with placebo (60% and 66%, respectively).

In addition to the primary efficacy endpoint, six ranked secondary efficacy endpoints were evaluated in both trials. These secondary endpoints relate to reduction of total MBL volume, reduction of MBL over time (at Month 6, 3, and 1), suppression of menstrual bleeding during treatment, and improvement in anemia (defined as an increase in hemoglobin of 2 g/dL by the end of treatment in subjects with a baseline hemoglobin ≤10.5 g/dL). Compared to placebo, treatment with Ela + E2+NETA successfully met all six secondary efficacy endpoints.

We conclude that the evidence provided by the Applicant, confirmed by our review, meets the statutory requirement to establish substantial effectiveness of this product for the indication sought.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Uterine fibroids, which are neoplasms of uterine smooth muscles, are the most common benign neoplasms in premenopausal women. Between 25% to 30% of women with uterine fibroids experience symptoms, including heavy and prolonged menstrual bleeding and bulk-related pelvic symptoms. Heavy menstrual bleeding is the most common symptom associated with uterine fibroids and can result in chronic anemia despite iron supplementation. Currently, FDA-approved medical treatment for HMB associated with uterine fibroids is short-term administration of gonadotropin-releasing hormone (GnRH) agonists for preoperative hematological improvement. Off-label use of combined hormonal contraceptives, progestational agents, progestin-containing intrauterine systems, and tranexamic acid for symptomatic management are also utilized. Surgical options for women with HMB from uterine fibroids range from less invasive and uterus-preserving procedures [such as endometrial ablation, uterine artery embolization, and magnetic resonance imaging (MRI)-guided radiofrequency ablation] to myomectomy. The only definitive treatment is hysterectomy (removal of the uterus). A safe and effective oral therapy for chronic use would provide another treatment option for HMB associated with uterine fibroids.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Uterine fibroids are benign, hormonally-sensitive tumors of the uterine smooth muscle. They are the most common benign tumors in pre-menopausal women and the leading indication for hysterectomies in the United States. Although the actual prevalence is unknown, a large prospective study in the U.S. in 95,000 women ages 25 to 44 reported an overall incidence rates of fibroids diagnosed by ultrasound and a hysterectomy of 9 per 1,000 woman-years. • Approximately 25-30% of women with uterine fibroids become symptomatic, most commonly with HMB and sometimes have	Uterine fibroids are a major source of morbidity for premenopausal women. HMB in women with uterine fibroids can result in iron-deficiency anemia, which may not be adequately mitigated with iron supplementation alone. In this clinical program, HMB is defined

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	concurrent bulk symptoms (e.g., pelvic pain, dyspareunia and interference of bladder or bowel function). • Women who have submucosal or intramural fibroids that distort the uterine cavity may also experience infertility and/or recurrent pregnancy loss.	as monthly blood loss volume >80 mL.
Current Treatment Options	• There are no FDA-approved medical therapies for the long-term management of heavy menstrual bleeding caused by uterine fibroids. • At this time, one gonadotropin releasing hormone (GnRH) agonist is the only FDA-approved medical therapy for symptomatic fibroids. Since 1999, leuprolide acetate via intramuscular depot injection has been approved for the preoperative hematologic improvement of patients with anemia caused by uterine fibroids. • Medical therapies not specifically approved for fibroid treatment but commonly used to treat fibroid-related symptoms include other gonadotropin-releasing hormone agonists approved for other indications, combined oral contraceptives (COCs), progestins, levonorgestrel-releasing intrauterine systems (LNG-IUS), tranexamic acid and non-steroidal anti-inflammatory drugs (NSAIDs). • The mainstay of treatment for uterine fibroids is surgical intervention, including myomectomy (hysteroscopic, laparoscopic or abdominal) and hysterectomy. • Interventional radiology therapeutic options include uterine artery embolization (UAE) and MRI-guided focused ultrasound (MRg-FUS) ablation. However, these options require specialized expertise and may not be universally accessible to patients.	• Use of GnRH agonists without concomitant hormone therapy has hypo-estrogenic side effects including bone loss; therefore, the approved duration of treatment is limited to three months or as a pre-operative measure to improve anemia caused by fibroids. • All surgical procedures and accompanying anesthesia carry the risks of complications or significant morbidity. • Multiple treatment options exist including medical treatment (limited duration of treatment with GnRH agonists), procedures (longer-term improvement, possibly definitive treatment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		if a woman is near menopause), and hysterectomy for definitive treatment.
Benefit	• The Applicant conducted two randomized, placebo-controlled, double-blind, Phase 3 clinical trials [Studies M12-815 (hereafter referred to as Study 815) and M12-817 (hereafter referred to as Study 817)] to evaluate efficacy and safety of elagolix in combination with E2/NETA in the management of HMB associated with uterine fibroids in adult premenopausal women. • A total of 395 subjects were randomized to the Ela + E2/NETA arm versus 196 subjects in the placebo arm. More than 50% of subjects were from sites in the United States. Nearly 70% of all subjects were Black or African American, reflecting a population that is representative of US women affected by HMB associated with fibroids. • The primary efficacy endpoint evaluated in these two trials were (1) the proportion of women whose menstrual blood loss (MBL) was less than 80 mL during the final (6^{th}) month, and (2) the proportion of women with at least 50% reduction in MBL volume from baseline to the final month. In both trials, these endpoints were met successfully. Compared to subjects receiving placebo, approximately 60% more subjects treated with Ela + E2/NETA met the primary efficacy endpoint. Six ranked secondary efficacy endpoints also were successfully met in each clinical trial. Compared to placebo, treatment with Ela + E2/NETA reduced MBL volume by more than 170 mL in six months, resulted in suppression of menstrual bleeding to spotting or no bleeding in approximately 60% of subjects. In subjects who have moderate	The Applicant has provided consistent data from two adequate and placebo-controlled clinical trials that convincingly demonstrate the effectiveness of Ela +E2/NETA in reducing HMB associated with uterine fibroids. The primary endpoint selected is clinically meaningful and represents resolution of HMB. The secondary endpoints evaluated in both clinical trials provide further support of clinical benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	anemia at baseline (with Hgb ≤10.5 g/dL), treatment with Ela + E2/NETA resulted in improvement in Hgb by at least 2 g/dL in approximately one third to one half more subjects, compared to placebo.	
Risk and Risk Management	• The safety of Ela + E2/NETA was also evaluated in Studies 815 and 817, and a Phase 3 open-label extension study (Study 816) in which most subjects who completed 6 months of treatment with either Ela BID alone or Ela BID and E2/NETA QD received their assigned treatment for another 6 months. • A total of 518 unique subjects were exposed to Ela + E2/NETA for six months in the Phase 2/3 uterine fibroid program. In Studies 815 and 817 combined, 395 subjects were exposed to Ela + E2/NETA for six months. An additional 58 subjects (who were randomized to the placebo arm in Studies 815/817) received Ela + E2/NETA in Study 816 for six months. The total number of unique subjects exposed in the Phase 3 program was 453 with the number of Phase 3 subjects who completed six months or more of treatment with Ela + E2/NETA was 312 (69%). A total of 182 subjects completed 12 months of treatment. • Two serious thromboembolic events (thrombosis in the calf and a pulmonary embolism) occurred in subjects receiving Ela + E2/NETA Phase 3 program. • Bone loss during treatment remains a safety concern because significant bone loss may result in an increased risk of fractures. The addition E2/NETA did not fully mitigate the hypoestrogenic effect of elagolix on bone in all women. Six subjects treated with Ela + E2/NETA experienced fracture events in the Phase 3 clinical program, with two being consistent with fragility fractures. Among women who received Ela + E2/NETA for 12 months, continued	• The safety profile contained sufficient data at 6 months and one year. • Identified safety concerns with this fixed dose combination product can be mitigated with labeling, although additional safety information on specific signals (bone, alopecia) will be needed during postmarketing. • Chronic use of hormone therapy has known identified safety risks, including thromboembolic. Based on the safety data from this program, the estrogen/progestin boxed warning for thromboembolic events (class warning) will also be applicable to labeling for this product. • A Warning and Precaution for bone loss is needed. This

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	bone loss was observed at the spine, total hip, and femoral neck in 24%, 32%, and 38%, respectively, at their 12-month post-treatment follow-up (PTFU). • Recovery of bone loss is also a concern as women who have lost bone may continue to be at risk for fragility fractures, particularly as many women with symptomatic fibroids may be peri-menopausal. In these two trials, bone recovery (to baseline) was reported in 31%, 36% and 24% of these subjects who lost bone at the spine, total hip, and femoral neck, respectively, at the end of the 12-month PTFU. • Two breast cancers were diagnosed in subjects who received Ela + E2/NETA in the Phase 3 program. An association between estrogen alone or estrogen and progestin combination and breast cancer in premenopausal women has not been conclusively established. • Consistent with findings with the clinical trials for elagolix alone, the incidences of depression and worsening mood change are higher with Ela + E2/NETA treatment than with placebo. • There was a numeric increase in hypertension events (4.1% versus 2.5%) compared to Ela alone. Treatment with Ela + E2/NETA resulted in a mean increase in systolic blood pressure of 5.1 mmHg at Month 5, and a mean increase in diastolic blood pressure of 2.1 mmHg at Month 4, as compared to placebo. • An higher incidence of alopecia events was seen in subjects treated with Ela + E2/NETA (3.5%) as compred to placebo subjects (1%). No consistent pattern of alopecia was seen. These events may be irreversible; 4 out of 14 women with alopecia (29%) reported no resolution at the end of the study. The underlying	W&P will also include the available information on delayed and incomplete recovery of BMD. As a result of the lack of recovery in up to one third of women, the duration of therapy will be limited to 24 months. Reassuring BMD data from an ongoing, 48-month trial are needed before revision of the limitation of use in duration of treatment can be considered. • Oriahnn includes hormone therapy containing estrogen and progestin administered chronically. As with use of other hormone therapies, use of Oriahnn will be contraindicated in women with current or past history of breast or other hormonally-sensitive malignancies. • Suicidal ideation/behavior and exacerbation of mood disorders will remain a Warning and Precaution.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cause of this alopecia is unknown and will require further assessment. • Hot flush was the most common adverse event (AE), followed by headache and fatigue. These symptoms are consistent with the safety profile for elagolix. • There is a potential risk of exposure during pregnancy as women with HMB may not realize they are pregnant.	• A Warning and Precaution for high blood pressure will be included in labeling. Use of Oriahnn in women with uncontrolled hypertension, coronary artery disease, and diabetes mellitus with vascular disease will be contraindicated. • Warning and Precaution for alopecia, including the potential that the pattern may not be reversible will be included. • A postmarketing requirement (PMR) for a prospective, observational study to assess the incidence, pattern, and reversibility of alopecia will be requested. • Administration during pregnancy is adequately mitigated by labeled instructions to start within seven days of menses. In addition, the Applicant agreed to include data from this product into the ongoing pregnancy registry and study

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		PMRs to capture any additional information on exposure in pregnancy to this FDC with elagolix.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO) As documented using the Uterine Bleeding Questionnaire (UBQ), which was administered in both Phase 3 clinical trials (Studies 815 and 817)	Section 8.1 Review of Relevant Individual Trials Used To Support Efficacy
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Uterine fibroids (leiomyomata) are benign neoplasms of smooth muscle origin and can cause symptoms such as heavy menstrual bleeding (HMB), dysmenorrhea, dyspareunia, and bulk-related bladder or bowel dysfunction. Because uterine fibroids are the most common neoplasms in premenopausal women, they are the most common reason for hysterectomy, the most common gynecologic surgical procedure in the United States. Leiomyomas may occur in the general population, but are more common in black women (three-fold increased risk)[1].

2.2. Analysis of Current Treatment Options

There are no FDA-approved medical therapies specifically for the management of heavy menstrual bleeding caused by uterine fibroid beyond three months duration as part of pre-operative care prior to hysterectomy. The recommended use of leuprolide injections is limited to one course (one injection of 11.25 mg for three months or three monthly injections of 3.75 mg) to improve anemia prior to myomectomy or hysterectomy. (b) (4)

Refer to Table 1 on the next page.

[1] Eltoukhi H, Modi M, Weston M, Armstrong A and Steward E, 2013, The Health Disparities of Uterine Fibroid Tumors for African American Women: A Publich Health Issue, Amer J of Obs and Gyn, 210(3):194-199.

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments for Abnormal Uterine Bleeding in Women with Uterine Fibroids						
Lupron ® (leuprolide acetate) depot injection	Preoperative hematologic improvement in women with anemia caused by fibroids	1995	Monthly injection of 3.75 mg for up to 3 months or one injection of 11.25 mg	Administration of Lupron depot and iron produced an increase of ≥6% hematocrit and ≥2 g/dL hemoglobin in 77% of patients at three months of therapy.	Duration of use is limited due to concern over bone safety	Must use concomitantly with iron therapy
FDA Approved Treatments for Menorrhagia but not Specifically for Bleeding in Women with Uterine Fibroids						
Tranexamic acid (Lysteda®)	Cyclic heavy menstrual bleeding	2009	1,300 mg (two 650 mg tablets) three times a day (3,900 mg for a maximum of 5 days during monthly menstruation Dose adjustment is needed in patients with renal impairment.		An antifibrinolytic, Lysteda is contraindicated in women who are using combined hormonal contraception and women with current or history of thromboembolic disease	Efficacy of tranexamic acid has not been demonstrated specifically in women with HMB due to fibroids

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Non-FDA Approved Treatments for Menorrhagia						
Oral contraceptive agents	Contraception	Initial 1961[2]	An example of a more recently approved dosing regimen is ethinyl estradiol 20 mcg and levonorgestrel 100 mcg for 21 days and placebo for 7 days (NDA 209405, approved in 2020)	Peer-reviewed literature	Thromboembolic events Contraindicated in women 35 years or older and who smoke	Dosing generally is the same as that used for prevention of pregnancy.

[2] NDA 10976 Enovid (mestranol and norethindrone), marketed by GD Searle LLC. DARRTS search May 4, 2020.

Surgical Treatments						
Endometrial ablation		1997	Multiple FDA-approved devices for global endometrial ablation (GEA), e.g., NovaSure, Minerva, Thermachoice	FDA approval is based on results of randomized controlled trials that compare the safety and effectiveness of the GEA device to the hysteroscopic roller ablation.[3]	Perforation of the uterus, burns to bowels, pulmonary edema	Can be done as an office procedure
Uterine artery embolization (a percutaneous angiographic procedure, performed by interventional radiologists under fluoroscopic guidance)	Also used to control postpartum hemorrahge	2000	Multiple FDA-approved embolic agents (e.g., tris-acryl gelatin microsphere, polyvinyl alcohol particles gelfoam,) used to occlude the artery		Embolism, loss of ovarian function and infertility, iatrogenic menopause, post-embolization syndrome (pain, fever, nausea)	Requires specialized expertise; short hospital stay; Cutoff of 10 cm size of fibroid; Need good renal function
MRI-guided focused ultrasound (MRgFUS)	FDA-approved to treat uterine fibroids	First approved in 2004 by FDA			Skin burns, sciatic nerve injury, vaginal discharge, focal abdominal wall edema	Require specialized expertise; outpatient procedure Cutoff of 10 cm size of fibroid Need acceptable renal function due to use of gadolinium
Myomectomy (hysteroscopic, laparoscopic, and abdominal)					Incurs surgical risks	Risk of recurrence
Hysterectomy				Definitive treatment	Incurs surgical risks	Loss of childbearing and potential loss of ovarian function

Source: Drugs@FDA and clinical review team

[3] FDA letter to Endometrial Ablation Industry 2015. https://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM470246.pdf

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Elagolix is a gonadotropin-releasing hormone (GnRH) antagonist, approved in 2018 as Orilissa® at doses of 150 mg and 200 mg in oral tablets for the management of moderate to severe pain in premenopausal women associated with endometriosis.[4]

Estradiol (E2), available in the US since 1954, is approved for multiple indications, including the treatment of vasomotor symptoms and vulvovaginal atrophy associated with menopause and prevention of osteoporosis. NETA, available in the US since 1982, is approved for the treatment of secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology. The FDC of orally-administered E2 1 mg and NETA 0.5 mg were approved in 1998 as Activella®, which is indicated for the treatment of moderate to severe vasomotor symptoms and vulvovaginal atrophy due to menopause and prevention of osteoporosis in postmenopausal women. As chronic administration of elagolix causes hypoestrogenic effects, especially on bone mineral density (BMD), the addition of E2/NETA is intended to attenuate the hypoestrogenic effects.

The Ela + E2/NETA combination has not been approved in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The clinical development of elagolix + E2/NETA was conducted under IND 115528, which was opened on November 30, 2012. Major regulatory activities, milestone submissions and communications are summarized below.

Pre-IND meeting (summary) held on July 30, 2012 (meeting minutes dated August 29, 2012)

- The proposed indication “heavy menstrual bleeding (HMB) associated with uterine fibroids” was acceptable to the Division.
- The general design of the Phase 2b, randomized, double-blind, placebo-controlled trial of elagolix 300 mg in combination with two strengths of add-back therapy was discussed.

[4] Orilissa Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210450s000lbl.pdf

- Adequate evidence of the add-back therapy appropriately minimizing the impact on bone mineral density (BMD) would be necessary to support the duration of use.
- The Division recommended that efficacy be defined as reduction in menstrual blood loss (MBL) to <80 mL **and** a reduction in MBL of at least 50% from baseline.
    - These assessments should be derived from alkaline hematin measurements.
    - Data on the bleeding endpoints for both "scheduled" (menstrual) bleeding and "unscheduled" (irregular or breakthrough) bleeding should be included in these analyses.
- The Division did not agree with assessing fibroid or uterine volume as secondary endpoints, as the clinical relevance of reduction in volume is undetermined.
- The Division recommended that the Sponsor exclude women with other etiologies for uterine bleeding (e.g., endometrial polyps and diffuse adenomyosis) by having baseline evaluations (endometrial biopsy at screening; saline infusion sonohysterography and MRI as needed).
- The Division encouraged the Sponsor to employ strict quality controls regarding fibroid and uterine volumetric imaging (especially with ultrasound imaging) due to differences between each machine, between types of machines, and inter-observer variation.
- The Division did not agree to the use of the Fibroid Symptom Diary (FSD, an 11-item Daily Uterine Fibroid Bleeding and symptom diary) or the Uterine Fibroid Symptom-Quality of Life (USF-QoL) instruments to support labeling claims because of concerns with the content validity of these instruments.

End-of-Phase 2 meeting (Summary) held on May 27, 2015 (meeting minutes dated June 19, 2015)

- The Sponsor stated they planned to take the 300 BID with addback regimen into Phase 3, due to better exposure and tolerability. This was acceptable to the Division. The Division advised the Sposnor that the clinical pharmacology data (e.g., food effect, intrinsic and extrinsic factor information) needed to support the proposed dosing regime).
- The Division recommended that the primary efficacy assessment compare the treatment effect of elagolix plus+ add-back versus placebo. Formal hypothesis testing would not be conducted for elagolix 300 mg BID alone treatment arm. However, the Division stated that the Sponsor would need to address the benefit of add-back in addition to the elagolix regimen and to provide a formal demonstration of the impact on safety parameters such as BMD.
- The Division agreed with the proposed sample size that would permit detection of ≥ 17% difference in responder rate with 80% power. The Sponsor clarified that non-responders would be defined as any women who discontinued prematurely due to adverse events, lack of efficacy, or surgical/interventional management of fibroids. For women who discontinue for other reasons, the Division

recommended using a model-based approach (Multiple Imputation method) to handle missing data.

- The Division recommended that the Sponsor specify all key secondary (or other non-primary) endpoints intended to support labeling claims. Secondary endpoints may be included in labeling if they are agreed upon in advance by the Division, appropriately addressed in the statistical analysis, and evaluated using an appropriately validated instrument. Secondary endpoints that are designated for inclusion in labeling will likely be reported regardless of whether the outcome is successful.
- Regarding safety, the Division recommended that the Sponsor provide safety information based on the requirements in ICH E1 guideline.
- The Division did not agree that reduction in uterine or fibroid volume or a 1g/dL increase in hemoglobin could be considered clinically meaningful.
- The Division was concerned that evaluation of BMD after six months of treatment was unlikely to provide a sufficient assessment of any impact on BMD. The Division recommended a standardized approach and stated that the number of subjects on whom 12-month data are obtained will be an important consideration.

SPA No Agreement Letter (October 1, 2015) - Summary

- Agreement was not reached on the entry criteria, secondary efficacy endpoints and safety assessments.
- Demonstration of the contribution of the treatment effect of E2/NETA to mitigate the adverse impact of elagolix on BMD is needed to address the combination drug rule.
- The Division proposed several options for the Sponsor to consider regarding an indication. As an example, a preoperative indication that focused on improvement of hematologic indices might be acceptable, although the primary endpoints used for the chronic HMB indication would not support this indication.

FDA Advice/Information Request (May 17, 2016)

The Division provided additional comments on the Phase 3 study protocol for Study M12-815.

- MBL volume in the last 28 days of treatment be calculated as the sum of all (not just the observed) AH data over this time period. If all AH data are missing in this time period, the MBL volume should be set as missing, not zero. If AH data are missing for some bleeding days, the Sponsor should impute the missing AH data using all sources. For example, if two out of four days of AH data are missing, the Sponsor should propose how to impute the missing AH data for the two missing days and derive the total MBL volume thereafter using both observed and imputed AH data.
- For analysis of percent change from baseline in bone mineral density (BMD), the Division recommended using the analysis of covariance (ANCOVA) with baseline BMD as a covariate in the model.

WRO (December 19, 2017)

- The Division provided feedback on the approach proposed by the Sponsor to bridge various drug products: the drug products used in the Phase 3 clinical trials (elagolix 300 mg tablet and E2/NETA tablets), the TBM drug product (elagolix + E2/NETA tablets in capsules), and the prototype drug product used in bioequivalence study M15-872 (a different formulation of elagolix/E2/NETA capsules).
- The Division stated that a food effect study for the TBM capsule was necessary.

WRO (August 3, 2018)

- The Division provided additional feedback on approach for bridging the three drug products. FDA disagreed with using comparative dissolution data to establish similarity between the prototype fixed dose combination capsule and the TBM FDC of elagolix/E2/NETA capsule and to support an in vivo bioequivalence waiver.
- The Division reiterated that a food effect study remains necessary as the Sponsor's PBPK model was not sufficient.

Guidance meeting held on December 10, 2018 (meeting minutes dated January 4, 2019)

- The FDA did not agree that the proposed safe space based on in vitro dissolution data, PBPK modeling, and clinical bioequivalence study data supported an in vivo bioequivalence waiver. The Sponsor agreed.
- The Sponsor stated their plan to submit the NDA as a 505 (b)(2) application, using a generic version of Activella tablet, containing 1 mg E2 and 0.5 mg NETA, as reference. The FDA verified that the marketing of Activella E2/NETA 1 mg/0.5 mg tablet remains active. The Sponsor was reminded that a scientific bridge to Activella should be established in their 505(b)(2) application.

FDA Advice/Information Request (April 16, 2019)

- The Division provided feedback on the statistical analysis plan (SAP) for the Phase 3 trials Studies 815 and 817:
    - — Impute as non-responders for subjects who have less than 28 days of treatment in your primary efficacy analysis.
    - — Subjects who withdraw from the trials due solely to adverse events should not be imputed as non-responders. For these subjects, include their efficacy data, up to the time of discontinuation, in the efficacy analysis.
    - — Define a per-protocol analysis set that includes subjects who do not have major protocol violations. Conduct a sensitivity assessment for the efficacy of the study drug using this analysis set.

— Perform secondary analyses of efficacy evaluating the data by pre-defined subgroups. These analyses should assess efficacy in groups defined by demographics and baseline characteristics such as age, race and region and subgroups of clinical interest.

Pre-NDA meeting held on June 13, 2019 (meeting minutes dated July 9, 2019)

- The Division agreed with the proposed format of and cross-references (to Activella NDA 020907 and Orilissa NDA 210450) in the planned NDA.
- The Division reminded the Applicant that for an FDC, all active ingredients need to be justified.
- For the ISS, the 3- and 6- month, Phase 2 data (M12-663 and M12-813) need to be included in the safety assessment and should be presented.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Four clinical sites participating in the two Phase 3 Studies providing primary support were selected for inspection by OSI (Drs. Samuel Simha, Amber Hatch, Phyllis Gee, and Kenneth Sekine). These sites were selected because of their relatively high subject enrollment, above-average site-specific efficacy results, and the lack of recent inspections.

Three sites were classified as No Action Indicated. Dr. Gee's site received a Voluntary Action Indicated (VAI) classification; the FDA Form 483 issued included the following issues:

- Subject (b) (6) had a baseline QTc >450 msec (QTc of 453 msec). A deviation report was submitted. As investigator did not believe subject was at any increased medical risk [remainder of electrocardiogram (ECG) was normal], subject could continue the study. Action: Applicant amended prequalification checklist to include requirement for lead researcher and principal investigator (PI) review document prior to subject enrollment.
- Two adverse events not captured: Subject (b) (6) had normal BP at baseline and medical history did not state hypertension. Lisinopril was started after starting investigational product (IP). "Hypertension" instead of "worsening hypertension" was recorded. Action: Staff retrained in proper documentation and timely reporting. Subject (b) (6) had worsening anemia on Day 1 labs that was not reported initially as only serious adverse events (SAEs) and protocol related nonserious AE would have been reported prior to initiation of IP. Subject was also delayed in responding to request to return for follow up.

- Subject (b) (6) had poor study drug compliance and should have triggered subject re-education. Multiple issues occurred at the site, personnel, and software levels. Action: Applicant added an area to source documents to capture IP compliance.
- Lack of consent for pharmacogenetic sub-study: Subject (b) (6) had blood drawn in error and specimens were discarded; Subjects (b) (6) and (b) (6) gave consent but did not have any specimens drawn.

Dr. Gee's responses to Form 483 observations were deemed acceptable by OSI (see FDA letter dated March 20, 2020).

Based on the results of these inspections, the OSI team concluded that Studies M12-815 and M12-817 were adequately conducted, and the clinical data generated appear acceptable in support of the proposed indication. For details, see OSI summary review dated March 9, 2020.

One clinical site, Dr. Naomi Akita (Site ID 102714), was terminated by the Applicant for cause. During the IND stage, a for-cause OSI inspection was conducted at Dr. Akita's site in response to a report submitted by the Applicant. OSI audited documents from 6 subjects enrolled in M12-817 and 4 subjects enrolled in M12-816. Form 483 cited a protocol violation [enrollment of a subject (# (b) (6)) with uncontrolled diabetes] and record keeping violations (inconsistent records in five subjects regarding fasting status of the lab samples collected during the treatment visits). Four subjects (#s (b) (6)) were enrolled in Protocol M12-817 and one subject (Subject (b) (6)) was enrolled in Protocol M12-816. OSI issued a VAI assessment (IND 115528, OSI letter dated May 7, 2019).

The Applicant terminated Dr. Akita's site for the following reasons:

- Demonstration of a lack of knowledge of the roles and responsibilities of the clinical investigator.
- Minimal oversight in the areas of informed consent review, eligibility assessments, medical history and concomitant medications.
- Safety letters were not reviewed.
- Discrepancy of the location of all the study documentation for both studies.
- Tasks delegated to study/site management organization staff were not performed in a manner compliant with the protocol.

Despite termination of Dr. Akita's site, her subjects were included in the efficacy and safety analyses. However, given the small number of subjects included, we do not consider their inclusion to affect the overall findings of efficacy and safety.

In summary, these deviations identified in the clinical database did not significantly impact the efficacy or safety analyses. We conclude that results obtained from the Phase 3 clinical trials can support this application.

4.2. Product Quality

From the perspective of the Office of Product Quality, this 505(b)(2) application for Oriahnn (elagolix, estradiol, and norethindrone acetates capsules; elagolix capsules) is recommended for approval. The Applicant has provide sufficient chemistry, manufacturing and controls information and supporting data in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of the drug product. An expiration dating period of 24 months for product stored in (b) (4) blisters at 20°C to 25°C is granted. All drug substance and product-related manufacturing, packaging and testing facilities have acceptable status per Current Good Manufacturing Principle (CGMP). An Overall Manufacturing Inspection Recommendation of APPROVE was issued on March 15, 2020. The recommendation remains current as of this review. The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

Oriahnn consists of elagolix capsules, 300 mg, co-packaged with elagolix, E2, and NETA capsules, 300 mg/1 mg/0.5 mg. Oriahnn is supplied as a weekly blister pack containing 7 elagolix capsules and 7 elagolix, E2, and NETA fixed-dose combination (FDC) capsules. (b) (4)

Elagolix capsules and FDC capsules are differentiated by capsule shell cap color and imprint.

The CMC information for the active ingredient elagolix sodium is documented in AbbVie's NDA 210450. Elagolix sodium, 310.5 mg, is equivalent to 300 mg elagolix free acid. Amneal's NDA 20907 cross-references Type II Drug Mater Files (DMFs) (b) (4) for E2 and NETA, respectively.

All inactive ingredients used in the manufacture of the drug product meet compendial requirements and are suitable for the intended use. The encapsulated elagolix tablets are manufactured by (b) (4)

The identity, strength, quality, purity, and bioavailability of the encapsulated tablets is ensured by in-process controls and the regulatory product specifications. The limits for degradation products are supported by nonclinical qualification studies (see Nonclinical Review). Appropriate dissolution test methods and acceptance criteria have been established to ensure the requisite performance of the capsules. A 24-month expiration

dating period for product stored at 20ºC to 25ºC is supported by long-term and accelerated stability data.

The manufacturing facilities assessment evaluated the CGMP status of the manufacturers of the three active ingredients (elagolix sodium, E2, and NETA), the manufacturer (b) (4), the commercial product manufacturer (AbbVie Ltd., Barceloneta, Puerto Rico), the primary packaging site (AbbVie (b) (4) Chicago), and other laboratory testing facilities. A Pre-Approval Inspection (PAI) of the commercial drug product manufacturing site was conducted, and a Form FDA 483 was issued on February 20, 2020. An initial recommendation of Withhold Approval was made. However, based on additional available information and on AbbVie's response to the 483, a final recommendation of Approval was made. Nevertheless, a post-approval inspection (PoAI) of AbbVie PR for process validation batches will be requested. We note that Phase 3 investigational product was not manufactured at AbbVie PR, and there is no evidence that the quality of the site-specific stability and pivotal BE batches manufactured there was compromised by the conditions identified in the 483. All other facilities also have acceptable CGMP status.

A combination of relative BE/BA studies (see Clinical Pharmacology Review) and comparative in vitro dissolution profile studies were used to link investigational products (elagolix tablet RC2, with and without estradiol and norethindrone acetate tablets) and commercial elagolix capsules (EN03) and commercial elagolix, E2 and NETA fixed-dose combination capsules (FDC4).

4.3. Clinical Microbiology

This section is not applicable because the product is an oral capsule.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable. There are device components or companion diagnostics.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were conducted to support this application. The Applicant has cross referenced NDA 210450 for elagolix (for which they are also the designated Applicant). The new dose of elagolix (300 mg BID) is higher than the previously approved high dose of 200 mg BID but is adequately supported by previously conducted nonclinical studies (see review of 210450). The Applicant has also

adequately justified the levels of impurities for the proposed higher dose of elagolix of 300 mg BID.

The Applicant has right of reference to NDA 20907 for E2/NETA and has submitted the nonclinical summary (but not original study reports) and all necessary literature to support approval. This is acceptable.

Per the March 24, 2020 nonclinical review submitted in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), the nonclinical review team concludes that this application is approvable.

5.2. Referenced NDAs, BLAs, DMFs

NDA 210450 and NDA 20907.

6. Clinical Pharmacology

6.1. Executive Summary

In current NDA submission, there are seven Phase 1 studies, two Phase 2 dose-finding studies and three Phase 3 studies (Table 17). In addition, 22 Phase 1 studies submitted in NDA 210450 were cross referenced to support the uterine fibroids indication proposed in this NDA. Additionally, the Applicant has obtained the right of reference for NDA 020907 Activella E2/NETA 1 mg/0.5 mg and E2/NETA 0.5 mg/0.1 mg to support the E2/NETA component of Oriahnn.

6.1.1. Clinical Pharmacology Recommendations

The Office of Clinical Pharmacology Divisions of Cardiometabolic and Endocrine Pharmacology, Pharmacometrics, and Translational and Precision Medicine have reviewed the information contained in NDA 213388 and recommend approval of this NDA. Key review issues with specific recommendations/comments are summarized in the table below:

Table 2: Recommendations and Comments From FDA

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Clinical pharmacology information provides dose/exposure-dependent evidence of effectiveness. The elagolix exposure-response analyses for the primary efficacy endpoint [the proportion of subjects who had menstrual blood loss (MBL) <80 mL during the final month and ≥ 50% reduction in MBL volume from baseline to the final month] support the effectiveness. Two Phase 2 dose-finding studies also support the effectiveness.
General dosing instructions	One capsule (elagolix 300 mg/E2 1 mg/NETA 0.5 mg) should be orally administered in the morning and one capsule (elagolix 300 mg) should be orally administered in the evening. Both morning and evening doses can be taken with or without food. We recommend that the duration of treatment with Oriahnn be limited to 24 months due to concern of bone safety.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Oriahnn is contraindicated in women with hepatic impairment.
Labeling	Refer to Section 11.1 for the our recommendations.
Bridge between the to-be-marketed and clinical trial formulations	The TBM morning and evening capsules have been demonstrated to meet the standard bioequivalence criteria to the tablets used in Phase 3 trials based upon elagolix, E2, and NETA concentrations measured in two bioequivalence studies.
Other (specify)	None.

E2 = estradiol; NETA = norethindrone acetate

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

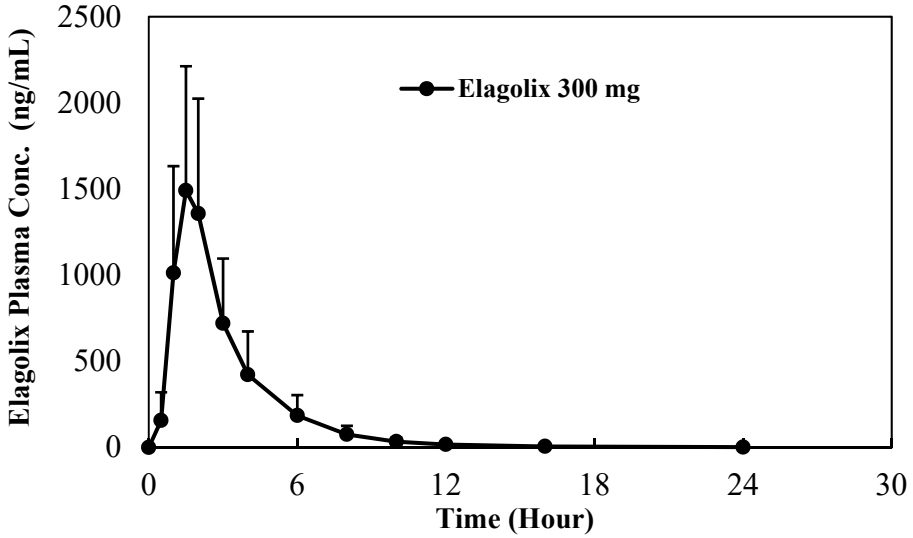
Oriahnn combines elagolix and E2/NETA. Elagolix is a GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of elagolix decreases blood concentrations of estradiol, and progesterone, and other ovarian sex hormones and reduces bleeding associated with uterine fibroids. To some extent, the add-back therapy of E2/NETA reduces the bone loss that can occur due to a decrease in circulating estrogen from elagolix alone treatment. Oriahnn is orally administered with or without food.

Absorption

Elagolix, E2, and NETA are rapidly absorbed upon oral administration with C_{max} occurring at approximately 1, 2, and 1 hour, respectively. The plasma concentration-time profiles of elagolix, E2, and NETA after oral administration of a single dose of Oriahnn morning dose under fasting conditions are shown in Figures 1 to 3. When Oriahnn morning dose was administered under fed conditions with a high-fat meal, the C_{max} values of elagolix, E2, and NETA were on average 36%, 23%, and 50% lower,

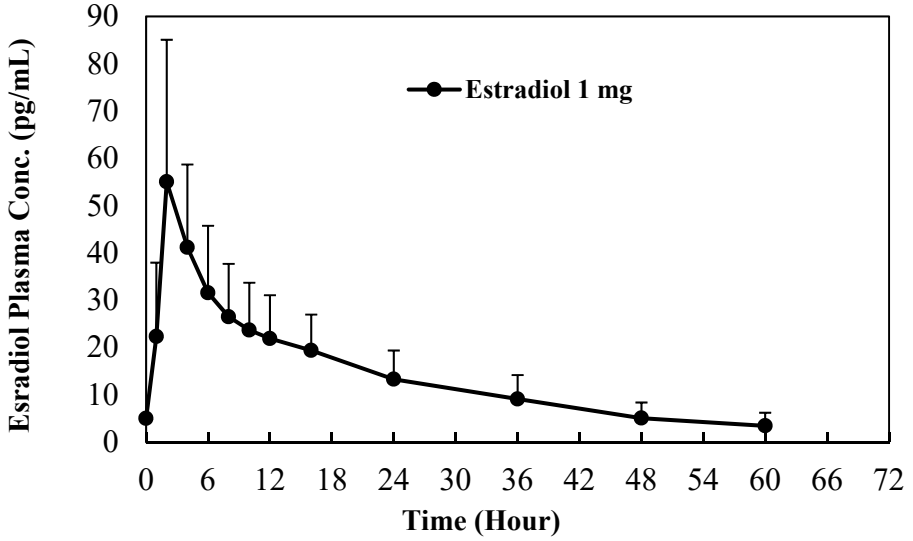
respectively, in comparison with that under fasting conditions. The high-fat meal decreased the area under the curve (AUC) of elagolix by 25% but increased the AUC of NETA by 23%. The meal did not affect the AUC of E2.

Figure 1: Plasma Concentration (Mean ± SD) –Time Profiles of Elagolix, in Healthy Female Subjects After Oral Administration of a Single Dose of Oriahnn Morning Formulation (N=164)



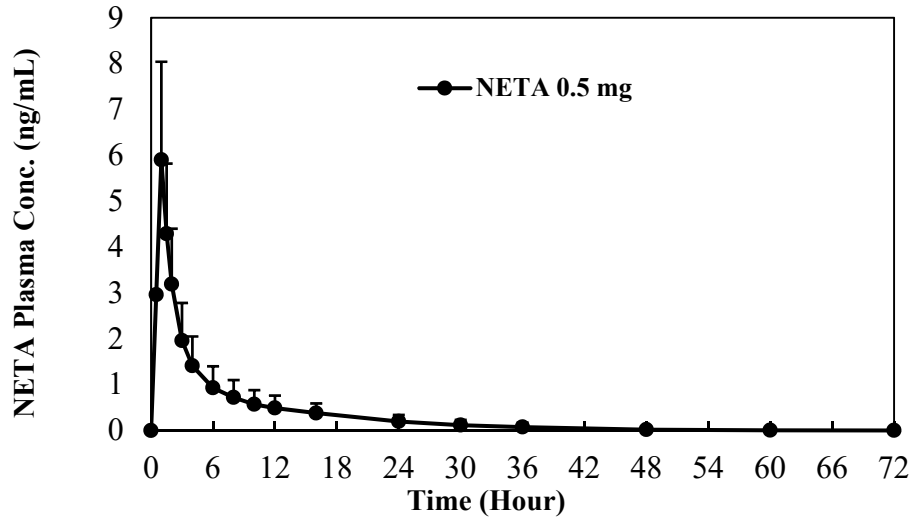
Source: Reviewer's plots based on Applicant's data from Study M16-856

Figure 2: Plasma Concentration (Mean ± SD) –Time Profiles of Estradiol, in Healthy Female Subjects After Oral Administration of a Single Dose of Oriahnn Morning Formulation (N=164)



Source: Reviewer's plots based on Applicant's data from Study M16-856

Figure 3: Plasma Concentration (Mean ± SD) –Time Profiles of Norethindrone Acetate, in Healthy Female Subjects After Oral Administration of a Single Dose of Oriahnn Morning Formulation (N=164)



Source: Reviewer's plots based on Applicant's data from Study M16-856
NETA = norethindrone acetate

Distribution

The apparent volume of distribution (V_d) of elagolix was 883 L after a single dose of 300 mg. After administration of a single dose of Oriahnn morning capsule, the V_d values of E2 and NETA were 27800 L and 336 L, respectively. Elagolix is approximately 80% bound to human plasma proteins. It preferentially partitions into plasma rather than blood cellular components with a blood-to-plasma ratio of approximately 0.6.

Metabolism

Elagolix is metabolized by multiple cytochrome P450 (CYP) enzymes with major contributions from CYP3A4. CYP2D6 is responsible for approximately 20% of the total metabolism. To a lesser extent, elagolix is metabolized by CYP2C8. The contribution from UDP-glucuronosyl transferase enzymes to drug metabolism is considered to be negligible. No major metabolites of elagolix were detected in human plasma.

Excretion

Elagolix is 90% excreted in the feces and 2.9% eliminated in the urine based on the recovery of total radioactivity. Biliary excretion contributes to the clearance of elagolix. The apparent terminal elimination half-lives ($T_{1/2}$) of elagolix, E2, and NETA are approximately 2.9, 14.5, and 9.2 hours, respectively.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The proposed dosing regimen is one capsule (elagolix 300 mg/E2 1 mg/NETA 0.5 mg) in the morning and one capsule (elagolix 300 mg) in the evening, to be taken orally with or without food for up to (b) (4) months. Treatment should start within 7 days from the onset of menses. Patients in Phase 3 studies were given morning and evening doses without regard to meals. The proposed dosing regimen is acceptable for the general population of premenopausal women with uterine fibroids.

Based on the therapeutic benefit and bone loss risk analysis, we recommend that the duration of treatment with Oriahnn be limited to 24 months.

6.2.2.2. Therapeutic Individualization

Hepatic Impairment

In a dedicated hepatic impairment study, following oral administration of a single dose of 150 mg elagolix, the AUC values of elagolix were comparable between subjects with normal hepatic function and subjects with mild hepatic impairment. Elagolix AUC values in subjects with moderate hepatic impairment and subjects with severe hepatic impairment were approximately 3-fold and 7-fold, respectively, of those from subjects with normal hepatic function. Also, estradiol is contraindicated in women with liver impairment or disease because of adverse effect and poor metabolism of estrogens in these patients. The Applicant proposed to contraindicate Oriahnn in women with hepatic impairment or disease. The Applicant's proposal is acceptable.

OATP1B1 Transporter Status

Pharmacogenetic analysis of 2077 DNA samples revealed 77% subjects with extensive transporter (ET) phenotype [i.e., *SLCO1B1* 521T/T genotype), 21% subjects with intermediate transporter (IT) phenotype (i.e., *SLCO1B1* 521T/C), and 2% subjects with poor transporter (PT) phenotype (i.e., *SLCO1B1* 521C/C genotype). Population pharmacokinetic (PK) analysis showed that the AUC of elagolix in subjects with IT phenotype or PT phenotype is expected to increase by 45% and 109%, respectively, compared to subjects with normal transporter function (i.e., subjects with ET phenotype who comprised the majority of the study population). The percentage of subjects who reported treatment-related adverse events was similar between subjects with IT phenotype and Phase 3 overall population. A 45% increase in the exposure of elagolix is not expected to have a clinically meaningful impact on the efficacy and safety of Oriahnn. Thus, no dose adjustment is needed for women with *SLCO1B1* 521T/C genotype. The frequency of *SLCO1B1* 521C/C is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on the efficacy and/or safety of elagolix has not been clearly established. We do not recommend dose adjustment for women with *SLCO1B1* 521C/C genotype.

Drug Interactions

The Applicant conducted 14 clinical drug interaction studies. (b) (4)

Four study reports were submitted in the current NDA. Major clinical drug interaction findings and management strategies are summarized in Table 3.

Table 3: The Major Clinical Drug Interaction Study Findings and Management Strategies for Elagolix

Evaluation	Results	The Applicant's Management Strategies	Review Team's Management Strategies
The Effects of Other Drugs on Elagolix			
CYP3A4 inhibition by ketoconazole, 400 mg QD (Study M12-660)	↑C_{max} by 77% ↑AUC by 120%	No dose adjustment is required.	Concomitant use of Oriahnn and strong CYP3A inhibitors is not recommended.
OATP1B1 inhibition by a single dose of rifampin, 600 mg (Study M12-659)	↑C_{max} by 337% ↑AUC by 458%	Concomitant use of Oriahnn and strong OATP1B1 inhibitors is contraindicated.	Concur with the Applicant.
CYP3A4/P-gp induction by Rifampin, 600 mg QD (Study M12-659)	↑C_{max} by 100% ↑AUC by 65%	Concomitant use of Oriahnn and rifampin is not recommended. Concomitant use of Oriahnn and strong CYP3A inducers may decrease elagolix, estradiol and norethindrone plasma concentrations.	The increased exposure to elagolix may have been due to the net effect of OATP1B1 inhibition and CYP3A induction. Pure CYP3A inducers are expected to decrease elagolix concentrations. Concomitant use of strong CYP3A inducers may reduce the efficacy of Oriahnn and is not recommended.

Evaluation	Results	The Applicant's Management Strategies	Review Team's Management Strategies
The Effects of Elagolix on Other Drugs			
BCRP/OATP1B1 inhibition by elagolix 300 mg BID (Study M13-756)	↓AUC by 40% ↔ C_{max} (rosuvastatin)	Consider increasing the dose of rosuvastatin.	Monitor lipid levels and adjust the dose of rosuvastatin, if necessary.
CYP3A4 induction by elagolix 150 mg QD and 300 mg BID (Study M15-629)	↓AUC by 35 - 55% ↓C_{max} by 19 – 44% (midazolam)	Consider increasing the dose of midazolam and individualize therapy based on patient's response.	Consider increasing the dose of midazolam by no more than 2-folds and individualize midazolam therapy based on the patient's response.
P-gp inhibition by elagolix 300 mg BID (PBPK simulation)	↑C_{max} by 78% ↑AUC by 28% (digoxin)	Clinical monitoring is recommended for digoxin when co-administered with elagolix. No dose adjustment or monitoring for other P-gp substrates with a wide therapeutic index.	Increase monitoring of digoxin concentrations and potential signs and symptoms of clinical toxicity when initiating or discontinuing Oriahnn in patients who are taking digoxin.
CYP2B6 induction by elagolix 300 mg BID (Study M16-850)	↔AUC ↑ C_{max} 25% (bupropion)	No dose adjustment is required for bupropion	Concur with the Applicant.
CYP2C19 inhibition by 300 mg elagolix BID (Study M16-855)	↑C_{max} by 95% ↑AUC by 78% (omeprazole)	No dose adjustment required for omeprazole	No dose adjustment needed for omeprazole 40 mg once daily or lower when co-administered with Oriahnn. When Oriahnn is used concomitantly with higher doses of omeprazole, consider dosage reduction of omeprazole. Co-administration with Oriahnn may increase plasma concentrations of drugs that are substrates of CYP2C19.

Evaluation	Results	The Applicant's Management Strategies	Review Team's Management Strategies
DDI between elagolix 300 mg BID and E2/NETA 1 mg/0.5 mg (Study M14-708)	↑C_{max} by 128% ↑AUC by 34% (E2) ↔AUC ↔ C_{max} (NETA)	No dose adjustment for E2 and NETA in Oriahnn is needed.	Advise women to use non-hormonal contraception during Oriahnn treatment because the use of estrogens and/or progestins may affect the efficacy and safety of Oriahnn.

AUC = area under the curve; BCRP = breast cancer resistance protein; BID = twice daily; C_{max} = maximum concentration; DDI = drug-drug interaction; E2/NETA = estradiol/norethindrone acetate; PBPK = physiologically-based pharmacokinetics; P-gp = P-glycoprotein; QD = once a day

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Parameter	Details
Pharmacology	
Mechanism of action	Elagolix is a GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of elagolix results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone and reduces bleeding associated with uterine fibroids. E2 acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a component of Oriahnn, the addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from elagolix alone. Progestins such as NETA act by binding to nuclear receptors that are expressed in progesterone-responsive tissues.
Active moieties	Elagolix, E2, and NETA
QT prolongation	No QT interval prolongation of clinical concern was observed at a single dose of 1200 mg. The effect of E2 and NETA on the QTc interval has not been studied.

Parameter	Details
General Information	
Bioanalysis	LC-MS/MS methods were used to measure elagolix, NETA, E2, and E2 metabolites in plasma, and E2 and progesterone in serum.
Healthy vs. patients	No dedicated comparative PK study between healthy subjects and patients was conducted. Population PK prediction showed that the average plasma concentration (C_{avg}) of elagolix in women with uterine fibroids was approximately 20% lower than that in healthy women.
Drug exposure at steady state (mean ± SD)	Elagolix 300 mg BID: AUC_{0-12} = 2826 ± 1231 ng*h/mL E2 and NETA: not available.
Range of effective dose or exposure	Effective dose range of elagolix: 100 mg BID to 300 mg BID or 600 mg QD
Maximally tolerated dose or exposure	Maximally tolerated doses of elagolix, E2, and NETA was not established. A single dose of 1200 mg elagolix and multiple doses of elagolix (400 mg BID for 21 days) were tested in healthy subjects. The doses of 300 mg BID with or without 1 mg E2/0.5 mg NETA QD were tested in women with uterine fibroids for 48 weeks. The doses of 600 mg QD with or without 1 mg E2/0.5 mg NETA QD were tested in women with uterine fibroids for 24 weeks.
Pharmacodynamics	Administration of elagolix results in dose-dependent suppression of LH and FSH, leading to decreased blood concentrations of the ovarian sex hormones, E2 and progesterone. The E2/NETA component supplements endogenous estrogen and progesterone. In Phase 3 trials in women with uterine fibroids administered Oriahnn for 6 months, the median concentrations of LH and FSH were approximately 0.40 to 0.70 mIU/mL and 1.8 to 2.5 mIU/mL respectively, resulting in median concentrations of estradiol of approximately 42 to 51 pg/mL, and progesterone of approximately 0.37 to 0.38 nM. In healthy women treated with Oriahnn, only appropriately 10% women reported ovulation.
Dose proportionality	For multiple-dose PK, on Day 1, elagolix shows dose-proportional increase in exposures (C_{max} and AUC) up to 200 mg and a more than dose-proportional increase from 200 mg to 1200 mg. At steady state (Day 21), elagolix shows a dose-proportional increase in exposures (C_{max} and AUC) up to 400 mg BID. Dose proportionality of E2 and NETA was not assessed.
Accumulation	Repeated daily administration of elagolix (QD or BID) at a dose ≥ 200 mg resulted in a decrease in drug exposure from Day 1 to Day 21. The accumulation ratio for elagolix was 0.78 for 300 mg BID dose. The accumulation ratios for E2, estrone (a major metabolite of E2), and NETA were 33-47% above concentrations following single dose administration.
Variability	Between-subject (in a BE study): elagolix C_{max} 44%, AUC 44%; E2 C_{max} 52%, AUC 41%; and NETA C_{max} 35%, AUC 45%.

Parameter	Details			
Absorption				
Bioavailability	The absolute bioavailability of elagolix, E2, and NETA in humans has not been established.			
Fasted T_{max} (median and range)	Elagolix: 1.5 h (1.0 – 4.0 h); E2: 2.0 (0.0 – 10.0 h); and NETA: 1.0 h (0.5 – 2.0 h)			
Food effect following a high-fat meal (Fed/fasted) [90% CI]	**Drug Name**	**$AUC_{0-\infty}$**	**C_{max}**	**T_{max} (Median, hour)**
	Elagolix	75% [66% - 84%]	64% [51% - 81%]	Fed: 3.0, Fasted: 1.5
	E2	105% [96% - 114%]	77% [65% - 91%]	Fed: 5.0, Fasted: 2.0
	NETA	123% [114% - 132%]	50% [43% - 59%]	Fed: 4.0, Fasted: 1.0
Distribution				
Volume of distribution	Elagolix: 883 L; E2: 27772 L; and NETA: 336 L			
Plasma protein binding	Elagolix: 80%; E2: 98%; and NETA: 97%			
Substrate transporter systems	Elagolix is a substrate of P-gp and OATP1B1. Population PK analysis showed OATP1B1 phenotype status was the only significant covariate on elagolix CL/F.			
Elimination				
Terminal elimination half-life (mean ± SD)	Elagolix: 2.9 ± 0.8 h; E2: 14.5 ± 6.6 h; and NETA: 9.2 ± 4.0 h			
CL/F (mean ± SD)	Elagolix: 79 ± 31 L/h; E2: 1246 ± 717 L/h; and NETA: 24 ± 12 L/h			
Metabolism				
Fraction metabolized (% dose)	Elagolix: 69% of dose recovered in feces and urine is metabolized.			
Primary metabolic pathway(s)	Elagolix is extensively metabolized in liver, primarily by CYP3A4, lesser extent by CYP2D6, and minor by CYP2C8. In human plasma, two oxidative metabolites (O-demethylated and N-dealkylated metabolites) constitute 2.4% and 3.3% of exposure relative to elagolix. E2 and NETA are metabolized partially by CYP3A. Other metabolic pathways for E2 and NEAT include sulfation and glucuronidation.			
Excretion				
Primary excretion pathways (% dose) ± SD	--Elagolix in feces: 90.1% (approximately 26.3% unchanged elagolix) --Elagolix in urine: 2.9% (approximately 2.6% unchanged elagolix)			
In vitro interaction liability (as a perpetrator)				
Inhibition/induction of metabolism	Elagolix is a time-dependent inhibitor of CYP3A4/5 (K_i 74 µM), CYP2C8 (K_i 82 µM), and CYP2C19 (K_i 34 µM), and an inducer of CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. E2 and NETA are substrates of CYP3A4.			
Inhibition/induction of transporter systems	Elagolix is an inhibitor of OATP1B1, OATP1B3, P-gp, and BCRP.			

6.3.2. Clinical Pharmacology Questions

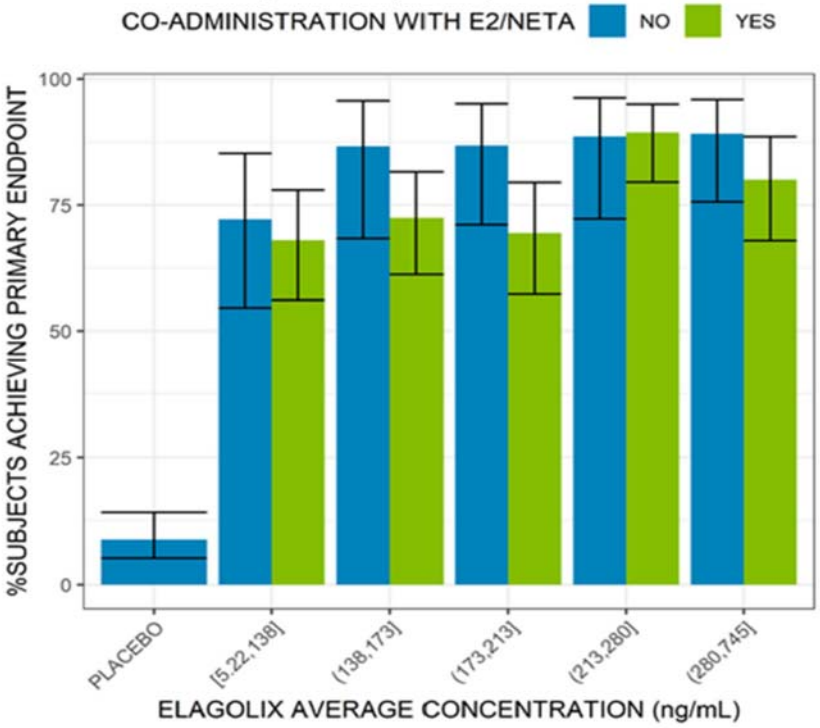
Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The clinical pharmacology information which provides supportive evidence of effectiveness includes: (1) elagolix exposure-response analyses for the primary efficacy endpoint [the proportion of subjects who had menstrual blood loss (MBL) <80 mL during

the final month and ≥ 50% reduction in MBL volume from baseline to the final month]; (2) dose-dependent efficacy observed in two Phase 2 studies; and (3) suppression effect of elagolix on E2 and progesterone in Phase 3 trials.

Elagolix Exposure-Response Information for Primary Efficacy Endpoint

Figure 4: Elagolix Average Concentration Quintile Plot for Proportion of Subjects that Met the Primary Efficacy Endpoint



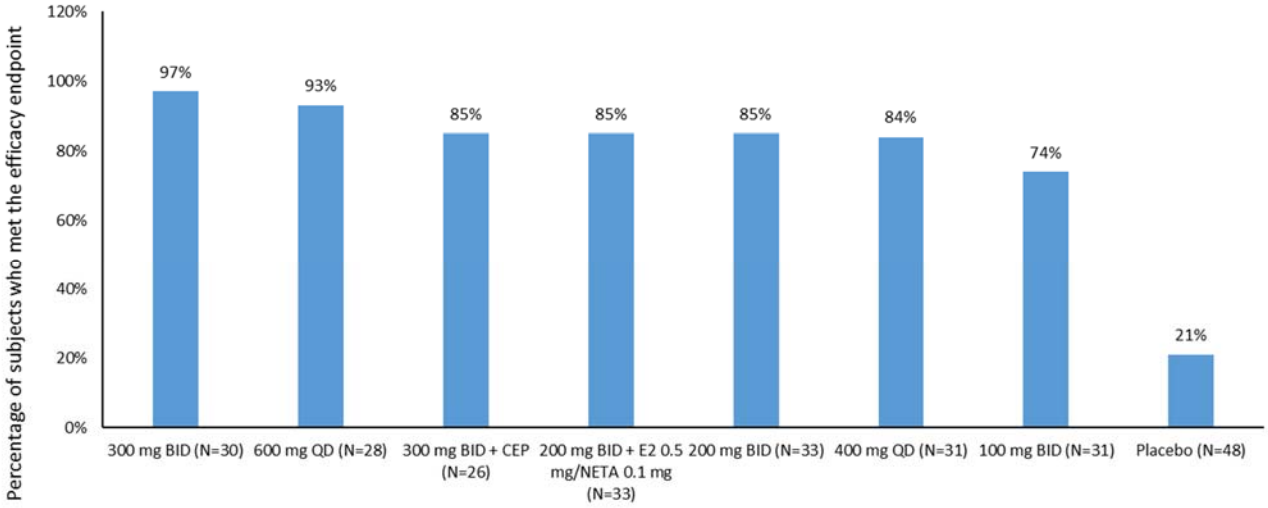
Source: Exposure-response analysis for efficacy study report (Report # RD190059), Figure 4.
Note: Bars plots represents observed proportions and error bars represents 95% binomial confidence intervals (CIs) of the observed proportions versus the model-predicted average elagolix concentration quintile
E2/NETA = estradiol/norethindrone acetate

To demonstrate the effectiveness of elagolix, the Applicant conducted exposure-response analysis for the primary efficacy endpoints using data from two Phase 3 trials: Study M12-815 and Study M12-817. The relationship between average plasma concentration of elagolix (C_{avg}) and percentage of subjects who met the primary efficacy endpoint was explored using quintile plots (Figure 4). For both elagolix 300 mg BID alone and elagolix 300 mg BID + E2/NETA groups, both exposure-response quintile plots and logistic regression analysis suggest that higher elagolix exposure is associated with higher probability of achieving the primary bleeding endpoint (see clinical pharmacology review in DARRTS for details). The addition of E2/NETA caused a small decrease (<10%) in the percentage of achieving the primary efficacy endpoint.

Dose-Dependent Efficacy Observed in Two Phase 2 Studies

In the Phase 2 dose-finding Study M12-663, the percentage of subjects who had MBL < 80 mL during the last 28 days of treatment and ≥ 50% reduction from baseline in MBL was used as an exploratory efficacy endpoint. The response was dose-dependent with 74% for elagolix daily dose of 200 mg, 84% to 85% for elagolix daily dose of 400 mg, and 85% to 97% for elagolix daily dose of 600 mg, compared with 21% for the combined placebo group (Figure 5).

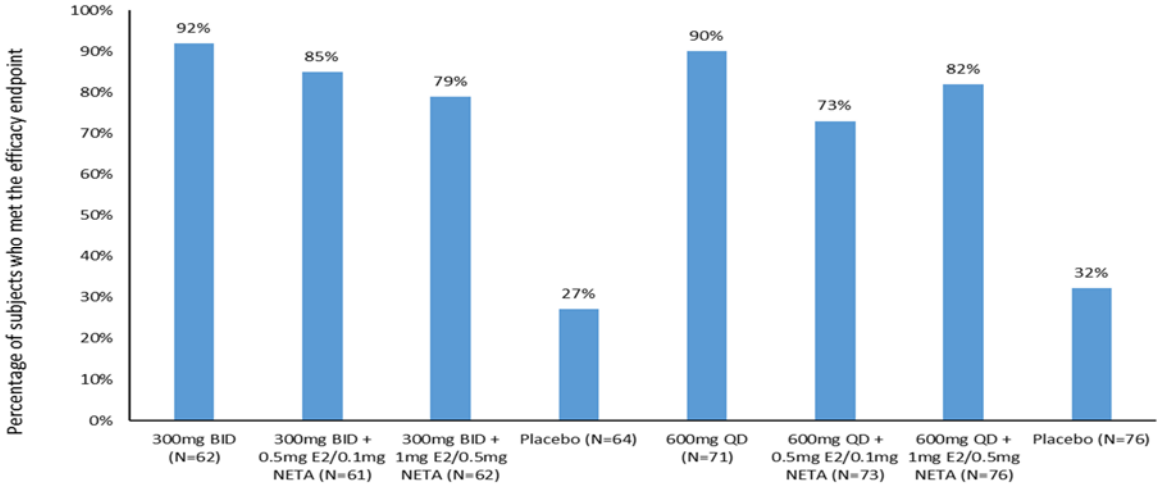
Figure 5: Analysis of Efficacy Endpoint for the Last 28 Days of Treatment Using Combined Placebo Group (Study M12-663)



Source: Study M12-663 report, Table 20.
Note: Efficacy endpoint: the percentage of subjects who had MBL < 80 mL during the last 28 days of treatment and ≥ 50% reduction in MBL volume from baseline to the final month.
BID = twice a day; CEP = combined Estrace (1 mg E2) and cyclical Prometrium (200 mg progesterone) administered QD; E2/NETA = estradiol/norethindrone acetate; QD = once a day

In the Phase 2b dose-finding Study M12-813, the Applicant assessed the effectiveness of elagolix at 300 mg BID or 600 mg QD alone and in combination with 2 different strengths of hormonal add-back therapies, E2 0.5 mg/NETA 0.1 mg or E2 1 mg/NETA 0.5 mg. As shown in Figure 6, all the treatment groups showed a statistically significantly greater proportion of responders who achieved MBL volume of < 80 mL at the final month and ≥50% reduction in MBL volume from baseline to the final month compared with that of the placebo group. The efficacy of elagolix was attenuated in a dose-dependent fashion by add-back therapy with E2/NETA.

Figure 6: Percentage of Subjects Who Met the Efficacy Endpoint by Treatment Group (Study M12-813)

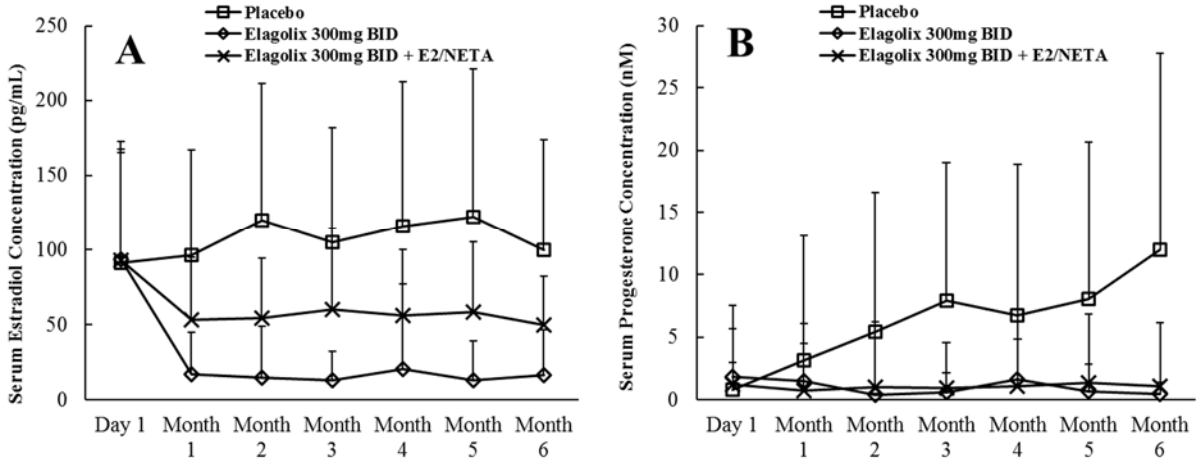


Source: Study M12-813 report, Table 19.
Note: Efficacy endpoint: the percentage of subjects who had MBL < 80 mL at the final month of treatment and ≥ 50% reduction in MBL volume from baseline to the final month.
BID = twice a day; E2/NETA = estradiol/norethindrone acetate; QD = once a day

Suppression on E2 and Progesterone in Phase 3 Trials

Elagolix reduces HMB primarily by suppressing ovarian sex hormones, estradiol and progesterone. To attenuate the hypoestrogenic effects (e.g., bone loss and hot flush) of elagolix alone treatment, E2/NETA was combined with elagolix as hormonal add-back therapy. In the uterine fibroids Phase 3 program, elagolix 300 mg BID + E2 1mg/NETA 0.5 mg was chosen as the TBM dose, and elagolix 300 mg BID alone was included as a reference arm to characterize the effect of E2/NETA. The effect of elagolix and add-back therapy on serum E2 and progesterone was assessed in Phase 3 trials. As shown in the Phase 3 Study M12-815 (Figure 7 below), compared with placebo, the overall Month 1 to Month 6 mean E2 concentration was reduced by approximately 84% and 49% in the elagolix 300 mg BID alone and elagolix 300 mg BID+E2/NETA groups, respectively. The overall Month 1 to Month 6 mean progesterone concentration was reduced by approximately 80% in both elagolix 300 mg BID alone and elagolix 300 mg BID+E2/NETA groups. Similar hormonal suppression results were observed in the pivotal Phase 3 Study M12-817 and Phase 3 extension Study M12-816. Furthermore, using pooled data from six studies (M12-813, M12-665, M12-667, M12-671, M12-821, and M12-673), the Applicant assessed the relationship between steady-state plasma E2 concentrations and elagolix daily dose, which revealed a dose-dependent suppression of E2.

Figure 7: Mean ± SD Serum (A) Estradiol and (B) Progesterone Concentration–Time Profiles by Treatment Group (Study M12-815)



Source: Study M12-815 report, Table 29 and Table 30.
BID = twice a day; E2/NETA = estradiol/norethindrone acetate

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dose regimen is appropriate for the management of HMB associated with uterine fibroids in premenopausal women. The proposed regimen is supported by clinical efficacy and safety data, exposure-response for safety, and QTc prolongation data. However, due to the loss in bone density observed in the Phase 3 trials, we recommend that the duration of treatment be limited to 24 months.

Efficacy

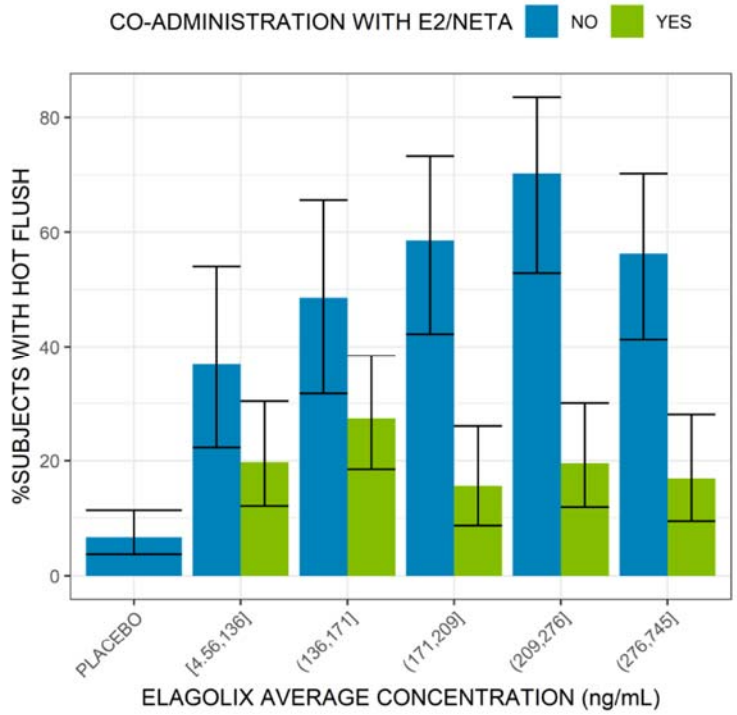
The efficacy of elagolix 300 mg BID + 1 mg E2/0.5 mg NETA QD dose in the management of HMB associated with uterine fibroids was demonstrated in two pivotal placebo-controlled Phase 3 studies (Studies M12-815 and M12-817) conducted in premenopausal women aged 18-51 years old. In both studies, 300 mg BID + E2/NETA significantly increased the responder rates at the final month compared to the placebo group. Refer to Section 8.1 Statistical and Clinical Evaluation of this review in for discussion on efficacy.

Exposure-Response Analysis for Hot Flush

In the two pivotal Phase 3 trials, 6.6%, 54.3%, and 20.0% subjects experienced hot flush in placebo, 300 mg BID, and 300 mg BID + E2/NETA groups, respectively. The relationship between average elagolix exposure C_{avg} and percentage of subjects with occurrence of hot flush was explored using quintile plots (Figure 8) and logistic regression analysis (See clinical pharmacology review in DARRTS for details). An increasing trend of incidence of hot flush was observed with increasing elagolix average

concentrations for 300 mg BID. For 300 mg BID + E2/NETA, no clear exposure-response relationship was identified between elagolix exposure and incidence of hot flush. The add-back therapy reduced the occurrence of hot flush caused by elagolix.

Figure 8: Exposure-Response Analysis for Hot Flush



Source: Exposure-response analysis for safety study report (Report # RD190282), Figure 19.
Note: Bars plots represents observed proportions and error bars represents 95% binomial CIs of the observed proportions at the model-predicted average concentration quintile.
E2/NETA = estradiol/norethindrone acetate

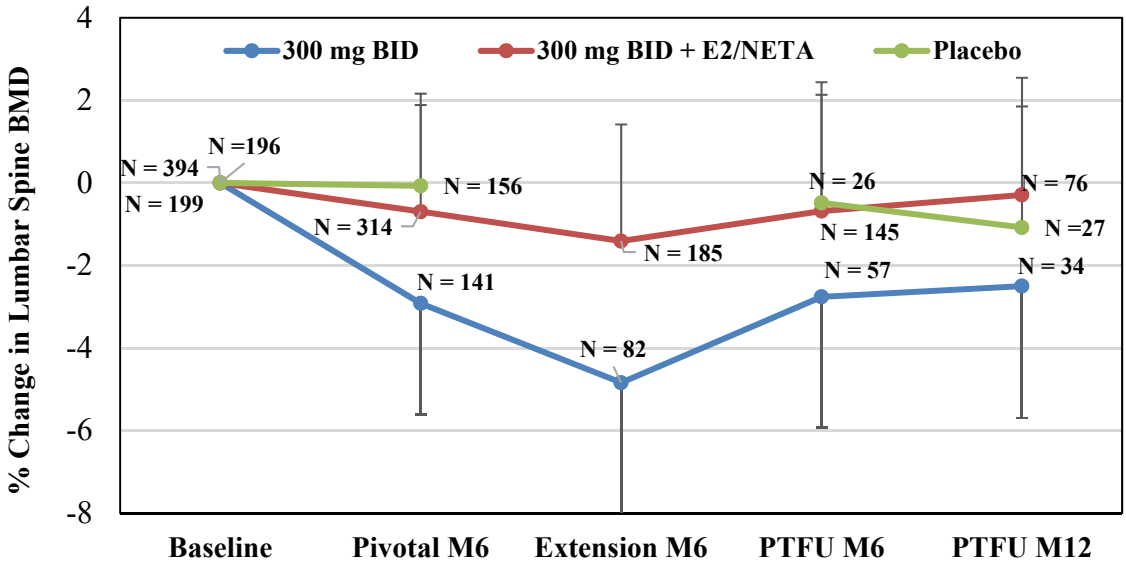
Bone Mineral Density

Long-term estradiol suppression by elagolix is expected to cause a decrease in BMD and E2/NETA add-back therapy can attenuate the bone loss. For subjects enrolled in Phase 3 trials, BMD of the lumbar spine, total hip, and femoral neck was assessed at baseline, Month 6 in the placebo-controlled pivotal studies, and Month 6 of the extension studies. Post-treatment recovery of BMD was assessed in post-treatment follow-up (PTFU) period (PTFU Month 6 and Month 12). As shown in Figure 9, treatment duration-dependent decrease in lumbar spine BMD was observed in both 300 mg BID and 300 mg BID + E2/NETA groups.

The Applicant developed a population exposure-BMD model for elagolix to simulate BMD changes in women with HMB associated with uterine fibroids using data available from three Phase 3 studies. Each simulated subject was treated with elagolix 300 mg BID + E2/NETA or placebo for 96 months and the % change from baseline BMD was predicted over the treatment period. The mean % change in lumbar spine BMD over time together with 95% confidence intervals (CIs) are shown in Figure 10. The

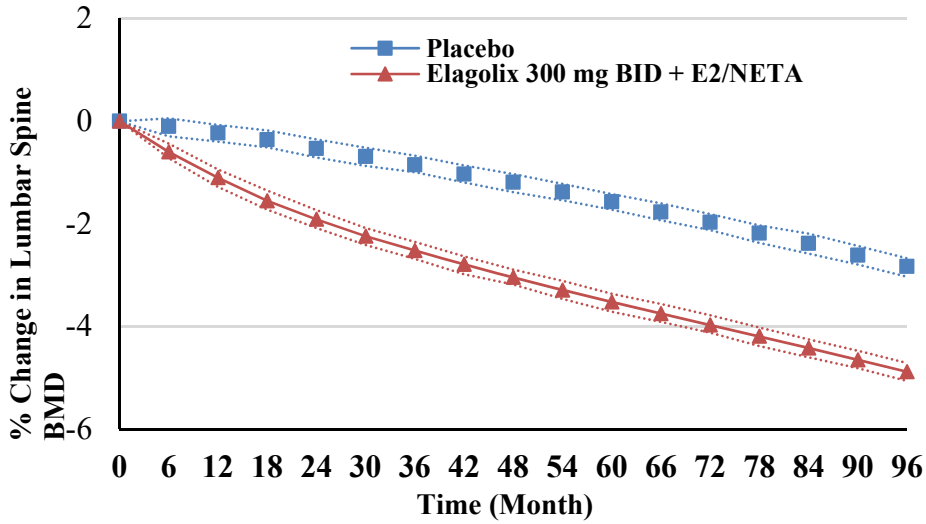
simulated mean % changes in lumbar spine BMD from baseline after 12-, 24-, 36-, and 48-month elagolix 300 mg BID + E2/NETA treatment were 1.10%, 1.91%, 2.52%, and 3.04%, respectively. The Applicant proposed continuous use of elagolix 300 mg BID + E2/NETA up to (b) (4) months. However, we noted that after continuous treatment with elagolix 300 mg BID + E2/NETA for 12 months in Phase 3 trials, 10.9% and 1.7% of subjects experienced >5% and ≥8% lumbar spine BMD decreases from baseline, respectively. Even after a 12-month post-treatment period, 5.4% of subjects in elagolix 300 mg BID + E2/NETA group still had >5% lumbar spine BMD decreases from baseline, indicating an incomplete recovery to baseline. Refer to Section 8.2.5.1 Bone Safety for details.

Figure 9: Observed Mean Percent Changes (Mean ± SD) in BMD During 12-Month Treatment Period and 12-Month Post-Treatment Period in Studies M12-815/M12-816/M12-817



Source: Applicant's IR response submitted on 1/15/2020, Table 5.
BID = twice a day; BMD = bone mineral density; E2/NETA = estradiol/norethindrone acetate; PTFU = post-treatment follow-up

Figure 10: Simulated Mean % Change in Lumbar Spine BMD From Baseline Over Time



Source: Exposure-response analysis for safety study report (Report # RD190282), Table 13.3-1.8.1.
Note: Dash lines represent 95% CIs.
BID = twice a day; BMD = bone mineral density; E2/NETA = estradiol/norethindrone acetate

In Phase 2 Study M12-813, the Applicant assessed the efficacy and safety of elagolix 300 mg BID and elagolix 600 mg QD groups with and without E2/NETA add back. It was found that the proportions of subjects who met the primary efficacy endpoint in the elagolix 300 mg BID and elagolix 600 mg QD groups were similar. However, better tolerability was seen with the elagolix 300 mg BID + E2/NETA regimen compared to the elagolix 600 mg QD + E2/NETA regimen. Furthermore, the Applicant assessed the attenuating effect of two add-back regimens (0.5 mg E2/0.1 mg NETA and 1 mg E2/0.5 mg NETA) on bone loss. As shown in Table 4, dose-dependent attenuating effect of E2/NETA on lumbar spine BMD decreases was observed. The add-back therapy with 1 mg E2/0.5 mg NETA more effectively attenuated the decrease in BMD compared to that with 0.5 mg E2/0.1 mg NETA.

Table 4: Mean Percentage Changes in Lumbar Spine Bone Mineral Density from Baseline to Month 6 in Phase 2 Study M12-813

Treatment	Month 6 Visit N	Mean % Change
Cohort 1		
Placebo	44	0.91
Elagolix 300 mg BID	48	-3.80
Elagolix 300 mg BID + 0.5 mg E2/0.1 mg NETA	48	-1.62
Elagolix 300 mg BID + 1 mg E2/0.5 mg NETA	48	-0.141
Cohort 2		
Placebo	58	-0.13
Elagolix 600 mg QD	57	-3.40
Elagolix 600 mg QD + 0.5 mg E2/0.1 mg NETA	46	-1.24
Elagolix 600 mg QD + 1 mg E2/0.5 mg NETA	52	-1.11

Source: Study M12-813 report, Table 97.
BID = twice a day; E2/NETA = estradiol/norethindrone acetate; QD = once a day

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes, Oriahnn is contraindicated in women with hepatic impairment.

Hepatic and Renal Impairment

The PK of elagolix was evaluated in women with renal and hepatic impairment at elagolix 200 mg and 150 mg, respectively. The study reports were submitted in NDA 210450. Refer to Clinical Pharmacology Review for NDA 210450 dated July 20, 2018 in DARRTS for more information. Comparable exposure of elagolix was observed in subjects with various renal function status. Renal impairment did not result in a significantly higher exposure of elagolix. No dose adjustment for elagolix was required in women with any degree of renal impairment or end-stage renal disease (including women on dialysis). The effect of renal impairment on the PK of E2/NETA has not been studied.

The mean AUC value of elagolix was comparable between subjects with normal hepatic function and subjects with mild hepatic impairment (Child-Pugh A). Elagolix AUC values in subjects with moderate hepatic impairment (Child-Pugh B) and subjects with severe hepatic impairment (Child-Pugh C) were approximately 3-fold and 7-fold, respectively, of the AUC values in subjects with normal hepatic function. The effect of hepatic impairment on the PK of E2/NETA has not been studied. Due to the adverse effect and poor metabolism of E2 in subjects with liver impairment or disease, Oriahnn is contraindicated in these subjects.

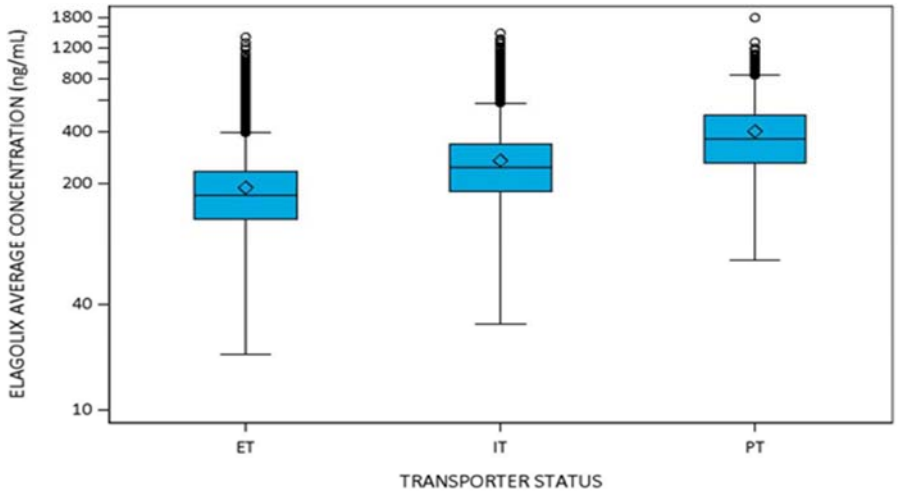
OATP1B1 Transporter Phenotype Status

Pharmacogenetic analysis of 2077 DNA samples collected from the Phase 1 and Phase 3 studies revealed 77% subjects with genotype-inferred extensive transporter phenotype (i.e., *SLCO1B1* 521T/T genotype), 21% subjects with IT phenotype (i.e.,

SLCO1B1 521T/C genotype), and 2% subjects with poor transporter phenotype (i.e., *SLCO1B1* 521C/C genotype). In the uterine fibroids Phase 3 trials (Studies M12-815, M12-816 and M12-817), five subjects (1 on placebo, 3 received elagolix+E2/NETA, 1 received elagolix alone) had PT phenotype and 74 subjects had PT and IT phenotype, respectively.

Population PK analysis identified that organic anion-transporting peptide (OATP) 1B1 phenotype status was a significant covariate on elagolix apparent clearance. Model simulations showed that subjects with phenotype status PT or IT had 2.09-fold and 1.45-fold higher exposures (i.e., C_{avg}), respectively compared to subjects with a phenotype status of ET (Figure 11 and Table 5).

Figure 11: Effect of OATP1B1 Phenotype on Elagolix Average Concentration



Source: Population PK study report, Figure 4.
Note: The box shows the interquartile range (IQR) with a median line in between. Lower/upper whiskers extend to the lowest/highest value within 1.5 * IQR.
ET = extensive transporter; IT = intermediate transporter; PT = poor transporter

Table 5: Elagolix Exposure Simulated by Population PK model – Subgroup Analysis by OATP1B1 Genotype

OTAP1B1	C_{avg} (ng/mL) Median (95% CI)	C_{max} (ng/mL) Median (95% CI)	C_{trough} (ng/mL) Median (95% CI)
Extensive	172 (78.6, 370)	631 (301, 1299)	2.06 (0.387, 11.7)
Intermediate	250 (115, 529)	917 (439, 1868)	3.03 (0.563, 16.9)
Poor	360 (152, 786)	1289 (621, 2719)	4.50 (0.736, 28.4)

Source: Population PK study report, Table 13.3-9.
C_{avg} = average concentration; C_{max} = maximum concentration; C_{trough} = lowest concentration reached before next dose is administered

Nineteen among 41 subjects (46.3%) with IT phenotype treated with Oriahnn in the Phase 3 trials reported adverse events, which was comparable to that of the overall patient population (50.4%) (Table 6). Furthermore, the percentages of subjects who

reported severe adverse events were similar between IT phenotype population (9.8%) and Phase 3 overall population (9.1%). Therefore, a 45% increase in the exposure of elagolix in the subjects with IT phenotype is not expected to have a clinically meaningful impact on efficacy and safety. No dose adjustment is needed or women with OATP1B1 IT phenotype.

Table 6. Treatment-Emergent Adverse Events: OATP1B1 Intermediate Transporter Phenotype versus Overall Phase 3 Population

	Number (%) of Subjects with Intermediate Transporter Phenotype			**Number (%) of Subjects in Overall Phase 3 Population[a]**		
		Elagolix 300 mg BID			Elagolix 300 mg BID	
	Placebo N = 22	Alone N = 22	+E2/NETA N = 41	Placebo N = 196	Alone N = 199	+E2/NETA N = 395
Any AE	16 (72.7)	13 (59.1)	27 (65.9)	130 (66.3)	166 (83.4)	283 (71.6)
Drug related AE[b]	7 (31.8)	13 (59.1)	19 (46.3)	73 (37.2)	143 (71.9)	199 (50.4)
Any SAE	1 (4.5)	0 (0)	4 (9.8)	10 (5.1)	20 (10.1)	36 (9.1)
Drug related SAE[b]	0	0 (0)	2 (4.9)	N.A.	N.A.	N.A.

Source: Summary of Clinical Safety, Table 8 and ISS safety adverse events dataset
AE = adverse event; SAE = severe adverse event; BID = twice a day; E2/NETA = estradiol/norethindrone acetate;
a. Placebo-Controlled Phase 3 Analysis Set
b. As assessed by the investigator; choices were reasonable poss bility and no reasonable possibility

The population PK model-simulated steady-state PK parameters for the five subjects with uterine fibroids and OATP1B1 PT phenotype in Phase 3 trials were shown in Table 7. Although the C_{avg} values of elagolix in the four subjects who received Ela + E2/NETA or elagolix alone are higher than the mean C_{avg} in uterine fibroids patients overall (211 ± 100 ng/mL, N=706), they are still within 95% CIs in uterine fibroids patients (median C_{avg} = 189 ng/mL and 95% CIs: 97 – 391 ng/mL). The three subjects ([(b) (6)]) who received elagolix 300 mg +E2/NETA for 12 months did not show significant lumbar spine BMD loss compared to the mean BMD loss in other subjects in 300 mg +E2/NETA group (Figure 12). Furthermore, no severe adverse events were reported among the five subjects with OATP1B1 PT genotype. Only Subject [(b) (6)] reported three moderate on-treatment adverse events (AEs; stiff neck, depression and migraine).

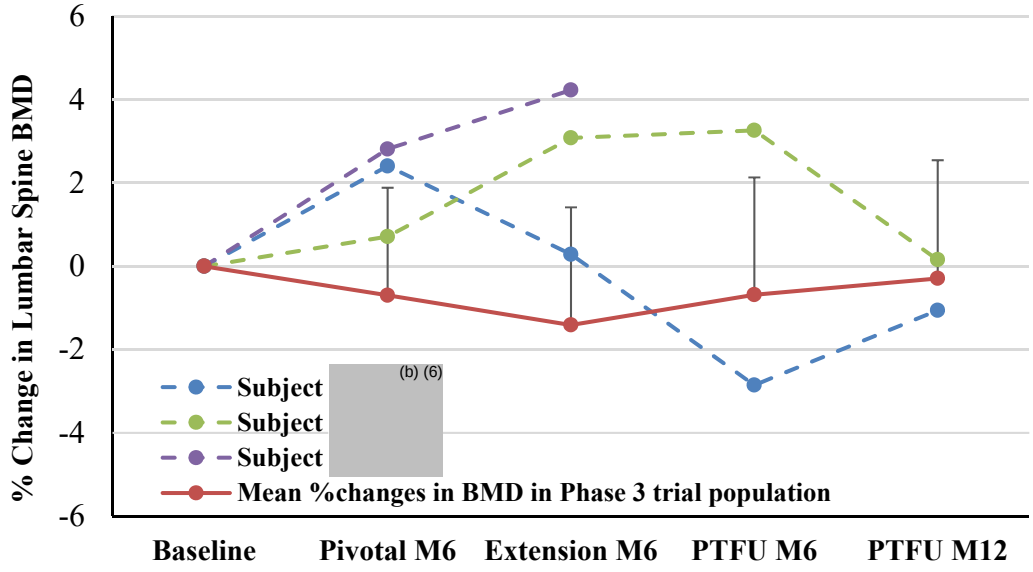
Table 7: Simulated Steady-State Pharmacokinetic Parameters of Elagolix in Subjects With Uterine Fibroids and OATP1B1 Poor Transporter Phenotype

Study # Subject ID	Treatment	CL/F (L/h)	V_2/F (L)	C_{avg} (ng/mL)
M12-815				
(b) (6)	Placebo/300 mg BID	87.8	184	285
M12-817				
(b) (6)	300 mg BID + E2/NETA	72.6	226	344
	300 mg BID + E2/NETA	66	160	379
	300 mg BID + E2/NETA	125	205	200
*	Placebo	N.A.	N.A.	N.A.

Source: Reviewer's analysis
* Subject was in placebo group therefore no PK data was available for simulation. N.A.- Not Available.
BID = twice a day; C_{avg} = average concentration; CL/F = apparent drug clearance; E2/NETA = estradiol/norethindrone acetate; N.A. = not available; V_2/F = volume of distribution after non-intravenous administration

A 109% increase in the exposure of elagolix may pose a safety risk in the subjects with PT phenotype. However, the frequency of OATP1B1 PT phenotype (i.e., *SLCO1B1* 521C/C genotype) is generally lower than 5% in most racial/ethnic groups. The limited safety data from three subjects showed that 12-month continuous treatment with elagolix 300 mg +E2/NETA did not result in severe AEs or significant bone loss in subjects with OTAP1B1 PT phenotype (see Figure 12 below). The impact of this polymorphism on the safety of elagolix has not been clearly established. We do not recommend dose adjustment for women with OATP1B1 PT phenotype. To mitigate potential safety risk, the following statement is added to Section 12.5 of drug label: "Adverse effects of elagolix have not been fully evaluated in subjects who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C)."

Figure 12: Observed Percent Changes in BMD During 12-Month Treatment Period and 12-Month Post-Treatment Period – Individual Subjects with OATP1B1 Poor Transporter Phenotype versus Phase 3 Trial Population



Source: Reviewer's analysis
BMD = bone mineral density; PTFU = post-treatment follow-up

Age

The 2168 subjects included in population PK analysis had an age range of 18 - 53 years and a mean age of 35.8 ± 7.8 years. Population PK analysis showed that subject age did not affect the clearance or volume of distribution of elagolix. Refer to Population PK Analyses in the clinical pharmacology review in DARRTS for more information. The effects of age on plasma steady-state levels of estrone sulfate was evaluated in the Activella NDA 20907 and no difference in the steady-state concentrations of estrone sulfate was observed between women aged above 65 and below 65 years. However, plasma E2 and NETA concentrations were not measured in the study. Therefore, a definitive conclusion cannot be drawn from this study.

The Applicant's subpopulation analysis for primary efficacy endpoint showed that the responder rates to 300 mg BID + E2/NETA treatment in subjects < 35 years old (77.3%), 35-40 years old (68.8%), 40-45 years old (75.8%), and ≥ 45 years old (69.5%) were comparable. No significant age effect on efficacy was observed for 300 mg BID + E2/NETA treatment.

The Applicant's subpopulation analysis for BMD showed that although 6-month treatment with 300 mg BID likely caused more bone loss in subjects < 40 years old, there was no apparent trend in mean percent changes in lumbar spine BMD from baseline corresponding with increasing age compared to placebo at Month 6 of 300 mg BID + E2/NETA treatment (Table 8).

Table 8: Mean Percent Changes in Lumbar Spine BMD by Age Compared to Placebo at Month 6 of Treatment

Treatments	<35 Years LS Mean (95% CI)	35-40 Years LS Mean (95% CI)	40-45 Years LS Mean (95% CI)	≥45 Years LS Mean (95% CI)
Placebo	-0.07 (-1.15, 1.02)	0.05 (-0.79, 0.88)	-0.74 (-1.57, 0.09)	0.19 (-0.42, 0.79)
300 mg BID	-3.57 (-4.96, -2.18)	-3.24 (-4.18, -2.30)	-2.74 (-3.50, -1.97)	-2.93 (-3.57, -2.29)
300 mg BID + E2/NETA	-1.42 (-2.22, -0.61)	-0.17 (-0.77, 0.43)	-0.82 (-1.37, -0.27)	-0.65 (-1.08, -0.22)

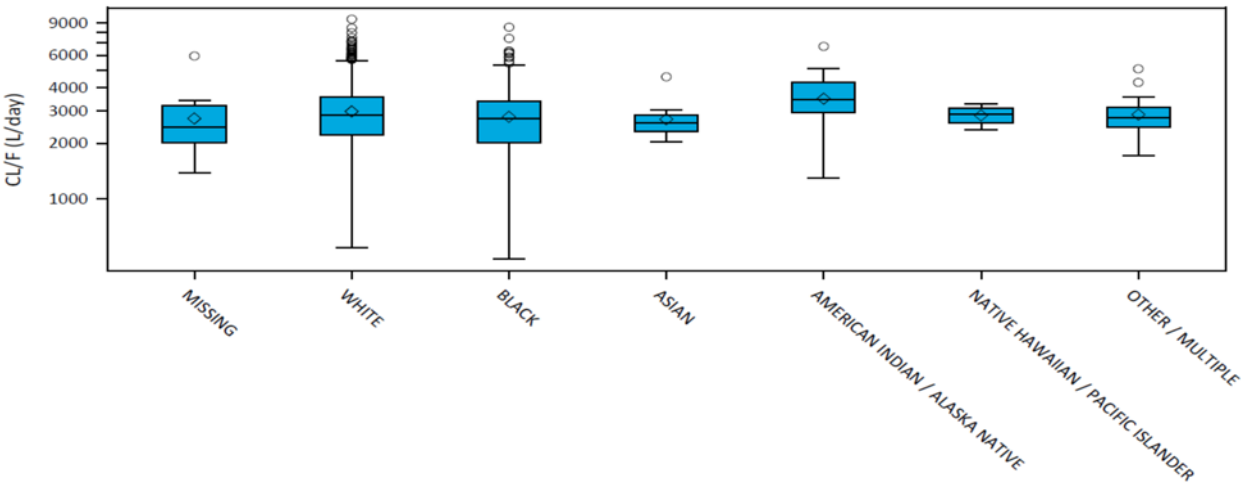
Source: Reviewer's summary from Integrated Study of Safety, TABLE 5.1-3.1.1.1
BID = twice a day; BMD = bone mineral density; E2/NETA = estradiol/norethindrone acetate; LS = least squares

Overall, consistent elagolix PK, efficacy and safety were observed in subjects aged 18 – 53 years. We agree with the Applicant that no age-based dose adjustment is recommended for premenopausal women with uterine fibroids.

Race and Ethnicity

The PK of elagolix was previously evaluated in healthy Asian women (Han Chinese and Japanese) in Phase 1 Study M12-654. The mean C_{max} and AUC values between Japanese and Han Chinese were found comparable. Population PK analysis for race/ethnicity effect on elagolix clearance did not identify a significant difference in elagolix clearance among White, Black, Asian, American Indian, native Hawaiian and other (Figure 13) or between Hispanic and others. The effect of race or ethnicity on the PK of E2 and NETA has not been assessed.

Figure 13: Effect of Race on Elagolix Clearance



Source: Population PK study report, Figure 13.3-3.
Note: The box shows the IQR with a median line in between. Lower/upper whiskers extend to the lowest/highest value within 1.5 * IQR.
CL/F = apparent drug clearance

The Applicant's subpopulation analysis for primary efficacy endpoint showed that the responder rates to 300 mg BID + E2/NETA treatment in Black subjects (71.8%), non-Black subjects (72.9%), Hispanic subjects (72.7%), and non-Hispanic subjects (72.1%) were comparable. Race-based subpopulation analysis for BMD changes showed that race did not affect the changes in lumbar spine BMD from baseline compared to placebo at Month 6 of 300 mg BID + E2/NETA treatment (Table 9).

Table 9: Mean Percent Changes in Lumbar Spine BMD by Race Compared to Placebo at Month 6 of Treatment

Treatments	Black or African American LS Mean (95% CI)	Others LS Mean (95% CI)
Placebo	0.10 (-0.38, 0.57)	-0.64 (-1.39, 0.10)
300 mg BID	-2.94 (-3.43, -2.45)	-3.04 (-3.84, -2.25)
300 mg BID + E2/NETA	-0.66 (-0.99, -0.32)	-0.78 (-1.30, -0.26)

Source: Reviewer's summary from Integrated Study of Safety, TABLE 5.1-3.2.1.1
BID = twice a day; BMD = bone mineral density; E2/NETA = estradiol/norethindrone acetate; LS = least squares

Body Weight and Body Mass Index

The subjects included in the population PK analysis had a body weight range of 40 – 160 kg and mean ± SD body weight of 79.4 ± 20.3 kg. The body mass index (BMI) range was 16.2 – 61.5 kg/m^2 and the mean ± SD BMI was 29.4 ± 7.3 kg/m^2. In the Applicant's population PK analysis, body weight was identified as a statistically significant covariate on apparent volume of distribution. However, the simulated individual subject's exposure to elagolix revealed that body weight ± 25 kg from the population median body weight of 76 kg did not affect elagolix average plasma concentrations (Table 10).

Table 10: Elagolix Exposure Simulated by Population PK Model – Subgroup Analysis by Body Weight

Body Weight	C_{avg} (ng/mL) Median (95% CI)	C_{max} (ng/mL) Median (95% CI)	C_{trough} (ng/mL) Median (95% CI)
Median (76 kg)	172 (78.6, 370)	631 (301, 1299)	2.06 (0.387, 11.7)
Median –25 kg	171 (79.6, 369)	658 (318, 1349)	1.95 (0.383, 10.8)
Median +25 kg	171 (79.1, 369)	611 (292, 1256)	2.13 (0.401, 12.4)

Source: Population PK study report, Table 13.3-9.
C_{avg} = average concentration; C_{max} = maximum concentration; C_{trough} = lowest concentration reached before next dose is administered; PK = pharmacokinetic

Subpopulation analysis for the primary efficacy endpoint showed that although the responder rate to 300 mg BID + E2/NETA treatment in the < 25 kg/m^2 group appeared low (59.2%), there was no apparent trend in responder rate corresponding with increasing BMI compared to placebo at Month 6 of 300 mg BID + E2/NETA treatment.

See also discussion on subpopulation in Section 8.1.3 Assessment of Efficacy Across Trials.

For the 300 mg BID group, overall, there was an apparent trend in mean percent changes in femoral neck, hip and lumbar spine BMD from baseline corresponding with increasing BMI compared to placebo (lower BMI, larger decrease in BMD) (Table 11). For the 300 mg BID + E2/NETA group, there was no clear trend in mean percent changes in femoral neck, hip and lumbar spine BMD from baseline corresponding with increasing BMI compared to placebo. Therefore, body weight or BMI based dose adjustment for Oriahnn is not needed.

Table 11: Mean Percent Changes in BMD by BMI Compared to Placebo at Month 6 of Treatment

Anatomic Region	<25 kg/m^2 LS Mean (95% CI)	25 to <30 kg/m^2 LS Mean (95% CI)	30 to <35 kg/m^2 LS Mean (95% CI)	35 to <40 kg/m^2 LS Mean (95% CI)	≥40 kg/m^2 LS Mean (95% CI)
Placebo					
Femoral neck	-0.25 (-1.35, 0.85)	-0.60 (-1.54, 0.35)	-0.42 (-1.56, 0.72)	-0.30 (-1.47, 0.88)	0.25(-1.37, 1.86)
Total hip	-0.37 (-1.19, 0.46)	-0.63 (-1.20, -0.07)	0.05 (-0.55, 0.65)	-0.05 (-0.80, 0.69)	0.06 (-0.72, 0.84)
Spine	-0.25 (-1.16, 0.67)	-0.28 (-1.00, 0.43)	-0.14 (-0.93, 0.65)	0.68 (-0.23, 1.59)	-0.69 (-1.82, 0.45)
300 mg BID					
Femoral neck	-2.85 (-3.91, -1.79)	-1.87 (-3.12, -0.61)	-2.40 (-3.56, -1.23)	-1.55 (-2.72, -0.38)	-1.01 (-2.50, 0.48)
Total hip	-2.69 (-3.47, -1.90)	-1.65 (-2.40, -0.91)	-2.31 (-2.92, -1.69)	-1.84 (-2.59, -1.10)	-1.50 (-2.22, -0.79)
Spine	-4.10 (-4.98, -3.21)	-2.91 (-3.86, -1.97)	-2.71 (-3.52, -1.90)	-3.09 (-4.01, -2.18)	-2.50 (-3.56, -1.44)
300 mg BID + E2/NETA					
Femoral neck	-0.04 (-0.83, 0.75)	-0.55 (-1.23, 0.12)	-0.34 (-1.12, 0.44)	-0.93 (-1.76, -0.11)	-0.90 (-2.05, 0.25)
Total hip	-0.36 (-0.95, 0.22)	-0.05 (-0.45, 0.35)	-0.12 (-0.53, 0.29)	-0.21 (-0.74, 0.32)	-0.20 (-0.75, 0.36)
Spine	0.04 (-0.61, 0.68)	-0.64 (-1.15, -0.14)	-0.71 (-1.25, -0.17)	-0.90 (-1.55, -0.26)	-0.94 (-1.75, -0.13)

Source: Reviewer's summary from Integrated Study of Safety
BID = twice a day; BMD = bone mineral density; BMI = body mass index; E2/NETA = estradiol/norethindrone acetate; LS = least squares

Patients Versus Healthy Subjects

The population PK model-simulated steady-state average plasma concentrations (C_{avg}) of elagolix 300 mg BID in women with uterine fibroids were approximately 20% lower than those in healthy women in Phase 1 studies (Table 12). Considering the small sample size of healthy subjects (N=28) and the inter-subject variability in PK (38-48%), a definitive conclusion regarding the impact of disease status on the PK of elagolix cannot be drawn.

Table 12: Population PK Model-Predicted Steady-State Exposure of Elagolix in Healthy Subjects and Patients

Population	N	C_{avg} (ng/mL) (GM, CV%)	C_{max} (ng/mL) (GM, %CV)
Healthy premenopausal women 300 mg BID	28	262 (243, 38)	2.06 (0.387, 11.7)
Premenopausal women 300 mg BID with uterine fibroids	706	211 (190, 48)	1.95 (0.383, 10.8)

Source: Clinical Pharmacology Study Summary, Table 15.
BID = twice a day; C_{avg} = average concentration; C_{max} = maximum concentration; GM = geometric mean; PK = pharmacokinetic

Bilirubin, Creatinine Clearance, Aspartate Amino Transferase and Alanine Amino Transferase

The levels of bilirubin, lab amino transferase (AST), alanine amino transferase (ALT) and creatinine, and creatinine clearance were used as covariates in the population PK analysis. None of them were found to be significantly associated with elagolix PK parameters.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes, the management strategies for drug-drug interactions (DDIs) are summarized in Table 3.

Food Effects

Two food effect studies (Study M16-856 and Study M19-648) were conducted with the TBM formulations (morning dose: an FDC capsule of elagolix/E2/NETA 300/1/0.5 mg and evening dose: elagolix 300 mg capsule) in healthy postmenopausal women. Following administration of an FDC capsule after a high-fat meal, the elagolix C_{max} and area under the curve from zero to infinity ($AUC_{0\text{-}inf}$) were 36% and 25% lower, respectively, when compared to exposures under fasting conditions. NETA C_{max} was 50% lower and $AUC_{0\text{-}inf}$ was 23% higher, while baseline-adjusted total estrone C_{max} and AUC were 44% and 14% lower, respectively. A high-fat meal reduced C_{max} of baseline-adjusted E2 by 23% but did not affect AUC. Data are shown in Table 13 below.

Table 13: The Effect of Food on the PK Parameters of To-Be-Marketed FDC Capsule (Study M16-856, N = 12)

	Least Squares Geometric Means		% Test/Ref Ratio
Parameters	**Fed [Test]**	**Fasting [Reference**	**(90% CI)**
Baseline-corrected E2			
$AUC_{0\text{-}inf}$ (pg•h/mL)	1081.2	1035.0	104.5 (95.5 – 114.3)
$AUC_{0\text{-}t}$ (pg•h/mL)	912.7	914.8	99.8 (92.7 – 107.4)
C_{max} (pg/mL)	41.29	53.72	76.9 (65.1 – 90.7)
T_{max} (h)*	5.0 (2.0 – 6.0)	2.0 (1.0 – 4.0)	N.A.
Baseline-corrected total estrone			
$AUC_{0\text{-}inf}$ (ng•h/mL)	163.3	189.1	86.4 (79.4 – 94.0)
$AUC_{0\text{-}t}$ (ng•h/mL)	159.6	185.4	86.1 (79.3 – 93.4)
C_{max} (ng/mL)	13.0	23.3	55.7 (45.1 – 68.9)
T_{max} (h)*	3.5 (2.0 – 6.0)	1.5 (1.0 – 2.0)	N.A.
Elagolix			
$AUC_{0\text{-}inf}$ (ng•h/mL)	3390.4	4536.5	74.7 (66.2 – 84.4)
$AUC_{0\text{-}t}$ (ng•h/mL)	3377.7	4524.0	74.7 (66.1 – 84.3)
C_{max} (ng/mL)	1078.5	1681.3	64.1 (50.7 – 81.1)
T_{max} (h)*	3.0 (2.0 – 6.0)	1.5 (1.0 – 2.0)	N.A.
NETA			
$AUC_{0\text{-}inf}$ (ng•h/mL)	26.38	21.53	122.5 (114.2 – 131.5)
$AUC_{0\text{-}t}$ (ng•h/mL)	24.20	19.51	124.1 (114.4 – 134.5)
C_{max} (ng/mL)	2.72	5.44	49.9 (42.6 – 58.5)
T_{max} (h)*	4.0 (1.0 – 6.0)	1.0 (1.0 – 1.0)	N.A.

Source: Reviewer's analysis
*Median (minimum – maximum).
$AUC_{0\text{-}inf}$ = area under the curve from 0 to infinity; $AUC_{0\text{-}t}$ = area under the curve from time 0 to time t; C_{max} = maximum concentration; E2 = estradiol; FDC = fixed=dose combination; N.A. = not available; NETA = norethindrone acetate; PK = pharmacokinetic; T_{max} = time to maximum concentration

Following administration of an evening dose capsule after a high-fat meal, the elagolix C_{max} and $AUC_{0\text{-}inf}$ were 40% and 28% lower, respectively when compared to exposures under fasting conditions, which was consistent with the food effect observed with morning dose formulation (FDC capsule). See Table 14 below.

Table 14: The Effect of Food on the PK Parameters of Evening Dose Capsule (Study M19-648, N=12)

	Least Squares Geometric Means		% Test/Ref Ratio
Parameters	**Fed [Test]**	**Fasting [Reference]**	**(90% CI)**
$AUC_{0\text{-}inf}$ (ng•h/mL)	2618	3634	72.03 (65.68 – 78.99)
$AUC_{0\text{-}t}$ (ng•h/mL)	2609	3630	71.88 (65.53 – 78.84)
C_{max} (ng/mL)	755	1262	59.79 (48.22 – 74.15)
T_{max} (h)*	3.0 (2.0 – 6.0)	1.75 (1.5 – 2.0)	N.A.

Source: Reviewer's analysis
*Median (minimum – maximum).
$AUC_{0\text{-}inf}$ = area under the curve from 0 to infinity; $AUC_{0\text{-}t}$ = area under the curve from time 0 to time t; C_{max} = maximum concentration; N.A. = not available; PK = pharmacokinetic; T_{max} = time to maximum concentration

Based on elagolix exposure-response relationship for efficacy, 25-28% decrease in elagolix AUC and up to 40% decrease in elagolix C_{max} under fed conditions are not expected to have a clinically meaningful impact on responder rates. In addition, both morning and evening doses were administered without regards to meals in Phase 3 trials. We concur with the Applicant that Oriahnn can be orally administered without regard to meals and no dose adjustment was recommended under fed conditions.

Drug-Drug Interactions

The Applicant submitted ten clinical DDI study reports and one physiologically-based pharmacokinetics (PBPK) modeling report in NDA 210450 submission. In the current NDA, the Applicant submitted four clinical DDI study reports and one PBPK modeling report. The clinical DDI study findings and management strategies are summarized in Table 3.

Study M12-660 showed that co-administration of ketoconazole 400 mg QD and a single dose of elagolix 150 mg caused an increase of elagolix AUC by 120%. Concomitant use of Oriahnn with a strong CYP3A inhibitor would result in a drug exposure around 660 mg BID elagolix administered alone. A single dose of rifampin 600 mg, which is expected to inhibit hepatic uptake transporter OATP1B1, caused an increase of elagolix AUC by 458% (Study M12-659). When co-administered with rifampin or another potent OATP1B1 inhibitor, the 300 mg BID dose of elagolix would result in a drug exposure around 1700 mg BID elagolix administered alone. The maximum single-dose exposure of elagolix in human was 1200 mg and the maximum multidose exposures in human were 400 mg BID for 21 days and 600 mg QD for 24 weeks. Currently, there are insufficient safety data to support concomitant use of Oriahnn with strong inhibitors of CYP3A or OATP1B1. Therefore, we concur with the Applicant that strong OATP1B1 inhibitors should be contraindicated. Also, concomitant use of Oriahnn and strong CYP3A inhibitors is not recommended.

Oral administration of rifampin 600 mg QD for 10 day is expected to inhibit OATP1B1, induce CYP3A enzymes and P-gp, and potentially also induce OATP1B1 transporters. The net effect of OATP1B1 inhibition and CYP3A/P-gp/OATP1B1 induction caused an increase of elagolix AUC by only 65% on Day 10. We concur with the Applicant that concomitant use of Oriahnn and rifampin should be avoided.

Co-administration of rosuvastatin 20 mg QD with elagolix 300 mg BID resulted in a decrease of rosuvastatin AUC by approximately 40%. The mechanisms for decrease in rosuvastatin AUC when co-administered with multiple-dose elagolix is unknown and OATP1B1 induction by elagolix may be one of the possible mechanisms. We agree with the Applicant that the dose of rosuvastatin may be increased, but only after monitoring of lipid levels confirms that dose adjustment is necessary.

PBPK simulation showed that the effect of elagolix 300 mg BID on the PK of digoxin is expected to be similar to that of elagolix 200 mg BID in an in vivo DDI study where the

C_{max} and AUC of digoxin was increased by approximately 70% and 30%, respectively. The Applicant proposed clinical monitoring for digoxin and no dose adjustment or monitoring for other P-gp substrates with a wide therapeutic index when co-administered with Oriahnn. While the proposal of no dose adjustment/monitoring for other P-gp substrates appears reasonable, we recommend increased monitoring of digoxin concentrations and potential signs and symptoms of clinical toxicity when initiating or discontinuing Oriahnn in patients who are taking digoxin.

Co-administration of a single dose of omeprazole with elagolix 300 mg BID resulted in an increase of omeprazole C_{max} and AUC by 95% and 77%, respectively. We recommend no dose adjustment for omeprazole 40 mg once daily or lower when co-administered with Oriahnn. However, doses up to 120 mg three times daily have been used in patients. When Oriahnn is used concomitantly with doses of omeprazole higher than 40 mg per day, dosage reduction for omeprazole is recommended.

Studies M14-708 and M13-757 showed that concomitant use of elagolix 300 mg BID increased the AUC and C_{max} of orally administered E2 but did not affect the PK of transdermally administered E2, indicating elagolix 300 mg BID might increase oral absorption of E2 by inhibiting CYP3A in gastrointestinal tract. Phase 3 trials showed that the steady-state average concentrations of E2 in patients treated with Oriahnn were approximately 50-60 pg/mL (Figure 7), which was slightly lower than the normal serum E2 level in healthy pre-menopausal women (65 ± 34 pg/mL). In addition, the Applicant's population PK simulation showed that the addition of 1mg E2/0.5 NETA did not affect the PK of elagolix. Therefore, the DDI between elagolix 300 mg BID and oral add-back E2 is not expected to have clinically meaningful impact on the efficacy and safety of Oriahnn. In the Phase 3 trials, however, the add-back of E2 reduced the efficacy of elagolix 300 mg alone treatment (Refer to Section 8.1.2, Table 28 for more information). We recommend that concomitant use of estrogens and/or progestins be prohibited during Oriahnn treatment.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

No, the TBM formulations (FDC capsule for morning dose and elagolix EN03 capsule for evening dose) are different from the Phase 3 trial formulations (elagolix RC2 300 mg immediate-release tablet and E2/NETA 1 mg/0.5 mg immediate-release tablet). The Applicant conducted two pivotal BE studies (Study M16-856 and Study M19-648) to bridge the TBM formulations to Phase 3 formulations. The BE study results for both morning dose formulation (Table 15) and evening dose formulation (Table 16) met the established BE criteria.

Table 15: Bioequivalence Assessment for Morning Dose Formulation (Study M16-856, N=165)

	Least Squares Geometric Means		% Test/Ref Ratio
Parameters	**FDC [Test]**	**RC2 +E2/NETA [Reference**	**(90% CI)**
Baseline-corrected E2			
$AUC_{0\text{-}inf}$ (pg•h/mL)	878.3	963.4	91.2 (87.6 – 94.9)
$AUC_{0\text{-}t}$ (pg•h/mL)	786.2	867.3	90.7 (87.8 – 93.6)
C_{max} (pg/mL)	52.8	55.7	94.8 (91.3 – 98.5)
Baseline-corrected total Estrone			
$AUC_{0\text{-}inf}$ (ng•h/mL)	166.0	178.4	93.0 (86.7 – 99.8)
$AUC_{0\text{-}t}$ (ng•h/mL)	163.1	174.9	93.3 (86.8 – 100.2)
C_{max} (ng/mL)	21.7	21.2	102.0 (96.1 – 108.3)
Elagolix			
$AUC_{0\text{-}inf}$ (ng•h/mL)	4297.9	4414.5	97.4 (94.7 – 100.1)
$AUC_{0\text{-}t}$ (ng•h/mL)	4226.6	4333.5	97.5 (94.8 – 100.3)
C_{max} (ng/mL)	1642.1	1806.2	90.9 (86.6 – 95.5)
NETA			
$AUC_{0\text{-}inf}$ (ng•h/mL)	22.03	22.93	96.1 (94.3 – 97.9)
$AUC_{0\text{-}t}$ (ng•h/mL)	19.84	20.67	96.0 (94.1 – 97.8)
C_{max} (ng/mL)	5.49	4.91	111.8 (108.5 – 115.3)

Source: Reviewer's analysis

$AUC_{0\text{-}inf}$ = area under the curve from 0 to infinity; $AUC_{0\text{-}t}$ = area under the curve from time 0 to time t; C_{max} = maximum concentration; E2/NETA =estradiol/norethindrone acetate; FDC = fixed-dose combination; RC2 = single dose of a 300 mg elagolix IR tablet

Table 16: Bioequivalence Assessment for Evening Dose Formulation (Study M19-648, N=45)

	Least Squares Geometric Means		% Test/Ref Ratio
Parameters	**EN03 [Test]**	**RC2 [Reference]**	**(90% CI)**
$AUC_{0\text{-}inf}$ (ng•h/mL)	3746	3875	96.7 (92.7 – 100.8)
$AUC_{0\text{-}t}$ (ng•h/mL)	3740	3869	96.7 (92.7 – 100.8)
C_{max} (ng/mL)	1313	1504	87.3 (80.7 – 94.6)

Source: Reviewer's analysis
$AUC_{0\text{-}inf}$ = area under the curve from 0 to infinity; $AUC_{0\text{-}t}$ = area under the curve from time 0 to time t; C_{max} = maximum concentrationEN03 = single dose of one elagolix 300 mg capsule formulation; RC2 = single dose of a 300 mg elagolix IR tablet

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

- The application includes the following key clinical studies to provide substantive evidence of effectiveness and safety. Two Phase 2, dose-ranging studies (for elagolix and hormonal add-back therapies) of 3- and 6-months duration in premenopausal women with HMB associated with uterine fibroids
- Two identical Phase 3, placebo-controlled, randomized, double-blind (DB) efficacy and safety trials in subjects with HMB associated with uterine fibroids of 6-month duration

- One Phase 3, open-label, safety extension trial in subjects with HMB associated with uterine fibroids of 6-month duration

The clinical Phase 2 dose-finding trials and Phase 3 trials are summarized in Table 17 below.

Table 17: Phase 2 and Phase 3 Clinical Trials in Premenopausal Women With HMB Associated With Uterine Fibroids

Trial Identity NCT no.	Trial Design	Regimen/ Schedule/ Route (no. entered/completed)	Study Endpoints	Treatment Duration/ Follow Up	Study Population	No. of Centers and Countries
Phase 2 Placebo Controlled Dose-Finding Studies						
M12-663 NCT01441635	Cohorts 1,2,4: R, DB, PC Cohorts 3,5,6: Open-label	Cohort 1: ELA 200 mg BID (35/28); Placebo (18/16) Cohort 2: ELA 300 mg BID (30/26); Placebo (16/14) Cohort 3: ELA 200 mg BID + Activella (E2/NETA [0.5 mg/0.1 mg]) QD (34/29) Cohort 4: ELA 100 mg BID (33/27); ELA 400 mg QD (32/26); Placebo (16/13) Cohort 5: ELA 600 mg QD (30/24) Cohort 6: ELA 300 mg BID + oral Estrace® 1 mg QD and cyclical Prometrium® 200 mg QD (27/25) Total 271/228	Mean change in MBL, measured by the AH method, from Baseline to the last complete menstrual cycle (last 28 days) during treatments	3 months/ 3 months	Premenopausal women ages 20-49 with uterine fibroids documented by pelvic US[a] and HMB[b]	45/U.S.
M12-813 NCT01817530	R, DB, PC	Cohort 1: ELA 300 mg BID (65/52); ELA 300 mg BID+E2/NETA 0.5 mg/0.1 mg QD (64/53) ELA 300 mg BID+E2/NETA 1 mg/0.5 mg QD (65/52); Placebo (65/50) Cohort 2: ELA 600 mg QD (77/58); ELA 600 mg QD+E2/NETA 0.5 mg/0.1 mg QD (76/53); ELA 600 mg QD+E2/NETA 1 mg/0.5 mg (77/53); Placebo (78/67) Total 567/438	The proportion of subjects meeting the following conditions: MBL volume (as assessed by AH) <80 mL during the final month, and ≥50%reduction in MBL volume from baseline to the final month	6 months/ 6 months	Premenopausal women ages 18-51 with uterine fibroids documented by pelvic US[d] and HMB[b]	86/U.S.[c], United Kingdom, Chile, Canada

Trial Identity NCT no.	Trial Design	Regimen/ Schedule/ Route (no. entered/completed)	Study Endpoints	Treatment Duration/ Follow Up	Study Population	No. of Centers and Countries
Pivotal Phase 3 Clinical Trials to Support Efficacy and Safety						
M12-815 NCT02654054	R, DB, PC	Placebo (102/83) ELA 300 mg BID (104/81) ELA 300 mg BID+E2/NETA 1 mg/0.5 mg QD (206/164) Total 412/328	The proportion of subjects meeting the following conditions: MBL volume <80 mL during the final month, and ≥50%reduction in MBL volume from baseline to the final month	6 months/ 12 months or enrollment in extension study M12-816	Premenopausal women ages 18-51 with uterine fibroids documented by pelvic US[e] and HMB[b]	76/U.S.[c]
M12-817 NCT02691494	R, DB, PC	Placebo (94/72) ELA 300 mg BID (95/69) ELA 300 mg BID+E2/NETA 1 mg/0.5 mg QD (189/148) Total 378/289	The proportion of subjects meeting the following conditions: MBL volume <80 mL during the Final Month, and ≥50% reduction in MBL volume from baseline to the final month	6 months/ ≤12 months	Premenopausal women ages 18-51 with uterine fibroids documented by pelvic US[e] and HMB[b]	77/ U.S. and Canada

Trial Identity NCT no.	Trial Design	Regimen/ Schedule/ Route (no. entered/completed)	Study Endpoints	Treatment Duration/ Follow Up	Study Population	No. of Centers and Countries
Phase 3 Extension Trial to M12-815 and M12-817 to Support Long-Term Safety						
M12-816 NCT02925494	R, DB	Placebo/ELA 300 mg QD (59/50) Placebo/ELA 300 mg BID +E2/NETA 1 mg/0.5 mg QD (58/43) ELA 300 mg QD/ELA 300 mg QD (98/79) ELA 300 mg BID +E2/NETA 1 mg/0.5 mg QD/ ELA 300 mg BID +E2/NETA 1 mg/0.5 mg QD (281/182) Total 496/354	Primary Endpoint: The proportion of subjects meeting the following conditions: MBL volume <80 mL during the final month, and ≥50% reduction in MBL volume from baseline to the final month	6 months/ ≤12 months	Subjects who completed the 6-month treatment period of their respective pivotal study (Study M12-815 or Study M12 817) and met study entry criteria.	U.S.[c] and Canada

[a] At least 1 intramural, submucosal non-pedunculated, or subserosal fibroid ≥2 cm in diameter or small multiple fibroids with a total uterine volume of ≥200 cm3 to ≥2,500 cm3.
[b] Evidenced by MBL >80 mL for each of 2 screening menstrual cycles as measured by the alkaline hematin method.
[c] Includes Puerto Rico
[d] Intramural, submucosal non-pedunculated, and large (≥4 cm) subserosal fibroids or subserosal fibroids in combination with intramural and/or submucosal fibroids; at least 1 fibroid with a diameter ≥3 cm (longest diameter) or multiple small fibroids with a total uterine volume of ≥200 cm3 to ≤2,500 cm3.
[e] Intramural, submucosal non-pedunculated fibroid with total diameter ≥2 cm [longest diameter]; subserosal fibroid ≥4 cm; or multiple fibroids with total uterine volume of ≥200 cm3 to ≤2,500 cm3.
BID = twice a day; BMD = bone mineral density; DB = double-blind; E2/NETA = estradiol/norethindrone acetate; ELA = elagolix; AH=a kaline hematin; HMB = heavy menstrual bleeding; max = maximum; MBL = menstrual blood loss; PC = placebo controlled; PO = orally (per os); QD = once a day; R = randomized; U.S. = United States; US = ultrasound

7.2. Review Strategy

The Phase 3 trials 815 and 817 as well as the 6-month uncontrolled extension trial M12-816 provide primary support for efficacy and safety of the product for the treatment of HMB associated with uterine fibroids. Evaluation of efficacy data was undertaken jointly by the clinical reviewer for efficacy, Linda Jaffe, MD, and the statistical reviewer Dr. Jia Guo, PhD. Primary efficacy endpoints and ranked secondary endpoints are reviewed in detail for labeling purposes. Assessment of safety was conducted by the clinical reviewer for safety, Marcea Whitaker, MD. Adverse events of special interest and overall safety using data from the profiles obtained in the pooled and individual phase 2 and 3 studies using MedDRA version 21.0 are reviewed.

The sources of data used for the evaluation of the efficacy and safety of Oriahnn for the proposed indication included final study reports submitted by the Applicant, datasets (Study Data Tabulation Model and Analysis Data Model) and literature references. This application was submitted in electronic common technical document format and is entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in Study Data Tabulation Model, and Analysis Data Model format are located at the following network path: \\cdsesub5\EVSPROD\NDA213388\0001\m5\datasets

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. Studies M12-815 and M12-817

Both Phase 3 pivotal trials (hereafter referred to as Studies 815 and 817, respectively) are entitled “A Phase 3 Study to Evaluate the Efficacy and Safety of Elagolix in Combination with Estradiol/Norethindrone Acetate for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women.” This section documents the virtually identical design of the two trials.

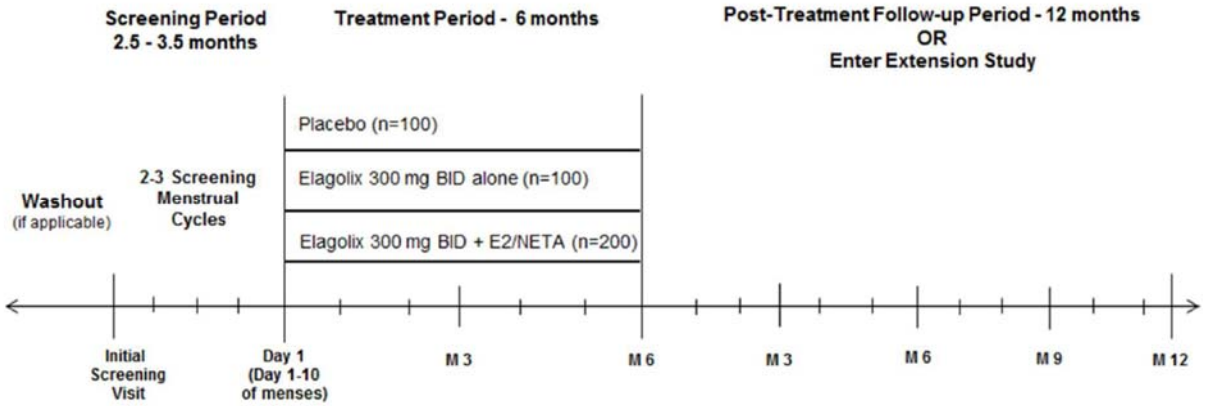
Trial Design

The objectives of both Studies 815 and 817 were to evaluate the safety, tolerability, and efficacy of elagolix 300mg BID in combination with E2/NETA (1 mg/0.5 mg) QD as compared to placebo for 6 months in the management of HMB associated with uterine fibroids and to characterize the effect of E2/NETA on the safety, tolerability and efficacy of elagolix. Both trials were randomized, double-blind, multicenter, placebo-controlled trials of 6 months duration in which subjects were randomized into one of three parallel dose arms – placebo, elagolix 300 mg BID (Ela), or elagolix 300 mg BID+E2/NETA (Ela

+ E2/NETA)- in a 1:1:2 ratio. Each study planned to enroll 400 subjects across 125 centers in the U.S. and Canada.

Each study consisted of a washout period from prohibited medications (if applicable), a screening period of 2.5 to 3.5 months), a 6-month treatment period, and for subjects who did not enter the 6-month extension trial, a PTFU period of up to 12 months. Subjects who prematurely withdrew from treatment would enter the PTFU period upon discontinuation of study drug. The overall study design for these studies is shown in Figure 14.

Figure 14: Study Design Schematic



Source: Study 815 Protocol-Amendment 3, Figure 1, pg. 47; Study M12817 Protocol-Amendment 2, Figure 1, pg. 48.
BID = twice a day; E2/NETA = estradiol/norethindrone acetate

The Washout Period was required for subjects who were taking prohibited medications including hormonal therapy or antifibrinolytics (see Table 18 below) and met the inclusion criteria for uterine fibroid(s) based on pelvic (transabdominal or transvaginal) US assessment. The duration of the Washout Period was based on the specific prohibited medication the subject was taking. For example, the minimum Washout Periods for medroxyprogesterone acetate injection, GnRH agonist 3-month depot injection, and hormonal contraceptives were 300 days, 90 days and 30 days, respectively. Subjects were required to have at least one menstrual period before proceeding to the Screening Period.

During the Screening Period, subjects' eligibility was determined by medical history, physical examination, screening laboratory assessment, assessment of MBL by the alkaline hematin method, and imaging studies which included pelvic ultrasound (US) and BMD assessment by dual-energy X-ray absorptiometry (DXA). Dual non-hormonal contraception was required. Iron supplementation was recommended for subjects who entered the study with anemia [hemoglobin (Hgb <12 g/dL as defined by the World Health Organization (WHO)] or who developed anemia during the study.

Key Inclusion Criteria:

(1) Premenopausal women ages 18 to 51 years (inclusive)
(2) Uterine fibroid(s) documented by pelvic US at screening as assessed by a central reader that meets one of the following criteria:
    (i) intramural, submucosal, non-pedunculated fibroid with longest total diameter ≥2 cm
    (ii) subserosal fibroid ≥4 cm, or
    (iii) multiple fibroids with a total uterine volume of 200 to 2500 cm^3 (inclusive)
(3) HMB defined as MBL >80 mL as determined by the alkaline hematin method during 2/2 consecutive or 2/3 nonconsecutive menstrual cycles during screening
(4) Adequate endometrial biopsy with no clinically significant pathology (adenomyosis was permissible as long as other criteria were met)
(5) Follicle-stimulating hormone <35 mIU/mL
(6) Negative urine and/or serum pregnancy test(s) during screening and just before first dose
(7) Willing to use two forms of non-hormonal contraception until completion of PTFU month 2 visit
(8) Normal mammogram within 3 months of screening if ≥ age 39

Key exclusion criteria:

(1) Pregnant, breast feeding, or planning pregnancy within 24 months, less than 6 months post-partum or post-pregnancy
(2) History of hysterectomy or bilateral oophorectomy; history of bariatric surgery within 6 months of screening
(3) Invasive treatment for uterine fibroid within the 6 months prior to screening, including myomectomy, uterine artery embolization, or high intensity focused ultrasound.
(4) Clinically significant gynecological disorder, including abnormal Pap smear at screening and active pelvic inflammatory disease (adenomyosis is acceptable), menstrual cycle length >38 days in the 3 months prior to screening, or endometrial ablation within 1 year prior to screening
(5) Screening BMD T-score ≤ -1.5 at the lumbar spine, femoral neck or total hip, other bone disease associated with low bone mass or fragility fracture, or the inability to obtain adequate BMD due to skeletal condition (surgery/hardware/scoliosis) or weight exceeding machine limit
(6) ≥2 blood transfusions within 9 months prior to screening or one within 60 days prior to Day 1 of treatment
(7) Clinically significant abnormalities in clinical chemistry, hematology, urinalysis, or ECG, including Hgb <8 g/dL, creatinine >2 mg/dL, ALT/AST ≥2-fold upper limit of normal (ULN), evidence of Hepatitis B, Hepatitis C, acute Hepatitis A or HIV, or QT interval corrected for heart rate (QTc) >450 msec
(8) History of major psychiatric disorder, including major depression or post-traumatic stress disorder within 2 years, or any history of suicidal ideation including results of the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening/Study Day 1
(9) History of bleeding or arterial or venous thromboembolic events

(10) Contraindications or intolerance to estrogen/progestins
(11) Use of prohibited medications (Table 18), including prior treatment with elagolix

Table 18: Prohibited Medications

Prohibited During the Washout, Screening, Treatment and Post-Treatment Follow-Up Periods	
Hormonal/Anti-Hormonal Medications[*,%], such as:	GnRH agonists leuprolide acetate (Lupron®), nafarelin acetate (Synarel®), goserlin acetate (Zoladex®) GnRH antagonists (other than elagolix) Danazol (Danocrine®) Medroxyprogesterone acetate (Depo-Provera®, Provera®) Oral contraceptives Estrogen preparations* Testosterone preparations Other progestins* (oral, vaginal, transdermal, implantable, IUD, or LNG-IUS, except emergency contraception) HCG or HCG products Glucocorticoids, oral or injectable (chronic use only) Mifepristone Selective Progesterone Receptor Modulators (e.g., Ulipristal acetate (except as emergency contraception, i.e., 30 mg) and Vilaprisan) Tamoxifen Bromocriptine (Parlodel®) Cabergoline (Dostinex®) Raloxifene (Evista®) Aromatase Inhibitors (e.g., Anastrozole [Arimidex®], Exemestane [Aromasin®])
Non-hormonal estrogen supplements[#]	Natural Estrogen preparations (e.g., soy-containing supplements, black cohosh)
Antifibrinolytics[%]	Tranexamic acid (Lysteda, Cyklokapron, Cyclo-f)
Moderate or strong CYP3A Inducers,[9] and Anti-epileptic medications, such as:	**Strong Inducers:** St. John's Wort Rifampin Carbamazepine Phenytoin Dexamethasone chronic use **Moderate Inducers:** Bosentan Efavirenz Etravirine Modafinil Nafcillin
Bisphosphonates, RANKL inhibitors, Anabolic Bone Agents or rPTH, such as:	Fosamax®, Fosamax Plus D®, Binosto®, Boniva®, Reclast®, Zometa®, Prolia®, XGEVA®, Forteo®, Actonel®, Atelvia®, Miacalcin®, Fortical®
Synthetic Prostaglandin E1 (PGE1) Analogs, such as:	Misoprostol (Cytotec®, Arthrotec®) Single use of PGE1 for cervical preparation prior to biopsy is allowed; chronic use is prohibited
Oral Retinoids (topical applications are permitted), such as:	Accutane® (isotretinoin)

Source: M12-815 Protocol Amendment 3, Table 3, pages 67-68
[*] E2/NETA will be taken by subjects randomized to the E2/NETA dose group
[#] Due to the extensive list of herbal remedies and supplements, please contact the AbbVie TA MD for any that may be prohibited
[%] Subjects may begin the use of hormonal contraceptives following completion of the Post-Treatment Follow-Up Month 2 Visit and return to menses. Tranexamic acid, if necessary, can be prescribed following completion of the Post-Treatment Follow-up Month 2 visit and the subject has returned to first full menses.
GnRH = gonadotropin-releasing hormone; IUD = intrauterine device; LNG-IUS = levonorgestrel-releasing intrauterine system; RANKL = receptor activator of nuclear factor kappa beta ligand; rPTH = recombinant parathyroid hormone

Pelvic Imaging Assessments

Pelvic Ultrasound (US)

Transabdominal (TAU) and transvaginal (TVU) ultrasound were used for screening and safety monitoring at baseline and during the treatment phase and PTFU. US assessments included endometrial thickness, presence of abnormal endometrial appearance/pathology, number and size of uterine fibroids, volume and location of the 3 largest fibroids, uterine volume, number size, location and characteristics (simple versus complex) of ovarian cyst(s), endometriomas >3.5 cm, solid ovarian lesions >1.5 cm. Saline Infusion Sonohysterography (SIS) was performed as screening to exclude endometrial polyp ≥1 cm and intracavitary submucosal pedunculated fibroid. Additional SIS was performed during the study as needed to further evaluate findings on TAU/TVU or magnetic resonance imaging (MRI).

MRI

An MRI substudy was performed to assess volume of the 3 largest fibroids as well as fibroid location, uterine volume, presence and characterization (dominant versus focal) of adenomyosis, and presence of any other concerning findings.

Assessment of MBL

Alkaline Hematin Assessment

Subjects were given sanitary products and sanitary product collection kits at the study sites. Venous blood samples and sanitary products were sent to a central Alkaline Hematin Laboratory for the alkaline hematin assessment.

Uterine Bleeding Questionnaire

The Uterine Bleeding Questionnaire (UBQ) consisted of the following questions:

Did the subject have any bleeding or spotting since her last study visit?

If yes, why were sanitary products not collected/returned? (subjects were to choose among seven response options listed)

UBQ was used as an indicator of menstrual bleeding only when AH data were not available, as described in the Statistical Analysis Plan section below.

Additional Instruments Used in Phase 3 Studies

- Pelvic US was used to assess fibroid and uterine volume at baseline (screening/Day 1), Month 3, and Month 6, or premature discontinuation. This endpoint, however, is considered exploratory because the clinical meaningfulness of this measure has not been determined.

  The following additional patient-reported outcome (PRO) and Quality of Life Instruments were used during the studies:

  — Uterine Fibroid Quality of Life (UFS-QoL) questionnaire

- Work Productivity and Activity Impairment Questionnaire: Uterine Fibroids (WPAI:UF)
- Patient Global Impression of Change on Menstrual Bleeding (PGIC-MB)
- Patient Global Impression of Change-Non-Bleeding Uterine Fibroids Symptoms
- EuroQol-5D 5 level
- C-SSRS
- Health Care Resource Utilization

The C-SSRS and Health Care Resource Utilization questionnaires were used for safety assessments. The other PRO instruments were used to assess multiple exploratory endpoints.

Dose Selection

The Applicant selected elagolix 300 mg BID, E2 1 mg and NETA 0.5 mg for their Phase 3 uterine fibroid program. They based their dose selection for elagolix and E2/NETA on the 3-month Phase 2a proof-of concept and dose finding study (M12-663) and the 6-month Phase 2b safety and efficacy study (M12-813). For a detailed discussion of dose-selection, refere to the discussion of exposure response in Section 6.3.2 Clinical Pharmacology Questions (Question 1).

In Study M12-813, 65 of the 567 enrolled subjects were randomized to elagolix 300 mg BID + E2 1 mg/NETA 0.5 mg, the regimen subsequently selected for the Phase 3 development program. Safety assessment demonstrated that fewer adverse events were observed in the Ela 300 mg BID groups compared to subjects receiving Ela 600 mg once daily. The addition of E2 1 mg/NETA 0.5mg to elagolix 300 mg BID reduced bone loss and ameliorated the vasomotor symptoms associated with elagolix monotherapy to a greater extent than E2 0.5 mg/NETA 0.1 mg. Hormonal add-back therapy with E2 1 mg/NETA 0.5 mg more effectively attenuated hot flushes and the reduction in BMD compared to E2 0.5 mg/NETA 0.1 mg and continued to demonstrate efficacy.

Randomization and Treatment

In both Phase 3 trials, Studies 815 and 817, eligible subjects were randomly assigned to one of three arms – placebo, Ela, or Ela +E2/NETA in a 1:1:2 ratio. Study site personnel and subjects remained blinded to treatment throughout the study.

Study drug consisted of elagolix 300 mg tablet or identical placebo tablet, which was self-administered twice daily, orally, and E2/NETA or identical capsule that was self-administered orally once daily in the morning without regard to food, for 6 months. Study drug was dispensed to subjects once monthly for 6 months in a carton that contained 5 blister cards, each supplying 7 days of medication. Subjects were instructed to return all study drug blister cards (used/unused/unopened) to the study site at each monthly visit

during the 6-month treatment period or upon premature discontinuation, and study site personnel documented compliance after scanning the returned study drug blister cards with scanning technology.

Alkaline hematin and safety laboratory assessments, were measured by a central laboratory. Pap smears and endometrial biopsies were also analyzed by a central laboratory. Imaging, including DXA, pelvic US, SIS and MRI were assessed by the (b) (4). Discrepancies between the local read and the central read regarding eligibility were reviewed by the Applicant and the readers on a case-by-case basis. An independent data monitoring committee was used to safeguard the interests of study subjects and to monitor the overall study conduct. The independent data monitoring committee recommended whether to continue, modify or stop the study for safety reasons.

Removal of subjects occurred if safety concerns developed, including elevation in liver enzymes (ALT or AST >5-fold ULN) or if the subject withdrew consent, used exclusionary medications, experienced HMB that required a blood transfusion during the treatment period any time after having taken 28 days of study drug, became pregnant, or had surgical or invasive procedure [including dilation and curettage (D & C)] for the treatment of HMB due to uterine fibroids. Subjects undergoing invasive procedures for HMB/fibroids during the PTFU period were not withdrawn unless they underwent hysterectomy and bilateral salpingo-oopherectomy and did not take post-operative hormone replacement therapy. Subjects who withdrew consent or were prematurely discontinued during the treatment period were expected to complete the Premature Discontinuation Visit and enter the 12-month PTFU period. Subjects who discontinued the PTFU period prematurely were expected to complete the PTFU Premature Discontinuation visit. Subjects with ongoing AEs or abnormal laboratory test results were followed until resolution.

If a subject became pregnant during the study, the subject was to be discontinued from study drug and from all procedures other than US. An US examination early in the first trimester of pregnancy to assess the conception date and document an intrauterine pregnancy was performed. Information regarding pregnancy occurrence and the outcome of the pregnancy was collected. For pregnancies that resulted in delivery of a live infant, the health of the infant was to be collected 6 to 12 months after delivery.

Study Endpoints

The primary efficacy endpoint for both studies was the proportion of responders. A responder was defined as any subject who met both of the following conditions:
(1) MBL volume <80 mL at the final month, and
(2) ≥50% reduction in MBL volume from Baseline to the final month

The Final Month is defined as the last 28 days prior to and including the Reference Day, which is defined as the last visit date in the Treatment Period (last treatment visit date)

or the last dose date if there are evaluable Alkaline Hematin data after the last treatment visit
date and prior to or on the last dose date.

Subjects who discontinued study drug prematurely because of an adverse event, lack of efficacy or required surgery or invasive intervention for the treatment of uterine fibroids were considered nonresponders regardless of whether the above criteria were met.

Secondary efficacy endpoints were ranked as follows:
(1) Change from Baseline in MBL volume to the Final Month
(2) Percentage of subjects with suppression of bleeding (no bleeding allowed, spotting allowed) at the Final Month
(3) Change from Baseline in MBL volume to Month 6
(4) Change from Baseline in MBL volume to Month 3
(5) Percentage of subjects with baseline hemoglobin (Hgb) ≤10.5 g/dL who had an increase in Hgb >2 g/dL at Month 6
(6) Change from Baseline in MBL volume to Month 1

There were numerous additional exploratory efficacy and safety endpoints related to menstrual bleeding, Hgb concentration, uterine and fibroid volume, and quality of life.

Statistical Analysis Plan

Sample Size Consideration

Both studies assumed responder rates of 60% and 30% for elagolix 300 mg BID + E2/NETA and placebo, respectively. Approximately 400 subjects were to be randomized in a 1:1:2 ratio to placebo (N=100), elagolix 300 mg BID (N=100), or elagolix 300 mg BID + E2/NETA (N=200). The sample size would provide at least 90% power to detect a difference in responder rate between the elagolix 300 mg BID + E2/NETA group and the placebo group based on a two-sides test at the significance level of 0.05.

Analysis Populations

The Applicant's statistical analysis plan for both studies predefined the full analysis set for all efficacy analyses and the safety analysis set for safety analyses. For both studies, the full analysis set and safety analysis set were identical, including all randomized subjects who had received at least one dose of study drug.

Handling of Missing Data

The missing data handling approach was discussed for each reviewed efficacy endpoint respectively in the section below when applicable.

Handling of Multiplicity

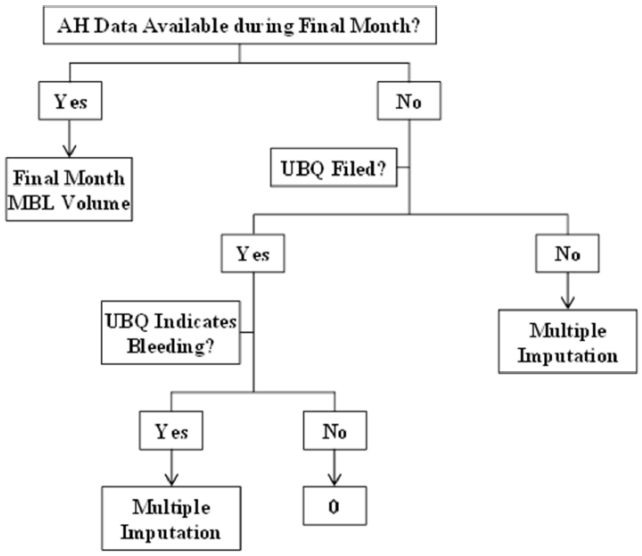
The primary comparison for all analyses were made between elagolix 300 mg BID + E2/NETA and placebo. The elagolix 300 mg BID alone group served as a reference arm. Therefore, no adjustment of the type I error rate (alpha) for primary analysis of the

primary endpoint was needed. Ranked secondary endpoints followed a fixed-sequence testing procedure.

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint, for both studies 815 and 817, was analyzed with multiple imputation for the missing final month MBL volume. The flow-chart below shows how the final month MBL volume was derived.

Figure 15: Flow-Chart for Deriving Final Month MBL Volume



Source:
AH = a kaline hematin; MBL = menstrual blood loss; UBQ = Uterine Bleeding Questionnaire

The primary analysis with multiple imputation, for both Studies 815 and 817, was carried out in the following steps:

(1) Multiple Imputation: 20 "complete" datasets of monthly MBL volume from Month 1 to Month 6 were generated using SAS PROC MI. The following covariates were considered in the imputation model:
    (i) Baseline MBL volume
    (ii) Randomized treatment group
    (iii) Baseline hemoglobin
    (iv) MBL volume in prior months
    (v) Age of the subject at Baseline

(2) Impute Final Month MBL Volume: In each of the 20 generated datasets, a subject's missing Final Month MBL volume was imputed using the MBL volume from the "complete" dataset with Month 1 – 6 MBL volume by looking at the corresponding month of the Reference Day using analysis time window. For example, if the Reference Day of a subject was > Day 154, then the Month 6 MBL volume from the "complete" dataset was used to impute Final Month MBL volume; if the Reference Day was > Day 126 and ≤ Day 154, then the Month 5 MBL volume was used to

impute Final Month MBL volume and so on. Subjects whose Reference Day were the same as Study Day 1 had their Final Month MBL volume imputed using their Month 1 MBL volume.

(3) Impute Responder Status: The responder status (yes/no) was derived from "complete" Final Month MBL volume, using the criteria as described for the primary efficacy endpoint. If a subject's Final Month MBL volume was non-missing, then the observed Final Month MBL volume was used in the analysis. If the subject prematurely discontinued due to "lack of efficacy," "requires surgery or invasive intervention for treatment of uterine fibroids," or adverse event, the subject was considered a non-responder, regardless of whether the Final Month MBL volume was observed or missing.
(4) Analysis: Each of the 20 imputed datasets was analyzed separately using a logistic regression model including treatment as the main effect and Baseline MBL volume as a covariate to compare each elagolix treatment group to placebo.
(5) Pooling: Estimates of the proportions of responders in each treatment group and the difference between the proportions from the M imputed datasets obtained from step 3 were combined into one overall result using PROC MIANALYZE in SAS.

Sensitivity Analyses for Primary Efficacy Endpoint

The Applicant also pre-specified sensitivity analyses for the primary efficacy endpoint using different approaches to handle prematurely discontinues subjects and missing final month MBL volume.

Each of the following sensitivity analyses for the primary endpoint was performed using a logistic regression model including treatment as the main effect and Baseline MBL volume as a covariate to compare each elagolix treatment group to placebo.

(1) The primary analysis was repeated with all subjects categorized as responders/nonresponders based on observed or imputed MBL volume data only (without taking into account their reasons for premature discontinuation of study drug). Multiple imputation was performed the same way as in the primary analysis.
(2) Last observation carried forward: The primary analysis was repeated with missing Final Month MBL volume imputed using the last observation carried forward.
(3) Non-responder imputation: All subjects who had missing Final Month MBL volume were considered as non-responders. No multiple imputation was performed.
(4) Observed cases: The primary analysis was repeated with the observed Final Month MBL volume. Subjects who had missing Final Month MBL volume were excluded from this analysis.
(5) The primary analysis was repeated using the total MBL volume collected from validated products only. All subjects were categorized as responders/nonresponders in the same manner as done in the primary analysis with exception that all AH data (including that for Baseline MBL volume) were based on the total MBL volume collected from validated products only.

Analysis of Ranked Secondary Efficacy Endpoints

The change and percent change from Baseline to the Final Month in MBL volume obtained from the primary analysis after multiple imputation were summarized by treatment group and compared between each elagolix treatment group and placebo, using one-way analysis of covariance with treatment as the main effect and Baseline MBL volume as a covariate. Baseline and Final Month MBL volumes obtained for the primary analysis were used.

The number and percentage of subjects achieving suppression of bleeding at Final Month APPEARS THIS WAY ON ORIGINAL were summarized by treatment group and were compared between each of the elagolix treatment groups and placebo using a Pearson's chi-square test or Fisher's exact test (if ≥20% of the cells had expected counts less than 5).

The comparison of change from Baseline in MBL volume to each month between each of the elagolix treatment groups and placebo was performed using a Mixed Model Repeated Measures model with observed MBL volume. The Mixed Model Repeated Measures analysis included the fixed categorical effects of treatment, month and treatment-by-month interaction, and the continuous fixed covariate of Baseline MBL volume.

The number and percentage of subjects who had Hgb Baseline ≤10.5 g/dL and had an increase in Hgb concentration >2 g/dL from Baseline were summarized for each month by treatment group and compared between each elagolix treatment group and placebo, using a Pearson's chi-square test or Fisher's exact test (if ≥20% of the cells had expected counts less than 5).

Protocol Amendments

There were three amendments to the protocol for Study 815. Amendments included requiring mammography for all subjects ≥39 years of age, updating the duration of washout period for prior treatments, updating acceptable forms of nonhormonal contraception, and recommending iron supplementation for all subjects with anemia. The requirement to obtain a repeat/duplicate Month 6 DXA scan based on results was removed. The PTFU period was extended from 6 to 12 months based on DXA results, and PTFU safety monitoring was enhanced.

There were two amendments and one administrative change to the protocol for Study 817. In addition to the amendments noted for Study 815, revised qualifying fibroids was changed to include all fibroids regardless of size. This change was unlikely to have had a major impacted efficacy results because the primary and secondary efficacy endpoints were determined by bleeding outcome measures. In addition, amendments clarified that subjects who underwent screening in Study 815 could enter Study 817 if enrollment had closed and updated eligibility for the extension study.

8.1.2. Study Results

Again, due to the replicative design of Studies 815 and 817, results from these two trials are presented together in Section 8.1.1.

Compliance with Good Clinical Practices

The Applicant attests that Studies 815 and 817 were both conducted in accordance with the protocol, International Conference on Harmonisation (ICH) guidelines, Good Clinical Practice guidelines, applicable regulations, and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. An Institutional Review Board ensured the ethical, scientific, and medical appropriateness of the study before it was conducted and approved all relevant documentation.

Patient Disposition

Subject disposition was similar in Study 815 and Study 817 (Table 19).

- Study 815 screened 3613 subjects and randomized 413 (11.4%). One subject (Subject (b) (6)) who was a screen failure (reason not provided) was randomized in error to elagolix 300 mg BID + E2/NETA but did not receive study drug and was subsequently discontinued. Therefore, the total number of subjects randomized and dosed was 412, with 206 in the elagolix 300 mg BID + E2/NETA group.
- Study 817 screened 3263 and randomized 378 (11.6%). Just under 80% of subjects in each study completed the 6-month treatment period, and just over half of subjects randomized and treated entered the 6-month extension study 816.

Table 19: Subject Disposition by Study and Treatment

Disposition	Placebo N (%)	Ela 300 mg BID N (%)	Ela 300 mg BID +E2/NETA N (%)	Total N (%)
Study 815				
Randomized and treated	102	104	206	412*
Completed	83 (81)	81 (78)	164 (80)	328 (80)
Discontinued	19 (19)	23 (22)	42 (20)	84 (20)
Entered extension	62 (61)	51 (49)	119 (58)	232 (56)
Study 817				
Randomized and treated	94	95	189	378
Completed	72 (77)	69 (73)	148 (78)	289 (77)
Discontinued	22 (23)	26 (27)	41 (22)	89 (24)
Entered extension	55 (59)	47 (49)	99 (52)	201 (53)

Source: Clinical Study Report Body 815, Table 2 and Figure 2; Clinical Study Report Body 817 Table 2 and Figure 2 (both in Module 5.3.5.1 of submission)
*excluded the one subject randomized in error and not dosed.
BID = twice daily; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix

The reasons for premature discontinuation during the treatment period as presented by the Applicant are shown in Table 20 and Table 21 for Study 815 and 817, respectively. In both studies, a greater proportion of subjects on active treatment discontinued the study prematurely due to AE(s) as compared to placebo, with a greater imbalance in Study 817. A greater proportion of subjects in the elagolix 300 mg + E2/NETA arm in Study 815 discontinued due to noncompliance with study drug, while a slightly greater proportion of placebo-treated subjects discontinued due to noncompliance with study drug in Study 817. A low incidence of invasive intervention for the treatment of uterine fibroids was reported in all three arms. Discontinuation rates for lack of efficacy in the treatment arms or pregnancy appeared to be low in both studies.

Table 20: Reasons for Premature Discontinuation During Treatment, Study 815

Reason for Discontinuation	Placebo N=102 n(%)	Ela 300 mg BID N=104 n(%)	Ela 300 mg BID +E2/NETA N=206 n(%)	Total N=412 n(%)
Adverse event (AE)	6 (6)	8 (8)	16 (8)	30 (7)
Lost to follow-up	6 (6)	6 (6)	6 (3)	18 (4)
Withdrew consent	3 (3)	4 (4)	10 (5)	17 (4)
Other*	3 (3)	2 (2)	3 (2)	8 (2)
Noncompliance with study drug	0	1 (1)	5 (2)	6 (2)
Surgery or invasive intervention for treatment of uterine fibroids	1 (1)	1 (1)	1 (1)	3 (1)
Lack of efficacy	0	0	1 (1)	1 (0)
Pregnancy	0	1 (1)	0	1 (0)
Exclusionary medication	0	0	0	0

Source: Clinical Study Report 815, Table 2, p 74
BID = twice daily; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix
*The majority of reasons were personal; one reason was protocol deviation and one subject (Subject (b) (6)) was ineligible after DXA scan was repeated.

Table 21: Reasons for Premature Discontinuation During Treatment, Study 817

Reason for Discontinuation	Placebo N=92 n(%)	Ela 300 mg BID N=95 n(%)	Ela 300 mg BID +E2/NETA N=189 n(%)	Total N=378 n(%)
Adverse event (AE)	3 (3)	10 (11)	15 (8)	28 (7)
Lost to follow-up	4 (4)	6 (6)	7 (4)	17 (5)
Withdrew consent	7 (7)	6 (6)	9 (5)	22 (6)
Other	1 (1)[a]	1 (1)[b]	5 (3)[c]	7 (2)
Noncompliance with study drug	3 (3)	1 (1)	4 (2)	8 (2)
Surgery or invasive intervention for treatment of uterine fibroids	2 (2)	2 (2)	0	4 (1)
Lack of efficacy	0	0	1 (1)	1 (0)
Pregnancy	2 (2)	0	0	2 (1)
Exclusionary medication	0	0	0	0

Source: Clinical Study Report 817, Table 2, p 75
[a] Abdominal pain and cervical mass; study drug discontinuation recommended by outside physician (Subject (b) (6)).
[b] Elected to have surgical management of uterine fibroids (Subject (b) (6))
[c] Subject was deployed by the Navy (b) (6)); subject did not meet inclusion/exclusion criteria (680028); personal reasons (b) (6)); subject moved away from the study site (b) (6)); subject had a positive hCG result due to concomitant hCG hormone medication (b) (6)).
BID = twice daily; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix

Several subjects in these two studies whose primary reason for premature treatment discontinuation was withdrawal of consent or "other" reasons also experienced an AE as a primary or secondary reason for discontinuation.

In Study 815, 4 subjects whose primary reason for discontinuation was "withdrawal of consent" also discontinued due to an AE (1 Ela, and 3 Ela + E2/NETA treated subjects); the AE was stated as part of the primary reason for withdrawal of consent for 2 of those subjects. Two subjects who prematurely discontinued study drug for "other" reasons (1 placebo and 1 Ela + E2/NETA treated subject) also reported AEs as additional reasons for discontinuation. The placebo treated subject's primary reason for drug discontinuation was that she desired surgery (Source: M12815 clinical study report [CSR] Table 14.1_9.1 and CSR Table 14.1_2.1).

In Study 817, 3 subjects (one in each treatment arm) whose primary reason for study drug discontinuation was "withdrawal of consent" also reported an AE as part of the primary or secondary reason for discontinuation (Source: M12817 CSR Table 14.1_9.1 and CSR Table 14.1_2.1). As noted in the pre-specified analysis, these subjects should have been considered nonresponders even if they met the primary efficacy endpoint (MBL <80 mL and reduction in MBL from baseline to month 6 ≥50%). However, given the treatment effect seen, this small number of subjects is unlikely to have impacted the efficacy results.

For both studies, subjects who completed the 6-month treatment period, and did not have exclusionary criteria or decline to participate, could enroll in a 6-month extension study M12-816 (hereafter, Study 816). Subjects who did not enter the extension study and subjects who withdrew early (except for pregnancy) were to enter the 12-month PTFU period. The number of subjects who entered the PTFU period and their disposition are shown in Table 22.

Table 22: Disposition During the Post-Treatment Follow-up Period

Disposition	Placebo N (%)	Ela N (%)	Ela + E2/NETA N (%)	Total N (%)
Study 815				
Entered PTFU	25	32	59	116
Completed	17 (68)	24 (75)	29 (49)	70 (60)
Premature discontinuation	8 (32)	8 (25)	30 (51)	46 (40)
Withdrew for invasive intervention of uterine fibroids	2 (8)	2 (6)	2 (3)	6 (5)
Study 817				
Entered PTFU	14	25	59	98
Completed	9 (64)	18 (72)	42 (71)	69 (70)
Premature discontinuation	5 (36)	7 (28)	17 (29)	29 (30)
Withdrew for invasive intervention of uterine fibroids	0	0	3 (5)	3 (3)

Source: 815 Clinical Study Report Table 4, p 77; 817 Clinical Study Report Table 4, p 78
E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; PTFU = post-treatment follow-up

In Study 815, approximately 5-6% of subjects in each treatment arm declined to participate in the extension study. In Study 817, 7-8% of subjects in the placebo and Ela + E2/NETA arms, and 4% in the Ela arm declined to participate in the extension study. No subject in either study was ineligible to participate because of abnormalities on TVU and only 1 subject in the placebo arm in Study 815 was ineligible based on endometrial biopsy result.

Subjects who experienced a decline in BMD of ≥8% at the lumbar spine, total hip or femoral neck at the end of the treatment period for Study 815 and Study 817 were also ineligible to participate in the extension study and were required to enter the PTFU period. In both studies 815 and 817, the largest percentage of subjects meeting this BMD exclusion criterion for Study 816 was in the Ela arm (3.8% and 3.2% in Studies 815 and 817 respectively) and is not unexpected, given the known pharmacodynamic effect of elagolix to decrease estrogen levels. One placebo treated subject in Study 815 also met this criterion, as did 1 subject (0.5%) in the Ela + E2/NETA arm in Study 815 and 3 subjects (1.6%) in the Ela + E2/NETA arm in Study 817. The reason for not entering the extension study was missing for approximately 20% of subjects in Study 815, and slightly more (22-27%) in Study 817. The other major reason for not entering the extension study was that it was closed to enrollment.

In Studies 815 and 817, the most common primary reasons for premature discontinuation during the PTFU period were withdrawal of consent or lost to follow-up. No subjects in either study discontinued due to an AE in the PTFU period. In Study 817,

one placebo treated subject discontinued for pregnancy, and one subject in the Ela arm elected to have a myomectomy.

Protocol Violations/Deviations

In Study 815, there were 22 protocol deviations involving approximately 5% of subjects. The most common protocol deviation was study entrance despite not satisfying entry criteria, and affected 1 (1%), 5 (5%) and 5 (3%) subjects in the placebo, Ela alone and Ela + E2/NETA arms, respectively. Of these 11 subjects, 4 had an abnormal electrocardiogram, 3 had osteoporosis/metabolic bone disease, and 3 had a clinically significant abnormality according to the investigator. Of 3 subjects who entered the study before DXA eligibility was confirmed, one subjects did not meet criteria and was withdrawn after receiving 42 days of study drug. She did not enter the PTFU period. Two subjects in the Ela + E2/NETA arm received the wrong treatment one time during the treatment period (exposure ≤27 days) and 2 subjects in each the Ela and Ela + E2/NETA arms (2% and 1%, respectively) received excluded concomitant treatment.

In Study 817, there were 29 protocol deviations involving approximately 7% of subjects. Similar to Study 815, the most common reason for protocol deviation was study entrance despite not satisfying entry criteria, and affected 4 (4%), 7 (7%) and 11 (6%) subjects in the placebo, Ela and Ela + E2/NETA arms, respectively. Nine of these 21 subjects had osteoporosis/metabolic bone disease. One subject in each the placebo and Ela + E2/NETA arms received the wrong treatment and 2 subjects in each the placebo and Ela + E2/NETA and 1 in the Ela arm received excluded concomitant treatment. The Applicant did not consider the protocol deviations that occurred in both trials substantial enough to have affected the study outcome or interpretation of study results or conclusions. We concur, and these subjects were included in the full analysis set and safety analysis set.

In addition to the protocol deviations summarized above, an error in the central imaging vendor's reference range used for the calculation of BMD T-scores affected T-score values for all subjects through the first 15 months of the study 815 and the first 13 months of Study 817. Respective Institutional Review Boards were notified, and the issue was resolved from those time points forward. After correcting T-scores, 5 subjects in Study 815 met DXA exclusion criteria at baseline (T-score ≤ -1.5 at any anatomic location). Of the 2 subjects still remaining in the study (one in the placebo arm) and one in the Ela + E2/NETA arm), both elected to complete the study and subsequently entered the extension study. Of the 3 subjects who withdrew prematurely, none did so because of a skeletal-related AE (i.e., fracture). In Study 817, 4 enrolled subjects (2 placebo, 1 Ela alone and 1 Ela + E2/NETA) met DXA exclusion criteria. All 4 chose to remain in the study after a discussion of the potential risks, and all 4 enrolled in the extension study (1 had already enrolled prior to notification of the error). Despite not meeting BMD eligibility criteria at baseline, the subjects who chose to continue participation met eligibility criteria for the extension study (decline in BMD of no more than 8% at any anatomic site at the end of the treatment period in the pivotal study).

This reference range correction did not significantly impact the assessment of the BMD safety information.

Finally, in Study 815, an unblinded notification was inadvertently issued by the interactive response technology system to blinded users at 6 sites, affecting 20 subjects (6 in Screening and 14 in the Treatment Period). The problem was corrected during the study, and the Applicant determined that the unblinding was not likely to significantly impact the study.

Overall, protocol deviations in both studies were infrequent and considered to be unlikely to impact data integrity or safety and efficacy results.

Table of Demographic Characteristics

Demographic characteristics of the study population for both studies are shown in Table 23 and Table 24. In both studies, approximately two-thirds of study participants were Black or African American and one-quarter to one-third were White, mean BMI was in the range of obesity (≥30 kg/m^2), and mean age was approximately 42 years.

Table 23: Demographic Characteristics, Study 815

Demographic Characteristic	Placebo N=102	Ela N=104	Ela + E2/NETA N=206	Total N=412
Race, n (%)				
White	30 (29)	27 (26)	59 (29)	116 (28)
Black/African American	70 (69)	69 (67)	141 (68)	280 (68)
Asian	1 (1)	2 (2)	3 (2)	6 (2)
American Indian/Alaska Native	0	0	2 (1)	2 (1)
Multi-race	1 (1)	4 (4)	1 (1)	6 (2)
Native Hawaiian or other Pacific Islander	0	1 (1)	0	1 (0)
Missing	0	1 (1)	0	1 (0)
Ethnicity n (%)				
Hispanic or Latino	19 (19)	4 (4)	34 (17)	57 (14)
Non-Hispanic or Latino	83 (81)	100 (96)	172 (84)	355 (86)
Age, yrs.				
Mean (SD)	42 (6)	43 (5)	43 (5)	42 (5)
BMI, kg/m^2				
Mean (SD)	34 (8)	33 (8)	33 (7)	34 (7)
Min, max	19, 58	20, 52	20, 53	19, 58

Source: Clinical Study Report 815 Table 7, p 88, Clinical Study Report 817, Table 7, p 86
BMI = body mass index; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix

These demographic characteristics for Study 815 are consistent with the U.S. population for whom the drug is intended.

Table 24: Demographic Characteristics, Study 817

Demographic Characteristic	Placebo N=94	Ela N=95	Ela + E2/NETA N=189	Total N=378
Race, n (%)				
White	30 (32)	27 (28)	59 (31)	116 (31)
Black/African American	63 (67)	66 (70)	124 (66)	253 (67)
Asian	1 (1)	2 (2)	0	3 (1)
American Indian/Alaska Native	0	0	0	0
Multi-race	0	0	3 (2)	3 (1)
Native Hawaiian or other Pacific Islander	0	0	2 (1)	2 (1)
Missing	0	0	1 (1)	1 (0)
Ethnicity n (%)				
Hispanic or Latino	11 (12)	17 (18)	31 (16)	59 (16)
Non-Hispanic or Latino	83 (88)	78 (82)	158 (84)	319 (84)
Age, yrs.				
Mean (SD)	43 (5)	42 (5)	43 (5)	42 (5)
BMI, kg/m^2				
Mean (SD)	34 (7)	35 (8)	33 (7)	34 (7)
Min, Max	20, 62	19, 55	19, 59	19, 62

Source: Clinical Study Report 815 Table 7, p 88, Clinical Study Report 817, Table 7, p 86
BMI = body mass index; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix

These demographic characteristics for Study 817 are also consistent with the U.S. population for whom the drug is intended.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline characteristics of the study populations are shown in Table 25 and Table 26.

Table 25: Baseline Characteristics, Study 815

Baseline Characteristic	Placebo N=102	Ela N=104	Ela + E2/NETA N=206
MBL volume (mL), Mean (SD)	255 (174)	249 (170)	238 (150)
Hemoglobin (g/dL), Mean (SD)	11 (1)	11 (2)	11 (2)
Min, max	8, 14	7, 15	7, 15
Hemoglobin ≤10.5 (g/dL), n (%)	39 (38)	51 (49)	68 (33)
Any prior uterine fibroid medication, n (%)	6 (6)	10 (10)	18 (9)
Systemic hormonal contraceptives, n (%)	3 (3)	3 (3)	9 (4)

Source: Clinical Study Report 815 Table 8 and Table 9 pp 89-91; Clinical Study Report 817, Table 8 and Table 9, pp 87-89
[a] Determined by TAU/TVU
[b] Determined by TAU/TVU or MRI
[c] Medications included are those used by ≥3% of subjects in any treatment group
E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; MBL = menstrual blood loss

Table 26: Baseline Characteristics, Study 817

Baseline Characteristic	Placebo N=94	Ela N=95	Ela + E2/NETA N=189
MBL volume (mL), Mean (SD)	254 (179)	225 (146)	229 (149)
Hemoglobin (g/dL), Mean (SD)	11 (2)	11 (2)	11 (25)
Min, max	7, 14	7, 14	7, 14
Hemoglobin ≤10.5 (g/dL), n (%)	31 (33)	34 (36)	64 (34)
Any prior uterine fibroid medication, n (%)	8 (9)	14 (15)	26 (14)
Systemic hormonal contraceptives, n (%)	2 (2)	6 (6)	14 (7)

Source: Clinical Study Report 815 Table 8 and Table 9 pp 89-91; Clinical Study Report 817, Table 8 and Table 9, pp 87-89
[a] Determined by TAU/TVU
[b] Determined by TAU/TVU or MRI
[c] Medications included are those used by ≥3% of subjects in any treatment group
E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; MBL = menstrual blood loss

MBL volume and Hgb were comparable across treatment arms within each study and between studies. While slightly more subjects in Study 817 had taken prior medication for the treatment of uterine fibroids, the vast majority of subjects in both studies had not. The most commonly used treatment was hormonal contraceptives.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Compliance was assessed throughout the study by scanning medication packets that were returned at each visit; however, measurements of treatment compliance were not collected. Nonetheless, duration of exposure was approximately 160 days in all treatment arms for both studies.

Concomitant Medications

The majority of subjects (>95%) took concomitant medications during the treatment period. The most commonly used medications were iron preparations , which is expected in a population with HMB. Also common were drugs to treat constipation, which is also expected in a population that has a pelvic mass (enlarged uterus with fibroids) and with a large percentage on iron preparations. Selected medications of interest according to treatment period are shown in Table 27 for Study 815, and patterns were generally similar in both studies. A slight increase in the use of anti-anemic preparations (iron) was seen during the treatment period and is consistent with the protocol recommendations to treat subjects with Hgb <12 g/dL with iron supplementation. There was no formal recommendation for prescribing calcium and/or vitamin D during the study, and only a minimal increase in the use of these supplements was observed. A slight increase in the use of SSRIs was also observed. See Section 8.2.5.5 Depression/Suicide for discussion of neuropsychiatric events. An increase in of the proportion of subjects treated with lipid modifying agents was seen in the treatment and PTFU periods for Study 815, most notably in the Ela alone arm, but was negligible in Study 817 (1 subject more in each placebo and Ela arms, and 2 fewer in the Ela + E2/NETA arm). See Section 8.2.4 Safety Results, Subsection Laboratory Findings for further discussion. Any pattern of changes in medication use from the treatment period to the PTFU period may not be generalizable and should be viewed with caution,

however, because the majority of subjects enrolled in the extension study and did not enter the PTFU period.

Table 27: Selected Concomitant Medications According to Study Period Taken During Study 815

Medication	Placebo N (%)	Ela N (%)	Ela + E2/NETA N (%)
Pretreatment	N=102	N=104	N=206
Anti-anemic medications[a]	75 (74)	73 (70)	146 (71)
Calcium	1 (1)	3 (3)	2 (1)
Vitamin D and analogues	5 (5)	9 (9)	16 (8)
SSRIs	1 (1)	3 (3)	8 (4)
Lipid modifying agents	8 (8)	11 (11)	14 (7)
Hormonal contraceptives (systemic)	0	0	0
Progestogens	0	0	0
Corticosteroids (systemic)	4 (4)	2 (2)	3 (2)
Treatment period	N=102	N=104	N=206
Anti-anemic medications[a]	87 (85)	79 (76)	159 (77)
Calcium	1 (1)	6 (6)	3 (2)
Vitamin D and analogues	7 (7)	10 (10)	17 (8)
SSRIs	2 (2)	5 (5)	9 (4)
Lipid modifying agents	11 (11)	18 (17)	18 (9)
Hormonal contraceptives (systemic)	0	1 (1)	1 (1)
Progestogens	0	0	1 (1)
Corticosteroids (systemic)	3 (3)	7 (7)	7 (3)
PTFU period	N=40	N=53	N=87
Anti-anemic medications[a]	33 (83)	39 (74)	62 (71)
Calcium	1 (3)	2 (4)	1 (1)
Vitamin D and analogues	0	2 (4)	9 (10)
SSRIs	3 (8)	2 (4)	7 (8)
Lipid modifying agents	4 (10)	7 (13)	10 (12)
Hormonal contraceptives (systemic)	2 (5)	2 (4)	3 (3)
Progestogens	2 (5)	1 (2)	0
Corticosteroids (systemic)	4 (10)	0	3 (3)

Source: Clinical Study Report 815 Table 11, pp 93-94
[a] Primarily iron supplementation
Source: Clinical Study Report 815 Table 11, pp 93-94 Efficacy Results – Primary Endpoint
E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; PTFU = post-treatment follow-up; SSRIs = selective serotonin reuptake inhibitors

The primary efficacy endpoint for both trials is the proportion of responders. A responder is defined as any subject who had (1) MBL volume <80 mL during the Final Month, and (2) ≥50% reduction in MBL volume from Baseline to the Final Month. The results for each study show statistically significant higher responder rates in the Ela + E2/NETA group versus placebo group .

Proportions of responders are comparable across Studies 815 and 817. Although the addition of E2/NETA to elagolix 300 mg BID appears to diminish the responder rates in both studies, these data nevertheless provide substantial evidence of effectiveness for

the to-be-marketed fixed combination product. An overview of the responder rates for these two studies is presented below.

Table 28: Study 815 – Proportion of Responders – Multiple Imputation (FAS)

Parameter	Placebo (N=102)	Ela (N=104)	Ela + E2/NETA (N=206)
Proportion (%)	9	84	69
Difference vs. placebo (%)		75	60
95% CI		(66, 85)	(51, 69)
P-value			<0.001

Source: Table 13 in Clinical Study Report.
The P value for test of difference between Ela + E2/NETA group and placebo is by pooling the results from a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate in each data set from multiple imputation.
E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; FAS = full analysis set

Table 29: Study 817 – Proportion of Responders – Multiple Imputation (FAS)

Parameter	Placebo (N=94)	Ela (N=95)	Ela + E2/NETA (N=189)
Proportion (%)	11	77	77
Difference vs. placebo (%)		66	66
95% CI		(56, 77)	(57, 75)
P-value			<0.001

Source: Table 13 in Clinical Study Report.
The P value for test of difference between Ela + E2/NETA group and placebo is by pooling the results from a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate in each data set from multiple imputation.
E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; FAS = full analysis set

Approximately 20% of subjects prematurely withdrew from the placebo-controlled trials, which is not unexpected in trials of HMB indications. Sensitivity analyses of the primary efficacy endpoint used different approaches to handle prematurely discontinued subjects and missing Final Month MBL volume showed that the responder rate difference between each active treat group versus placebo was similar to that of the primary analysis. This suggests that the missing data due to premature discontinuation did not impact the efficacy conclusions with respect to the primary endpoint.

Data Quality and Integrity

The statistical reviewer was able to reproduce analyses results from the two studies using the submitted analysis datasets.

Dose/Dose Response

A single dose of the fixed combination of Ela + E2/NETA was investigated in Studies 815 and 817. The pharmacodynamic response of this fixed combination drug is discussed in Section 6.

Durability of Response

In Studies 815 and 817, the ranked and non-ranked secondary endpoints (mean change from baseline in MBL volume at different treatment durations) inform the onset and durability of the response. In both studies, a significant reduction in MBL volume as compared to placebo was seen in Ela + E2/NETA treated subjects from Month 1 to Month 6. Maximum reduction was achieved at Month 3, and was maintained throughout the 6-month treatment period in both studies 815 and 817 (see Table 30 and Table 31, and Figure 16 and Figure 17 below).

Persistence of Effect

The majority of subjects from Studies 815 and 817 entered the open-label extension Study 816. In Studies 815 and 817, 116 and 98 subjects, respectively, entered the PTFU period. Of those, 60-70% completed the PTFU period. After six months of therapy with Ela + E2/NETA, resumption of menses was reported by 39%, 68% and 73% of women within 1, 2, and 6 months respectively for Study 815 and 39%, 85% and 92% within 1, 2, and 6 months respectively for Study 817. After 12 months of therapy with Ela + E2/NETA (Studies 815 or 817, then Study 816), resumption of menses was reported by 43%, 82% and 90% of women within 1, 2, and 6 months after stopping treatment, respectively. The resumption of menses is expected given the short half-life of elagolix and benefit beyond the end of treatment would not be expected. FDA accepts the Applicants proposal to include information regarding resumption of menses in labeling.

Efficacy Results – Ranked Secondary Endpoints

Results of the ranked secondary endpoints for both studies are shown in the two tables (Table 30 and Table 31) below; these are considered acceptable by the FDA for labeling purposes. The Ela + E2/NETA arm shows statistically significant treatment benefit versus placebo on all ranked secondary efficacy endpoints.

Table 30: Study 815 – Summary of Ranked Secondary Efficacy Endpoints – (FAS)

Secondary Endpoint Time Statistic	Placebo (N=102)	Ela (N=104)	Ela + E2/NETA (N=206)
MBL volume (mL)			
Change from baseline to final month			
Mean (SD)	255 (174)	249 (170)	238 (150)
LS mean (SE)	1 (15)	-222 (15)	-177 (10)
Difference vs. placebo		-222 (21)	-178 (18)
95% CI		(-263, -182)	(-213, -142)
P-value[a]			<0.001

Secondary Endpoint Time Statistic	Placebo (N=102)	Ela (N=104)	Ela + E2/NETA (N=206)
Change from baseline to Month 6			
n	71	67	132
Mean (SD)	249 (187)	267 (178)	229 (131)
LS mean (SE)	-2 (14)	-236 (14)	-195 (10)
Difference vs. placebo		-234 (19)	-193 (17)
95% CI		(-272, -197)	(-224, -160)
P-value[c]			<0.001
Change from baseline to Month 3			
n	85	83	172
Mean (SD)	264	256	231
LS mean (SE)	6 (15)	-235 (15)	-192 (11)
Difference vs. placebo		-241 (22)	-198 (19)
95% CI		(-284, -198)	(-235, -161)
P-value[c]			<0.001
Change from baseline to Month 1			
n	95	97	187
Mean (SD)	259(177)	255 (174)	230(137)
LS mean (SE)	-19 (16)	-209 (16)	-135 (11)
Difference vs. placebo		-190 (23)	-116 (20)
95% CI		(-235, -146)	(-155, -77)
P-value[c]			<0.001
Suppression of bleeding			
Final month			
n/N (%)	4/91 (4)	79/94 (84)	104/183(57)
Difference vs. placebo		80	52
95% CI		(71, 88)	44, 61
P-value[b]			<0.001
Baseline Hgb ≤10.5 g/dL & increase >2 g/dL			
Month 6			
n/N (%)	5/31 (16)	27/41 (66)	32/52 (62)
Difference vs. placebo		50	45
95% CI		(30, 69)	(27, 64)
P-value[b]			<0.001

Source: FDA analysis. Table 14.2_3.1.1, Table 14.2_5.1, Table 14.2_3.2, Table 14.2_3.3, Table 14.2_10.4, Table 14.2_3.4 in study 815 report.
[a] The P value for test of difference between each elagolix treatment group and placebo is by pooling the results from an ANCOVA model with treatment as the main effect and baseline MBL volume as a covariate in each dataset from multiple imputation.
[b] The P value is calculated based on chi-square test (or Fisher's exact test if ≥20% of the cells have expected cell count <5).
[c] The P value is from MMRM with treatment, month, and an interaction between treatment and month as fixed-effect factors, and baseline MBL volume as a covariate comparing each elagolix treatment group with placebo.
E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; Hgb = hemoglobin; LS = least squares; MBL = menstrual blood loss

Table 31: Study 817 – Summary of Ranked Secondary Efficacy Endpoints – (FAS)

Secondary Endpoint Time Statistic	Placebo (N=94)	Ela (N=95)	Ela + E2/NETA (N=189)
MBL volume (mL)			
Change from baseline to final month			
Mean (SD)	254 (179)	225(146)	229(149)
LS mean (SE)	-4 (15)	-199 (15)	-169 (11)
Difference vs. placebo		-195 (22)	-164 (19)
95% CI			
P-value[a]			<0.001
Change from baseline to Month 6			
n	64	53	124
Mean (SD)	283 (203)	230 (157)	219 (149)
LS mean (SE)	29 (17)	-224 (18)	-198 (12)
Difference vs. placebo		-252 (25)	-227 (21)
95% CI		(-301, -204)	(-267, -186)
P-value[c]			<0.001
Change from baseline to Month 3			
n	78	72	157
Mean (SD)	263 (190)	227 (145)	225 (148)
LS mean (SE)	-14 (12)	-211 (12)	-200 (8)
Difference vs. placebo		-197 (17)	-186 (14)
95% CI		(-230, -164)	(-214, -158)
P-value[c]			<0.001
Change from baseline to Month 1			
n	88	83	175
Mean (SD)	259 (183)	225 (140)	229 (151)
LS mean (SE)	-2 (14)	-197 (15)	-127 (10)
Difference vs. placebo		-195 (21)	-125 (18)
95% CI		(-235, -154)	(-160, -90)
P-value[c]			<0.001
Suppression of bleeding			
Final month			
n/N (%)	4/86 (5)	72/81 (89)	105/172 (61)
Difference vs. placebo		84	56
95% CI		(76, 92)	(48, 65)
P-value[b]			<0.001
Baseline Hgb ≤10.5 g/dL & increase >2 g/dL			
Month 6			
n/N (%)	5/24 (21)	10/25 (40)	24/48 (50)
Difference vs. placebo		19	29
95% CI		(-6, 44)	(8, 51)
P-value[b]			0.017

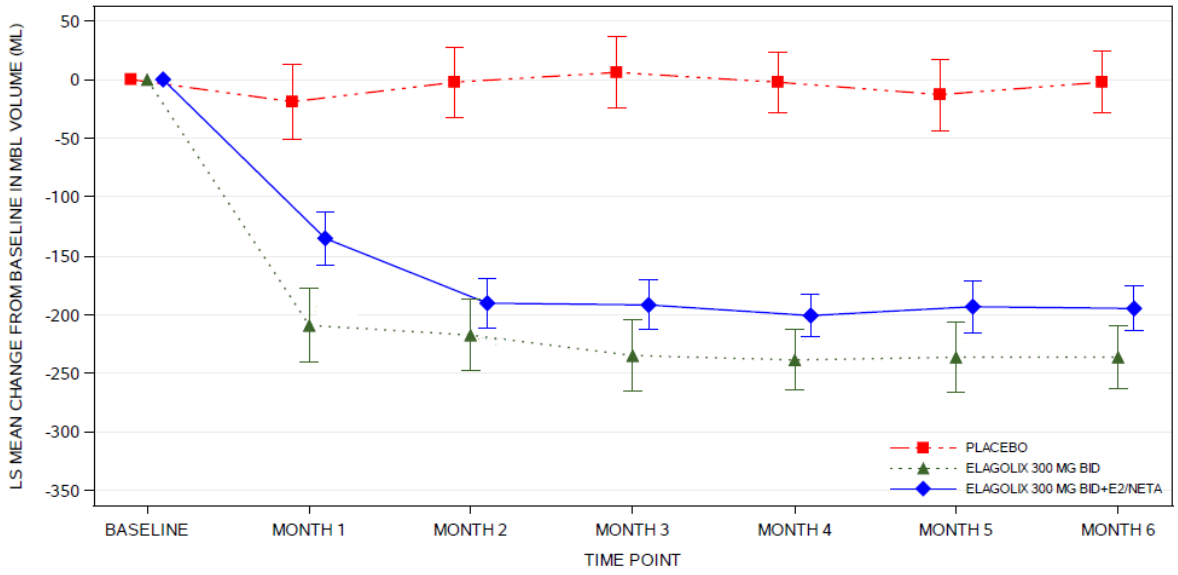
Source: FDA analysis; Table 14.2_3.1.1, Table 14.2_5.1, Table 14.2_3.2, Table 14.2_3.3, Table 14.2_10.4, Table 14.2_3.4 in study 817 report.
[a] The P value for test of difference between each elagolix treatment group and placebo is by pooling the results from an ANCOVA model with treatment as the main effect and baseline MBL volume as a covariate in each dataset from multiple imputation.
[b] The P value is calculated based on chi-square test (or Fisher's exact test if ≥20% of the cells have expected cell count <5).
[c] The P value is from MMRM with treatment, month, and an interaction between treatment and month as fixed-effect factors, and baseline MBL volume as a covariate comparing each elagolix treatment group with placebo.
E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; Hgb = hemoglobin; LS = least squares; MBL = menstrual blood loss

In both studies, MBL volume was reduced by approximately 200 mL as compared to placebo at Month 3 and this reduction persisted through Month 6. As compared to placebo, the treatment difference for the proportion of Ela + E2/NETA treated subjects with suppression of menstrual bleeding (defined as no days of bleeding but any number of days of spotting) at the Final Month of treatment was over 50%.

These data provide additional clinical evidence for the effectiveness of Ela + E2/NETA to reduce HMB associated with uterine fibroids. The proportion of subjects with baseline hemoglobin ≤10.5 g/dL who had an improvement in anemia (defined as an increase in hemoglobin >2 g/dL) was 45% and 29% in Studies 815 and 817, respectively. The clinical benefit of this increase in hemoglobin, such as reduction in the number of blood transfusions or improvement in symptoms of anemia was not evaluated. These results met the ranked secondary efficacy endpoint agreed upon with the Applicant and will be included in labeling.

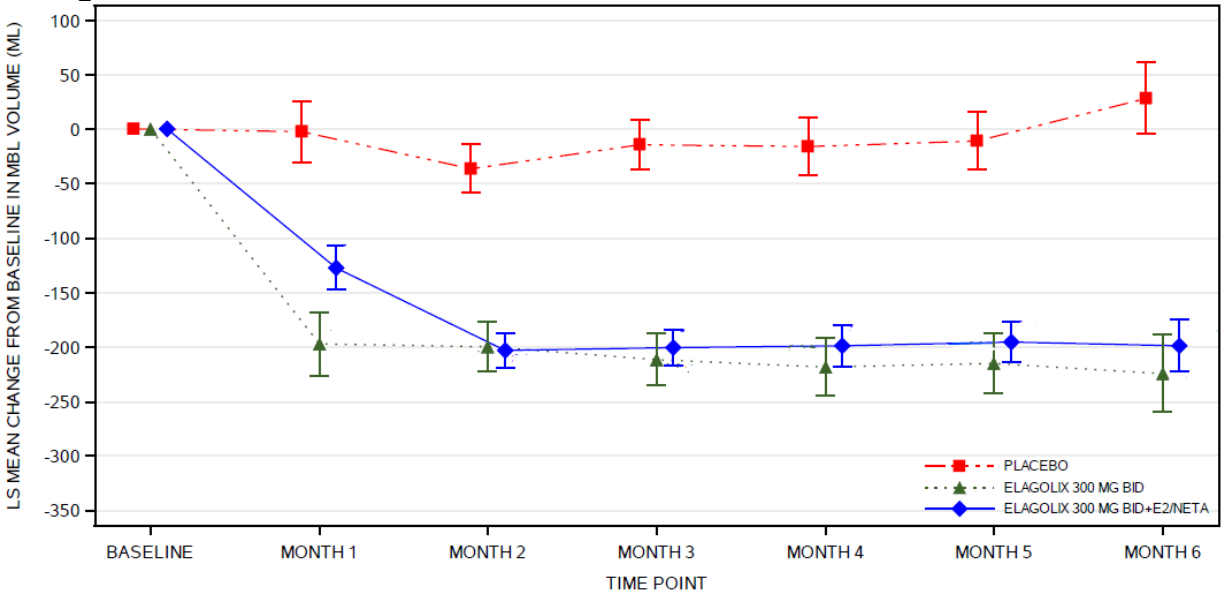
Figure 16 and Figure 17 demonstrated the estimated change from baseline in MBL volume overtime during the treatment period with the 95% CI. Continued reduction in mean MBL volume were seen in the first two months and the reduction maintained thereafter until the end of the treatment period.

Figure 16: Study 815 – LS Mean Change From Baseline in MBL Volume by Month During the Treatment Period



Source: Figure 3 in study 815 report.
Note: LS mean estimates are obtained from MMRM treatment, month, and an interaction between treatment and month as fixed effect factors, and baseline MBL volume as a covariate comparing each elagolix treatment group with placebo.
The bars above and below the data points are the 95% confidence limits on the mean values.
BID = twice a day; E2/NETA = estradiol I mg/norethindrone acetate 0.5 mg; LS = least squares; MBL = menstrual blood loss

Figure 17: Study 817 – LS Mean Change From Baseline in MBL Volume by Month During the Treatment Period



Source: Figure 3 in study 817 report.
Note: LS mean estimates are obtained from MMRM treatment, month, and an interaction between treatment and month as fixed effect factors, and baseline MBL volume as a covariate comparing each elagolix treatment group with placebo.
The bars above and below the data points are the 95% confidence limits on the mean values.
BID = twice a day; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; LS = least squares; MBL = menstrual blood loss

The results of the mean changes by month are exploratory, but are useful in determining that maximum benefit is likely reached by Month 3.

Other PRO instruments evaluated in the pivotal studies included the UFS-QoL questionnaire, WPAI:UF, PGIC-MB, Patient Global Impression of Change-Non-Bleeding Uterine Fibroids Symptoms, and EurolQol-5D 5 level. These questionnaires are considered exploratory by the FDA, and results from these instruments were not relied upon to inform efficacy or for labeling purposes.

Additional Subgroup Sensitivity Analyses Conducted on the Individual Trial Data

Subgroup Analyses for the Primary Efficacy Endpoint

To determine whether race, age, or BMI might be effect-modifiers, the Applicant submitted post hoc subgroup analyses results for the primary efficacy endpoint per FDA's request. As shown in Table 32 and Table 33, the proportion of responder were generally consistently higher for Ela + E2/NETA compared to placebo across the categories of race, age and BMI.

Table 32: Study 815 – Subgroup Analyses for Proportion of Responders – Multiple Imputation (FAS)

Subgroup Category	Placebo (N=102) N (%)	Ela (N=104) N (%)	Ela + E2/NETA (N=206) N (%)
Race			
Black of African American	70 (11)	69 (80)	141 (67)
Not Black or African American	32 (4)	34 (91)	65 (72)
Age (years)			
≤35	14 (2)	11 (77)	24 (84)
>35	88 (10)	93 (85)	182 (67)
BMI			
Normal (<25 kg/m^2)	13 (10)	18 (89)	28 (53)
Overweight (25 -<30 kg/m^2)	22 (5)	19 (74)	40 (72)
Obese (≥30 kg/m^2)	67 (10)	67 (86)	137 (71)

Source: Table 99_1 in agency-response-2019-oct-09-publ.pdf, submitted on 10/24/2019.
The P value for test of difference between Ela + E2/NETA group and placebo is by pooling the results from a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate in each data set from multiple imputation.
BMI = body mass index; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; FAS = full analysis set

Table 33: Study 817 – Subgroup Analyses for Proportion of Responders – Multiple Imputation (FAS)

Subgroup Category	Placebo (N=94) N (%)	Ela (N=95) N (%)	Ela + E2/NETA (N=188) N (%)
Race			
Black of African American	63 (8)	66 (79)	124 (78)
Not Black or African American	31 (15)	29 (72)	64 (74)
Age (years)			
≤35	8 (25)	12 (67)	23 (71)
>35	86 (9)	83 (78)	166 (77)
BMI			
Normal (<25 kg/m^2)	8 (25)	14 (74)	21 (70)
Overweight (25 -<30 kg/m^2)	20 (13)	14 (75)	46 (77)
Obese (≥30 kg/m^2)	66 (8)	67 (78)	122 (78)

Source: Table 99_2 in agency-response-2019-oct-09-publ.pdf, submitted on 10/24/2019.
The P value for test of difference between Ela + E2/NETA group and placebo is by pooling the results from a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate in each data set from multiple imputation.
BMI = body mass index; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; FAS = full analysis set

8.1.3. Assessment of Efficacy Across Trials

The Applicant submitted two replicate six-month Phase 3 trials that support the effectiveness of Ela + E2/NETA to reduce HMB associated with uterine fibroids. In these studies, HMB was determined using the objective alkaline hematin method, which is considered the “gold-standard” method, and was defined as MBL >80 mL, the accepted threshold commonly used in clinical trials. The trials were conducted primarily in the U.S., and the study population was representative of the target population for whom the drug is intended. The demographic and baseline characteristics of study subjects were

similar across trials, and results from these trials were consistent. In addition, consistent results for the subset of woman treated with the to-be-marketed product in the Phase 2b study M12-813 (where the primary efficacy endpoint is identical to that in the Phase 3 trials) provide additional supportive evidence of effectiveness.

Primary Endpoints

As shown in Table 28 and Table 29, in both Phase 3 trials (Studies 815 and 817), a significantly greater proportion of subjects treated with Ela + E2/NETA achieved the primary efficacy endpoint of MBL volume <80 mL during the Final Month and ≥50% reduction in MBL volume from Baseline to the Final Month as compared to placebo. In both Studies 815 and 817, the proportion of responders at baseline (those meeting the primary endpoint) were low (8.7% and 10.5%, respectively). After 6 months of treatment with Ela 300 mg + E2/NETA, approximately two thirds of treated subjects met the responder definition. The placebo-adjusted difference in the proportion of responders in the Ela + E2/NETA arms was 60% and 66%, in Study 815 and 817, respectively. Together, these two Phase 3 trials provide results showing consistent and robust support to establish efficacy of Ela 300 mg + E2/NETA in the management of HMB associated with uterine fibroids.

Secondary and Other Endpoints

Both studies met all six ranked secondary endpoints as shown in Table 30 and Table 31 above. These data provide evidence that treatment with Ela + E2/NETA resulted in statistically significant reductions in MBL volume at Months 1, 3, and 6 of treatment period (Figure 16 and Figure 17). Overall, compared to placebo, Ela + E2/NETA resulted in a significant reduction in MBL volume of 178 mL and 173 mL at the Final Month, respectively in each trial. Suppression of menstrual bleeding, defined as amenorrhea, with any number of days spotting allowed, was observed in over 50% of Ela + E2/NETA treated subjects as compared to placebo treated subjects.

Additionally, in both studies, a greater proportion of subjects with more severe anemia (hemoglobin ≤10.5 g/dL) experienced an increase in hemoglobin of at least 2 g/dL (45% and 29%, in Studies 815 and 817, respectively). However, the clinical meaningfulness of this change in mean laboratory finding was not assessed in the studies.

Subpopulations

Exploratory subgroup analyses performed at FDA's request demonstrated that efficacy results were consistently across categories of race, age and BMI.

Additional Efficacy Considerations

Other exploratory endpoints that the Applicant evaluated during drug development (e.g. uterine and fibroid volume) were not considered in the FDA's assessment of efficacy for this product. Refer to the Regulatory History section.

8.1.4. Integrated Assessment of Effectiveness

Based on the totality of the clinical data submitted by the Applicant, elagolix 300 mg BID + E2 1 mg/NETA 0.5 mg QD reduced heavy menstrual bleeding associated with uterine fibroids in premenopausal women.

The Applicant provided data from the two replicate, adequately powered, placebo-controlled Phase 3 trials (Studies 815 and 817), which included 395 women treated with elagolix 300 mg BID + E2 1 mg/NETA 0.5 mg QD and 196 women treated with placebo. These data support the following conclusions:

- Treatment with Ela + E2/NETA by six months reduced MBL volume to <80 mL (the threshold used to define HMB), and reduced MBL volume by at least 50% from pre-treatment baseline.
- Compared to placebo, 60% to 66% of women responded to treatment by achieved reduction in HMB as defined above.
- As compared to placebo, treatment reduced MBL volume by approximately 170 mL from baseline to the Final Month of treatment.
- Reductions in MBL volume were observed at Months 1, 3, and 6 after initiation of treatment. Maximum reduction in MBL volume was achieved at Month 3 and persisted for the duration of the treatment period.
- As compared to placebo, 29% to 45% of subjects with baseline Hgb ≤10.5 g/dL had an increase in Hgb of more than 2 g/dL at Month 6.

The highly consistent results across the two adequate and well-controlled placebo-controlled Phase 3 clinical trials and the Phase 2b study, establish substantial evidence of effectiveness for Ela + E2/NETA as a treatment for HMB associated with uterine fibroids in the target population.

8.2. Review of Safety

8.2.1. Safety Review Approach

This safety review evaluates pooled and individual study data from the two identical Phase 3, randomized, placebo- and active-controlled clinical trials (Studies 815 and 817) and the extension study (816). During pre-NDA meeting (see IND 115528 Meeting Minutes, dated July 13, 2019), it was agreed that the Summary of Clinical Safety in Module 2 would contain Phase 3 safety data (two pivotal studies pooled), one extension study, and a separate written analysis from each of the Phase 2 studies which used different doses of elagolix and required vitamin D and calcium intake. Only one of the Phase 2 studies enrolled a subset of subjects (from Cohort 1) randomized to the to-be-marketed dose (Ela 300 mg + E2/NETA). Therefore, Phase 2 data were not pooled with Phase 3 results. An Integrated Summary of Safety (ISS) was also to be submitted. Upon submission, the ISS contained only tables and figures which were referenced in the Summary of Clinical Safety. There was no explicit agreement for this ISS structure

but the Applicant's submitted ISS was deemed adequate for review at filing and during the review.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 1511 subjects have been exposed to elagolix (with and without E2/NETA) at doses ≥600 mg, including 518 unique subjects exposed to elagolix 300 mg BID + E2/NETA in the Phase 2/3 uterine fibroid clinical program (see Table 34 below). In Phase 3 clinical trials for the uterine fibroid indication, 395 subjects were randomized into the placebo-controlled treatment phase for six months and an additional 58 subjects, who were on placebo in Studies 815 and 817, were slated to receive elagolix 300 mg BID + E2/NETA in the extension study 816 for six months. This meets or exceeds ICH E1 requirements. Additionally, 65 subjects were randomized to the elagolix 300 mg BID + E2/NETA treatment in one Phase 2 study (M12-813). Exposure data are also available from elagolix in the endometriosis program; however, these data pertain to lower elagolix doses (up to 200 mg BID) and not included in this review. Overall exposure data for the uterine fibroid program are shown in Table 35.

Table 34: Safety Population for Elagolix 300 mg BID + E2/NETA

Clinical Trial Groups	Ela 300 mg BID + E2/NETA (N=562)	Ela 300 mg BID Active Control (N=323)	Placebo (N=261)
Controlled trials conducted for this indication			
Pivotal Phase 3	395	199	196
Extension study (previously on PBO in pivotal trials)	58	59	N/A
All other than controlled trials conducted for this indication			
Phase 2 Study (M12-813)	65	65	65
Phase 1	44		

Source: Compiled by Reviewer from safety datasets
BID = twice a day; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; PBO = placebo

Table 35: Overall Exposure Data for Elagolix 300 mg BID With and Without Addback

Dosage	≥ 1 Dose	≥ 6 Months[a]	≥ 12 Months[a]
Total elagolix daily dose ≥ 600 mg	1511	804	263
Uterine fibroid Phase 2 and 3 studies	1222	804	263
Phase 1 studies[b]	289	0	0
Elagolix 300 mg BID + E2/NETA 1 mg/0.5 mg QD	562	391	182
Uterine fibroid Phase 2 and 3 studies	518	391	182
Phase 1 studies[b]	44	0	0

Source: Table 2, Summary of Clinical Safety (Module 2.7.4), page 21 of 158
BID = twice a day; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; PBO = placebo
[a] six- and 12- month exposures are defined as ≥ 168 days and ≥ 336 days, respectively.
[b] Phase 1 studies include subjects who received elagolix alone or with add-back therapy (E2/NETA) or with other drugs.

The two placebo-controlled Phase 3 trials were identical and were pooled for the safety analysis. Demographics were similar across treatment groups (see Table 23 and Table 24 in Section 8.1.2). Over half of the subjects (55%) had anemia at baseline (defined as Hgb < 12 g/dL). Nearly a quarter (22%) of subjects were classified as iron deficiency and 50% were taking iron supplementation. Despite the mean BMI (33 kg/m^2), obesity was a baseline characteristic in only 13%. Approximately 26% of subjects had hypertension at baseline. Overall, the population had regular menstrual cycles (mean of every 27 days), with the mean bleeding duration of 6.6 days. Alcohol and tobacco use were similar across groups. At baseline, 10% of subjects used medication for uterine fibroids with the most common being sex hormones and genito-urinary modulators (estrogen/progesterone-like). Approximately 8% were taking vitamin D or analogues. No clinically concerning differences in demographics between treatment arms or between the two studies was identified by the Applicant or the FDA.

The Phase 2 studies were not included in the pooled database as they also evaluated other elagolix doses and add back regimens. Data from the Phase 2 study M12-813, that included an elagolix 300 BID + E2/NETA arm, were included in the submission but are presented separately below.

Adequacy of the Safety Database

The safety database and exposure for the to-be-marketed product (elagolix 300 mg BID + E2 1.0mg/NETA 0.5mg) are acceptable and the population represents the expected target population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of this submission was generally adequate. Two minor issues were noted and addressed by the Applicant during the review:

- The Applicant reported errors in the central imaging vendor's calculation of BMD T-scores for the first 15 and 13 months of Studies 815 and 817, respectively. The updated dataset was submitted with the original NDA and the Applicant confirmed that the corrected dataset had been submitted in Response to Information Request dated January 15, 2020.

- Additional analyses with accompanying datasets were requested for bone safety modeling analyses using 12-month data (Information Request dated December 18, 2019) regarding Clinical Study Report RD190282, entitled "Exposure-Safety Analyses of Elagolix Effects on Changes in Bone Mineral Density and Incidence of Hot Flush in Subjects with Heavy Menstrual Bleeding Associated with Uterine Fibroids Based on Data from Three Phase 3

Studies. These datasets are presented in the Clinical Pharmacology section of this review.

Categorization of Adverse Events

The categorization of AEs, SAEs and treatment-emergent AEs was acceptable using standard MedDRA coding. The definitions of AEs and SAEs are consistent with those outlined in 21 CFR 312.32. Additional AEs included: amenorrhea (no return to menses by the Post-Treatment Follow-up Month 2) and subjects were to be followed until resolution; BMD decrease that leads to study discontinuation or a BMD decrease at any anatomic location with a T-score < –1.5; and elective surgery due to deterioration of pre-existing condition (note: planned surgeries would not be AEs). Other AEs of special interest (AESIs) included rash/hypersensitivity, fracture, neuro-psychiatric (depression, mood swings, etc.), and vasomotor symptoms (hot flush, night sweats). Treatment-emergent adverse events (TEAEs) were defined as AEs with a start date on or after the first dose of the study drug and within 30 days of the last dose of the study drug.

Adverse events were monitored and recorded at each study visit during the treatment period and then monthly in the PTFU period, including phone visits. All AEs reported from the time of study drug administration through Month 6 or Month 12 in the Post-Treatment Follow-Up Period, (if applicable) were to be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related, nonserious AEs were collected from the time the subject signed the study-specific informed consent. Severity was categorized as mild, moderate, or severe.

Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 was used in the Phase 3 trials and the ISS datasets. MedDRA version 18.0 was used for Phase 2 study M12-813 and datasets were converted to version 21.0.

Routine Clinical Tests

Routine laboratory tests included chemistry, lipid panel, hematology and were collected at screening and monthly (up to Month 6) in the placebo-controlled phase and every 3 months in the 12 month PTFU period. Follicle-stimulating hormone, luteinizing hormone, estradiol (E2), progesterone, elagolix and NETA levels were collected at screening and monthly in the DB phase. Apoliprotein A and B were collected at screening and every 3 months in the placebo-controlled phase and PTFU. Creatinine phosphokinase and urinalysis were collected at screening and every 3 months in the placebo-controlled phase, with urinalysis measurement continuing in the PTFU. Urine pregnancy was collected at screening and monthly throughout DB and PTFU with serum pregnancy tests collected at screening, Day 1, Month 6 of treatment and Month 12 of PTFU. Thyroid stimulating hormone and thyroglobulin were collected at screening and Month 6 of placebo-controlled treatment. Although the protocols are unclear with regards to fasting instructions to the patients, in response to an Information Request, the Applicant

has clarified that the chemistry and lipid panels were to be obtained in the morning following an overnight fast. Central laboratory vendors were used for all clinical labs (b) (4), formerly (b) (4)), and imaging (including DXA) was done by (b) (4) (b) (4).

Additional safety monitoring included endometrial biopsy, pelvic ultrasound, abdominal MRI and saline infusion sonohysterography for endometrial safety, ECGs and DXA scans.

8.2.4. Safety Results

Deaths

Two deaths occurred in this clinical program; neither was considered by the Applicant or the FDA as related to the treatment.

- One 48 year-old WF (ID (b) (6)) committed suicide during the screening period of Study 815. She had not received study drug.
- A 31 year-old BF who received placebo in Study 817 and Ela + E2/NETA in extension Study 816 suffered a cardiovascular (CV)-related death on Day 245 of the extension phase (85 days after last dose of Ela + E2/NETA). She had a history of aplastic anemia and received a bone marrow transplant at age 4. Per patient's mother, the subject was intoxicated and subsequently passed out and stopped breathing (ethanol level elevated to 266 mg/dL). Resuscitation by paramedics was not successful. The autopsy report listed the primary cause of death as hypertensive cardiovascular disease with a secondary cause of obesity (BMI of 32.9).

Serious Adverse Events

A total of 23 subjects reported 31 SAEs in the placebo-controlled phase in Studies 815 and 817. The number of subjects with SAEs was numerically lower in the Ela + E2/NETA group overall (2.5%) compared to the placebo group (3.1%) or with Ela alone (3.5%). Differences in the number of subjects with events between groups were minimal (<1%) and no trends in a specific SAE were seen (Table 36). SAEs occurring in 2 or more subjects across groups include anemia, cholelithiasis, uterine leiomyoma and menorrhagia. There were two subjects with SAEs of anemia (placebo group) and uterine leiomyoma (Ela alone group).

Table 36: Treatment-Emergent SAEs in Pivotal Phase (Number of Subjects (%))

Serious Adverse Event	Ela 300 mg BID + E2/NETA (N=395)	Ela 300MG BID (N=199)	Placebo (N=196)	Total (N=791)
Total SAEs	13 (3.3)	10 (5.0)	8 (4.1)	31 (3.9)
N subjects	10 (2.5)	7 (3.5)	6 (3.1)	23 (2.9)
Abortion complete	0	0	1 (0.5)	1 (0.1)
Abortion spontaneous	0	1 (0.5)	0	1 (0.1)
Anemia	1 (0.3)	0	2 (1.0)	3 (0.4)
Anxiety	1 (0.3)	0	0	1 (0.1)
Appendicitis	0	1 (0.5)	0	1 (0.1)
Cellulitis	1 (0.3)	0	0	1 (0.1)
Cholelithiasis	1 (0.3)	1 (0.5)	0	2 (0.3)
Dermatitis	1 (0.3)	0	0	1 (0.1)
Dysfunctional uterine bleeding	1 (0.3)	0	0	1 (0.1)
Dysmenorrhea	1 (0.3)	0	0	1 (0.1)
Dyspnea exertional	0	0	1 (0.5)	1 (0.1)
Ectopic pregnancy	0	1 (0.5)	0	1 (0.1)
Exostosis	1 (0.3)	0	0	1 (0.1)
Hyperthyroidism	1 (0.3)	0	0	1 (0.1)
Intervertebral disc protrusion	1 (0.3)	0	0	1 (0.1)
Menorrhagia	1 (0.3)	1 (0.5)	1 (0.5)	3 (0.4)
Obesity	1 (0.3)	0	0	1 (0.1)
Osteoarthritis	0	0	1 (0.5)	1 (0.1)
Oxygen saturation decreased	0	0	1 (0.5)	1 (0.1)
Palmoplantar keratoderma	1 (0.3)	0	0	1 (0.1)
Pelvic pain	0	1 (0.5)	0	1 (0.1)
Prolapse	0	1 (0.5)	0	1 (0.1)
Small intestinal obstruction	0	1 (0.5)	0	1 (0.1)
Suicidal ideation	0	0	1 (0.5)	1 (0.1)
Uterine leiomyoma	0	2 (1.0)	0	2 (0.3)

Source: (b) (4).
Columns - Dataset: Demographics; Filter: None.
Table Section 1 - Dataset: Adverse Events; Filter: AESER = 'Y'.
BID = twice a day; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; Ela = elagolix; SAE = serious adverse event

One event occurred for each SAE in the Ela + E2/NETA group and narratives are provided below. Among the 10 subjects with SAEs, three (two with heavy uterine bleeding requiring transfusion, and one with symptomatic cholelithiasis requiring laparoscopic cholecystectomy) are possibly related to treatment with Ela + E2/NETA. Narratives for these three cases were considered possibly related to study drug are are shown in Table 37.

Table 37: Ela + E2/NETA SAE Narratives

ID	Age Race	Day of Onset	AECODE	Narrative
M12817-[redacted] (b) (6)	53 B	18	Anemia, Dysfunctional uterine bleeding	On Day 18, the subject (with uterine fibroids, metrorrhagia, menorrhagia, and anemia) experienced severe dysfunctional uterine bleeding and severe, worsening anemia. She presented to study site with weakness, pallor, and very heavy bleeding, and was referred to the ER, where she had blood pressures of 90/51 mmHg and 98/45 mmHg, heart rate of 78 bpm, and hemoglobin of 7.7 g/dl. She was admitted, given medroxyprogesterone and 2 units of red blood cells. Study drug was permanently discontinued due to these events with the last scheduled dose administered on Day 17. She was discharged from the hospital on Day 21.
M12817-[redacted] (b) (6)	46 B	180	Dysmenorrhea Menorrhagia	The subject with history of uterine fibroids, menorrhagia, and dysmenorrhea completed the study drug treatment period with the last scheduled dose administered on Day 182, and she entered the study follow-up period. On Day 183 (Post-Treatment Day 1), The subject was admitted for menorrhagia/anemia and given 2 units of red blood cells. Laboratory values during hospitalization were not provided. On Day 185 (Post-Treatment Day 3), the subject underwent a hysteroscopy with removal of a fibroid. She was treated with methylergometrine for the event of menorrhagia. She was discharged and the events were considered resolved on Day 186 (Post-Treatment Day 4).
M12817-[redacted] (b) (6)	43 B	95	Cholelithiasis	The subject, with history of gastric sleeve surgery, high cholesterol and morbid obesity, was hospitalized on Day 95 with symptoms of epigastric pain and jaundice. Liver function tests were reported to be abnormal (results not provided). CT and abdominal ultrasound revealed distended gallbladder with multiple stones present. Endoscopic retrograde cholangiopancreatography revealed sludge. Study drug was interrupted. On Day 99, a laparoscopic cholecystectomy revealed choledocholithiasis and cholelithiasis and a laparoscopic excision of right ovarian mass revealed a benign cyst. Treatment medications included piperacillin/tazobactam, Augmentin, and hydrocodone. The subject was discharged from the hospital and the event was considered resolved on Day 99. The study drug was restarted on Day 100. The prior event of hypercholesterolemia was considered resolved on Day 144.

Source: M12-815 and M12-817 CSR narratives
AECODE = adverse event code; B = black; ER = emergency room; µIU/mL = micro international units/milliliter; W = white

In the long-term extension phase, there were 12 SAEs (excluding one death, described in Section 8.2.4, subsection Deaths). Of the 9 subjects with SAEs who received Ela + E2/NETA, 6 had events that could potentially be caused by the study drug include 2 subjects with breast cancer (see narratives in Section 8.2.9, subsection Human Carcinogenicity and Tumor Development) and one each with spontaneous abortion, metrorrhagia (electing to undergo myomectomy), worsening menorrhagia and pelvic pain (electing to undergo hysterectomy), and hysterectomy (due to "return of heavy bleeding").

Dropouts and/or Discontinuations Due to Adverse Effects

The rate of premature discontinuation in the Ela + E2/NETA group (21.0%) was similar to placebo (20.9%) and both were less than the Ela alone group (24.6%). The top reasons for discontinuation (Ela + E2/NETA versus placebo) were adverse event (7.8% versus 4.6%), withdrawal of consent (4.8% versus 5.1%) and lost to follow-up (3.3% versus 5.1%), respectively.

Five additional subjects (four in Ela + E2/NETA group, one in PBO group) were identified in the disposition dataset (ds.xpt) who were coded as "Withdrawal by the subject" but who actually discontinued due to an AE. Four of the five subjects were captured in the separate adverse event dataset (ae.xpt). The missing subject was (b) (6) who received Ela + E2/NETA and had an event of heavy bleeding Day 36.

In the placebo-controlled phase, the most common adverse events leading to drug discontinuation in Ela + E2/NETA compared to placebo were nausea (1.3% versus 1.0%), alopecia (1.0% versus 0), headache (1.0% versus 0.5%), metrorrhagia (1% versus 0), hot flush (0.8% versus 0.5%), lower abdominal pain (0.5% versus 0). See Table 38 for the complete listing.

Table 38: Discontinuations Due to Adverse Events in Phase 3 Placebo-Controlled Phase (and > 0 in Ela + E2/NETA)

Adverse Event	Ela + E2/NETA N=395 n (%)	Ela BID N=199 n (%)	Placebo N=196 n (%)	TOTAL N=790 n (%)
Nausea	5 (1.3)	2 (1.0)	2 (1.0)	9 (1.1)
Alopecia	4 (1.0)	1 (0.5)	0	5 (0.6)
Headache	4 (1.0)	3 (1.5)	1 (0.5)	8 (1.0)
Menorrhagia	4 (1.0)	1 (0.5)	3 (1.5)	8 (1.0)
Metrorrhagia	4 (1.0)	0	0	4 (0.5)
Hot flush	3 (0.8)	5 (2.5)	1 (0.5)	9 (1.1)
Abdominal pain lower	2 (0.5)	0	0	2 (0.3)
Arthralgia	2 (0.5)	2 (1.0)	0	4 (0.5)
Menometrorrhagia	2 (0.5)	1 (0.5)	0	3 (0.4)
Night sweats	2 (0.5)	1 (0.5)	0	3 (0.4)
Weight increased	2 (0.5)	0	0	2 (0.3)
Abdominal pain	1 (0.3)	1 (0.5)	0	2 (0.3)
Affect lability	1 (0.3)	0	0	1 (0.1)

Adverse Event	Ela + E2/NETA N=395 n (%)	Ela BID N=199 n (%)	Placebo N=196 n (%)	TOTAL N=790 n (%)
Anemia	1 (0.3)	0	2 (1.0)	3 (0.4)
Angina pectoris	1 (0.3)	0	0	1 (0.1)
Back pain	1 (0.3)	0	0	1 (0.1)
Depression	1 (0.3)	0	1 (0.5)	2 (0.3)
Dysfunctional uterine bleeding	1 (0.3)	0	0	1 (0.1)
Dysmenorrhea	1 (0.3)	0	0	1 (0.1)
Dyspnea	1 (0.3)	0	0	1 (0.1)
Fatigue	1 (0.3)	1 (0.5)	1 (0.5)	3 (0.4)
Hair growth abnormal	1 (0.3)	0	0	1 (0.1)
Hepatic enzyme increased	1 (0.3)	0	0	1 (0.1)
Homicidal ideation	1 (0.3)	0	0	1 (0.1)
Hypertension	1 (0.3)	1 (0.5)	0	2 (0.3)
Irritability	1 (0.3)	0	0	1 (0.1)
Lethargy	1 (0.3)	0	0	1 (0.1)
Libido decreased	1 (0.3)	0	0	1 (0.1)
Lichen nitidus	1 (0.3)	0	0	1 (0.1)
Memory impairment	1 (0.3)	0	0	1 (0.1)
Neck pain	1 (0.3)	0	0	1 (0.1)
Nightmare	1 (0.3)	0	0	1 (0.1)
Pain	1 (0.3)	1 (0.5)	0	2 (0.3)
Peripheral swelling	1 (0.3)	0	0	1 (0.1)
Pruritus generalized	1 (0.3)	0	0	1 (0.1)
Thrombosis	1 (0.3)	0	0	1 (0.1)
Urinary incontinence	1 (0.3)	0	0	1 (0.1)
Urticaria	1 (0.3)	0	0	1 (0.1)
Vertigo	1 (0.3)	0	1 (0.5)	2 (0.3)
Vomiting	1 (0.3)	0	0	1 (0.1)

Source: Compiled by reviewer, ISS ae.xpt dataset, TRTEM1FL, "Y"; AEDD01FL "Y"
BID = twice a day; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; ELA = elagolix; PBO = placebo

With the exception of alopecia, no specific trends in discontinuation were identified in the treated population (see additional discussion in Section 8.2.5.4 Alopecia). When combined with the extension phase, 3.7% of 218 subjects receiving Ela + E2/NETA for 12 months discontinued due to adverse reactions.

Significant Adverse Events

Significant adverse events of special interest that are associated with either GnRH analog or hormone therapy use include thromboembolic and cardiovascular events (discussed in Section 8.2.5.3) and bone-related events, BMD change, fractures (discussed in Section 8.2.5.1), and alopecia (discussed in Section 8.2.5.4).

The Applicant also presented SMQs for non-bone related hypoestrogenic effects (see Section 8.2.5.6), depression and suicide/self-injury (see Section 8.2.5.5), drug related hepatic disorders (see section Laboratory Findings below), and cardiac arrhythmias (see Section 8.2.5.3).

Severity categories were defined as “mild” (AE is transient and easily tolerated), “moderate” (AE causes discomfort and interrupts usual activities) and “severe” (AE causes considerable interference with usual activities and may be incapacitating or life-threatening).

Adverse events of special interest identified in the Orilissa submission and were reviewed include rash/hypersensitivity, fracture, neuro-psychiatric (depression, mood swings, etc.), vasomotor symptoms (hot flush, night sweats) or serious adverse events (consistent with definitions in 21 CFR 312.32).

Treatment Emergent Adverse Events (TEAEs) and Adverse Reactions

Overall, there was an increase in TEAEs in the Ela + E2/NETA group (72%) compared to placebo (66%). However, the incidences of TEAEs in the Ela + E2/NETA group were lower than those in the elagolix alone group (83%). The most frequent events by system organ class were infections and infestations (similar across groups), vascular (more events in Ela alone group), reproductive and breast disorders (greatest in placebo group), and gastrointestinal disorders (similar to placebo).

Treatment-emergent events occurring in >2% of subjects in the placebo-controlled phase are listed in Table 39 and are consistent with the Applicant’s analysis. Combined hot flushes or night sweats were the most frequently reported events in Ela + E2/NETA. However, the rates of vasomotor symptoms were approximately one-third of those with elagolix alone, showing that addition of E2/NETA mitigated these hypoestrogenic symptoms in some subjects associated with elagolix. However, it is unclear to what extent the symptoms were mitigated.

Neuropsychiatric events including depression also occurred at a higher rates in Ela + E2/NETA compared to elagolix alone although not suicidal ideation or completed suicide. Headache, fatigue, metrorrhagia, libido decreased, hypertension, alopecia, influenza, abdominal distension, vomiting, increased creatine phosphokinase (CPK), and irritability all occurred at greater rates in Ela + E2/NETA than in placebo. This issue is discussed further in Specific Safety Issues below (Section 8.2.5.5 Depression/Suicide)

Additionally, the rate of anemia in Ela + E2/NETA (1.8%) was similar to that in Ela alone (1.5%); both were reduced when compared the placebo group (5.1%).

Table 39: TEAEs in Phase 3 Placebo-Controlled Studies-Number (%) of Subjects

Adverse Event	Ela 300 MG BID + E2/NETA (N=395)	Ela 300 MG BID (N=199)	Placebo (N=196)	Total (N=790)
Total	283 (72)	166 (83)	130 (66)	579 (73)
Hot flush	79 (20)	108 (54)	13 (7)	200 (25)
Headache	37 (9)	30 (15)	14 (7)	81 (10)
Nausea	37 (9)	11 (6)	19 (10)	67 (9)
Night sweats	34 (9)	52 (26)	8 (4)	94 (12)
Fatigue	24 (6)	4 (2)	7 (4)	35 (4)
Dysmenorrhea	20 (5)	1 (1)	10 (5)	31 (4)
Metrorrhagia	20 (5)	1 (1)	1 (1)	22 (3)
Nasopharyngitis	20 (5)	10 (5)	12 (6)	42 (5)
Libido decreased	17 (4)	8 (4)	2 (1)	27 (3)
Arthralgia	15 (4)	9 (5)	5 (3)	29 (4)
Diarrhea	15 (4)	4 (2)	8 (4)	27 (3)
Hypertension	15 (4)	5 (3)	6 (3)	26 (3)
Urinary tract infection	15 (4)	5 (3)	8 (4)	28 (4)
Alopecia	14 (4)	3 (2)	2 (1)	19 (2)
Influenza	14 (4)	4 (2)	1 (1)	19 (2)
Mood swings	14 (4)	13 (7)	4 (2)	31 (4)
Abdominal distension	13 (3)	2 (1)	1 (1)	16 (2)
Upper respiratory tract infection	13 (3)	6 (3)	5 (3)	24 (3)
Menorrhagia	12 (3)	3 (2)	5 (3)	20 (3)
Vomiting	12 (3)	1 (1)	3 (2)	16 (2)
Weight increased	12 (3)	7 (4)	2 (1)	21 (3)
Back pain	10 (3)	5 (3)	7 (4)	22 (3)
Blood creatine phosphokinase increased	10 (3)	1 (1)	3 (2)	14 (2)
Insomnia	10 (3)	10 (5)	7 (4)	27 (3)
Acne	9 (2)	5 (3)	4 (2)	18 (2)
Pelvic pain	9 (2)	2 (1)	4 (2)	15 (2)
Anxiety	8 (2)	3 (2)	4 (2)	15 (2)
Bacterial vaginosis	8 (2)	1 (1)	7 (4)	16 (2)
Depression	8 (2)	2 (1)	1 (1)	11 (1)
Irritability	8 (2)	3 (2)	2 (1)	13 (2)
Low density lipoprotein increased	8 (2)	4 (2)	2 (1)	14 (2)
Sinusitis	8 (2)	4 (2)	3 (2)	15 (2)

Source: (b) (4).
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section 1 - Dataset: Adverse Events; Filter: TRTEM1FL = 'Y'.
BID = twice a day; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; ELA = elagolix; TEAE = treatment-emergent adverse event

Th events above were reviewed and those occurring ≥5% and greater than placebo will be included in labeling.

Laboratory Findings

Liver Assessment Tests

No subjects met the definition for Hy's law for potential liver injury and no concerning safety signals or trends in liver function were identified. There were no elevations in total bilirubin outside the upper limit of normal on treatment.

In the placebo-controlled Phase 3 trials (Studies 815 and 817), no placebo subjects had elevations in AST, ALT, or total bilirubin levels. A total of 7 subjects had AST elevations >3x ULN in placebo-controlled phase: five subjects out of 379 (1.3%) in Ela + E2/NETA group (up to 6x ULN) and two subjects in Ela group (up to 4X ULN). Two subjects had AST elevations in the extension phase at Month 1 (5x ULN) and Month 2 (7X ULN), respectively. In the latter subject, AST declined but remained elevated at 132 U/L in the extension follow-up period. All subjects had normal baseline value.

In the placebo-controlled phase, four subjects out of 379 (1.1%) in Ela + E2/NETA group had an ALT >3x ULN range (8x ULN). Four subjects in the Ela group during the placebo-controlled phase had ALT elevation (up to 9x ULN); one subject receiving Ela in the extension phase had also ALT elevation (11x ULN). In all but one subject these abnormal ALT returned to normal range. Subject (b) (6) (who received ELA alone and was withdrawn at Month 2 of the placebo-controlled phase (peak ALT 423) had her last recorded ALT at 80; it is not known whether her ALT returned to normal level. One additional subject in Phase 2 (Study M12-663) had an ALT elevation >3x ULN. There were five subjects with both AST and ALT elevations.

One subject in the Ela + E2/NETA group in the placebo-controlled phase had alkaline phosphatase elevation 3x ULN at Month 4 (658 IU/L).

Serum Lipids

Ela + E2/NETA and Ela 300 mg BID led to increases in total cholesterol, LDL, triglycerides (TG) and apolipoprotein B compared to placebo. Compared to the Ela alone group, these increases were numerically less prominent in the Ela + E2/NETA group at Month 6. The increases in serum lipid values occurred within 3 months of treatment initiation and remained stable during treatment with levels generally returned to normal 3 months after drug cessation. Shift tables show one subject in each active cohort in the placebo-controlled phase had a shift in LDL from Grade 0 to Grade 3 (≥400-500 mg/dl). The following outliers in lipid changes are also notable:

- One subject ((b) (6)), previously treated with for hypertriglyceridemia, in Ela/Ela group extension study had a shift in TG from Grade 1 to 4 (peak 1224 mg/dL). Although some improvement in TG levels in this patient was seen upon

resumption of lipid-lowering medication (down to 299 mg/dL), her last known level was 502 mg/dL; it is unknown whether her treatment for hypertriglyceridemia required further adjustment.

- One subject in Phase 2 (Study M12-663, Subject (b) (6)) developed pancreatitis after receiving elagolix 600 mg QD. She is a 35 year-old black female (BF) who presented to the emergency room on Day 73 with complaints of intractable nausea, vomiting, diarrhea, and abdominal pain for one week. Peak lipase was 172 (normal range 6-51 U/L) and TG were 190 mg/dL on Day 61. The event lasted 4 days. Study drug was interrupted but resumed. The etiology was unknown but relationship with elagolix cannot be definitely ruled out.

Small mean increases in HDL were seen following 6 months of treatment compared to baseline in the placebo-controlled phase. Increases ranged from 0.2 mg/dl to 1.9 mg/dl in Study 815 and Study 817, respectively for ELA + E2/NETA, compared to 0.9 mg/dl in both studies for placebo. Increases in ELA alone ranged from 2.9 mg/dl in Study 815 and 0.8 mg/dl in Study 817. In these studies, Shifts from Grade 0 to 1 (defined as HDL <40) occurred in 4.7% and 7.3% of subjects in ELA+E2/NETA, respectively, compared to 8.9% and 8.1% in placebo, respectively, (and 7.6% and 4.0%, respectively, in ELA) following 6 months of treatment. No trends were seen between studies. No conclusion can be made regarding beneficial effects of study drug on HDL across both studies with study drug.

Elagolix and estrogen therapy are independently known to have determinantal effect on lipids. While it appears that the combination of elagolix and E2/NETA may have partially mitigated this effect (compared to elagolix alone), mean elevations were seen compared to placebo. Labeling will reflect the mean increases in lipid parameters (total cholesterol, LDL, trigylcerides, apolipoprotein) compared to placebo.

Hemoglobin

Hematology assessments were conducted at screening and monthly in the placebo-controlled phase. The mean hemoglobin at baseline was 11.1, 10.7, and 11.0 g/dL, and the mean percent change at Month 6 was 13%, 18% and 3.3%, respectively for Ela + E2/NETA, Ela alone and placebo groups. Anemia led to study drug discontinuation in 1 subject (0.3%) in Ela + E2/NETA and 2 subjects (1%) in placebo. There were no anemia AEs in the Ela alone group. Improvement in anemia (defined as an increase in hemoglobin of 2 g/dL by the end of treatment in subjects with a baseline hemoglobin ≤10.5 g/dL) was identified as a benefit of treatment and as a ranked effectiveness endpoint – refer to section Efficacy Results – Ranked Secondary Endpoints in the Efficacy discussion.

Vital Signs

No significant changes in systolic (SBP) or diastolic blood pressure (DBP) were anticipated following treatment with elagolix alone; however, the addition of estrogen

could lead to elevations in blood pressure. Temperature, systolic and diastolic blood pressures (seated single readings), pulse and heart rate were obtained at monthly visits prior to scheduled blood collections.

Mean change in SBP (placebo subtracted) peaked at Month 5 (5.1 mmHg, 95% CI 2.68, 7.59) in the placebo-controlled phase following treatment with Ela + E2/NETA compared to 4.3 mmHg for Ela alone (95% CI 1.43, 7.13). Mean changes were lower in the PTFU period and returned to baseline or below baseline by PTFU Month 12. Peak diastolic mean changes (placebo subtracted) occurred at Month 4 (2.1 mmHg, 95% CI 0.43, 3.84). DBP values returned to baseline or below baseline by PTFU Month 1. Mean SBP and DBP changes were statistically different from placebo.

Outliers (and selected patient summaries) during the placebo-controlled phase as follows. See Table 40 for full listing:

- SBP ≥160 mmHg: There were 20 subjects (5.1%) in the Ela + E2/NETA (max reading 204 mmHg, see narrative below) with SBP ≥160 compared to seven subjects (3.6%) in Ela and four subjects (2.0%) in placebo. The greatest number of elevations occurred from Month 1 to Month 4. The difference between Ela + E2/NETA and placebo groups over the study visits ranged from 0-1.8%.
  - 42 year-old BF (# (b) (6)) without history of HTN had BP of 204/112 mmHg at Month 3 (Day 71) (baseline 136/70 mmHg), coded as hypertension AE. Antihypertensive medication was added during the study. No narrative was submitted. No symptoms reported.
- DBP ≥100 mmHg: There were 43 subjects (10.9%) in the Ela + E2/NETA (max reading 128 mmHg) with DBP ≥100 compared to 16 (8%) in Ela and 12 (6.1%) in placebo. The greatest number of elevations occurred between Months 2 and 4.
  - 43 year-old black female (# (b) (6)) with history of HTN BP of 180/128 at Month 1 (baseline 128/84) and recorded as an AE. Narrative was not submitted. No symptoms reported.
- Increase in SBP by 20mmHg and >140 mmHg: There was an overall, 1% increase in rates in Ela + E2/NETA compared to placebo at Months 3 and 4. (Source: advs.xpt, PIVEXT = Pivotal, Aphase = treatment, CRIT6= ≥140 and ≥20 mmHg).
- Increase in DBP by 15 mmHg (and >90 mmHg): Few outliers in elagolix arms, none in placebo group. (Source advs.xpt, PIVEXT = Pivotal, Aphase = treatment, CRIT6= >90 and ≥15 mmHg).

There were 15 subjects (3.8%) with treatment-emergent HTN AEs who received ELA + E2/NETA, which was similar to the number in the placebo group, 6 subjects (3.1%). There were 5 (2.5%) subjects in the ELA alone group

Table 40: Listing of Treatment-Emergent Hypertension AEs – Placebo-controlled Phase (Exposure to ELA + E2/NETA)

Subject#	Day of onset	Summary of Clinical Data
(b) (6) severe	36, 71	42 BF without prior history of HTN, smoker, with BP 181/101 on Day 36 and 204/112 on Day 71 of PC phase (baseline 136/70). Next recorded reading 130/80 on Day 86. Chest pain and chest discomfort was recorded on Day 70 and 72. ECG was negative. She completed the PC phase and entered the EXT phase. No mention of either event in narrative.
(b) (6) severe	130	39 BF without prior history of HTN, with BP 158/116 on Day 130, 128/100 on Day 144, and 153/117 on day 157 (baseline 115/76). Concomitant medication started included lisinopril, HCTZ and hydralazine. She completed PC and EXT phases. No narrative was submitted.
(b) (6) severe	55	48 BF with history of HTN on amlodipine and valsartan, BP of 186/100 on Day 55, and 142/100 on Day 169 (baseline 140/92). She completed the PC and EXT phases. No narrative submitted.
(b) (6)	84	43 BF with history of HTN and congestive heart failure who was taking HCTZ, losartan, metoprolol, who had BPs of 160/110 on Day 84, 158/102 on Day 112, 142/102 on Day 118, and 160/100 on Days 175/176 (baseline 128/84). . She completed PC and EXT phases. No narrative for HTN submitted.
(b) (6)	168	42 BF with history of HTN on lisinopril, BP 158/104 on Day 168 (Month 6) (baseline 134/86). She completed the PC phase and was lost to follow in PTFU.
(b) (6)	56	46 BF with history of "elevated blood pressure" taking chlorthalidone who had BP of 145/94 on Day 56 (baseline 128/89) Completed PC and EXT phases. (Subject reportedly received the wrong treatment or incorrect dose, no additional information recorded in protocol deviation dataset)
(b) (6)	119	44 WF with history of HTN, hypertriglyceridemia, taking amlopidine, carvedilol, lisinopril, ASA, nitroglycerin with BP 150/92 on Day 57, 143/74 in PTFU (Day 323) (baseline 136/87). She completed the PC and PTFU phases.
(b) (6)	113	47 BF with history of HTN (on amlopidine) and high cholesterol, BP was 166/91 on Day 113 (baseline 140/84). She completed PC and EXT phases.
(b) (6)	28	32 BF with history of high blood pressure on with BP 140/105 on Day 28. Her labetolol dose was doubled. She completed the PC phase and PTFU.
(b) (6)	84	48 BF with history of HTN (amlodipine, lisinopril and hydrochlorthiazide [HCTZ]) with BP of 164/100 on Day 84, 163/107 on Day 115, and 181/122 on Day 114. (Baseline 136/88) She completed PC and EXT phases.
(b) (6)	141 113	48 BF with history of HTN on clonidine, HCTZ, BP 176/110 on Day 113, and 168/90 on Day 141, BP 140/90 at follow up visit (Baseline 148/82). She completed the PC phase, entered EXT but discontinued due to "other" reason. No narrative submitted.
(b) (6)	35	45 BF with HTN, migraine and anemia, alcohol user taking amlopidine, and atorvastatin. BP 163/122 on Day 35. Recurrence of reading on Day 85 (post treatment day 28. She refused to go to the ER and was evaluated by a personal physician drug, Study drug was discontinued. Narrative was submitted.
(b) (6)	64	41 BF with history of HTN and ventricular arrhythmia on Prinivil, HCTZ, Toprol XL, spironolactone, with 144/82 on Day 64 (baseline 129/92). She completed DB and EXT phases and sought other nonsurgerical treatment during PTFU (Subject enrolled despite PC phase above threshold for entry)
(b) (6)	28	48 WF history of HTN on HCTZ, with a BP of 150/102 at Day 28 (baseline 130/88). She completed PC and EXT phases.
(b) (6)	73	44 BF with history of HTN, on lisinopril, who had BP with BP 157/114 on Day 87 and 155/116 on Day 115. (BP of 158/103 in screening period, qualifying

		baseline of 132/88). She completed PC and EXT phases. No narrative was submitted.

Source: Compilied by reviewer from CSRs M12-815, M12-817 and submitted datasets (vs.xpt, ds.xpt, cm.xpt, mh.xpt.)
PC = placebo-controlled phase; EXT = extension phase

In the extension study, there were similar percentages of subjects with 1) SBP ≥160 and ≥20 mmHg increase and 2) SBP ≥160 mmHg in both elagolix-treated groups (12-month duration) approximately 17% and 7%, respectively. Percentage of subjects with DBP elevations (>90mmHg and ≥15 mmHg increase, and ≥100 mmHg) was numerically greater in the Ela/Ela group compared to Ela+E2+NETA/Ela+E2+NETA group. The Applicant also identified subjects who had potentially clinically significant vital changes over three consecutive visits. There were six subjects in the Ela + E2+NETA/Ela + E2+NETA group who met this criterion with two subjects having hypertension AEs.

- # (b) (6): 48 year-old with SBP of 178 mmHg on Day 110 of extension study (Baseline SBP 130 mmHg at screening for the placebo-controlled phase)
- # (b) (6): 44 year-old with DBP of 122 Day 82 of extension study (Baseline 107 at screening for the placebo-controlled phase; multiple repeats of DBP showing 90, 97, 103, and 88 mmHg when she qualified for the study)

Three subjects in the Ela/Ela group met the potentially clinically significant vital sign changes over three consecutive visits criteria.

Elevations in blood pressure are included in both Section 5 (Warnings and Precautions) and Section 6 (Adverse Reactions).

No significant changes were seen in pulse rate or weight, although a trend in decreased weight was seen over the treatment period.

ECGs

Resting 12-lead ECGs were obtained at screening and Month 6 (or premature discontinuation) and read by investigator (or cardiologist, if necessary). Subjects were excluded for any clinically significant abnormal ECG or ECG with corrected QT interval >450 msec at Screening. Abnormal ECGs were seen in in 5 subjects in Ela + E2/NETA group (outlined in Table 41 below), two subjects in Ela alone and one subject in placebo in Studies 815 and 817. One subject ((b) (6)) in Ela + E2/NETA group was evaluated for abnormal T waves on post-treatment Day 26; however, because the abnormal findings were also noted to be present at baseline, the findings were not considered to be related to the study drug. Another subject ((b) (6)) on Ela + E2/NETA had chest pain and “cardiac flutter” on Day 189. In response to our Information Request, her narrative submitted (March 30, 2020 Response to Information Request), showed that the decreased R wave was seen on ECG on post-treatment Day 86. Upon referral for cardiology follow-up, her evaluation showed no evidence of cardiac injury and she was not given any treatment.

Table 41: Abnormal ECGs in Ela + E2/NETA Group, Phase 3 Placebo-Controlled Trials

Subject Number	Age/Race	Day	AE	Comment
(b) (6)	43 year-old WF	170	"abnormal ECG" "cannot rule out MI, probably old"	Referred to cardiology, who determined ECG was unremarkable, in sinus rhythm
(b) (6)	43 year-old BF	178	Abnormal T waves	Referred to cardiology
(b) (6)	42 year-old BF	174	Sinus bradycardia	Referred to cardiology; ECHO with mild left atrial/ right atrial enlargement, mild LVH, trivial pericardial effusion Stress test: no evidence of ischemia
(b) (6)	40 year-old BF w/ iron def anemia	127 PT 62	Abnormal T waves	Extensive T waves changes suggestive of MI (described as worsening T-wave abnormality) and recorded as "clinically significant. Although the study report states the subject had the same findings prior to study drug administration Subject was evaluated by family practitioner, who ordered blood testing, no report provided. PTFU Day 62 laboratory data show CK 189 (normal range, 0-190 U/L, baseline value 164). No further action was taken.
(b) (6)	45 year-old BF w/iron deficiency	183	QRS Axis Abnormal (No R wave in V3 compared with Baseline)	Evaluated by family practitioner No diagnostic or therapeutic procedures were performed. Follow up on Day 305 (PTFU 122); no diagnostics reported. No further action. Ongoing at end of study.
		189 PT 6	Chest discomfort, cardiac flutter	Events occurred from Day 189 through Day 233. Study drug was not discontinued, and she completed PTFU. Cardiology evaluation did not reveal evidence of myocardial injury.

Source: Narratives, CSR M12-815 and M12-817
AE = adverse event; BF = black female; ECHO = echocardiogram; LVH = left ventricular hypertrophy; MI = myocardial infarction; PTFU = post-treatment follow-up; PT= post treatment; WF = white female, BF = black female

After review, we conclude that EKG changes do not need to be included in labeling.

QT

A thorough QT study (M12-661) was conducted under the endometriosis clinical program in support of NDA 210450 (Orilissa) and evaluated single dose of elagolix 300 mg and 1200 mg. No QT signal was suggested. The additive effect of E2 and NETA on the QTc interval has not been studied (See Clinical Pharmacology section), but is not required given the decades of substantial information on cardiovascular effects of hormone therapy.

Immunogenicity

Two subjects in Ela + E2/NETA treatment group in the placebo-controlled phase had a reported allergic reaction:

- M12817-(b) (6): A 47 year-old BF who, on day 48, had drug hypersensitivity, localized urticarial rash on the face which did not progress. The investigator attributed the effect to codeine taken 1 day prior for arthralgia.
- M12817-(b) (6): A 41 year-old BF who experienced moderate drug hypersensitivity on day 36, reported as allergic reaction to prinivil and further described as bilateral lip swelling.

These events had reasonable alternative explanations and do not appear to be related to Ela + E2/NETA.

One additional occurrence in placebo-controlled phase involved subject #(b) (6), a 34 year-old BF on Ela 300 mg BID. On Day 15, she reported symptoms of headache, nausea, vomiting, and/or diarrhea. Additionally, she experienced swelling of the eyelids lips, neck, arms and hands and skin irritation with itching. She was treated with diphenhydramine, ibuprofen, calcium carbonate, and bismuth subsalicylate. Study drug was permanently discontinued on Day 20. On Day 21, the subject was evaluated in the emergency room. On that same day, prednisone, famotidine, and cetirizine were added to her treatment.

8.2.5. Analysis of Submission-Specific Safety Issues

Safety issues of special interest included bone safety, endometrial safety, cardiovascular safety, lipid effects, and alopecia.

8.2.5.1. Bone Safety

Changes in BMD at the lumbar spine, total hip and femoral neck were assessed by DXA as these are the standard sites used to monitor for bone loss. In the placebo-controlled Phase 3 studies, DXA scans were performed at baseline and end of treatment Month 6 using Hologic or GE Lunar machines. No DXA scan was obtained if early termination occurred before Month 3 unless a bone-related AE was reported. Subjects with bone loss of ≥8% at any anatomic site were not eligible for the extension study; they were required to enter the PTFU period and have DXA scans at PTFU Month 6 and PTFU Month 12. In the extension study, DXA scans were performed at the end of the 6 Month extension (treatment Month 12). An additional scan was performed at extension Month 3, if ≥5% bone loss was observed at spine or total hip at the end of pivotal phase. Additional DXA scans were obtained at PTFU Month 6 and PTFU Month 12 to monitor for recovery of bone loss. A central imaging center was responsible for quality control of DXA scanners and interpretation of BMD data. Subjects were encouraged to have all their scans on the same DXA machine made by the same manufacturer each time.

Comparing BMD at Month 6 to baseline, mean bone loss occurred and was less with Ela + E2/NETA than with Ela alone, showing that hormonal add-back therapy attenuates BMD loss. However, approximately 30% had no change or gained bone during treatment. Categorical BMD decreases at the lumbar spine in placebo-controlled phase are shown in below in Table 42.

Table 42. Number and Percentage of Subjects with Lumbar Spine BMD Decreases from Baseline to Month 6: Placebo-Controlled Phase 3 Analysis Set

	Ela 300 mg BID + E2/NETA	Ela 300 mg alone	Placebo
Decrease[a]	N = 305	N = 139	N = 150
> 3%	56 (18%)	67 (48%)	15 (10%)
> 5%	17 (6%)	26 (19%)	3 (2%)
> 8%	0	4 (3%)	0

Source: Table 27, Summary of Clinical Safety, p 104
a = categories are not mutually exclusive.
BID = twice a day; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; ELA = elagolix;

Table 43 Placebo-subtracted mean changes in BMD from baseline to Month 6 from Studies 815 and 817 are shown in Table 43 for three anatomical sites. At Month 6, the change in BMD in the Ela + E2/NETA was -0.55% at the lumbar spine, 0.01% at the total hip, and -0.34% at femoral neck.

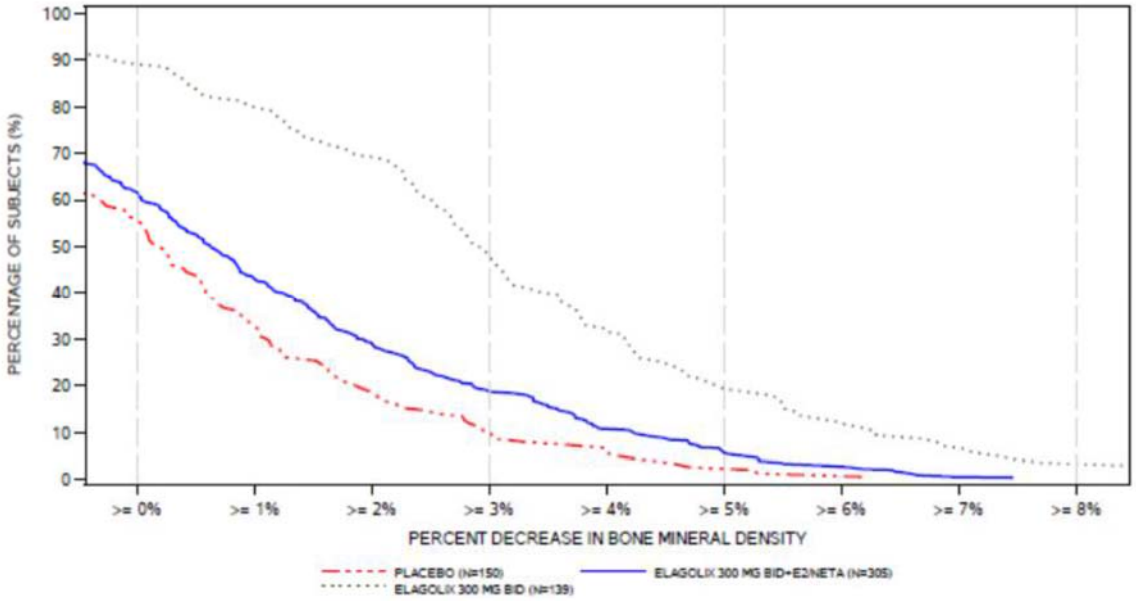
Table 43: LS Mean Difference % Change at Month 6 (Placebo-Controlled Phase) IQR Corrected (Placebo-Subtracted) >3% at the lumbar spine, >4% at the total hip, and >5% at the femoral neck

	Lumbar Spine			Total Hip			Femoral Neck		
Subgroup	N	LSMD	95% CI	N	LSMD	95% CI	N	LSMD	95% CI
Ela 300 BID	139	-2.80	(-3.39 -2.22)*	140	-1.79	(-2.24, -1.35)*	140	-1.61	(-2.40, -0.82)*
Ela + E2/NETA	305	-0.55	(-1.04, -0.06)*	304	0.01	(-0.38, 0.38)	304	-0.34	(-1.01, 0.330)

Source: Table 5.1, ISS section 1.2.1.1, p 1615/2176
*p<0.05
BID = twice a day; CI = confidence interval; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; ELA = elagolix;
IQR = interquartile range; LSMD = least square mean difference

Categorical assessment of bone loss was performed for the lumbar spine, total hip and femoral neck. A graphical presentation of the differences in the degree of bone loss between the Ela + E2/NETA, Ela alone and placebo groups at the lumbar spine is shown in Figure 18 below. Separation between the Ela + E2/NETA and placebo remains.

Figure 18: Cumulative Distribution for Percent Change from Baseline in Lumbar Spine BMD at Month 6 (Placebo-Controlled Phase 3 Analysis Set)



Source: Summary of Clinical Safety, Figure 9, p. 102
BID = twice a day; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg

The Applicant provides a discussion of subjects with ≥8% bone loss at any site and attributes this substantial degree of bone loss to potential confounding factors (alcohol use, tobacco use, concomitant medicatons, etc.). We evaluated the Applicant's discussion and do not agree that these factors could result in the degree of BMD loss seen (i.e., alcohol use was <2 drinks/day, nonsmokers or <0.5 pack per day). At the lumbar spine, no subjects in the Ela + E2/NETA arm had ≥8% bone loss compared to 4 subjects (2%) in the Ela alone arm. At the femoral neck, five subjects (1.6%) receiving Ela + E2/NETA had ≥8% bone loss compared to two subjects (1.4%) in the Ela arm and one subject (0.7%) in the placebo arm. At the total hip, no subjects in the Ela + E2/NETA arm had ≥8% bone loss compared to 1 subject (0.7%) in the Ela alone arm.

The proportion of subjects with bone loss ≥8% was greater in the Ela alone arm compared to Ela + E2/NETA and supports the addition of E2/NETA to partially attenuate bone loss. Additional risk factors for this degree of bone loss (other than elagolix exposure) could not be identified in these cases.

Following 12 months of continuous treatment with Ela + E2/NETA (long term extension data) and before entering PTFU, continued bone loss (compared to baseline) of 1.5%, 0.7%, and 0.8% at the lumbar spine, total hip and femoral neck, respectively, was seen compared with declines of 4.8%, 3.3% and 3.0% following Ela alone. Table 44 shows the mean percentage change from baseline in the lumbar spine BMD for the Ela +

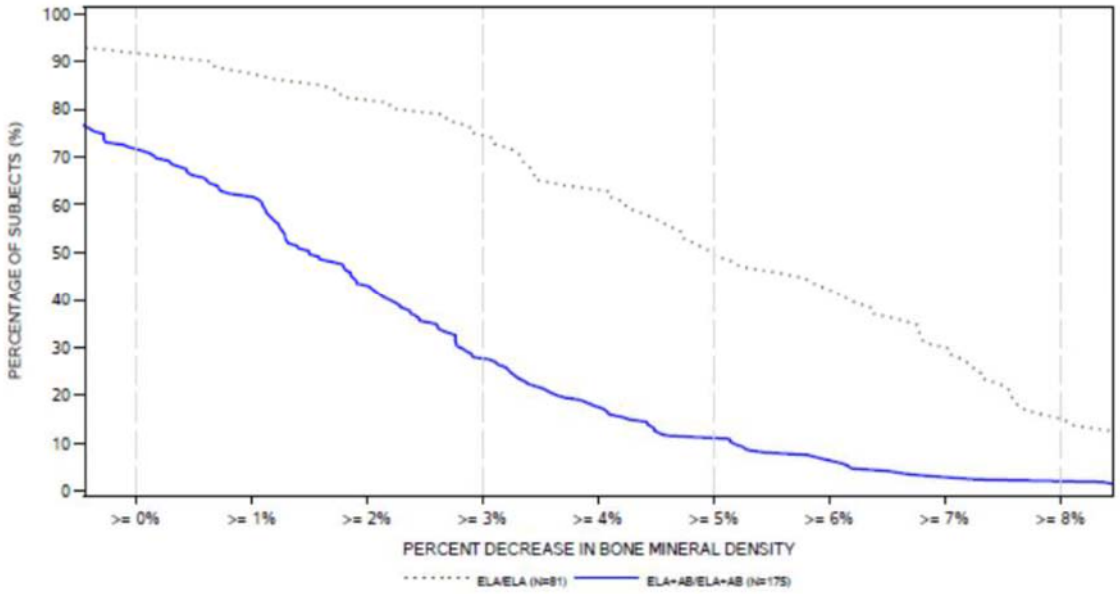
E2/NETA group and the placebo group at Months 6 in Studies 815 and 817 and at Month 23 in Study 816.

Table 44: Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD in Women with Fibroids at Month 6 in Studies 815 and 816 and Month 12 in Study 816

	Studies 815 and 817 Treatment Month 6		Study 816 Treatment Month 12
	Placebo	**Ela + E2/NETA**	**Ela + E2/NETA**
Number of Subjects	150	305	175
Percent Change from Baseline	-0.1	-0.7	-1.5
Treatment Difference, % (95% CI)		-0.6 (-1.0, -0.1)	
CI: Confidence interval			

The cumulative distribution curve for percent change from baseline in lumbar spine following 12 months of active therapy (Ela + E2/NETA versus Ela alone) (Figure 19) shows attenuation of bone loss with Ela + E2/NETA compared to Ela alone, but 30% of subjects still experienced substantial bone loss (30% with ≥3% loss, 10% with ≥5% loss and 5% with ≥8% loss). Because no subjects received placebo in the extension phase, a direct comparison between Ela + E2/NETA with placebo for 12 months is not feasible.

Figure 19: Cumulative Distribution Function for Percent Change From Baseline in Lumbar Spine Following 12 Months of Active Therapy



Source: Figure 10, Summary of Clinical Safety, p. 106/158.
BID = twice a day; E2/NETA = estradiol I mg/norethindrone acetate 0.5 mg; ELA = elagolix

Phase 2 data that included the to-be-marketed dose of Ela + E2/NETA arm showed similar trends in BMD.

Recovery of Bone Loss

After the treatment period in each study, subjects were monitored for recovery of bone loss for up to 12 months. In Study 816, following 12 months of treatment with Ela + E2/NETA, at post-treatment month 6, 30% of subjects did not recover any bone losses or had further decline at lumbar spine (LS) and total hip (TH), and 40% did not recover losses or had further decline at femoral neck (FN). After 12 months off treatment, 25-30% did not recover any bone losses at LS and TH and 40% did not recover at the FN. Notably, these rates of non-recovery were generally higher in the long-term Ela +E2/NETA group across bone sites (with the exception of PTFU Month 6 data at TH) when compared to long-term Ela group.

For the remaining subjects, it was reassuring that approximately one-third of total subjects had full recovery of bone losses and one-third of total subjects had partial recovery. The time to full bone loss recovery has not been determined but it is clear that monitoring is needed to determine which patients do not achieve adequate recovery. This information will be included in labeling.

Three subjects who had substantial bone loss from Baseline to Final On-Treatment DXA (defined in this analysis as >3% at the lumbar spine, >4% at the total hip, and >5% at the femoral neck) continued to lose a similar degree of bone mass during the PTFU

period at the same anatomic site affected during treatment; one of these three received 12 months of Ela + E2/NETA treatment and the other two received 12 months of Ela alone. Therefore, the complete data set was used to report BMD changes on treatment and post-treatment in labeling. Review of the subject narratives for the 3 subjects who met the definitions of bone loss for this analysis suggests that each subject had possible confounding factors that could have contributed to bone loss.

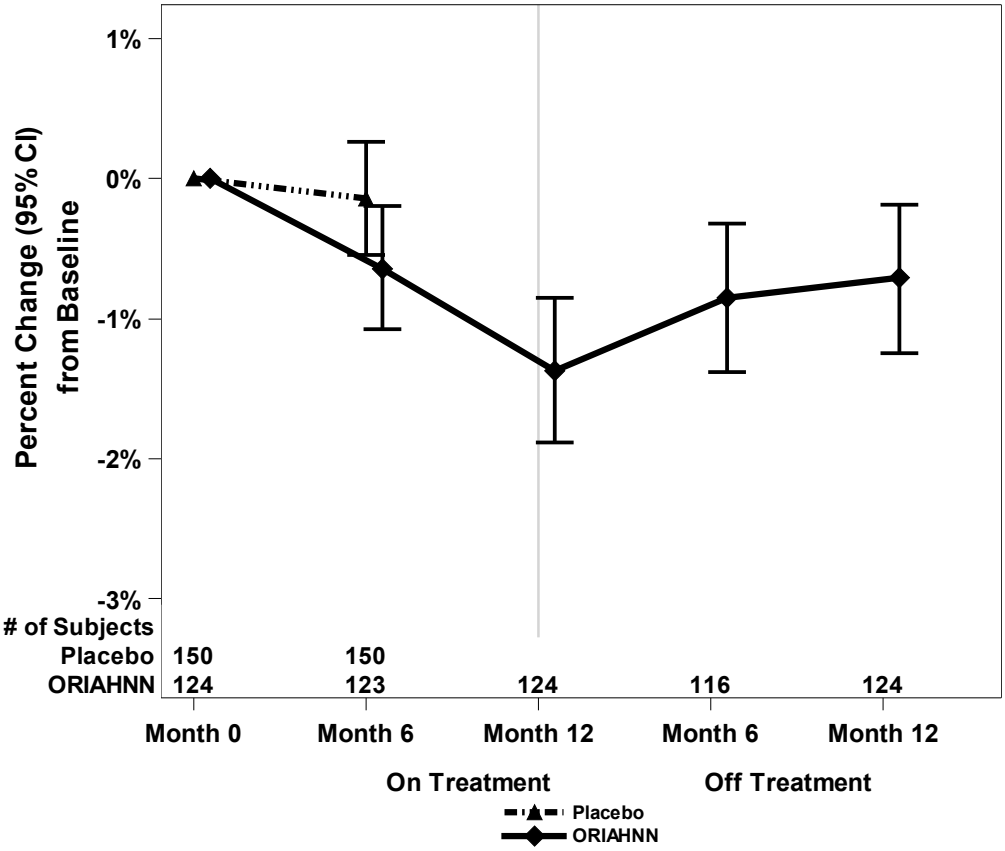
Ela + E2/NETA group:

- Subject (b) (6): 49 year-old white female with BMI of 32. She had bone loss of 5.5% at lumbar spine at the end of treatment. At PTFU Month 6, bone loss from baseline was 8.5%. No data are available at PTFU Month 12. Other history was positive for tobacco use (0.2 ppd), alcohol use (<2 drinks per day), return to menses within 4 months (i.e., amenorrhea suggesting hypoestrogenemia for 4/6 months of the PTFU period over which her BMD was monitored) and nasal fluticasone use.

Ela/Ela group:

- Subject (b) (6): 42 year-old BF with tobacco and alcohol use (<2 drinks per day), taking esomeprazole throughout the study and paroxetine from the end of the placebo-controlled trial through PTFU Day 77. She had bone loss of 7.3% at the lumbar spine at the end of treatment. At PTFU Month 6 and PTFU Month 12, bone losses from baseline at the lumbar spine were 3.5% and 10%, respectively.
- Subject (b) (6): 43 year-old WF with BMI of 34, alcohol use, daily nasal steroids throughout the study, intramuscular corticosteroid injection and prednisone 10 mg use x 8 days during the treatment phase. She also had a history of hypocalcemia. She had bone loss of 6.9% at the total hip at the end of treatment. At PTFU Month 6 and PTFU Month 12, bone loss from baseline at the TH was 7.1% and 15%, respectively. At the femoral neck, bone loss was 4%, 10%, and 17% at end of treatment, PTFU Month 6 and PTFU Month 12, respectively.

Figure 20 Mean Percent Change From Baseline in Lumbar Spine BMD in Women Who Received 12 Months of ORIAHNN (On-Treatment) and 12 Month of Follow Up (Off Treatment)



There was a subset of subjects (n=23) who did not lose bone during the 6 or 12 month treatment period but then had a decline in BMD during the PTFU period of >3% at the lumbar spine, >4% at the total hip, and >5% at the femoral neck. In response to an Information Request, the Applicant provided the following additional information (February 14, 2020). Overall, these subjects tended to be older and have higher BMI than the mean for the study population as a whole. The results are inconsistent across bone sites, but the distribution shows a trend in more subjects with delayed bone loss following 6- and 12-month treatment with Ela + E2/NETA overall (Table 45). There were no trends seen in risk factors although subjects in the Ela + E2/NETA group did have higher BMIs. In contrast to the Applicants perspective, most subjects (14/23) had no identifiable risk factors for bone loss. Four subjects in the continuous Ela + E2/NETA arm, two in the continuous Ela arm, and 1 of each of the two other arms used medications during the PTFU period that might have contributed to bone loss. One subject treated with 12 months of Ela + E2/NETA and one treated with 12 months of Ela each had amenorrhea during the PTFU period. There does not appear to be biologic plausibility for delayed bone loss after Ela + E2/NETA discontinuation based on the

known mechanism of action and the pharmacokinetics of elagolix. Whether withdrawal of E2/NETA and/or entering perimenopause contributed to bone loss is unknown.

Table 45: Subjects With Delayed Bone Loss in PTFU Phase (>3% at Lumbar Spine, >4% at Total Hip, and >5% at Femoral Neck).

Site of Bone Loss	PBO/ELA N=59	PBO/ELA+E2/NETA N=58	ELA/ELA N=98	ELA+E2/NETA:ELA+E2/NETA N=218
Any site	2 (3%)	4 (7%)	4 (4%)	13 (6%)
Lumbar spine	1 (2%)	4 (7%)	0	4 (2%)
Total hip	1 (2%)	0	2 (2%)	2 (1%)
Femoral neck	0	0	3 (3%)	7 (3%)

Source: Response to Information Request, dated February 14, 2020
BID = twice a day; E2/NETA = estradiol I mg/norethindrone acetate 0.5 mg; ELA = elagolix; PBO = placebo; PTFU = post-treatment follow-up

Fracture Adverse Events

Overall, in the Phase 3 program, there were 9 bone fractures in 9 subjects (including a single tibular/fibular fracture reported separately in the dataset), none of whom had bone loss ≥8% while on treatment. The ≥8% cutoff is an arbitrary threshold historically used to define excessive bone loss in postmenopausal women and may be an inappropriate threshold for pre-menopausal women who are not expected to have BMD losses. Seven subjects received Ela + E2/NETA (four in the placebo-controlled phase, three in the extension study), one received Ela in the placebo-controlled phase (wrist fracture, held up in self-defense), and one received placebo (foot fracture due to trauma).

Narratives for the seven subjects with fractures exposed to Ela + E2/NETA are provided below. All seven subjects had some decline in in BMD compared to the pretreatment baseline. Four of the seven subjects had events occurring in the post treatment follow-up phase. The fractures described for subject (b) (6) is consistent with a fragility fracture and is denoted with an asterisk below(*).

Subjects who received Ela + E2/NETA in the placebo-controlled trial only (did not enter extension study):

- Subject (b) (6)0: 42 year-old BF with Type II DM and vit D deficiency taking ergocalciferol, pantoprazole and using steroid intermittently, experienced left ankle malleolus and syndesmosis fracture after falling from standing height on Day 369 (post treatment day 172) in PTFU period of Study 815. Month 6 (on treatment) DXA scan showed BMD change from baseline of -3% at LS and FN and -7% at TH. PTFU M6 (off treatment), DXA scan showed continued loss at TH (-9%) but some recovery at FN (-2%). PTFU M12 DXA showed additional loss at TH (-10%) and FN (-5%) but recovery at LS (-1.3%).

- Subject (b) (6): 31 year-old BF with left hand MCP, nondisplaced finger fracture on Day 3 of Study 815. She remained in the study; her Month 6 DXA scan showed changes from baseline of -1.5% at LS, -0.2% at TH, -6% at FN.
- Subject (b) (6): 50 year-old WF who sustained a left tibula/fibula fracture following a bicycle crash on Day 454 in PTFU of Study 815 (post treatment day 275). Month 6 DXA scan showed BMD change from baseline of -2.2% at LS, 0.3 at TH, -0.8 at FN. PTFU Month 12 DXA scan showed BMD change from baseline of -8.9% at LS, -1.7% at TH, -3.8 at FN.

Subjects who received Ela + E2/NETA in the placebo-controlled trial and in the extension study:

- Subject (b) (6): 42 year-old BF with BMI of 39 had a left hand fracture after falling from a height of 2 steps) on Day 96 of Study 817. Month 6 DXA scan showed BMD change from baseline of -3.5% at LS, -2.2% at FN. She continued to receive Ela + E2/NETA in the extension Study 816.
- *Subject (b) (6): 49 year-old BF with distal radial fracture after a fall (tripped on curb), Day 459 PTFU of extension (post treatment Day 294). She had progressive declines in her femoral neck BMD with BMD changes from baseline of -2.4%, -2.8% and -4% at Month 6, PTFU Month 6 and PTFU Month 12, respectively, while she had gains in BMD at the LS and TH.
- Subject (b) (6): 51 year-old BF with right foot fracture (toe) on Day 125 in PTFU (post treatment Day 91). Ela + E2/NETA was discontinued on Day 30 due to SAE of pulmonary embolism (PE) in the extension phase. She was treated with rivaroxaban for the PE. Day 48 DXA scan showed BMD changes from baseline of 0, -1.0% and -2.4% at the LS, TH and FN, respectively. By PTFU Month 12, she had BMD changes from baseline of -2.9% and -2.4% at the LS and FN, respectively, while she had gained 0.6% at the TH.
- Subject (b) (6): 37 year-old BF with foot fracture on Day 216 in PTFU. During 6 months of Ela + E2/NETA treatment, bone losses of 2.9 to 4.1% were seen across bone sites. By the end of PTFU, BMD changes of 4.4% at LS, 3.8% at TH, and 3.6% at FN from baseline were reported. This subject was not included in the ISS fracture dataset.

In Phase 2, four fractures were reported, all occurring in M12-813. One occurred in Ela + E2/NETA group (narrative below); one following Ela alone, and two in the placebo group.

- Subject (b) (6): 42 year-old BF who received Ela + E2/NETA sustained a left index finger fracture on Day 244 (post treatment Day 62). Mechanism of injury was not provided. BMD at PTFU Month 6 showed BMD gains of 4.3% at LS, 1.4% at TH, and 3.1% at FN.

While the addition of add back therapy to elagolix 300 mg BID provided some attenuation of bone loss, this was not seen in all subjects. The magnitude of bone loss

after treatment durations greater than 12 months is unknown and could be clinically important even in younger patient populations who are not expected to lose bone. Ela + E2/NETA also appears to be associated with continued bone loss after drug cessation in some women. We considered all these factors in the risk-benefit assessment and determined that this information be prominently presented in labeling.

Duration of Therapy

The Applicant initially proposed a 4-year duration of use based on submitted modeling and available BMD information (see Clinical Pharmacology Section 6); however, clinical data are currently only available for 12 months of use. Using the model and BMD data to support the proposed duration of use is problematic because the correlation between BMD and fractures remains limited in this population.

For Oriahnn, a long term extension study, M16-283, a Phase 3b, randomized, placebo-controlled, 4-year clinical trial is in progress to evaluate the long term safety of elagolix with E2/NETA in premenopausal women 18 to 50 years of age with heavy menstrual bleeding associated with uterine fibroids.. The trial consists of a 12-month placebo controlled assessment of Ela + E2/NETA followed by a 36-month open label period. DXA scans will be collected at 6 months intervals through Month 48 and for 12 months post treatment. This study may support a longer duration of use contingent on the updated benefit-risk assessment . Until results from this trial are reviewed and continued efficacy is demonstrated, the duration of use should be limited to 24 months given the available information on bone loss and recovery.

8.2.5.2. Endometrial Safety

Endometrial safety was assessed using endometrial biopsy at screening and at Month 6. Transvaginal or transabdominal ultrasound was also conducted at screening, Day 1, Month 3, Month 6, PTFU Month 3, and PTFU Month 6 to measure endometrial thickness as early in the menstrual cycle as possible. A subset of subjects (including 37 subjects in Ela + E2/NETA group) also had MRI performed at screening or Day 1, Month 6 and PTFU Month 3.

None of the endometrial biopsies in elagolix-treated subjects showed endometrial pathology (hyperplasia or malignancy). Eleven subjects (2.8%) in the Ela + E2/NETA group had insufficient tissue for analysis compared to 4% in ELA and 3.6% in placebo group. One complex hyperplasia without atypia was seen in the placebo group. One subject with a documented polyp on MRI had a saline infusion sonohysteroscopy.

In Phase 2, one subject ((b) (6) in Study M12-813) in the elagolix 300 mg BID arm was diagnosed with endometrial adenocarcinoma on Day 202 (post-treatment day 30).

The Applicant proposed labeling based on ultrasound measurements, Ela + E2/NETA resulted in a decrease from baseline to Month 6 in mean endometrial thickness. This

language will be deleted from labeling because the ultrasound measurements were not standardized and neither Phase 3 trial was powered to assess the differences in endometrial safety.

8.2.5.3. Embolic and Thrombotic Events and Cardiovascular Safety

There were no major adverse thromboembolic or cardiovascularevents[5] in the 12 months following Ela + E2/NETA treatment or any arm in the Phase 3 studies.

In Studies 815 and 817, there were imbalances between Ela + E2/NETA versus Ela alone treatment arms in in the following SMQs: cardiac arrythmia (2.5% versus 1%), cardiomyopathy (2.5% versus 1.0%), ischemic heart disease (3.0% versus 0.5%), embolic/thrombotic 0.3% (one event) versus 0.

Table 46 (CV TEAEs in Studies 815 and 817) shows treatment emergent CV events in Phase 3 placebo-controlled trials. There was a numeric increase in hypertension (HTN) events in the Ela + E2/NETA group (4.1%) compared versus Ela alone (2.5%); however, this rate was similar to that seen in the PBO group (3.6%). There was one event of angina in the Ela + E2/NETA group.

Table 46: CV TEAEs in Phase 3 DB Phase

Event	ELA + E2/NETA N=395 n (%)	ELA N=199 n (%)	PBO N=196 n (%)
Hypertension	16 (4.1)	5 (2.5)	7 (3.6)
Palpitations	3 (0.8)	1 (0.5)	2 (1.0)
Tachycardia	2 (0.5)	0	0
Angina	1 (0.3)	0	0
Cardiac flutter	1 (0.3)	0	0
Hypotension	1 (0.3)	0	0
Sinus bradycardia	1 (0.3)	0	0
Thrombosis	1 (0.3)	0	0
PVD	0	0	1 (0.5)

Source: compiled by reviewer using adverse event dataset (ae.xpt)
CV = cardiovascular; DB = double blind; E2/NETA = estradiol l mg/norethindrone acetate 0.5 mg; ELA = elagolix; PBO = placebo; PVD = peripheral vascular disease; TEAE = treatment-emergent adverse event

In the extension phase, one event of pulmonary embolism occurred in a subject (who received Ela + E2/NETA both placebo-controlled and extension phase) versus none in Ela/Ela group. Additionally, two subjects receiving Ela + E2/NETA in both placebo-controlled and extension phase had angina (versus none in the Ela/Ela), 10 subjects had HTN versus (2 in Ela/Ela) and 1 subject with sinus tachycardia (versus 0 in Ela/Ela). One subject receiving Ela alone in both placebo-controlled and extension phase had hypotension.

[5] Defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Selected narratives for those treated with Ela +E2/NETA follow:

Thrombosis (1 case in placebo-controlled Phase, 1 case in extension)

M12817-(b) (6): 50 year-old BF diagnosed with left calf deep vein thrombosis on Day 30 of treatment with Ela +E2/NETA in Study 817. Her medical history is significant for anemia, HTN, obesity (Weight 111 kg) and vitamin D deficiency, and taking Zestoretic, iron, and other supplements. Ela + E2/NETA was withdrawn. Subject treated with oral apixaban.

M12815-(b) (6): 51 year-old BF with history of anemia and cardiac ablation for Wolff-Parkinson White-Syndrome who completed Ela + E2/NETA in placebo-controlled phase and entered extension Study 816. On Day 30 of extension study (total treatment duration of 226 days), she reported shortness of breath, chest discomfort, racing heart, and fatigue. Computed tomography scan on Day 34 confirmed subsegmental pulmonary embolism in the lower lobe of right lung with likely a similar small thrombus in the left lower lobe. Ela + E2/NETA was discontinued; She was treated with rivaroxaban as an out-patient. Lower extremity doppler was negative and the 2D echocardiogram was normal on Day 37. Twelve days after study drug was stopped, she presented to the emergency room with complaints of shortness of breath and chest pain. Her symptoms were determined to be consistent with the diagnosis of pulmonary embolism; no additional medication was given. Follow-up computed tomography scan on post-treatment Day 197 revealed no evidence of pulmonary embolism. She completed rivaroxaban on post treatment Day 249. The investigator did not consider this event to be an SAE but thought the event “reasonably possibly related to the study drug.” We feel that this event qualifies as an SAE (medically significant) and is reasonably likely related to the study drug.

In the Phase 2 M12-813, one subject in the elagolix 300 mg BID group in Cohort 1 had SAEs of deep vein thrombosis and pulmonary embolism. The subject was hospitalized, and the events were ongoing at the end of the study. The subject has a family history of factor V Leiden mutation, which may explain her hypercoagulability.

Angina (1 case in placebo-controlled Phase, 2 cases in extension)

M12817-(b) (6): 44 year-old BF presented with two-day history of angina pectoris reported as cardiac chest pain on Day 22 of treatment with Ela + E2/NETA. Her medical history is notable for Type II DM, hyperlipidemia (LDL 209), taking glipizide, metformin, and naproxen. Study drug was discontinued. The event was not deemed serious by investigator. An ECG was not obtained during the event, subject did not follow up with a cardiologist and no treatment was provided. A post treatment ECG was normal on Day 55, post treatment day 26.

M12817-(b) (6): 49 year-old BF with anemia and hyperlipidemia taking iron supplements and started on oral krill and salmon oil during the study (Day 33) received treatment with Ela + E2/NETA. On Day 176, abnormal ECG findings, sinus bradycardia and left atrial enlargement (deemed not clinically significant) were noted. During the extension study, an event of angina pectoris was reported as cardiac chest pain and characterized as intermittent and mild in severity. On Day 83 of the extension, the subject was evaluated by a cardiologist. A stress ECG was normal showing no evidence of exercise induced ischemia. A transthoracic echo showed normal chamber sizes and wall motion with tricuspid regurgitation. Study drug was not interrupted, and no further action was taken. The event was considered resolved on Day 106 of the extension.

M12817-(b) (6): 46 year-old female with history of anemia and HTN on long-acting nifedipine received treatment with Ela + E2/NETA. On Day 71 of the extension study, the subject experienced an event of angina pectoris, reported as cardiac chest pain of moderate severity, with a concurrent event of back pain reported as intermittent, acute bilateral thoracic back pain. The patient was seen in the emergency room the same day and had physical exam, urine testing and x-ray; she was treated with intravenous ketorolac, oxycocet, and paracetamol. Follow up with her internist on Day 80 reported a normal ECG and unspecified blood and urine testing. Study drug was not interrupted. The subject completed the extension and follow up phases.

In summary, none of the reports of “angina” appear to result in myocardial injury requiring cardiac follow-up or treatment. Increased thromboembolic risk is expected with the addition of estrogen (class labeling) and a box warning will be included in labeling.

8.2.5.4. Alopecia

An imbalance was noted in the number of cases of alopecia, hair thinning and hair loss in the Ela + E2/NETA group (3.5%) compared to Ela alone (1.5%) and placebo (1.0%) (see Table 47). Alopecia was the reason for study drug discontinuation in one-third of affected subjects. The onset of alopecia and related events ranged from Day 7 to Month 5 of treatment with most cases having continuing hair loss at the end of the study/treatment.

A Response to an Information Request (received March 13, 2020) showed 19 subjects in the placebo-controlled studies and 5 subjects in the extension study with treatment-emergent alopecia, hair thinning or hair loss (a total of 24 subjects, see Table 48). The incidence rates of alopecia events were similar between African American and non-African American subjects for the Ela + E2/NETA group; however, the difference from placebo was greater in the African American population. No potential etiology (e.g., androgenic alopecia) for alopecia could be discerned.

Table 47: Incidence of Alopecia in Placebo-Controlled Phase

	All Subjects, n (%)			African American Subjects, n (%)			Non-African American Subjects, n (%)		
Parameter	PBO N=196	ELA N=199	ELA+AB N=395	PBO N=133	ELA N=135	ELA+AB N=265	PBO N=63	ELA N=63	ELA+AB N=129
AE of alopecia	2 (1.0)	3 (1.5)	14 (3.5)	1 (0.8)	1(0.7)	9 (3.4)	1 (1.6)	2 (3.2)	4 (3.1)
Drug DC	0	1 (0.5)	4 (1.0)	0	1(0.7)	3 (1.1)	0	0	1 (0.8)

Source: compiled by reviewer using adverse event dataset (ae.xpt)
AE = adverse event; DC = discontinuation; E2/NETA = estradiol I mg/norethindrone acetate 0.5 mg; ELA = elagolix; PBO = placebo;

Table 48: Review of Alopecia Cases in Phase 3

Subject	Age/race	Treatment	Pattern/severity	Onset	Other	Resolution?
(b) (6)	42 BF	ELA+E2/NETA	None reported "mild"	D 63	Iron def anemia Hb 12.8 to 12.1 MCV 94	Day 347 (PT D 177)
	45 BF	ELA+E2/NETA	Right occipital localized bald spot "moderate"	D 20	Iron def anemia Hb 12.3 to 11.8 MCV 83 to 81	D/c'd study drug Resolution on Day 50 (PT D30)
	42 WF	ELA+E2/NETA	None reported "moderate"	D 7	Hypothyroidism Hb 12.1 to 13.5 MCV 87 to 85	Ongoing
	39 BF	ELA+E2/NETA	None reported "mild"	D 116	Anemia Hb 11.7 to 11.4 MCV 98 to 97	D108 of Extension
	44 BF	ELA+E2/NETA	None reported "mild"	D 152	Acne – onset D 112 Hb 11.7 to 13.5 MCV 94 to 94	Ongoing
	45 BF	ELA+E2/NETA	Patchy hair loss "mild"	D 70	Anemia Hb 10.3 to 9.5 MCV 84 to 79	Day 246 (PT D 133)
	34 BF	ELA+E2/NETA	None reported "mild"	D 26	Anemia, vitiligo Hb 10.6 to 11.8 MCV 71 to 72	Resolved on D 215 (PT D 42)
	35 BF	ELA+E2/NETA	None reported "Mild"	D15	Anemia Hb 9.1 to 10.5 MCV 69 to 70	Resolved on D 34
	46 BF	ELA+E2/NETA	None reported "mild"	D 19	Chronic anemia Hb 11.8 to 11.9 MCV 80 to 84	Resolved D120
	49 unk	ELA+E2/NETA	None reported "mild"	D 105	Hb 13.5 to 14.4 MCV 96 to 95	Resolved D 406 (PT D 241)
	31 BF	ELA+E2/NETA	None reported "mild"	D 31	Acne Hb 10.7 to 12.2 MCV 77 to 88	Ongoing
	44 WF	ELA+E2/NETA	None reported "mild"	D 148	Anemia Hb 9.7 to 13.2 MCV 69 to 83	Resolved D 193 (PT D 24)

Subject	Age/race	Treatment	Pattern/severity	Onset	Other	Resolution?
(b) (6)	43 WF	ELA+E2/NETA	None reported "mild"	D 55	Iron def anemia Hb 9.6 to 12.9 MCV 64 to 79	Resolved D 310 (PT D 144)
	50 WF	ELA+E2/NETA	None reported "moderate"	D 42	Anemia Hb 12 to 12 MCV 91 to 94	Ongoing
	41 B	PBO: ELA + E2/NETA	None reported "mild"	D 20 EXT	Anemia Hb 11.1 to 11.6 MCV 78 to 79	Resolved D 51
	43 WF	ELA	None reported "mild"	D 20	Anemia Hb 10 to 15.6 MCV 78 to 96	Ongoing
	40 BF	ELA	Top left side of head "severe"	D 99	Iron def anemia Hb 10.8 to 12.2 MCV 76 to 77	D/c'd study drug Resolved D 417 (PT D 251)
	36 WF	ELA	None reported "mild"	D 65	None known	Resolved D 333 (PT D 159)
	48 BF	ELA:ELA	None reported "mild"	D 8 EXT	Anemia Hb 11.2 to 12.8 MCV 78 to 78	Ongoing
	42 BF	PBO:ELA	None reported "mild"	D 45 EXT	DM type 2 Goiter Iron def anemia Hb 10.5 to 10.7 MCV 73 to 73	Resolved D 244 (PT D 75)
	41 BF	PBO:ELA	None reported "moderate"	D 76 EXT	Anemia Hb 9.3 to 13.9 MCV 81 to 90	Resolved D 125
	46 BF	PBO:ELA	None reported "moderate"	D 62 EXT	Iron def anemia DM type 2 Hb 12.9 to 15.9 MCV 84 to 86	Resolved D 130 (PT D 29)
	44 WF	PBO	None reported "Severe" D 109 "moderate" D 32	D 32	Anemia Hb 12.4 to 12.8 MCV 93 to 103	Ongoing
	50 BF	PBO	None reported "mild"	D 199	Anemia Hb 9.0 to 9.3 MCV 79 to 73	Resolved D 342 (PT D 173)

Source: Response to Information Request (SD 18) submitted March 13, 2020
BF = black female; E2/NETA = estradiol I mg/norethindrone acetate 0.5 mg; ELA = elagolix; Hb = hemoglobin; PBO = placebo; PTFU = post-treatment follow-up; MCV = mean corpuscular volume; WF = white female; DM = diabetes mellitus

Onset and Resolution

- For the 15 subjects who received Ela + E2/NETA, onset of alopecia ranged from Day 7 to Day 158 of treatment.
- For the seven subjects receiving elagolix alone, onset ranged from Day 20 to Day 176 of treatment.

- Two placebo subjects also reported alopecia. Event onset was Day 32 and Day 199, respectively.
- Seven of the 24 subjects (30%) reported that alopecia had not resolved at the end of the study. Notably, four of these seven received Ela + E2/NETA.

Severity

- In Ela +E2/NETA group, there three moderate cases and 11 mild cases. There were no severe cases in the Ela+ E2/NETA group. The Ela alone and placebo groups each had one severe case of alopecia.

Hair Loss Pattern

- The pattern of hair loss was reported in 3 subjects (1 right occipital, 1 left temporal, and 1 patchy), all from the Ela + E2/NETA arm in the placebo-controlled phase. No specific hair loss pattern was reported by the remaining 21 subjects.

It is unclear what the etiology of this alopecia represents. The Warnings and Precautions section of labeling will include alopecia, as this may be potentially irreversible. There does not seem to be an increased propensity for alopecia in the African American population but more data are needed to determine the type of alopecia identified, the duration of recovery and whether the alopecia is reversible. A Post-Marketing Requirement for a prospective study will be requested to characterize the incidence, pattern, and reversibility of alopecia.

8.2.5.5. Depression/Suicide

Use of elagolix is associated with new onset or worsening depression, including suicidal ideation and behavior. In the endometrial program conducted for Orilissa, subjects also had a higher incidence of depression and mood changes compared to placebo, and while on Orilissa, subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history (Orilissa labeling). One completed suicide occurred in clinical trials for Orilissa.

In the Phase 3 placebo-controlled trials (Studies 815 and 817) for Oriahnn, there were no events of suicide in subjects exposed to either elagolix or elagolix +E2/NETA. One suicide occurred in the screening period prior to receiving study drug. One placebo subject (# (b) (6)) reported suicidal ideation. Of the total of 11 subjects with treatment-emergent depression in Phase 3, 8 subjects (2%) were in the Ela +E2/NETA group compared to 2 subjects (1%) in the Ela alone group, and 1 (0.5%) in the placebo group.

The Applicant conducted an SMQ for depression and suicide/self-injury, including terms such as depressed mood, mood swings/mood altered and tearfulness. In Studies 815 and 817, the query identified 36 subjects (9.1%) in Ela + E2/NETA, 18 subjects (9%) on

Ela alone 7 (3.6%) in placebo group. AEs in the depression and suicide/self-injury SMQ led to study drug discontinuation for 0.8% of subjects in the Ela + E2/NETA group, 0.5% of subjects in the elagolix alone group, and 1.5% of subjects in the placebo group. The percentage of subjects with AEs in the depression and suicide/self-injury SMQ in the Phase 2 studies was lower than in the Phase 3 studies.

In the extension phase, depression, depressed mood, and/or tearfulness were reported for 5 subjects (2.3%) in the Ela + E2+NETA/Ela + E2+NETA group and 4 subjects (4.1%) in the Ela/Ela group. Mood change events (i.e., mood swings and mood altered) were reported for 6.4% of subjects in the Ela + E2+NETA/Ela + E2+NETA group and 8.2% of subjects in the Ela/Ela group.

Suicidality was also assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS) at baseline and during treatment in both placebo-controlled trials and the extension study. Two subjects receiving Ela + E2/NETA responded “yes” to the screening questions (indicating suicidal ideation) and are described below.

- Subject (b) (6) experienced two AEs of affect lability (coded as nonserious) in Study M12-817, one on Day 10 (moderate) and one on Day 33 (severe). Study drug was discontinued on Day 33, but no medication was prescribed, and the subject was not referred to a mental healthcare provider.
- Subject (b) (6) who had a history of depression and anxiety reported mild depression, on Day 130 of Study M12-815 and was treated with clonazepam; the event was ongoing at the end of the Treatment Period when she entered the extension study.

It is unclear from this data that addition of hormone therapy to elagolix mitigates the mood changes reported with use of elagolix alone. After review of the safety database from studies 815 and 817, the Warning and Precaution for depression in Orlissa is included in Oriahnn labeling.

8.2.5.6. Hypoestrogenic Effects (Hot Flush)

The incidence of hot flush and/or night sweats was attenuated with the addition of E2/NETA to elagolix. The rates in Studies 815 and 817 were 20% in Ela + E2/NETA, 54% in Ela alone, and 6.6% in placebo group. The incidence of the occurrence of these symptoms, likely related to GnRH analog use, will be included in labeling.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

In Phase 3 trials, subjects were administered the UFS-QoL questionnaire, the WPAI:UF, and the PGIC-MB. These questionnaires are exploratory and were not relied upon to inform on safety or tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

No overall differences were seen among exploratory analyses by age, race, BMI, and ethnicity subgroup across all treatment groups.

Age: The overall AE rates were similar to the overall population. However, in the < 35 years group, more AEs were reported by placebo subjects compared to Ela + E2/NETA subjects.

Race: Approximately two-thirds of subjects enrolled in the clinical program were African American; more adverse events occurred in the Ela + E2/NETA group compared to placebo (73% versus 64%, respectively) in this population. In the non-African American population, the overall AEs events were numerically similar between Ela + E2/NETA and placebo groups.

BMI: Effect of BMI by treatment group was similar to overall population.

None of these exploratory analyses yielded results that raised new effectiveness or safety concerns that would require additional data or analyses.

8.2.8. Specific Safety Studies/Clinical Trials

No special safety studies were conducted.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The administration of estrogens and/or progestins has a known association of increased risk of the frequency of hormone-dependent malignancies.

During the development of Oriahnn for uterine fibroids, two breast cancer cases were reported as SAEs (%) in the elagolix with E2 and NETA .

Subject (b) (6) was a 46 year-old BF receiving Ela + E2+NETA/Ela + E2+NETA. She was diagnosed with Stage 2 breast cancer on Day 34 of the extension study (total 217 days of Oriahnn exposure). Study drug was discontinued on Day 113. The event was deemed by the investigator and the Applicant as unrelated to the study drug.

Subject (b) (6) was a 52 year-old BF who received Placebo/Ela + E2+NETA and was diagnosed with non-metastatic, poorly differentiated carcinoma of the right breast on Day 167 of the extension study. The subject underwent partial mastectomy and chemotherapy. She completed the treatment period but did not enter the PTFU. For this case, the investigator and the Applicant did not attribute the breast cancer to study drug.

It is known that use of hormone therapy is associated with an increased risk of breast cancer and this is outlined in current labeling for E2/NETA. Based on this, Oriahnn will carry a similar contraindication in women with current or past history of breast cancer and other hormonally-sensitive malignancies.

Human Reproduction and Pregnancy

While there is no definitive teratogenic signal based on available nonclinical studies, the risk of early pregnancy loss is assumed based on the mechanism of elagolix.

The adpreg.xpt dataset was queried and five pregnancies were identified in subjects on-treatment in Studies 815 and 817; two subjects were treated with Ela + E2/NETA (summarized below). The Applicant correctly reported four pregnancies from Phase 3 trials; the discrepancy with the dataset queried was due to one subject having a positive testing due to subcutaneous hCG hormone treatment for weight loss. Thus, in Phase 3 trials, one pregnancy each occurred in Ela + E2/NETA and Ela alone arm, respectively; two pregnancies occurred in the placebo group.

One subject on Ela + E2/NETA:

- (b) (6): 36 year-old BF in extension study (received Ela + E2+NETA/Ela + E2+NETA). After a treatment duration of 89 days in extension phase (total exposure 257 days), she experienced a spontaneous abortion (<6 weeks gestation).

Additionally, a 40 year-old WF on Ela 300 mg BID (subject (b) (6)), who received 9 days of therapy, had a spontaneous abortion between 6 and 13 weeks of gestation. In the Phase 2 uterine fibroid studies, two pregnancies were reported. Both women opted to terminate the pregnancy; they received 2 days and 8 days of Elagolix 600 mg QD, respectively.

The Applicant reports one congenital malformation (talipes equinovarus of the right foot). This subject ((b) (6)) was a 40 year-old Asian female with two prior pregnancies (election abortion and full-term) who received Ela 300 BID in the placebo-controlled phase and extension study. The pregnancy occurred in the follow-up period of the extension phase and the birth was on Day 468 (post-treatment day 299). This case is considered to be hereditary (father also has talipes equinovarus) because an association with elagolix would be temporally implausible.

The Applicant calculated the annualized pregnancy rates during the treatment period to be 2.4% for placebo, 0.7% for elagolix 300 mg BID, and 0.4% for elagolix 300 mg BID + E2/NETA (per ISS Table 7.1_3). The use of Oriahnn will be contraindicated in pregnancy. Currently, Orilissa has two postmarketing requirement studies (a prospective pregnancy registry and a pharmacoepidemiology surveillance study). These

two studies are expected to include women with uterine fibroids who are treated with Oriahnn once approved.

Pediatrics and Assessment of Effects on Growth

Elagolix + E2/NETA for uterine fibroids is not intended for use in the pediatric population as uterine fibroids are extremely rare in this population. The Applicant has submitted a request for pediatric waiver and we concur. See Section 10 Pediatrics for additional details.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

All three active ingredients in this product have previously been approved and neither component (Orilissa and Activella) in this combination product is scheduled under the Controlled Substances Act (CSA). The Applicant conducted a MedDRA query designed to identify preferred terms related to abuse liability in women enrolled in all three Phase 3 trials and concluded that there was no new abuse-related safety signal. The Applicant proposes that Oriahnn not be added to any schedule as defined by the CSA. Per a review dated April 28, 2020, the Controlled Substance Staff concluded that Oriahnn does not warrant scheduling under the CSA and that no additional abuse liability assessments are not needed unless postmarketing surveillance identifies a signal for abuse. We concur with the Applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Post marketing experience with elagolix drug substance is available from the Orilissa endometriosis program. Two events of self-injury/self-injurious ideation have been reported in the postmarketing period.

- ([(b) (6)]) 32 year-old with ideation few days after initiation of Orilissa therapy. Patient discontinued Orilissa on her own after 4 days and sought help. Symptoms stopped within 24 hours. Patient has a history of depression while on leuprorelin and medroxyprogesterone acetate.
- Self-injury (initially reported as suicide in postmarketing period; consumer report [(b) (6)]) A 27 year-old who intentionally caused self-injury after initiation of Orilissa for endometriosis. Patient was upset because her endometriosis pain came back. Orilissa was discontinued, outcome of event is unknown.

One event of pelvic fracture was reported: (medically confirmed report 2787493) in a 29 year-old. She experienced a pelvic fracture during 6th month of Orilissa treatment for endometriosis. Limited information was contained in the report.

Postmarketing reports of suicidality and fracture are being followed through pharmacovigilance.

Expectations on Safety in the Postmarket Setting

An ongoing long-term safety study is being conducted to assess the effect of continuous therapy up to 4 years (See Bone Safety). These results are expected in the post marketing period and may result in additional labeling considerations.

8.2.11. Integrated Assessment of Safety

A total of 518 unique subjects have been exposed to elagolix 300 mg BID + E2 1 mg/NETA 0.5 mg in the Phase 2/3 uterine fibroid clinical program. In Phase 3 placebo-controlled clinical trials for the uterine fibroid indication (Studies 815 and 817), 395 subjects were exposed for six months and an additional 58 subjects, who received placebo in Studies 815 and 817, received Ela + E2/NETA in the extension study 816 for six months. Additionally, 65 subjects received Ela + E2/NETA in one Phase 2 study (M12-813) for 6 months. Among the 276 subjects who received Ela + E2/NETA in Studies 815 and 817 and entered extension study 816, 182 were exposed for 12 months.

The most common AEs occurring in > 5% of subjects in clinical trials were hot flushes, headache, fatigue, and metrorrhagia. These AEs are expected in this population during use of a GnRH analog. Less common but significant safety issues are highlighted below.

Thromboembolic and Vascular events
Approved labeling for estrogen and progestin combinations (in combined hormonal contraceptive products intended for women of reproductive potential and in hormone therapies intended for postmenopausal women) includes a Box Warning regarding thromboembolic disorders. In the clinical program, two thromboembolic events: one subject with thrombosis in the calf after 30 days of treatment with Ela + E2/NETA and another subject with bilateral pulmonary embolism after receiving 226 days of Ela + E2/NETA. Because Oriahnn is a fixed-dose combination containing E2/NETA, contraindications and Warnings & Precautions related to thromboembolic events are included in product labeling.

Bone Loss
The adverse effect of elagolix, a GnRH antagonist, on bone is well known. The total daily dose of elagolix, 600 mg per day in Oriahnn, is also higher than previously approved (150 mg QD for 24 months and 200 mg BID for 6 months). The addition of E2/NETA did attenuate bone loss, but the attenuation was incomplete. Among the subjects who received 12 months of treatment with Ela + E2/NETA and followed for an additional 12 months, continued bone loss was observed at the spine, total hip, and femoral neck in 24%, 32%, and 38%, respectively. These findings show that E2/NETA do not totally mitigate bone loss in all subjects. Therefore, labeling will include baseline and annual assessment for BMD to monitor bone safety.

Full recovery of bone loss was only observed in 31%, 36% and 24% of subjects who lost bone at the spine, total hip, and femoral neck, respectively. Significantly, seven subjects treated with Ela + E2/NETA experienced fracture events. In one of the seven, the fractures were consistent with fragility fractures. Although the Applicant proposed a treatment duration of (b) (4) months, clinical data provided in this application pertain only to 12 months of use. Because the target population of women with heavy menstrual bleeding due to uterine fibroids tend to be older than women with endometriosis-associated pain, the concern over delayed bone loss and incomplete recovery does not support clinical use of longer than 24 months.

Use of Oriahnn in women with known osteoporosis will be contraindicated because of known potential for bone loss and the limited data on recovery.

Hormonally-Sensitive Malignancies
In postmenopausal women, the use of estrogen alone and estrogen/progestin combinations may be associated with an increased risk for hormonally-sensitive malignancies, including breast cancer. This association has not been conclusively established in premenopausal women. In this program, two women treated with Ela + E2/NETA were diagnosed with breast cancer (%), after 202 days and 167 days of treatment, respectively. Given the occurrence of these cancers in the treatment arm of the development program, labeling for E2/NETA will be applied. Use of Oriahnn will be contraindicated in women with a current or past history of, or at high risk for (such as those with BRCA mutations) hormonally-sensitive malignancies.

Suicidal Ideation/Behavior and Exacerbation of Mood Disorders
Elagolix alone is known to worsen symptoms of depression. In the clinical program for Orilissa, one subject committed suicide. In this Studies 815 and 817, subjects receiving Ela + E2/NETA had a higher incidence of depression and mood changes compared to placebo subjects (3% versus 1%, respectively). This safety concern will remain under Section 5 Warnings and Precautions.

Elevated Blood Pressure
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In the placebo-controlled trials (Studies 815 and 817), treatment with Ela + E2/NETA resulted in a mean increase in systolic blood pressure of 5.1 mmHg (95% CI 2.68, 7.59) at Month 5, and a mean increase in diastolic blood pressure of 2.1 mmHg (95% CI 0.43, 3.84) at Month 4, as compared to placebo. Use of Oriahnn will be contraindicated in women with uncontrolled hypertension.

Embryo-Fetal Loss
Lower doses of elagolix (in Orilissa) did not completely suppress ovulation and an unexpectedly high number of pregnancies occurred in the Orilissa clinical program. Because of its mechanism, elagolix may cause embryo-fetal loss if taken early in pregnancy. Only one pregnancy occurred with Ela + E2/NETA treatment in this clinical

program; therefore, the number of pregnancies is too small to assess the effect of Oriahnn on pregnancy and fetal/neonatal outcome. The use of Oriahnn will be contraindicated in pregnancy and women will be advised to use non-hormonal contraception during treatment for Oriahnn because does not prevent pregnancy. Additionally, women who start treatment on Oriahnn and become pregnancy will be included two ongoing studies being conducted to address the postmarketing requirements for Orilissa.

Alopecia
In Studies 815 and 817, hair loss and hair thinning occurred at a greater rate in subjects treated with Ela + E2/NETA than in placebo subjects (3.5% versus 1%). Based on the safety database, the pattern of hair loss or reversibility could not be determined. Alopecia will be included in Section 5 Warnings and Precautions because these adverse cosmetic effects may be important to women contemplating initiating or continuing therapy with Oriahnn. A postmarketing requirement to conduct a prospective observational study will be requested to evaluate the incidence, pattern and reversibility of alopecia in women being treated with Oriahnn.

8.3. Statistical Issues

There were no statistical issues identified in this development program. The Applicant followed their pre-specified statistical analysis plan and, from the statistical perspective, demonstrated the effectiveness of elagolix 300 mg BID + E2 1 mg/NETA 0.5 mg for the management of heavy menstrual bleeding associated with uterine fibroids.

8.4. Conclusions and Recommendations

Based on the totality of the efficacy and the safety database presented in this application, we conclude that elagolix 300 mg BID + E2 1 mg/NETA 0.5 mg QD (Oriahnn) shows statistically significant efficacy for the treatment of heavy menstrual bleeding due to uterine fibroids in premenopausal women. In both Phase 3, randomized, double-blind, placebo-controlled clinical trials, a significantly greater proportion of subjects treated with Oriahnn achieved the primary efficacy endpoint of MBL volume < 80 mL during the final Month and ≥ 50% reduction in MBL volume from baseline to the final month as compared to placebo.

All the safety concerns identified during this review can be adequately mitigated through labeling, evaluated through enhanced Pharmacovigilance Program, or evaluated via postmarketing requirements. Availability of this product will provide a new, longer-term treatment option to women desiring non-invasive therapies. The benefit-risk profile of Oriahnn is favorable and the product should be approved.

Based on labeling and the safety review, the Division has recommended enhanced pharmacovigilance plan for key safety concerns: thromboembolic disorders and vascular events, bone mineral density decrease, hormonally-sensitive malignancies, exacerbation of mood disorders and suicidality, elevated hepatic transaminases, elevated blood pressure, gallbladder disease, pregnancy outcomes, adverse effects on carbohydrate and lipid metabolism.

9. Advisory Committee Meeting and Other External Consultations

The Division determined that the application did not raise issues requiring external expert advice. Therefore, an advisory committee was not convened to discuss this application.

10. Pediatrics

The Applicant seeks a full waiver from the requirements to obtain pediatric data under the Pediatric Research Equity Act (PREA). The Applicant submitted an initial pediatric study plan (iPSP) on July 13, 2015, and a final Pediatric Study Plan (PSP) on February 19, 2016, requesting a full waiver to conduct pediatric studies in girls <18 years and all boys. Reasons provided by the Applicant to justify a full waiver include:

- The necessary studies are impossible or highly impractical, given the extremely rare occurrence of symptomatic uterine fibroids in the pediatric population.
- Boys are not affected by heavy menstrual associated with uterine fibroids.

On March 17, 2016, FDA issued an Agreed iPSP. Uterine fibroids are so rare in the adolescent female population such that clinical studies in this population would not be feasible. In addition, this condition does not occur in premenarchal girls or boys. For these reasons, heavy menstrual bleeding associated with uterine fibroids is included in the list of conditions that qualifies for a full waiver under PREA. Further, we would not recommend studying this product in the adolescent female population because adolescence is a critical time of bone mass accrual; the potential adverse effects on achieving peak bone mass, increasing fracture risk, and developing osteoporosis later in life are major concerns that alter the benefit/risk for this population.

The Pediatric Review Committee (PeRC) reviewed the Applicant's request on February 11, 2020 and agrees with granting a full waiver of studies in pediatric patients because studies are impossible or highly impracticable. The final PeRC decision is documented in the meeting minutes dated February 24, 2020.

11. Labeling Recommendations

11.1. Prescription Information

The proposed proprietary name, Oriahnn, is determined by Division of Medication Error Prevention to be conditionally acceptable. This decision was documented in a letter conveyed to the Applicant on January 7, 2020.

Table 49 presents the key aspects of the Prescribing Information (PI) first submitted by the Applicant and the approved PI:

Table 49: Summary of Significant Labeling Changes

Section	Recommended Changes in Labeling
Highlight	• Revised Box Warning to add contraindication of women with current or history of thromboembolic disorders • Multiple additions based on edits in the Full Prescribing Information
Section 1	• Added Limitation of Use to limit duration of use to 24 months due to potential of irreversible bone loss
Section 2	• Added clarifying edits for dosing instructions
Section 4	• Added clarifying edits
Section 5	• Significantly revised each safety concerns to add information from clinical trials and mitigation strategy • Added a Warning for events of alopecia given findings of safety review • Added required a Warning for risk of allergic reactions due to inactive ingredient FD&C yellow number 5 (per regulation)
Section 6	• Revised exposure information • Significantly revised sections in Less Common Adverse Reactions
Section 7	• Significantly revised clinical recommendations to minimize risks of adverse drug-drug interactions
Section 8	• Revised Risk Summary in 8.1 (pregnancy) and Data in 8.2 (Lactation)
Section 12	• Revised language in 12.1 (Mechanism of Action) and deleted statements of promotional nature related to NETA • Revised pharmacokinetic information in 12.3 based on review • Revised pharmacogenomic information in 12.5 based on exposure of subjects with OATP1B1 polymorphism
Section 14	• Significantly revised language to delete promotional statements
Section 17	• Significantly revised based on the extensive changes in Sections 5 and 7

11.2. Patient Labeling

The Patient Labeling Team and Office of Prescription Drug Promotion in the Office of Medical Policy collaborated with the core review disciplines on the review of the Prescribing Information and the Medication Guide to ensure readability, consistency and that the materials are truthful and not misleading. See separate consult reviews in DARRTS, dated April 20, 2020 for further details.

11.3. Carton and Container Labeling

Reviewers in the Division of Medical Error Prevention and Analysis and the Office of Product Quality collaborated with the core review disciplines on the review of carton and container labeling. Final agreement is pending and the only outstanding issue from the medication error perspective is how the nonproprietary names of the active ingredients will be presented. See separate reviews in DARRTS and Panorama, respectively, for further details.

12. Risk Evaluation and Mitigation Strategies (REMS)

FDA has determined that a REMS is not necessary to ensure the benefits outweigh the risks of this product. Labeling is adequate to inform providers and patients of the risks identified during development of Oriahnn.

13. Postmarketing Requirements and Commitment

Our safety review of data submitted in this NDA showed an imbalance for the AEs of alopecia, including hair loss and hair thinning. In the two Phase 3 clinical trials (Studies M12-815 and M12-817), more women experienced alopecia, hair loss and hair thinning with elagolix 300 mg + E2/NETA (3.5%) compared to placebo (1.0%). No specific pattern was discernable. In most of these women, hair loss was continuing when treatment was stopped. In consultation with DEPI and DPV, the Division has determined that a postmarketing requirement is needed to further assess the incidence rate, time to onset, pattern, extent, and reversibility of alopecia in treated women. We the Applicant conduct a prospective observational study to evaluate this event of interest.

There are two ongoing PMRs for the approved elagolix drug product. These were required because as a GnRH receptor antagonist, elagolix may cause a decrease in progesterone production in early pregnancy and in turn increase the risk for pregnancy outcomes, including embryofetal loss. Because an unexpectedly high number of pregnancies (49 on treatment) occurred in the clinical program of Orilissa, the Division requested two pregnancy-related PMRs with Orilissa's approval.

- Issued under PMR 3390-1, the Division requested a prospective pregnancy registry to evaluate the effects of elagolix on pregnancy and maternal and fetal/neonatal outcomes. The study protocol was finalized as of January 2020.

- Issued under PMR 3390-2, the Division also requested a retrospective cohort study in a claims-based database to evaluate the effects of elagolix on pregnancy-related outcomes. The study protocol is currently under review.

Since the pre-approval safety database for elagolix + E2/NETA was too limited to draw any conclusions about its effect on pregnancies, maternal and fetal/neonatal outcomes, the Division has determined that these two pregnancy-related PMRs issued for Orilissa should also enroll women who are treated with Oriahnn. Two new PMR numbers will be assigned under this NDA but the PMRs will be linked to Orilissa's PMR 3390-1 and PMR 3390-2, respectively.

14. Appendices

14.1. Financial Disclosure

Six clinical studies provided pivotal information in support of this application and were reviewed by the clinical reviewer, Dr. Marcea Whitaker. Three were Phase 3 studies: M12-815, M12-817, M12-816. Three were clinical pharmacology studies: M16-856, M15-872, and M19-648. Studies M16-856 (bioequivalence and food effect study) and M15-872 (bioavailability study) were partially conducted in AbbVie-owned clinical pharmacology unit. M19-648 was a pivotal bioequivalence (BE) study conducted in AbbVie owned clinical pharmacology unit.

All investigators involved in the three clinical pharmacology studies are AbbVie employees; no financial certifications or disclosures were submitted for these investigators. A listing of investigators with disclosable interest (i.e., participating in the three Phase 3 studies who received payments >$25,000 from the Applicant) and the number of enrolled subjects at their clinical site is shown in Table 50 below. An FDA Form 3455 is provided for each investigator. The payments were for Speaker fees pertaining to Orilissa, except for review of M12-817 study report (Dr. (b) (6)), and consulting (Dr. (b) (6)). Dr. (b) (6) site had the greatest enrollment but review of OSI site selection tool did not identify disproportionate efficacy or safety results at that site. Inspection was not requested as Dr. (b) (6) site had been recently inspected in 2018 and received an assessment of No Action Indicated.

The financial disclosure reporting and information provided appears acceptable and no additional information or concerns were identified.

Table 50: Investigators With Payments >$25,000 (No of Subjects Enrolled)

M12-815	M12-817	M12-816
(b) (6)		

Our review of the financial disclosure information specific to each of six pivotal studies is presented below.

Covered Clinical Study (Name and/or Number): M12-815

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 80		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 11		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: No Significant payments of other sorts: 11 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Stock: 0 Sponsor of covered study: AbbVie, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Covered Clinical Study (Name and/or Number): M12-817

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 88		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Stock: 0 Sponsor of covered study: AbbVie, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Covered Clinical Study (Name and/or Number): M12-816

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 123		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 12		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Stock: 0 Sponsor of covered study: AbbVie, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Covered Clinical Study (Name and/or Number): M16-856

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Stock: 0 Sponsor of covered study: AbbVie, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Covered Clinical Study (Name and/or Number): M15-872 (BA study)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Stock: 0 Sponsor of covered study: AbbVie, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Covered Clinical Study (Name and/or Number): M19-648 (pivotal BE study)

Was a list of clinical investigators provided:	Yes ☐	No ☒ (Request list from Applicant) one investigator and he is listed under other studies
Total number of investigators identified: 1 (Kent Kamradt MD)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 exempt		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Stock: 0 Sponsor of covered study: AbbVie, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) N/A Investigator exempt
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A Investigator exempt
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A Investigator exempt

14.2. Nonclinical Pharmacology/Toxicology

For details, refer to Pharmacology/Toxicology Review for in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) dated March 24, 2020.

14.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

For details, refer to Clinical Pharmacology Review in DARRTS, dated May 8, 2020.

14.4. Additional Clinical Outcome Assessment Analyses

For details, refer to Clinical Outcome Assessments Review in DARRTS dated February 21, 2020.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINA Y CHANG
05/21/2020 03:09:33 PM

AUDREY L GASSMAN
05/29/2020 07:40:03 AM
I concur with the review team's Approval recommendation - refer to the Addendum for additional information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	213388
Supporting document/s:	SDN 1
Applicant's letter date:	7-31-2019
CDER stamp date:	7-31-2019
Product:	Elagolix + estradiol (E2) / norethindrone acetate (NETA)
Indication:	Management of heavy menstrual bleeding associated with uterine fibroids
Applicant:	Abbvie, Inc
Review Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT Kimberly Hatfield, PhD
Acting Division Director:	Christine Nguyen, MD
Project Manager:	Maria Wasilik

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 213388 are owned by Abbvie or are data for which Abbvie has obtained a written right of reference. Any information or data necessary for approval of NDA 213388 that Abbvie does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Abbvie does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 213388.

1 Executive Summary

1.1 Recommendations

None

1.1.1 Approvability

The application is approvable.

1.1.2 Additional NonClinical Recommendations

None

1.1.3 Labeling

The label for Oriahnn® is derived from the labels for Orilissa® (elagolix alone) and Activella® (E2/NETA). The nonclinical team reviewed the pharmacologic class in Highlights, and Sections 8.1-8.3, 12, and 13. The label initially proposed by the sponsor underwent significant revision. For that reason, we show here only the final labeling language for these sections without intermediate edits. Section 12 appears last.

Sponsor-proposed label	Final label
INDICATIONS AND USAGE Oriahnn (b) (4) indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids).	**INDICATIONS AND USAGE** Oriahnn (b) (4) indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.
8. Use in Specific Populations There is a pregnancy registry that monitors pregnancy outcomes in women who become pregnant while on treatment with Oriahnn. Patients should be encouraged to enroll by calling 1 877 311 8972. **8.1 Pregnancy** **Risk Summary** Exposure to Oriahnn early in pregnancy may increase the risk of early pregnancy loss. Use of Oriahnn is contraindicated in pregnant women. Discontinue Oriahnn if pregnancy occurs during treatment.	**8. Use in Specific Populations** **8.1 Pregnancy** Pregnancy Exposure Registry There is a pregnancy registry that monitors outcomes in women who become pregnant while treated with ORIAHNN. Pregnant patients should be encouraged to enroll by calling 1-833-782-7241. Risk Summary Use of ORIAHNN is contraindicated in pregnant women. Exposure to elagolix early in pregnancy may increase the risk of early pregnancy loss. Discontinue ORIAHNN if pregnancy occurs during treatment.

When pregnant rats and rabbits were orally dosed with elagolix during the period of organogenesis, postimplantation loss was observed in pregnant rats at doses 12 times the maximum recommended human dose (MRHD). Spontaneous abortion and total litter loss was observed in rabbits at doses 4 and 7 times the MRHD. There were no structural abnormalities in the fetuses at exposures up to 25 and 7 times the MRHD for the rat and rabbit, respectively *(see Data)*.	The limited human data with the use of elagolix in pregnant women are insufficient to determine whether there is a risk for major birth defects or miscarriage *[see Data].*
(b) (4)	When pregnant rats and rabbits were orally dosed with elagolix during the period of organogenesis, postimplantation loss was observed in pregnant rats at doses 12 times the maximum recommended human dose (MRHD). Spontaneous abortion and total litter loss were observed in rabbits at doses 4 and 7 times the MRHD. There were no structural abnormalities in the fetuses at exposures up to 25 and 7 times the MRHD for the rat and rabbit, respectively *[see Data]*.
	Data
Human Data There was one pregnancy reported (b) (4) the 453 women who received Oriahnn in the Phase 3 uterine fibroids clinical trials. The pregnancy resulted in a spontaneous abortion and the estimated fetal exposure to Oriahnn occurred during the first 18 days of pregnancy.	*Human Data* There was one pregnancy reported in the 453 women who received ORIAHNN in the Phase 3 uterine fibroids clinical trials. The pregnancy resulted in a spontaneous abortion and the estimated fetal exposure to ORIAHNN occurred during the first 18 days of pregnancy.
Animal Data Embryofetal development studies were conducted in the rat and rabbit. Elagolix was administered by oral gavage to pregnant rats (25 animals/dose) at doses of 0, 300, 600 and 1200 mg/kg/day and to rabbits (20 animals/ dose) at doses of 0, 100, 150, and 200 mg/kg/ day, during the period of organogenesis (gestation day 6-17 in the rat and gestation day 7-20 in the rabbit). In rats, maternal toxicity was present at all doses and included six deaths and decreases in body weight gain and food consumption. Increased post implantation losses were present in the mid dose group, which was 12 times the MRHD based on AUC. In rabbits, three spontaneous abortions and a single total litter loss were observed at the highest, maternally toxic dose, which was 7 times the MRHD based on AUC. A single total litter loss occurred at a lower non-maternally toxic dose	*Animal Data* *There were no changes to the sponsor's submitted text in this section.*

of 150 mg/kg/day, which was 4 times the MRHD. No fetal malformations were present at any dose level tested in either species even in the presence of maternal toxicity. At the highest doses tested, the exposure margins were 25 and 7 times the MRHD for the rat and rabbit, respectively. However, because elagolix binds poorly to the rat gonadotropin-releasing hormone (GnRH) receptor (~1000 fold less than to the human GnRH receptor), the rat study is unlikely to identify pharmacologically mediated effects of elagolix on embryofetal development. The rat study is still expected to provide information on potential non-target-related effects of elagolix. In a pre- and postnatal development study in rats, elagolix was given in the diet to achieve doses of 0, 100 and 300 mg/kg/day (25 per dose group) from gestation day 6 to lactation day 20. There was no evidence of maternal toxicity. At the highest dose, two dams had total litter loss, and one failed to deliver. Pup survival was decreased from birth to postnatal day 4. Pups had lower birth weights and lower body weight gains were observed throughout the pre-weaning period at 300 mg/kg/day. Smaller body size and effect on startle response were associated with lower pup weights at 300 mg/kg/day. Post-weaning growth, development and behavioral endpoints were unaffected. Maternal plasma concentrations in rats on lactation day 21 at 100 and 300 mg/kg/day (47 and 125 ng/mL) were 0.04-fold and 0.1-fold the maximal elagolix concentration (C_{max}) in humans at the MRHD. Because the exposures achieved in rats were much lower than the human MRHD, this study is not predictive of potentially higher lactational exposure in humans.	

8.2 Lactation Risk Summary (b) (4) [redacted] Data There is no information on the presence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen and progestin combinations. There are no adequate animal data on excretion of (b) (4) [redacted] in milk. **8.3 Females and Males of Reproductive Potential** Based on the mechanism of action, there is a risk of early pregnancy loss if Oriahnn is administered to a pregnant woman *[see Use in Specific Populations (8.1), Clinical Pharmacology (12.1)]*.	**8.2 Lactation** Risk Summary There is no information on the presence of elagolix in human milk, the effects on the breastfed child, or the effects on milk production. When estrogen and progestins are administered to lactating women, these compounds and/or their metabolites are detected in human milk and can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. Advise the nursing female to use non-hormonal contraception until she discontinues breast-feeding. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for ORIAHNN and any potential adverse effects on the breast-fed child from ORIAHNN or from the underlying maternal condition *[see Data]*. Data There is no information on the presence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen and progestin combinations. There are no adequate animal data on excretion of **elagolix** in milk. **8.3 Females and Males of Reproductive Potential** Based on the mechanism of action of elagolix, there is a risk of early pregnancy loss if ORIAHNN is administered to a pregnant woman *[see Use in Specific Populations (8.1), Clinical Pharmacology (12.1)]*.

Pregnancy Testing Exclude pregnancy before initiating treatment with Oriahnn. Perform pregnancy testing if pregnancy is suspected during treatment with Oriahnn and discontinue treatment if pregnancy is confirmed *[see Warnings and Precautions (5.8)]*. Contraception Advise women to use non-hormonal contraception during treatment with Oriahnn and for one week after discontinuing Oriahnn *[see Warnings and Precautions (5.8)]*.	Pregnancy Testing ORIAHNN may delay the ability to recognize the occurrence of a pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding *[see Adverse Reactions (6.1)]*. Exclude pregnancy before initiating treatment with ORIAHNN. Perform pregnancy testing if pregnancy is suspected during treatment with ORIAHNN and discontinue treatment if pregnancy is confirmed *[see Contraindications (4) and Warnings and Precautions (5.8)]*. Contraception *There were no changes to the sponsor's submitted text in this section.*
13 Nonclinical Toxicology **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Elagolix Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) that administered elagolix by the dietary route revealed no increase in tumors in mice at up to 11.9-fold the MRHD based on AUC. In the rat, there was an increase in thyroid (male and female) and liver (males only) tumors at the high dose (7.7 to 8.1-fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans. Elagolix was not genotoxic or mutagenic in a battery of tests, including the *in vitro* bacterial reverse mutation assay, the *in vitro* mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, and the *in vivo* mouse micronucleus assay. In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/	**13 Nonclinical Toxicology** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Elagolix *There were no changes to the sponsor's submitted text in this section.* *Note that margins of exposure values have been adjusted to account for the higher dose of elagolix in ORIAHNN as compared to ORILISSA.*

day in female rats is approximately 2.9-fold. However, because elagolix has low affinity for the GnRH receptor in the rat *[see Use in Specific Populations (8.1)]*, and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans. E2/NETA Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.	 E2/NETA Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver *[see Warnings and Precautions (5.3)].*

12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action**	**12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action**
(b) (4)	ORIAHNN combines elagolix and estradiol/ norethindrone acetate (E2/NETA), a combination of estrogen and progestin. Elagolix is a GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of elagolix results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone and reduces bleeding associated with uterine fibroids. E2 acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a component of ORIAHNN, the addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from elagolix alone. Progestins such as NETA act by binding to nuclear receptors that are expressed in progesterone-responsive tissues. As a component of ORIAHNN, NETA may protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

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/s/

LESLIE C MCKINNEY
05/26/2020 12:44:24 PM

KIMBERLY P HATFIELD
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I concur with Dr. McKinney.

Office of Clinical Pharmacology Review

NDA or BLA Number	213388
Link to EDR	\\CDSESUB1\evsprod\NDA213388\213388.enx
Submission Date	SDN 001, 7/31/2019; SDN 012, 1/15/2020; SDN 014, 2/4/2020
Submission Type	Standard
Brand Name	Oriahnn®
Generic Name	Elagolix, estradiol and norethindrone
Dosage Form and Strength	Capsule, elagolix 300 mg + estradiol/norethindrone acetate 1 mg/0.5 mg or elagolix 300 mg alone
Route of Administration	Oral administration
Proposed Indication	Management of heavy menstrual bleeding (HMB) associated with uterine leiomyomas
Applicant	Abbvie Inc.
Associated IND	IND 115528
OCP Review Team	Peng Zou, PhD; Yanhui Lu, PhD; Fang Li, PhD; Jingyu Yu, PhD; Xinyuan Zhang, PhD; Yuching Yang, PhD; Oluseyi Adeniyi, PharmD; Christian Grimstein, PhD
OCP Final Signatory	Yanhui Lu Team Leader Office of Clinical Pharmacology

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1. EXECUTIVE SUMMARY

Elagolix (ABT-620, A-1278823), an oral, nonpeptide, gonadotropin-releasing hormone (GnRH) antagonist, was approved by the FDA in July 2018 for the management of moderate to severe pain associated with endometriosis and is marketed as Orilissa® (NDA 210450). In the current NDA 213388, AbbVie Inc. (AbbVie) developed elagolix, estradiol (E2) and norethindrone acetate (NETA) as a fixed-dose combination (FDC) oral capsule for the management of heavy menstrual bleeding (HMB) associated with uterine leiomyomas (uterine fibroids or UF). The proposed dosing regimen is elagolix 300 mg twice a day (BID) + E2/NETA 1 mg/0.5 mg once a day (QD) (hereinafter referred to as elagolix 300 mg BID + E2/NETA). Elagolix 300 mg is administered twice daily: once as an FDC capsule (elagolix 300 mg + E2/NETA 1 mg/0.5 mg) in the morning and once as a capsule containing elagolix 300 mg alone in the evening.

In current NDA submission, there are seven Phase 1 studies, two Phase 2 dose-finding studies and three Phase 3 studies (Table 1). In addition, 22 Phase 1 studies submitted in NDA 210450 were cross referenced to support the uterine fibroids indication proposed in this NDA. Additionally, the Applicant has obtained the right of reference for NDA 020907 Activella® E2/NETA 1 mg/0.5 mg and E2/NETA 0.5 mg/0.1 mg to support the E2/NETA component of Oriahnn®.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Cardiometabolic and Endocrine Pharmacology, Pharmacometrics, and Translational and Precision Medicine have reviewed the information contained in NDA 213388 and recommend approval of this NDA. Key review issues with specific recommendations/comments are summarized in the table below:

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Clinical pharmacology information provides dose/exposure-dependent evidence of effectiveness. The elagolix exposure-response analyses for the primary efficacy endpoint [the proportion of subjects who had menstrual blood loss (MBL) <80 mL during the final month and ≥ 50% reduction in MBL volume from baseline to the final month] support the effectiveness. Two Phase 2 dose-finding studies also support the effectiveness.
General dosing instructions	One capsule (elagolix 300 mg/E2 1 mg/NETA 0.5 mg) should be orally administered in the morning and one capsule (elagolix 300 mg) should be orally administered in the evening. Both morning and evening doses can be taken with or without food. The review team recommends that the duration of treatment with Oriahnn be limited to 24 months due to concern of bone safety.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Oriahnn is contraindicated in women with hepatic impairment.
Labeling	Refer to Section 2.4 for the review team's recommendations.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed morning and evening capsules have been demonstrated to meet the standard bioequivalence criteria to the tablets used in Phase 3 trials based upon elagolix, E2, and NETA concentrations measured in two bioequivalence studies.
Other (specify)	None.

1.2 Post-Marketing Requirements and Commitments

None.

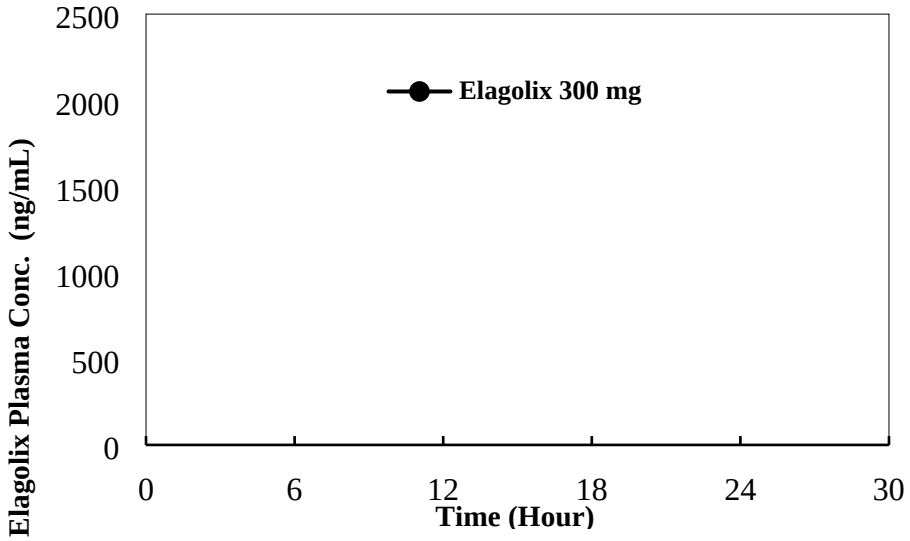
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

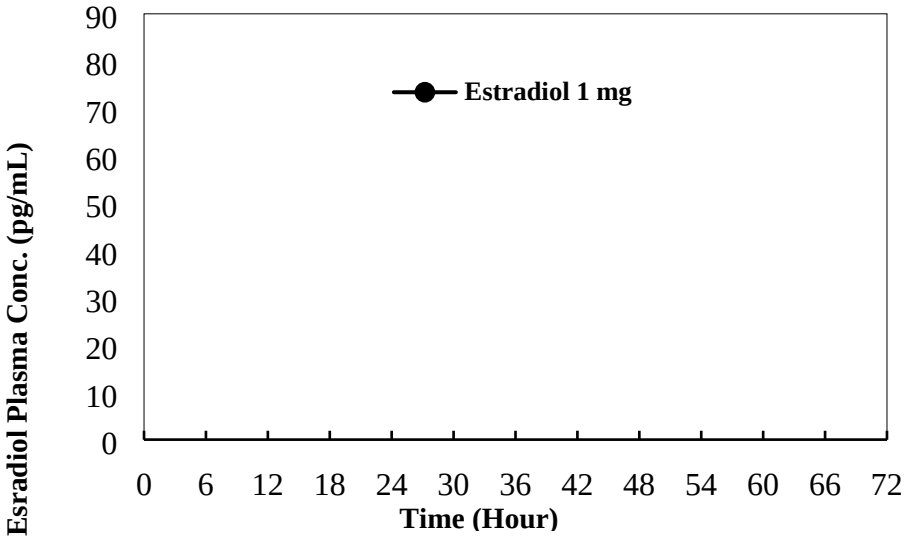
2.1 Pharmacology and Clinical Pharmacokinetics

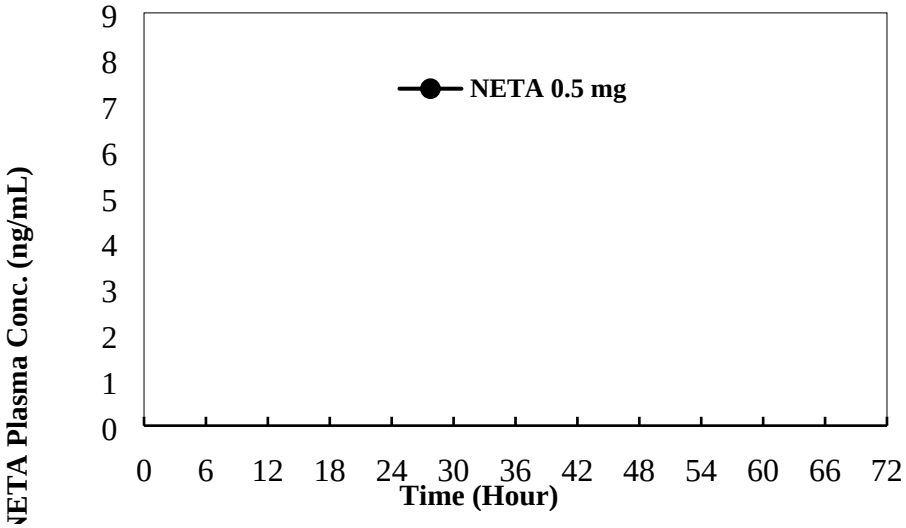
Oriahnn combines elagolix and E2/NETA. Elagolix is a GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of elagolix decreases blood concentrations of ovarian sex hormones, estradiol, and progesterone and reduces bleeding associated with uterine fibroids. To some extent, the add-back therapy of E2/NETA reduces the bone loss that can occur due to a decrease in circulating estrogen from elagolix alone treatment. Oriahnn is orally administered with or without food.

Absorption: Elagolix, E2, and NETA are rapidly absorbed upon oral administration with Cmax occurring at approximately 1, 2, and 1 hour, respectively. The plasma concentration-time profiles of elagolix, E2, and NETA after oral administration of a single dose of Oriahnn morning dose under fasting conditions are shown in **Figure 2.1-1**. When Oriahnn morning dose was administered under fed conditions with a high-fat meal, the Cmax values of elagolix, E2, and NETA were on average 36%, 23%, and 50% lower, respectively, in comparison with that under fasting conditions. The high-fat meal decreased the area under the curve (AUC) of elagolix by 25% but increased the AUC of NETA by 23%. The meal did not affect the AUC of E2.

Figure 2.1-1. Plasma Concentration (Mean ± SD) -Time Profiles of Elagolix, E2, and NETA in Healthy Female Subjects After Oral Administration of a Single Dose of Oriahnn Morning Formulation (N = 164)







Source: Reviewer's plots based on Applicant's data from Study M16-856.

Distribution: The apparent volume of distribution (V_d) of elagolix was 883 L after a single dose of 300 mg. After administration of a single dose of Oriahnn morning capsule, the V_d values of E2 and NETA were 27800 L and 336 L, respectively. Elagolix is approximately 80% bound to human plasma proteins. It preferentially partitions into plasma rather than blood cellular components with a blood-to-plasma ratio of approximately 0.6.

Metabolism: Elagolix is metabolized by multiple cytochrome P450 (CYP) enzymes with major contributions from CYP3A4. CYP2D6 is responsible for approximately 20% of the total metabolism. To a lesser extent, elagolix is metabolized by CYP2C8. The contribution from UDP-glucuronosyl transferase (UGT) enzymes to drug metabolism is negligible. No major metabolites of elagolix were detected in human plasma.

Excretion: Elagolix is 90% excreted in the feces and 2.9% eliminated in the urine based on the recovery of total radioactivity. Biliary excretion contributes to the clearance of elagolix. The apparent terminal

elimination half-lives ($T_{1/2}$) of elagolix, E2, and NETA are approximately 2.9, 14.5, and 9.2 hours, respectively.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is one capsule (elagolix 300 mg/E2 1 mg/NETA 0.5 mg) in the morning and one capsule (elagolix 300 mg) in the evening, to be taken orally with or without food for up to (b) (4) months. Treatment should start within 7 days from the onset of menses. Patients in Phase 3 studies were given morning and evening doses without regard to meals. The proposed dosing regimen is acceptable for the general population of premenopausal women with uterine fibroids.

Based on the therapeutic benefit and bone loss risk analysis, the review team recommends that the duration of treatment with Oriahnn be limited to 24 months.

2.2.2 Therapeutic individualization

Hepatic Impairment: In a dedicated hepatic impairment study, following oral administration of a single dose of 150 mg elagolix, the AUC values of elagolix were comparable between subjects with normal hepatic function and subjects with mild hepatic impairment. Elagolix AUC values in subjects with moderate hepatic impairment and subjects with severe hepatic impairment were approximately 3-fold and 7-fold, respectively, of those from subjects with normal hepatic function. Also, estradiol is contraindicated in women with liver impairment or disease because of adverse effect and poor metabolism of estrogens in these patients. The Applicant proposed to contraindicate Oriahnn in women with hepatic impairment or disease. The Applicant's proposal is acceptable.

OATP1B1 Transporter Status: Pharmacogenetic analysis of 2077 DNA samples revealed 77% subjects with extensive transporter (ET) phenotype [i.e., *SLCO1B1* 521T/T genotype), 21% subjects with intermediate transporter (IT) phenotype (i.e., *SLCO1B1* 521T/C), and 2% subjects with poor transporter (PT) phenotype (i.e., *SLCO1B1* 521C/C genotype). Population PK analysis showed that the AUC of elagolix in subjects with IT phenotype or PT phenotype is expected to increase by 45% and 109%, respectively, compared to subjects with normal transporter function (i.e., subjects with ET phenotype who comprised the majority of the study population). The percentage of subjects who reported treatment-related adverse events was similar between subjects with IT phenotype and Phase 3 overall population. A 45% increase in the exposure of elagolix is not expected to have a clinically meaningful impact on the efficacy and safety of Oriahnn. Thus, no dose adjustment is needed for women with *SLCO1B1* 521T/C genotype. The frequency of *SLCO1B1* 521C/C is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on the efficacy and/or safety of elagolix has not been clearly established. The review team does not recommend dose adjustment for women with *SLCO1B1* 521C/C genotype.

Drug Interactions: The Applicant conducted 14 clinical drug interaction studies. Among the 14 studies, 10 study reports were submitted in NDA 210450 and cross referenced in the current NDA. Four study reports were submitted in the current NDA. Major clinical drug interaction findings and management strategies are summarized in **Table 2.2.2-1**.

Table 2.2.2-1. The Major Clinical Drug Interaction Study Findings and Management Strategies for Elagolix

Evaluation	Results	The Applicant's Management Strategies	Review Team's Management Strategies
The Effects of Other Drugs on Elagolix			
CYP3A4 inhibition by ketoconazole, 400 mg QD (Study M12-660)	↑C_{max} by 77% ↑AUC by 120%	No dose adjustment is required.	Concomitant use of Oriahnn and strong CYP3A inhibitors is not recommended.
OATP1B1 inhibition by a single dose of rifampin, 600 mg (Study M12-659)	↑C_{max} by 337% ↑AUC by 458%	Concomitant use of Oriahnn and strong OATP1B1 inhibitors is contraindicated.	Concur with the Applicant.
CYP3A4/P-gp induction by Rifampin, 600 mg QD (Study M12-659)	↑C_{max} by 100% ↑AUC by 65%	Concomitant use of Oriahnn and rifampin is not recommended. Concomitant use of Oriahnn and strong CYP3A inducers may decrease elagolix, estradiol and norethindrone plasma concentrations.	The increased exposure to elagolix may have been due to the net effect of OATP1B1 inhibition and CYP3A induction. Pure CYP3A inducers are expected to decrease elagolix concentrations. Concomitant use of strong CYP3A inducers may reduce the efficacy of Oriahnn and is not recommended.
The Effects of Elagolix on Other Drugs			
BCRP/OATP1B1 inhibition by elagolix 300 mg BID (Study M13-756)	↓AUC by 40% ↔ C_{max} (rosuvastatin)	Consider increasing the dose of rosuvastatin.	Monitor lipid levels and adjust the dose of rosuvastatin, if necessary.
CYP3A4 induction by elagolix 150 mg QD and 300 mg BID (Study M15-629)	↓AUC by 35 - 55% ↓C_{max} by 19 – 44% (midazolam)	Consider increasing the dose of midazolam and individualize therapy based on patient's response.	Consider increasing the dose of midazolam by no more than 2-folds and individualize midazolam therapy based on the patient's response.
P-gp inhibition by elagolix 300 mg BID (PBPK simulation)	↑C_{max} by 78% ↑AUC by 28% (digoxin)	Clinical monitoring is recommended for digoxin when co-administered with elagolix. No dose adjustment or monitoring for other P-gp substrates with a wide therapeutic index.	Increase monitoring of digoxin concentrations and potential signs and symptoms of clinical toxicity when initiating or discontinuing Oriahnn in patients who are taking digoxin.
CYP2B6 induction by elagolix 300 mg BID (Study M16-850)	↔AUC ↑ C_{max} 25% (bupropion)	No dose adjustment is required for bupropion	Concur with the Applicant.
CYP2C19 inhibition by 300 mg elagolix BID (Study M16-855)	↑C_{max} by 95% ↑AUC by 78% (omeprazole)	No dose adjustment required for omeprazole	No dose adjustment needed for omeprazole 40 mg once daily or lower when co-administered with Oriahnn. When Oriahnn is used concomitantly with higher doses of omeprazole, consider dosage reduction of omeprazole. Co-administration with Oriahnn may increase plasma concentrations of drugs that are substrates of CYP2C19.

Evaluation	Results	The Applicant's Management Strategies	Review Team's Management Strategies
DDI between elagolix 300 mg BID and E2/NETA 1 mg/0.5 mg (Study M14-708)	↑C_{max} by 128% ↑AUC by 34% (E2) ↔AUC ↔ C_{max} (NETA)	No dose adjustment for E2 and NETA in Oriahnn is needed.	Advise women to use non-hormonal contraception during Oriahnn treatment because the use of estrogens and/or progestins may affect the efficacy and safety of Oriahnn.

AUC = area under the curve; BCRP = breast cancer resistance protein; BID = twice daily; C_{max} = maximum concentration; DDI = drug-drug interaction; E2/NETA = estradiol/norethindrone acetate; PBPK = physiologically-based pharmacokinetics; P-gp = P-glycoprotein; QD = once a day

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following Labeling recommendation and comments:

Section 7.1: Elagolix is a weak inhibitor of CYP2C19. Co-administration with Oriahnn may increase plasma concentrations of drugs that are substrates of CYP2C19 (e.g., omeprazole and esomeprazole).
Section 7.2: Concomitant use of Oriahnn and strong CYP3A inhibitors (e.g., ketoconazole) is not recommended.

(b) (4)

Section 12.1: The language for mechanism of action was revised.
Section 12.3, Table 6: The ranges of Tmax for elagolix, E2 and NETA were added. The terminal half-lives were revised.
Section 12,3, Drug Interaction Studies: The effect of co-administered rosuvastatin, sertraline or fluconazole on E2/NETA has not been studies.

(b) (4)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Oriahnn is a fixed-dose combination (FDC) product of elagolix, E2, and NETA that is being sought for the management of heavy menstrual bleeding (HMB) associated with uterine leiomyomas (or uterine fibroids). The clinical trials that support the safety and efficacy of Oriahnn were conducted under IND 115528. The Phase 1 studies supporting the NDA were conducted under IND 64802. Additionally, to support the E2/NETA component of Oriahnn, the Applicant cross referenced Activella® NDA 020907 for the nonclinical sections and general clinical pharmacology information (e.g. metabolism and drug-drug interactions) and has submitted literature as summarized in NDA 020907. The End of Phase 2 and pre-NDA meetings with the FDA were held on May 27, 2015 and June 13, 2019, respectively.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Elagolix is a GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland.

	Administration of elagolix results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone and reduces bleeding associated with uterine fibroids. E2 acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a component of Oriahnn, the addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from elagolix alone. Progestins such as NETA act by binding to nuclear receptors that are expressed in progesterone-responsive tissues.
Active Moieties	Elagolix, E2, and NETA
QT Prolongation	No QT interval prolongation of clinical concern was observed at a single dose of 1200 mg. The effect of E2 and NETA on the QTc interval has not been studied.
General Information	
Bioanalysis	LC-MS/MS methods were used to measure elagolix, NETA, E2, and E2 metabolites in plasma, and E2 and progesterone in serum.
Healthy vs. Patients	No dedicated comparative PK study between healthy subjects and patients was conducted. Population PK prediction showed that the average plasma concentration (C_{avg}) of elagolix in women with uterine fibroids was approximately 20% lower than that in healthy women.
Drug exposure at steady state (Mean ± SD)	Elagolix 300 mg BID: AUC_{0-12} = 2826 ± 1231 ng*h/mL E2 and NETA: not available.
Range of effective dose or exposure	Effective dose range of elagolix: 100 mg BID to 300 mg BID or 600 mg QD
Maximally tolerated dose or exposure	Maximally tolerated doses of elagolix, E2, and NETA was not established. A single dose of 1200 mg elagolix and multiple doses of elagolix (400 mg BID for 21 days) were tested in healthy subjects. The doses of 300 mg BID with or without 1 mg E2/0.5 mg NETA QD were tested in women with uterine fibroids for 48 weeks. The doses of 600 mg QD with or without 1 mg E2/0.5 mg NETA QD were tested in women with uterine fibroids for 24 weeks.
Pharmacodynamics	Administration of elagolix results in dose-dependent suppression of LH and FSH, leading to decreased blood concentrations of the ovarian sex hormones, E2 and progesterone. The E2/NETA component supplements endogenous estrogen and progesterone. In Phase 3 trials in women with uterine fibroids administered Oriahnn for 6 months, the median concentrations of LH and FSH were approximately 0.40 to 0.70 mIU/mL and 1.8 to 2.5 mIU/mL respectively, resulting in median concentrations of estradiol of approximately 42 to 51 pg/mL, and progesterone of approximately 0.37 to 0.38 nM. In healthy women treated with Oriahnn, only appropriately 10% women reported ovulation.
Dose Proportionality	For multiple-dose PK, on Day 1, elagolix shows dose-proportional increase in exposures (C_{max} and AUC) up to 200 mg and a more than dose-proportional increase from 200 mg to 1200 mg. At steady state (Day 21), elagolix shows a dose-proportional increase in exposures (C_{max} and AUC) up to 400 mg BID. Dose proportionality of E2 and NETA was not assessed.
Accumulation	Repeated daily administration of elagolix (QD or BID) at a dose ≥ 200 mg resulted in a decrease in drug exposure from Day 1 to Day 21. The accumulation ratio for elagolix was 0.78 for 300 mg BID dose. The

	accumulation ratios for E2, estrone (a major metabolite of E2), and NETA were 33-47% above concentrations following single dose administration.			
Variability	Between-subject (in a BE study): elagolix C_{max} 44%, AUC 44%; E2 C_{max} 52%, AUC 41%; and NETA C_{max} 35%, AUC 45%.			
Absorption				
Bioavailability	The absolute bioavailability of elagolix, E2, and NETA in humans has not been established.			
Fasted T_{max} (Median and Range)	Elagolix: 1.5 h (1.0 – 4.0 h); E2: 2.0 (0.0 – 10.0 h); and NETA: 1.0 h (0.5 – 2.0 h)			
Food Effect Following a High-Fat Meal (Fed/fasted) [90% CI]	**Drug component**	**$AUC_{0-\infty}$**	**C_{max}**	**T_{max} (Median, hour)**
	Elagolix	75% [66% - 84%]	64% [51% - 81%]	Fed: 3.0, Fasted: 1.5
	E2	105% [96% - 114%]	77% [65% - 91%]	Fed: 5.0, Fasted: 2.0
	NETA	123% [114% - 132%]	50% [43% - 59%]	Fed: 4.0, Fasted: 1.0
Distribution				
Volume of Distribution	Elagolix: 883 L; E2: 27772 L; and NETA: 336 L			
Plasma Protein Binding	Elagolix: 80%; E2: 98%; and NETA: 97%			
Substrate transporter systems	Elagolix is a substrate of P-gp and OATP1B1. Population PK analysis showed OATP1B1 phenotype status was the only significant covariate on elagolix CL/F.			
Elimination				
Terminal Elimination half-life (Mean ± SD)	Elagolix: 2.9 ± 0.8 h; E2: 14.5 ± 6.6 h; and NETA: 9.2 ± 4.0 h			
CL/F (Mean ± SD)	Elagolix: 79 ± 31 L/h; E2: 1246 ± 717 L/h; and NETA: 24 ± 12 L/h			
Metabolism				
Fraction metabolized (% dose)	Elagolix: 69% of dose recovered in feces and urine is metabolized.			
Primary metabolic pathway(s)	Elagolix is extensively metabolized in liver, primarily by CYP3A4, lesser extent by CYP2D6, and minor by CYP2C8. In human plasma, two oxidative metabolites (O-demethylated and N-dealkylated metabolites) constitute 2.4% and 3.3% of exposure relative to elagolix. E2 and NETA are metabolized partially by CYP3A. Other metabolic pathways for E2 and NEAT include sulfation and glucuronidation.			
Excretion				
Primary excretion pathways (% dose) ±SD	--Elagolix in feces: 90.1% (approximately 26.3% unchanged elagolix) --Elagolix in urine: 2.9% (approximately 2.6% unchanged elagolix)			
In vitro interaction liability (as a perpetrator)				
Inhibition/Induction of metabolism	Elagolix is a time-dependent inhibitor of CYP3A4/5 (K_i 74 μM), CYP2C8 (K_i 82 μM), and CYP2C19 (K_i 34 μM), and an inducer of CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. E2 and NETA are substrates of CYP3A4.			
Inhibition/Induction of transporter systems	Elagolix is an inhibitor of OATP1B1, OATP1B3, P-gp, and BCRP.			

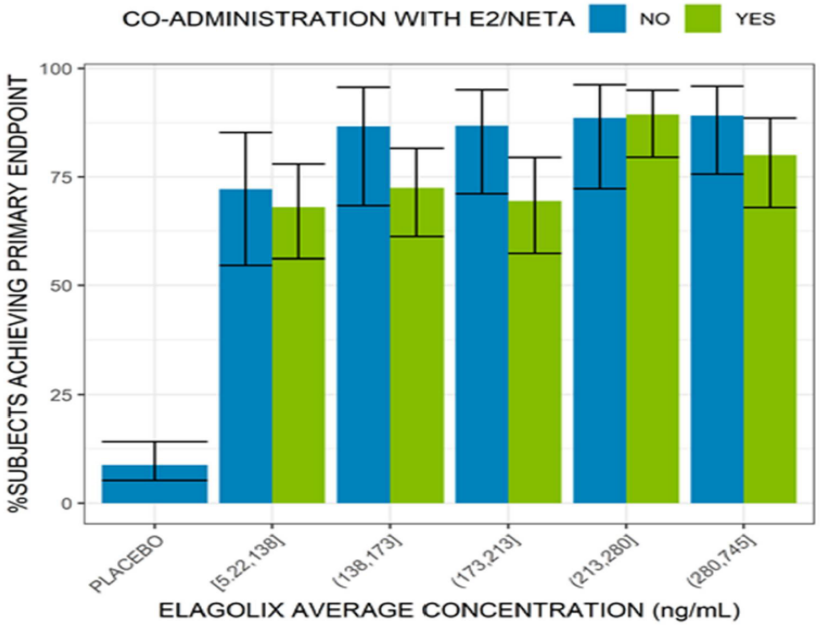
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology information which provides supportive evidence of effectiveness includes: (1) elagolix exposure-response analyses for the primary efficacy endpoint [the proportion of subjects who had menstrual blood loss (MBL) < 80 mL during the final month and ≥ 50% reduction in MBL volume from baseline to the final month]; (2) dose-dependent efficacy observed in two Phase 2 studies; and (3) suppression effect of elagolix on E2 and progesterone in Phase 3 trials.

Elagolix exposure-response information for primary efficacy endpoint:

Figure 3.3.1-1. Elagolix Average Concentration Quintile Plot for Proportion of Subjects that Met the Primary Efficacy Endpoint.



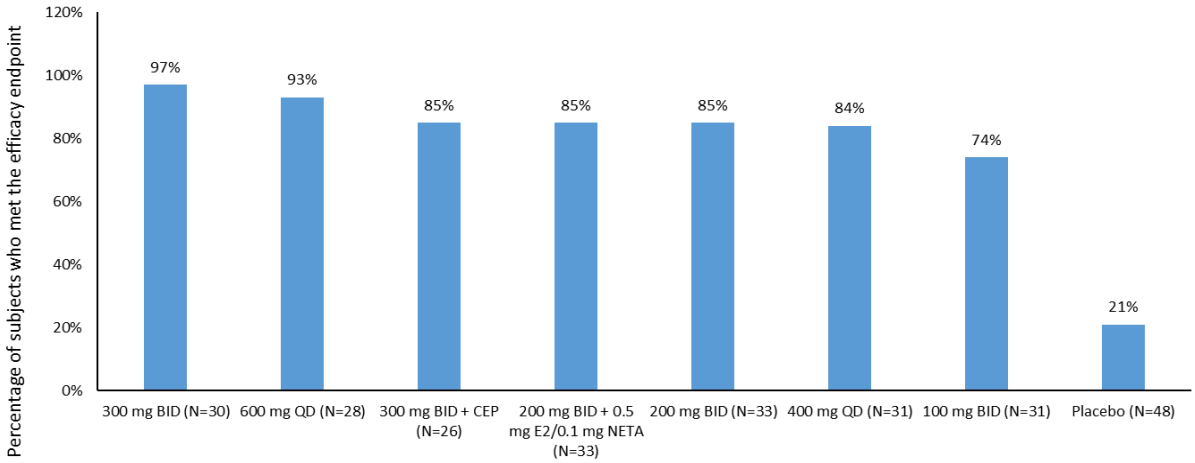
Note: Bars plots represents observed proportions and error bars represents 95% binomial confidence intervals (CIs) of the observed proportions versus the model-predicted average elagolix concentration quintile
Source: Exposure-response analysis for efficacy study report (Report # RD190059), Figure 4.

To demonstrate the effectiveness of elagolix, the Applicant conducted exposure-response analysis for the primary efficacy endpoints using data from two Phase 3 trials: Study M12-815 and Study M12-817. The relationship between average plasma concentration of elagolix (C_{avg}) and percentage of subjects who met the primary efficacy endpoint was explored using quintile plots (**Figure 3.3.1-1**). For both elagolix 300 mg BID alone and elagolix 300 mg BID + E2/NETA groups, both exposure-response quintile plots and logistic regression analysis suggest that higher elagolix exposure is associated with higher probability of achieving the primary bleeding endpoint (see Appendices 4.6 for details). The addition of E2/NETA caused a small decrease (<10%) in the percentage of achieving the primary efficacy endpoint.

Dose-dependent efficacy observed in two Phase 2 studies:
In the Phase 2 dose-finding Study M12-663, the percentage of subjects who had MBL < 80 mL during the last 28 days of treatment and ≥ 50% reduction from baseline in MBL was used as an exploratory efficacy endpoint. The response was dose-dependent with 74% for elagolix daily dose of 200 mg, 84% to 85% for elagolix daily

dose of 400 mg, and 85% to 97% for elagolix daily dose of 600 mg, compared with 21% for the combined placebo group (**Figure 3.3.1-2**).

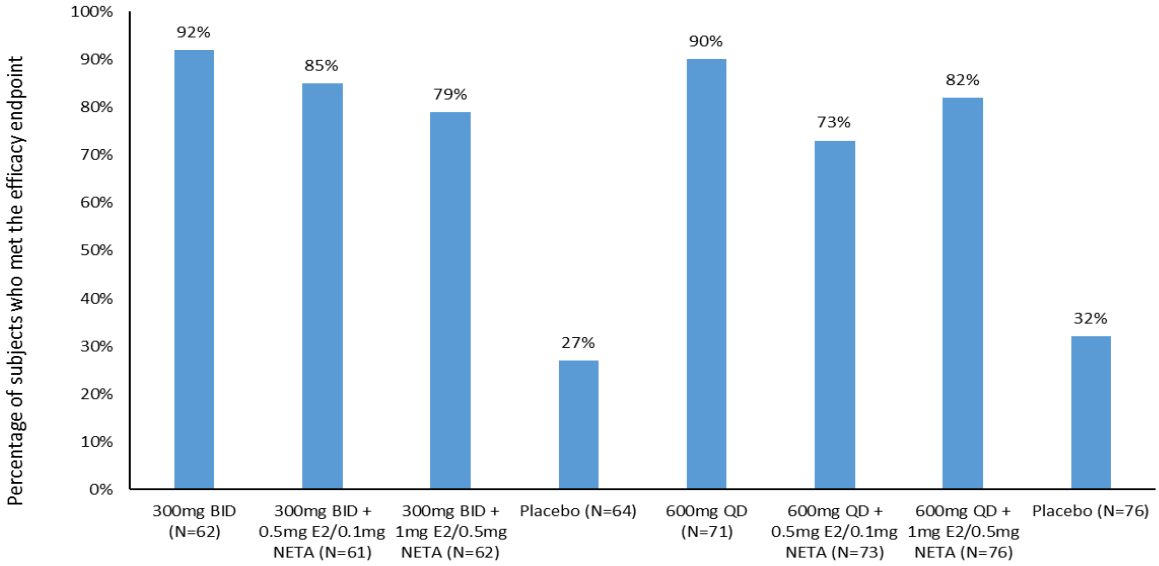
Figure 3.3.1-2. Analysis of Efficacy Endpoint for the Last 28 Days of Treatment Using Combined Placebo Group (Study M12-663)



Note: Efficacy endpoint: the percentage of subjects who had MBL < 80 mL during the last 28 days of treatment and ≥ 50% reduction in MBL volume from baseline to the final month.
BID = twice a day; CEP = combined Estrace (1 mg E2) and cyclical Prometrium (200 mg progesterone) administered QD; E2/NETA = estradiol/norethindrone acetate; QD = once a day
Source: Study M12-663 report, Table 20.

In the Phase 2b dose-finding Study M12-813, the Applicant assessed the effectiveness of elagolix at 300 mg BID or 600 mg QD alone and in combination with 2 different strengths of hormonal add-back therapies, 0.5 mg E2/0.1 mg NETA or 1 mg E2/0.5 mg NETA. As shown in **Figure 3.3.1-3**, all the treatment groups showed a statistically significantly greater proportion of responders who achieved MBL volume of < 80 mL at the final month and ≥50% reduction in MBL volume from baseline to the final month compared with that of the placebo group. The efficacy of elagolix was attenuated in a dose-dependent fashion by add-back therapy with E2/NETA.

Figure 3.3.1-3. Percentage of Subjects Who Met the Efficacy Endpoint by Treatment Group (Study M12-813)

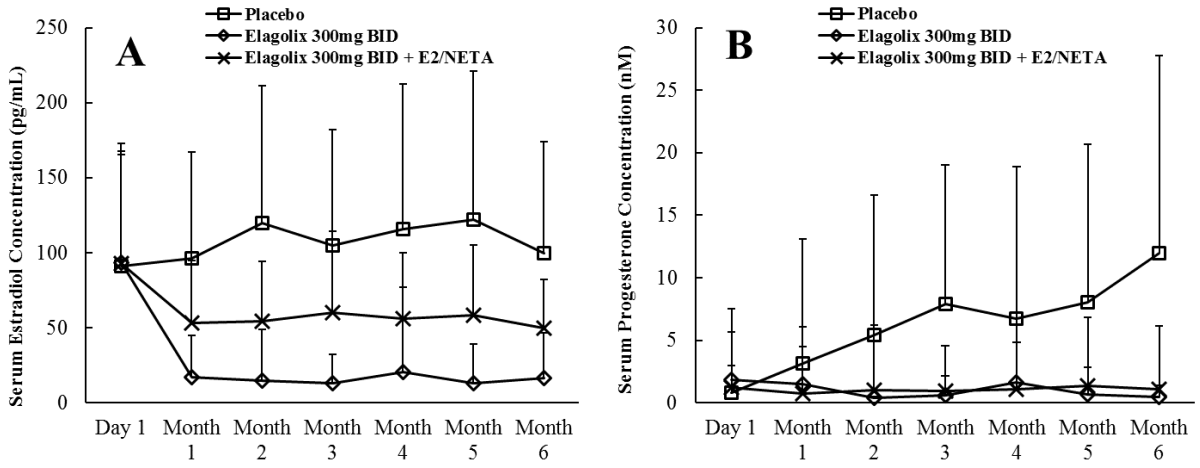


Note: Efficacy endpoint: the percentage of subjects who had MBL < 80 mL at the final month of treatment and ≥ 50% reduction in MBL volume from baseline to the final month. BID = twice a day; E2/NETA = estradiol/norethindrone acetate; QD = once a day

Source: Study M12-813 report, Table 19.

Suppression on E2 and progesterone in Phase 3 trials:

Figure 3.3.1-4. Mean ± SD Serum (A) Estradiol and (B) Progesterone Concentration–Time Profiles by Treatment Group (Study M12-815).



Source: Study M12-815 report, Table 29 and Table 30.

Elagolix reduces HMB primarily by suppressing ovarian sex hormones, estradiol and progesterone. To attenuate the hypoestrogenic effects (e.g., bone loss and hot flush) of elagolix alone treatment, E2/NETA was combined with elagolix as hormonal add-back therapy. In the uterine fibroids Phase 3 program, elagolix 300 mg BID + 1 mg E2/0.5 mg NETA was chosen as the to-be-marketed dose, and elagolix 300 mg BID alone was included as a reference arm to characterize the effect of E2/NETA. The effect of elagolix and add-back therapy on serum E2 and progesterone was assessed in Phase 3 trials. As shown in the Phase 3 Study M12-815 (**Figure 3.3.1-4**), compared with placebo, the overall Month 1 to Month 6 mean E2 concentration was reduced by approximately 84% and 49% in the elagolix 300 mg BID alone and elagolix 300 mg BID+E2/NETA groups, respectively. The overall Month 1 to Month 6 mean progesterone concentration was reduced by approximately 80% in both elagolix 300 mg BID alone and elagolix 300 mg BID+E2/NETA groups. Similar hormonal suppression results were observed in the pivotal Phase 3 Study M12-817 and Phase 3 extension Study M12-816. Furthermore, using pooled data from six studies (M12-813, M12-665, M12-667, M12-671, M12-821, and M12-673), the Applicant assessed the relationship between steady-state plasma E2 concentrations and elagolix daily dose, which revealed a dose-dependent suppression of E2.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

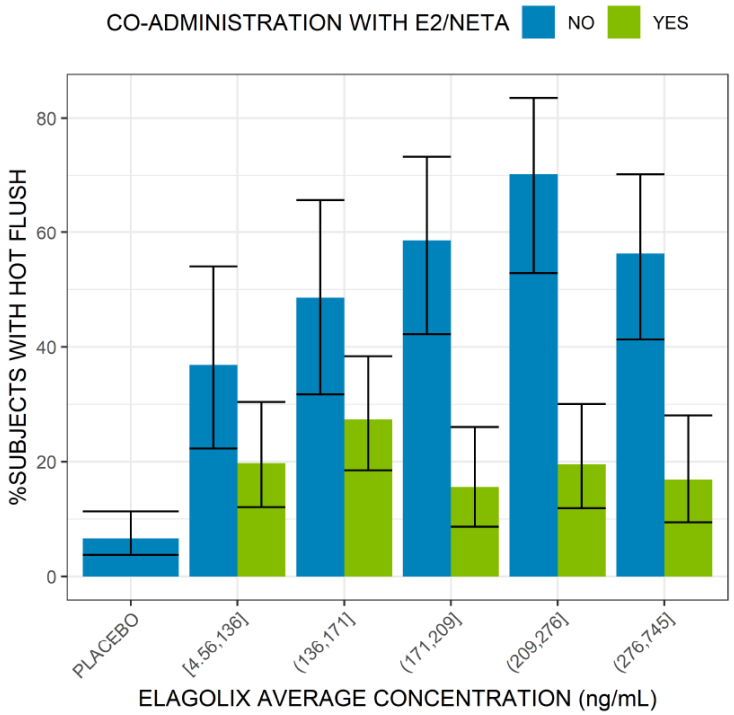
Yes, the proposed dose regimen is appropriate for the management of HMB associated with uterine fibroids in premenopausal women. The proposed regimen is supported by clinical efficacy and safety

data, exposure-response for safety, and QTc prolongation data. However, due to the loss in bone density observed in the Phase 3 trials, we recommend that the duration of treatment be limited to 24 months.

Efficacy:
The efficacy of elagolix 300 mg BID + 1 mg E2/0.5 mg NETA QD dose in the management of HMB associated with uterine fibroids was demonstrated in two pivotal placebo-controlled Phase 3 studies (Study M12-815 and M12-817) conducted in premenopausal women aged 18-51 years old. In both studies, 300 mg BID + E2/NETA significantly increased the responder rates at the final month compared to the placebo group. Refer to Section 8.1 Statistical and Clinical Evaluation of the multi-disciplinary review for discussion on efficacy.

Exposure-Response Analysis for Hot Flush:
In the two pivotal Phase 3 trials, 6.6%, 54.3%, and 20.0% subjects experienced hot flush in placebo, 300 mg BID, and 300 mg BID + E2/NETA groups, respectively. The relationship between average elagolix exposure C_{avg} and percentage of subjects with occurrence of hot flush was explored using quintile plots (**Figure 3.3.2-1**) and logistic regression analysis (See Appendices 4.6 for details). An increasing trend of incidence of hot flush was observed with increasing elagolix average concentrations for 300 mg BID. For 300 mg BID + E2/NETA, no clear exposure-response relationship was identified between elagolix exposure and incidence of hot flush. The add-back therapy reduced the occurrence of hot flush caused by elagolix.

Figure 3.3.2-1. Exposure-Response Analysis for Hot Flush



Note: Bars plots represents observed proportions and error bars represents 95% binomial CIs of the observed proportions at the model-predicted average concentration quintile.
Source: Exposure-response analysis for safety study report (Report # RD190282), Figure 19.

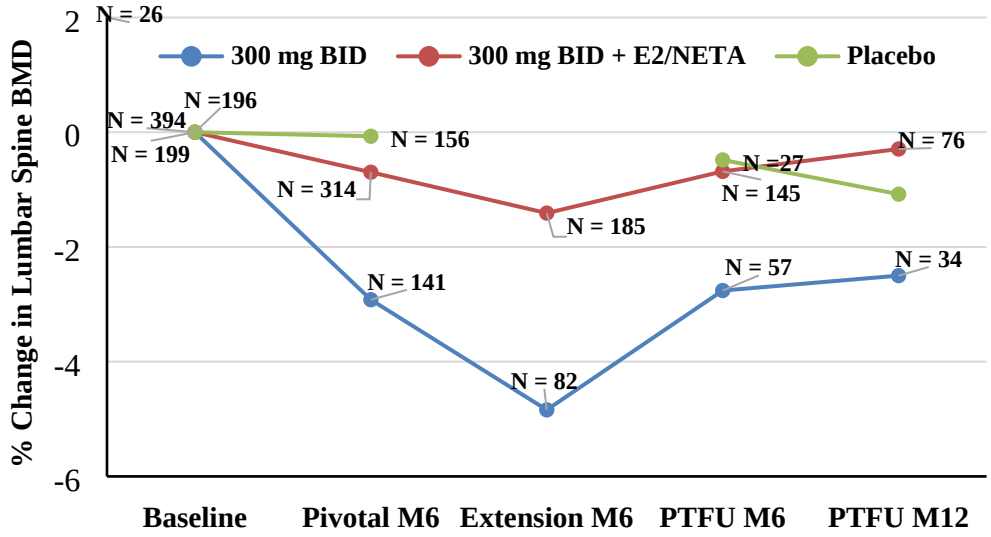
QTc prolongation:
In Phase 1 studies, a single dose of 1200 mg elagolix and multiple doses of elagolix (400 mg BID for 21 days) were well tolerated in healthy subjects. The effect of elagolix on QT prolongation was evaluated in healthy premenopausal women and no significant QTc prolongation effect of elagolix (single-dose 300

mg and 1200 mg) was detected. The supratherapeutic dose of 1200 mg produced mean (± SD) C_{max} value of 13229 (± 4218) ng/mL which is ~9-fold of the mean (± SD) C_{max} of 1479 (± 530) ng/mL at the therapeutic dose of 300 mg BID. The study reports were submitted in NDA 210450. The effect of E2 and NETA on QT prolongation was not evaluated.

Bone Mineral Density:
Long-term estradiol suppression by elagolix is expected to cause a decrease in bone mineral density (BMD) and E2/NETA add-back therapy can attenuate the bone loss. For subjects enrolled in Phase 3 trials, BMD of the lumbar spine, total hip, and femoral neck was assessed at baseline, Month 6 in the placebo-controlled pivotal studies, and Month 6 of the extension studies. Post-treatment recovery of BMD was assessed in post-treatment follow-up (PTFU) period (PTFU Month 6 and Month 12). As shown in **Figure 3.3.2-2**, treatment duration-dependent decrease in lumbar spine BMD was observed in both 300 mg BID and 300 mg BID + E2/NETA groups.

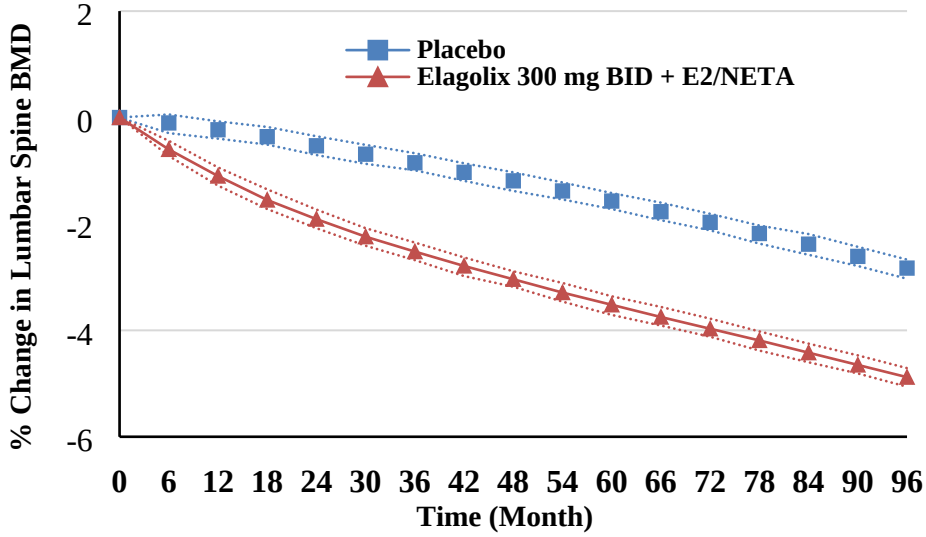
The Applicant developed a population exposure-BMD model for elagolix to simulate BMD changes in women with HMB associated with uterine fibroids using data available from three Phase 3 studies. Each simulated subject was treated with elagolix 300 mg BID + E2/NETA or placebo for 96 months and the % change from baseline BMD was predicted over the treatment period. The mean % change in lumbar spine BMD over time together with 95% confidence intervals (CIs) are shown in **Figure 3.3.2-3**. The simulated mean % changes in lumbar spine BMD from baseline after 12-, 24-, 36-, and 48-month elagolix 300 mg BID + E2/NETA treatment were 1.10%, 1.91%, 2.52%, and 3.04%, respectively. Based on the threshold of 3% BMD loss from baseline, the Applicant proposed continuous use of elagolix 300 mg BID + E2/NETA up to (b) (4) months. However, the review team noted that after continuous treatment with elagolix 300 mg BID + E2/NETA for 12 months in Phase 3 trials, 10.9% and 1.7% of subjects experienced >5% and ≥8% lumbar spine BMD decreases from baseline, respectively. Even after a 12-month post-treatment period, 5.4% of subjects in elagolix 300 mg BID + E2/NETA group still had >5% lumbar spine BMD decreases from baseline, indicating an incomplete recovery to baseline.

Figure 3.3.2-2. Observed Mean Percent Changes in BMD During 12-Month Treatment Period and 12-Month Post-Treatment Period in Studies M12-815/M12-816/M12-817



Source: Applicant's IR response submitted on 1/15/2020, Table 5.

Figure 3.3.2-3. Simulated Mean % Change in Lumbar Spine BMD From Baseline Over Time



Note: Dash lines represent 95% CIs.
Source: Exposure-response analysis for safety study report (Report # RD190282), Table 13.3-1.8.1.

In Phase 2 Study M12-813, the Applicant assessed the efficacy and safety of elagolix 300 mg BID and elagolix 600 mg QD groups with and without E2/NETA add back. It was found that the proportions of subjects who met the primary efficacy endpoint in the elagolix 300 mg BID and elagolix 600 mg QD groups were similar. However, better tolerability was seen with the elagolix 300 mg BID + E2/NETA regimen compared to the elagolix 600 mg QD + E2/NETA regimen (refer to individual study review in Appendix for more details). Furthermore, the Applicant assessed the attenuating effect of two add-back regimens, 0.5 mg E2/0.1 mg NETA and 1 mg E2/0.5 mg NETA, on bone loss. As shown in **Table 3.3.2-1**, dose-dependent attenuating effect of E2/NETA on lumbar spine BMD decreases was observed. The add-back therapy with 1 mg E2/0.5 mg NETA more effectively attenuated the decrease in BMD compared to that with 0.5 mg E2/0.1 mg NETA.

Table 3.3.2-1. Mean Percentage Changes in Lumbar Spine Bone Mineral Density from Baseline to Month 6 in Phase 2 Study M12-813

	Treatment	Month 6 Visit N	Mean % Change
Cohort 1	Placebo	44	0.91
	Elagolix 300mg BID	48	-3.80
	Elagolix 300mg BID + 0.5 mg E2/0.1 mg NETA	48	-1.62
	Elagolix 300mg BID + 1 mg E2/0.5 mg NETA	48	-0.141
Cohort 2	Placebo	58	-0.13
	Elagolix 600mg QD	57	-3.40
	Elagolix 600mg QD + 0.5 mg E2/0.1 mg NETA	46	-1.24
	Elagolix 600mg QD + 1 mg E2/0.5 mg NETA	52	-1.11

Source: Study M12-813 report, Table 97.
BID = twice a day; E2/NETA = estradiol/norethindrone acetate; QD = once a day

3.3.3 Is there a management strategy required for subpopulations based on intrinsic factors?

Yes, Oriahnn is contraindicated in women with hepatic impairment.

Hepatic and Renal Impairment:

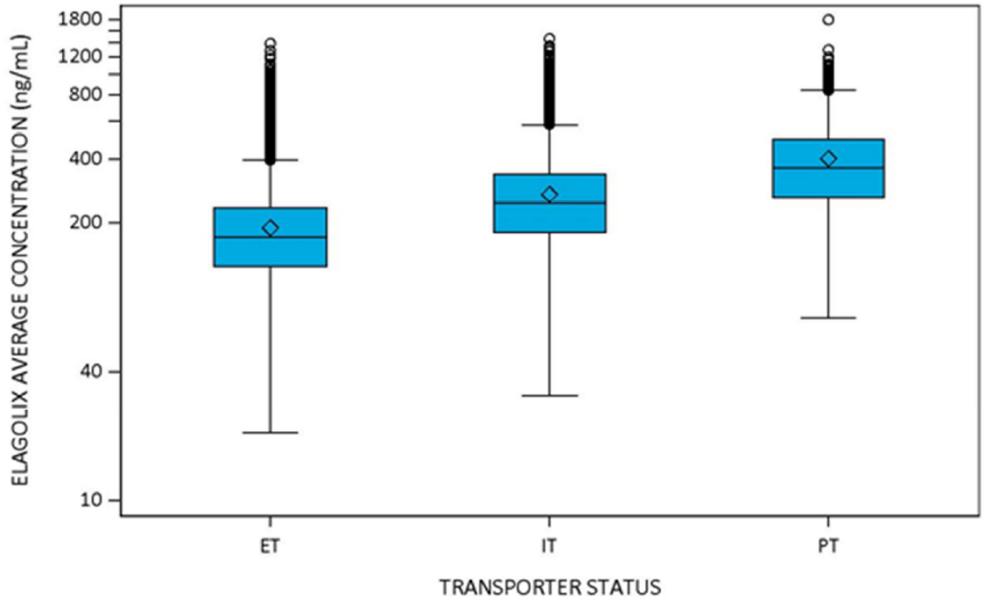
The PK of elagolix was evaluated in women with renal and hepatic impairment at elagolix 200 mg and 150 mg, respectively. The study reports were submitted in NDA 210450. Refer to Clinical Pharmacology Review for NDA 210450 dated 7/20/2018 in DARRTS for more information. Comparable exposure of elagolix was observed in subjects with various renal function status. Renal impairment did not result in a significantly higher exposure of elagolix. No dose adjustment for elagolix was required in women with any degree of renal impairment or end-stage renal disease (including women on dialysis). The effect of renal impairment on the PK of E2/NETA has not been studied.

The mean AUC value of elagolix was comparable between subjects with normal hepatic function and subjects with mild hepatic impairment (Child-Pugh A). Elagolix AUC values in subjects with moderate hepatic impairment (Child-Pugh B) and subjects with severe hepatic impairment (Child-Pugh C) were approximately 3-fold and 7-fold, respectively, of the AUC values in subjects with normal hepatic function. The effect of hepatic impairment on the PK of E2/NETA has not been studied. Due to the adverse effect and poor metabolism of E2 in subjects with liver impairment or disease, Oriahnn is contraindicated in these subjects.

OATP1B1 Transporter Phenotype Status:
Pharmacogenetic analysis of 2077 DNA samples collected from the Phase 1 and Phase 3 studies revealed 77% subjects with genotype-inferred extensive transporter phenotype (ET, i.e., *SLCO1B1* 521T/T genotype), 21% subjects with intermediate transporter phenotype (IT, i.e., *SLCO1B1* 521T/C genotype), and 2% subjects with poor transporter phenotype (PT, i.e., *SLCO1B1* 521C/C genotype). In the uterine fibroids Phase 3 trials (Studies M12-815, M12-816 and M12-817), five subjects (1 on placebo, 3 received elagolix+E2/NETA, 1 received elagolix alone) had PT phenotype and 74 subjects had PT and IT phenotype, respectively.

Population PK analysis identified that organic anion-transporting peptide (OATP) 1B1 phenotype status was a significant covariate on elagolix CL/F. Model simulations showed that subjects with phenotype status PT or IT had 2.09-fold and 1.45-fold higher exposures (i.e., C_{avg}), respectively compared to subjects with a phenotype status of ET (**Figure 3.3.3-1** and **Table 3.3.3-1**).

Figure 3.3.3-1. Effect of OATP1B1 Phenotype on Elagolix Average Concentration



Note: The box shows the interquartile range (IQR) with a median line in between. Lower/upper whiskers extend to the lowest/highest value within 1.5 * IQR.

Source: Population PK study report, Figure 4.
ET = extensive transporter; IT = intermediate transporter; PT = poor transporter

Table 3.3.3-1. Elagolix Exposure Simulated by Population PK model – Subgroup Analysis by OATP1B1 Genotype

	Simulated Elagolix Exposure (Median and 95% CIs)		
OTAP1B1	**Cavg (ng/mL)**	**Cmax (ng/mL)**	**Ctrough (ng/mL)**
Extensive	172 (78.6, 370)	631 (301, 1299)	2.06 (0.387, 11.7)
Intermediate	250 (115, 529)	917 (439, 1868)	3.03 (0.563, 16.9)
Poor	360 (152, 786)	1289 (621, 2719)	4.50 (0.736, 28.4)

Source: Population PK study report, Table 13.3-9.
Cavg = average concentration; Cmax = maximum concentration; Ctrough = lowest concentration reached before next dose is administered

Nineteen among 41 subjects (46.3%) with IT phenotype treated with Oriahnn in the Phase 3 trials reported adverse events, which was comparable to that of the overall patient population (50.4%) (**Table 3.3.3-2**). Furthermore, the percentages of subjects who reported severe adverse events were similar between IT phenotype population (9.8%) and Phase 3 overall population (9.1%). Therefore, a 45% increase in the exposure of elagolix in the subjects with IT phenotype is not expected to have a clinically meaningful impact on efficacy and safety. No dose adjustment is needed or women with OATP1B1 IT phenotype.

Table 3.3.3-2. Treatment-Emergent Adverse Events: OATP1B1 Intermediate Transporter Phenotype versus Overall Phase 3 Population

	Number (%) of Subjects with Intermediate Transporter Phenotype			**Number (%) of Subjects in Overall Phase 3 Population[a]**		
		Elagolix 300 mg BID			Elagolix 300 mg BID	
	Placebo N = 22	Alone N = 22	+E2/NETA N = 41	Placebo N = 196	Alone N = 199	+E2/NETA N = 395
Any AE	16 (72.7)	13 (59.1)	27 (65.9)	130 (66.3)	166 (83.4)	283 (71.6)
Drug related AE[b]	7 (31.8)	13 (59.1)	19 (46.3)	73 (37.2)	143 (71.9)	199 (50.4)
Any SAE	1 (4.5)	0 (0)	4 (9.8)	10 (5.1)	20 (10.1)	36 (9.1)
Drug related SAE[b]	0	0 (0)	2 (4.9)	N.A.	N.A.	N.A.

Source: Summary of Clinical Safety, Table 8 and ISS safety adverse events dataset
AE = adverse event; SAE = severe adverse event; BID = twice a day; E2/NETA = estradiol/norethindrone acetate;

a. Placebo-Controlled Phase 3 Analysis Set
b. As assessed by the investigator; choices were reasonable possibility and no reasonable possibility

The population PK model-simulated steady-state PK parameters for the five subjects with uterine fibroids and OATP1B1 PT phenotype in Phase 3 trials were shown in **Table 3.3.3-3**. Although the C_{avg} values of elagolix in the four subjects who received elagolix + E2/NETA or elagolix alone are higher than the mean C_{avg} in uterine fibroids patients (211 ± 100 ng/mL, N = 706), they are still within 95% CIs in uterine fibroids patients (median C_{avg} = 189 ng/mL and 95% CIs: 97 – 391 ng/mL). The three subjects ((b) (6), (b) (6)) who received elagolix 300 mg +E2/NETA for 12 months did not show significant lumbar spine BMD loss compared to the mean BMD loss in other subjects in 300 mg +E2/NETA group (**Figure 3.3.3-2**). Furthermore, no severe adverse events (AEs) were reported among the five subjects

with OATP1B1 PT genotype. Only Subject (b) (6) reported three moderate on-treatment AEs (stiff neck, depression and migraine).

Table 3.3.3-3. Simulated Steady-State Pharmacokinetic Parameters of Elagolix in Subjects with Uterine Fibroids and OATP1B1 Poor Transporter Phenotype

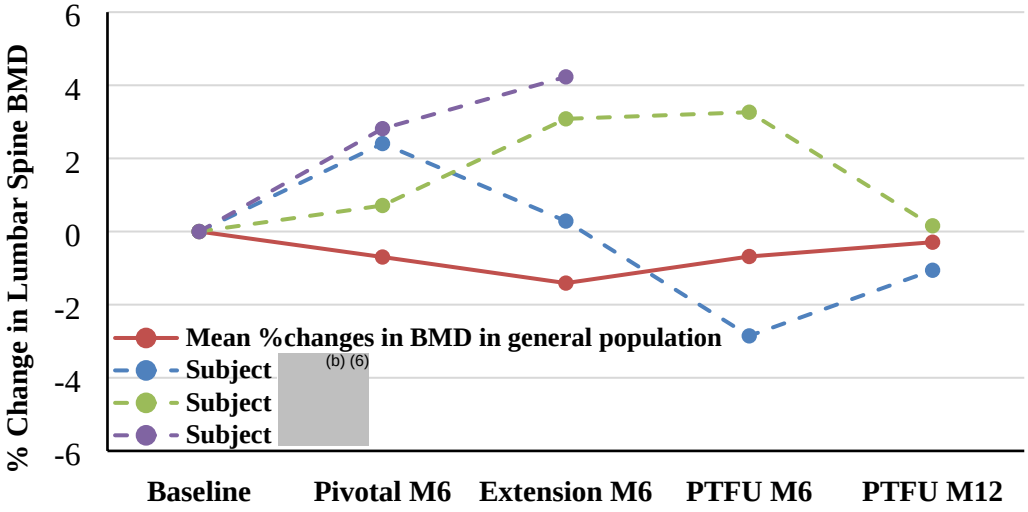
Study # Subject ID	Treatment	CL/F (L/h)	V_2/F (L)	C_{avg} (ng/mL)
M12-815				
(b) (6)	Placebo/300 mg BID	87.8	184	285
M12-817				
(b) (6)	300 mg BID + E2/NETA	72.6	226	344
	300 mg BID + E2/NETA	66	160	379
	300 mg BID + E2/NETA	125	205	200
*	Placebo	N.A.	N.A.	N.A.

Source: Reviewer's analysis

* Subject was in placebo group therefore no PK data was available for simulation. N.A.- Not Available.
BID = twice a day; Cavg = average concentration; CL/F = apparent drug clearance; E2/NETA = estradiol/norethindrone acetate; N.A. = not available; V2/F = volume of distribution after non-intravenous administration

A 109% increase in the exposure of elagolix may pose a safety risk in the subjects with PT phenotype. However, the frequency of OATP1B1 PT phenotype (i.e., SLCO1B1 521C/C genotype) is generally lower than 5% in most racial/ethnic groups. The limited safety data from three subjects showed that 12-month continuous treatment with elagolix 300 mg +E2/NETA did not result in severe AEs or significant bone loss in subjects with OTAP1B1 PT phenotype (see **Figure 3.3.3-2** below). The impact of this polymorphism on the safety of elagolix has not been clearly established. We do not recommend dose adjustment for women with OATP1B1 PT phenotype. To mitigate potential safety risk, the following statement is added to Section 12.5 of drug label: "Adverse effects of elagolix have not been fully evaluated in subjects who have two reduced function alleles of the gene that encodes OATP 1B1 (*SLCO1B1 521T>C*)."

Figure 3.3.3-2. Observed Percent Changes in BMD During 12-Month Treatment Period and 12-Month Post-Treatment Period – Individual Subjects with OATP1B1 Poor Transporter Phenotype versus General Population



Source: Reviewer's analysis

Age:
The 2168 subjects included in population PK analysis had an age range of 18 - 53 years and a mean age of 35.8 ± 7.8 years. Population PK analysis showed that subject age did not affect the clearance or volume of distribution of elagolix. Refer to Appendices 4.5 Population PK Analyses for more information. The effects of age on plasma steady-state levels of estrone sulfate was evaluated in the Activella NDA 20907 and no difference in the steady-state concentrations of estrone sulfate was observed between women aged above 65 and below 65 years. However, plasma E2 and NETA concentrations were not measured in the study. Therefore, a definitive conclusion cannot be drawn from this study.

The Applicant's subpopulation analysis for primary efficacy endpoint showed that the responder rates to 300 mg BID + E2/NETA treatment in subjects < 35 years old (77.3%), 35-40 years old (68.8%), 40-45 years old (75.8%), and ≥ 45 years old (69.5%) were comparable. No significant age effect on efficacy was observed for 300 mg BID + E2/NETA treatment.

The Applicant's subpopulation analysis for BMD showed that although 6-month treatment with 300 mg BID likely caused more bone loss in subjects < 40 years old, there was no apparent trend in mean percent changes in lumbar spine BMD from baseline corresponding with increasing age compared to placebo at Month 6 of 300 mg BID + E2/NETA treatment (**Table 3.3.3-4**).

Table 3.3.3-4. Mean Percent Changes in Lumbar Spine BMD by Age Compared to Placebo at Month 6 of Treatment

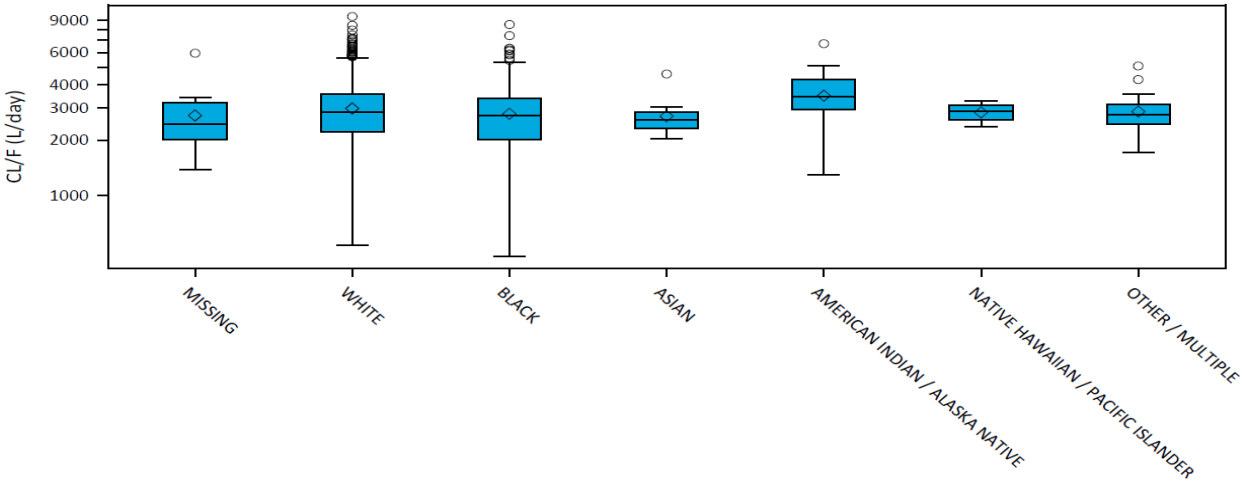
Percent Changes (%) in Lumbar Spine BMD Compared to Placebo by Age Group Least Squares Mean (95% CI)				
Treatments	**< 35 Years**	**35 – 40 Years**	**40 – 45 Years**	**≥ 45 Years**
Placebo	-0.07 (-1.15, 1.02)	0.05 (-0.79, 0.88)	-0.74 (-1.57, 0.09)	0.19 (-0.42, 0.79)
300 mg BID	-3.57 (-4.96, -2.18)	-3.24 (-4.18, -2.30)	-2.74 (-3.50, -1.97)	-2.93 (-3.57, -2.29)
300 mg BID + E2/NETA	-1.42 (-2.22, -0.61)	-0.17 (-0.77, 0.43)	-0.82 (-1.37, -0.27)	-0.65 (-1.08, -0.22)

Source: Reviewer's summary from Integrated Study of Safety, TABLE 5.1-3.1.1.1
BID = twice a day; BMD = bone mineral density; CI = Confidence Interval; E2/NETA = estradiol/norethindrone acetate

Overall, consistent elagolix PK, efficacy and safety were observed in subjects aged 18 – 53 years. The review team agrees with the Applicant that no age-based dose adjustment is recommended for premenopausal women with uterine fibroids.

Race and Ethnicity:
The PK of elagolix was previously evaluated in healthy Asian women (Han Chinese and Japanese) in Phase 1 Study M12-654. The mean C_{max} and AUC values between Japanese and Han Chinese were found comparable. Population PK analysis for race/ethnicity effect on elagolix clearance (CL/F) did not identify a significant difference in elagolix CL/F among White, Black, Asian, American Indian, native Hawaiian and other (**Figure 3.3.3-3**) or between Hispanic and others. The effect of race or ethnicity on the PK of E2 and NETA has not been assessed.

Figure 3.3.3-3. Effect of Race on Elagolix Clearance



Note: The box shows the IQR with a median line in between. Lower/upper whiskers extend to the lowest/highest value within 1.5 * IQR.
Source: Population PK study report, Figure 13.3-3.

The Applicant's subpopulation analysis for primary efficacy endpoint showed that the responder rates to 300 mg BID + E2/NETA treatment in Black subjects (71.8%), non-Black subjects (72.9%), Hispanic subjects (72.7%), and non-Hispanic subjects (72.1%) were comparable. Race-based subpopulation analysis for BMD changes showed that race did not affect the changes in lumbar spine BMD from baseline compared to placebo at Month 6 of 300 mg BID + E2/NETA treatment (**Table 3.3.3-5**).

Table 3.3.3-5. Mean Percent Changes in Lumbar Spine BMD by Race Compared to Placebo at Month 6 of Treatment

Percent Changes (%) in Lumbar Spine BMD Compared to Placebo by Race Group Least Squares Mean (95% CI)		
Treatments	**Black or African American**	**Others**
Placebo	0.10 (-0.38, 0.57)	-0.64 (-1.39, 0.10)
300 mg BID	-2.94 (-3.43, -2.45)	-3.04 (-3.84, -2.25)
300 mg BID + E2/NETA	-0.66 (-0.99, -0.32)	-0.78 (-1.30, -0.26)

Source: Reviewer's summary from Integrated Study of Safety, TABLE 5.1-3.2.1.1
BID = twice a day; BMD = bone mineral density; CI = Confidence Interval; E2/NETA = estradiol/norethindrone acetate

Body Weight and Body Mass Index (BMI):
The subjects included in the population PK analysis had a body weight range of 40 – 160 kg and mean ± SD body weight of 79.4 ± 20.3 kg. The BMI range was 16.2 – 61.5 kg/m^2 and the mean ± SD BMI was 29.4 ± 7.3 kg/m^2. In the Applicant's population PK analysis, body weight was identified as a statistically significant covariate on apparent volume of distribution. However, the simulated individual subject's exposure to elagolix revealed that body weight ± 25 kg from the population median body weight of 76 kg did not affect elagolix average plasma concentrations (**Table 3.3.3-6**).

Table 3.3.3-6. Elagolix Exposure Simulated by Population PK model – Subgroup Analysis by Body Weight

	Simulated Elagolix Exposure, Median (95% CI)		
Body Weight	**C_{avg} (ng/mL)**	**C_{max} (ng/mL)**	**C_{trough} (ng/mL)**

Median (76 kg)	172 (78.6, 370)	631 (301, 1299)	2.06 (0.387, 11.7)
Median – 25 kg	171 (79.6, 369)	658 (318, 1349)	1.95 (0.383, 10.8)
Median + 25 kg	171 (79.1, 369)	611 (292, 1256)	2.13 (0.401, 12.4)

Source: Population PK study report, Table 13.3-9.
C_{avg} = average concentration; CI = Confidence Interval; C_{max} = maximum concentration; C_{trough} = lowest concentration reached before next dose is administered; PK = pharmacokinetics

Subpopulation analysis for the primary efficacy endpoint showed that although the responder rate to 300 mg BID + E2/NETA treatment in the < 25 kg/m^2 group appeared low (59.2%), there was no apparent trend in responder rate corresponding with increasing BMI compared to placebo at Month 6 of 300 mg BID + E2/NETA treatment (**Table 3.3.3-7**). See also discussion on subpopulation in Section 8.1.3 Assessment of Efficacy Across Trials in the multi-disciplinary review.

Table 3.3.3-7. Proportion of Subjects Who Met the Primary Endpoint – Subgroup Analysis by BMI

Subgroup	**Placebo**		**300 mg BID**		**300 mg BID + E2/NETA**	
	N	%	N	%	N	%
< 25 kg/m^2	21	16.0	32	81.6	49	59.2
25 to < 30 kg/m^2	42	8.0	33	73.8	86	74.4
30 to < 35 kg/m^2	53	10.3	48	80.4	113	71.3
35 to < 40 kg/m^2	43	9.3	43	82.3	79	80.4
≥ 40 kg/m^2	37	5.8	43	83.4	67	70.2

Source: Summary of Clinical Efficacy, Table 20.

For the 300 mg BID group, overall, there was an apparent trend in mean percent changes in femoral neck, hip and lumbar spine BMD from baseline corresponding with increasing BMI compared to placebo (lower BMI, larger decrease in BMD) (**Table 3.3.3-8**). For the 300 mg BID + E2/NETA group, there was no clear trend in mean percent changes in femoral neck, hip and lumbar spine BMD from baseline corresponding with increasing BMI compared to placebo. Therefore, body weight or BMI based dose adjustment for Oriahnn is not needed.

Table 3.3.3-8. Mean Percent Changes in BMD by BMI Compared to Placebo at Month 6 of Treatment

		Percent Changes (%) in BMD Compared to Placebo by BMI Least Squares Mean (95% CI)				
Treatments	**Anatomic Region**	**< 25 kg/m^2**	**25 to < 30 kg/m^2**	**30 to < 35 kg/m^2**	**35 to < 40 kg/m^2**	**≥ 40 kg/m^2**
Placebo	Femoral neck	-0.25 (-1.35, 0.85)	-0.60 (-1.54, 0.35)	-0.42 (-1.56, 0.72)	-0.30 (-1.47, 0.88)	0.25(-1.37, 1.86)
	Total hip	-0.37 (-1.19, 0.46)	-0.63 (-1.20, -0.07)	0.05 (-0.55, 0.65)	-0.05 (-0.80, 0.69)	0.06 (-0.72, 0.84)
	Spine	-0.25 (-1.16, 0.67)	-0.28 (-1.00, 0.43)	-0.14 (-0.93, 0.65)	0.68 (-0.23, 1.59)	-0.69 (-1.82, 0.45)
300 mg BID	Femoral neck	-2.85 (-3.91, -1.79)	-1.87 (-3.12, -0.61)	-2.40 (-3.56, -1.23)	-1.55 (-2.72, -0.38)	-1.01 (-2.50, 0.48)
	Total hip	-2.69 (-3.47, -1.90)	-1.65 (-2.40, -0.91)	-2.31 (-2.92, -1.69)	-1.84 (-2.59, -1.10)	-1.50 (-2.22, -0.79)
	Spine	-4.10 (-4.98, -3.21)	-2.91 (-3.86, -1.97)	-2.71 (-3.52, -1.90)	-3.09 (-4.01, -2.18)	-2.50 (-3.56, -1.44)
300 mg BID + E2/NETA	Femoral neck	-0.04 (-0.83, 0.75)	-0.55 (-1.23, 0.12)	-0.34 (-1.12, 0.44)	-0.93 (-1.76, -0.11)	-0.90 (-2.05, 0.25)
	Total hip	-0.36 (-0.95, 0.22)	-0.05 (-0.45, 0.35)	-0.12 (-0.53, 0.29)	-0.21 (-0.74, 0.32)	-0.20 (-0.75, 0.36)
	Spine	0.04 (-0.61, 0.68)	-0.64 (-1.15, -0.14)	-0.71 (-1.25, -0.17)	-0.90 (-1.55, -0.26)	-0.94 (-1.75, -0.13)

Source: Reviewer's summary from Integrated Study of Safety
BID = twice a day; BMD = bone mineral density; BMI = body mass index; CI = Confidence Interval; E2/NETA = estradiol/norethindrone acetate

Patients versus Healthy Subjects:
The population PK model-simulated steady-state average plasma concentrations (C_{avg}) of elagolix 300 mg BID in women with uterine fibroids were approximately 20% lower than those in healthy women in Phase 1 studies (**Table 3.3.3-9**). Considering the small sample size of healthy subjects (N = 28) and the

inter-subject variability in PK (38-48%), a definitive conclusion regarding the impact of disease status on the PK of elagolix cannot be drawn.

In addition, the presence of adenomyosis in women with uterine fibroids was used as a covariate in the population PK analysis. No difference in the PK of elagolix was detected between patients with (N =104) and without adenomyosis (N = 724).

Table 3.3.3-9. Population PK Model-Predicted Steady-State Exposure of Elagolix in Healthy Subjects and Patients.

Population	**Mean (Geometric Mean, CV%)**		
	N	**C_{avg} (ng/mL)**	**C_{max} (ng/mL)**
Healthy Premenopausal Women 300 mg BID	28	262 (243, 38%)	2.06 (0.387, 11.7)
Premenopausal Women 300 mg BID with Uterine Fibroids	706	211 (190, 48%)	1.95 (0.383, 10.8)

Source: Clinical Pharmacology Study Summary, Table 15.

Bilirubin, Creatinine Clearance, Aspartate Amino Transferase and Alanine Amino Transferase:
The levels of bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT) and creatinine, and creatinine clearance were used as covariates in the population PK analysis. None of them were found to be significantly associated with elagolix PK parameters.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes, the management strategies for drug-drug interactions (DDIs) are summarized in **Table 2.2.2-1**.

Food Effects:
Two food effect studies (Study M16-856 and Study M19-648) were conducted with the to-be-marketed (TBM) formulations (morning dose: an FDC capsule of elagolix/E2/NETA 300/1/0.5 mg and evening dose: elagolix 300 mg capsule) in healthy postmenopausal women. Following administration of an FDC capsule after a high-fat meal, the elagolix C_{max} and area under the curve from zero to infinity ($AUC_{0\text{-}inf}$) were 36% and 25% lower, respectively, when compared to exposures under fasting conditions. NETA C_{max} was 50% lower and $AUC_{0\text{-}inf}$ was 23% higher, while baseline-adjusted total estrone C_{max} and AUC were 44% and 14% lower, respectively. A high-fat meal reduced C_{max} of baseline-adjusted E2 by 23% but did not affect AUC. Data are shown in **Table 3.3.4-1** below.

Table 3.3.4-1. The Effect of Food on the PK Parameters of To-Be-Marketed FDC Capsule (Study M16-856, N = 12)

Parameters	**Least Squares Geometric Means**		**% Test/Ref Ratio (90% CI)**
	Fed [Test]	**Fasting [Reference]**	
Baseline-corrected E2			
$AUC_{0\text{-}inf}$ (pg•h/mL)	1081.2	1035.0	104.5 (95.5 – 114.3)
$AUC_{0\text{-}t}$ (pg•h/mL)	912.7	914.8	99.8 (92.7 – 107.4)
C_{max} (pg/mL)	41.29	53.72	76.9 (65.1 – 90.7)
T_{max} (h)*	5.0 (2.0 – 6.0)	2.0 (1.0 – 4.0)	N.A.
Baseline-corrected total estrone			
$AUC_{0\text{-}inf}$ (ng•h/mL)	163.3	189.1	86.4 (79.4 – 94.0)

AUC_{0-t} (ng•h/mL)	159.6	185.4	86.1 (79.3 – 93.4)
C_{max} (ng/mL)	13.0	23.3	55.7 (45.1 – 68.9)
T_{max} (h)*	3.5 (2.0 – 6.0)	1.5 (1.0 – 2.0)	N.A.
Elagolix			
AUC_{0-inf} (ng•h/mL)	3390.4	4536.5	74.7 (66.2 – 84.4)
AUC_{0-t} (ng•h/mL)	3377.7	4524.0	74.7 (66.1 – 84.3)
C_{max} (ng/mL)	1078.5	1681.3	64.1 (50.7 – 81.1)
T_{max} (h)*	3.0 (2.0 – 6.0)	1.5 (1.0 – 2.0)	N.A.
NETA			
AUC_{0-inf} (ng•h/mL)	26.38	21.53	122.5 (114.2 – 131.5)
AUC_{0-t} (ng•h/mL)	24.20	19.51	124.1 (114.4 – 134.5)
C_{max} (ng/mL)	2.72	5.44	49.9 (42.6 – 58.5)
T_{max} (h)*	4.0 (1.0 – 6.0)	1.0 (1.0 – 1.0)	N.A.

*Median (minimum – maximum).

Source: Reviewer's analysis

AUC_{0-inf} = area under the curve from 0 to infinity; AUC_{0-t} = area under the curve from time 0 to time t; C_{max} = maximum concentration; E2 = estradiol; FDC = fixed=dose combination; N.A. = not available; NETA = norethindrone acetate; PK = pharmacokinetic; T_{max} = time to maximum concentration

Following administration of an evening dose capsule after a high-fat meal, the elagolix C_{max} and AUC_{0-inf} were 40% and 28% lower, respectively when compared to exposures under fasting conditions, which was consistent with the food effect observed with morning dose formulation (FDC capsule). See **Table 3.3.4-2** below.

Table 3.3.4-2. The Effect of Food on the PK Parameters of Evening Dose Capsule (Study M19-648, N = 12)

Parameters	**Least Squares Geometric Means**		**% Test/Ref Ratio (90% CI)**
	Fed [Test]	**Fasting [Reference]**	
AUC_{0-inf} (ng•h/mL)	2618	3634	72.03 (65.68 – 78.99)
AUC_{0-t} (ng•h/mL)	2609	3630	71.88 (65.53 – 78.84)
C_{max} (ng/mL)	755	1262	59.79 (48.22 – 74.15)
T_{max} (h)*	3.0 (2.0 – 6.0)	1.75 (1.5 – 2.0)	N.A.

*Median (minimum – maximum).

Source: Reviewer's analysis

AUC_{0-inf} = area under the curve from 0 to infinity; AUC_{0-t} = area under the curve from time 0 to time t; C_{max} = maximum concentration; N.A. = not available; PK = pharmacokinetic; T_{max} = time to maximum concentration

Based on elagolix exposure-response relationship for efficacy, 25-28% decrease in elagolix AUC and up to 40% decrease in elagolix C_{max} under fed conditions are not expected to have a clinically meaningful impact on responder rates. In addition, both morning and evening doses were administered without regards to meals in Phase 3 trials. The review team concurs with the Applicant that Oriahnn can be orally administered without regard to meals and no dose adjustment was recommended under fed conditions.

Drug-Drug Interactions:

The Applicant submitted ten clinical DDI study reports and one physiologically-based pharmacokinetics (PBPK) modeling report in NDA 210450 submission. In the current NDA, the Applicant submitted four clinical DDI study reports and one PBPK modeling report. The clinical DDI study findings and management strategies are summarized in **Table 2.2.2-1**.

Study M12-660 showed that co-administration of ketoconazole 400 mg QD and a single dose of elagolix 150 mg caused an increase of elagolix AUC by 120%. Concomitant use of Oriahnn with a strong CYP3A inhibitor would result in a drug exposure around 660 mg BID elagolix administered alone. A single dose of rifampin 600 mg, which is expected to inhibit hepatic uptake transporter OATP1B1, caused an increase of elagolix AUC by 458% (Study M12-659). When co-administered with rifampin or another potent OATP1B1 inhibitor, the 300 mg BID dose of elagolix would result in a drug exposure around 1700 mg BID elagolix administered alone. The maximum single-dose exposure of elagolix in human was 1200 mg and the maximum multidose exposures in human were 400 mg BID for 21 days and 600 mg QD for 24 weeks. Currently, there are insufficient safety data to support concomitant use of Oriahnn with strong inhibitors of CYP3A or OATP1B1. Therefore, we concur with the Applicant that strong OATP1B1 inhibitors should be contraindicated. Also, concomitant use of Oriahnn and strong CYP3A inhibitors is not recommended.

Oral administration of rifampin 600 mg QD for 10 day is expected to inhibit OATP1B1, induce CYP3A enzymes and P-gp, and potentially also induce OATP1B1 transporters. The net effect of OATP1B1 inhibition and CYP3A/P-gp/OATP1B1 induction caused an increase of elagolix AUC by only 65% on Day 10. We concur with the Applicant that concomitant use of Oriahnn and rifampin should be avoided.

Co-administration of rosuvastatin 20 mg QD with elagolix 300 mg BID resulted in a decrease of rosuvastatin AUC by approximately 40%. The mechanisms for decrease in rosuvastatin AUC when co-administered with multiple-dose elagolix is unknown and OATP1B1 induction by elagolix may be one of the possible mechanisms. We agree with the Applicant that the dose of rosuvastatin may be increased, but only after monitoring of lipid levels confirms that dose adjustment is necessary.

PBPK simulation showed that the effect of elagolix 300 mg BID on the PK of digoxin is expected to be similar to that of elagolix 200 mg BID in an in vivo DDI study where the Cmax and AUC of digoxin was increased by approximately 70% and 30%, respectively. The Applicant proposed clinical monitoring for digoxin and no dose adjustment or monitoring for other P-gp substrates with a wide therapeutic index when co-administered with Oriahnn. While the proposal of no dose adjustment/monitoring for other P-gp substrates appears reasonable, we recommend increased monitoring of digoxin concentrations and potential signs and symptoms of clinical toxicity when initiating or discontinuing Oriahnn in patients who are taking digoxin.

Co-administration of a single dose of omeprazole with elagolix 300 mg BID resulted in an increase of omeprazole Cmax and AUC by 95% and 77%, respectively. We recommend no dose adjustment for omeprazole 40 mg once daily or lower when co-administered with Oriahnn. However, doses up to 120 mg three times daily have been used in patients. When Oriahnn is used concomitantly with doses of omeprazole higher than 40 mg per day, dosage reduction for omeprazole is recommended.

Studies M14-708 and M13-757 showed that concomitant use of elagolix 300 mg BID increased the AUC and Cmax of orally administered E2 but did not affect the PK of transdermally administered E2, indicating elagolix 300 mg BID might increase oral absorption of E2 by inhibiting CYP3A in gastrointestinal tract. Phase 3 trials showed that the steady-state average concentrations of E2 in patients treated with Oriahnn were approximately 50-60 pg/mL (**Figure 3.3.1-4**), which was slightly lower than the normal serum E2 level in healthy pre-menopausal women (65 ± 34 pg/mL). In addition, the Applicant's population PK simulation showed that the addition of 1mg E2/0.5 NETA did not affect the

PK of elagolix. Therefore, the DDI between elagolix 300 mg BID and oral add-back E2 is not expected to have clinically meaningful impact on the efficacy and safety of Oriahnn. In the Phase 3 trials, however, the add-back of E2 reduced the efficacy of elagolix 300 mg alone treatment (**Table 2.2.2-1**). The review team recommends that concomitant use of estrogens and/or progestins be prohibited during Oriahnn treatment.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

No, the TBM formulations (FDC capsule for morning dose and elagolix EN03 capsule for evening dose) are different from the Phase 3 trial formulations [elagolix RC2 300 mg immediate-release (IR) tablet and E2/NETA 1 mg/0.5 mg IR tablet]. The Applicant conducted two pivotal bioequivalence (BE) studies (Study M16-856 and Study M19-648) to bridge the TBM formulations to Phase 3 formulations. The BE study results for both morning dose formulation (**Table 3.3.5-1**) and evening dose formulation (**Table 3.3.5-2**) met the established BE criteria.

Table 3.3.5-1. Bioequivalence Assessment for Morning Dose Formulation (Study M16-856, N = 165)

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CI)
	FDC [Test]	RC2 +E2/NETA [Reference]	
Baseline-corrected E2			
AUC_{0-inf} (pg•h/mL)	878.3	963.4	91.2 (87.6 – 94.9)
AUC_{0-t} (pg•h/mL)	786.2	867.3	90.7 (87.8 – 93.6)
C_{max} (pg/mL)	52.8	55.7	94.8 (91.3 – 98.5)
Baseline-corrected total Estrone			
AUC_{0-inf} (ng•h/mL)	166.0	178.4	93.0 (86.7 – 99.8)
AUC_{0-t} (ng•h/mL)	163.1	174.9	93.3 (86.8 – 100.2)
C_{max} (ng/mL)	21.7	21.2	102.0 (96.1 – 108.3)
Elagolix			
AUC_{0-inf} (ng•h/mL)	4297.9	4414.5	97.4 (94.7 – 100.1)
AUC_{0-t} (ng•h/mL)	4226.6	4333.5	97.5 (94.8 – 100.3)
C_{max} (ng/mL)	1642.1	1806.2	90.9 (86.6 – 95.5)
NETA			
AUC_{0-inf} (ng•h/mL)	22.03	22.93	96.1 (94.3 – 97.9)
AUC_{0-t} (ng•h/mL)	19.84	20.67	96.0 (94.1 – 97.8)
C_{max} (ng/mL)	5.49	4.91	111.8 (108.5 – 115.3)

Source: Reviewer's analysis

AUC_{0-inf} = area under the curve from 0 to infinity; AUC_{0-t} = area under the curve from time 0 to time t; C_{max} = maximum concentration; E2/NETA =estradiol/norethindrone acetate; FDC = fixed-dose combination

Table 3.3.5-2. Bioequivalence Assessment for Evening Dose Formulation (Study M19-648, N = 45)

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CI)
	EN03 [Test]	RC2 [Reference]	
AUC_{0-inf} (ng•h/mL)	3746	3875	96.7 (92.7 – 100.8)
AUC_{0-t} (ng•h/mL)	3740	3869	96.7 (92.7 – 100.8)

C_{max} (ng/mL)	1313	1504	87.3 (80.7 – 94.6)

Source: Reviewer's analysis
$AUC_{0\text{-inf}}$ = area under the curve from 0 to infinity; $AUC_{0\text{-t}}$ = area under the curve from time 0 to time t; C_{max} = maximum concentration

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

PK Assays:

High performance liquid chromatography tandem mass spectrometry (LC-MS/MS) methods were developed and validated for the quantitative determination of elagolix, E2, unconjugated estrone, total estrone, and NETA in human plasma. The validation reports for each method and analytical study reports for each PK study were submitted. Method specifications and validation parameters are listed in **Table 4.1-1**.

Table 4.1-1. Bioanalytical Method Specifications and Validation Parameters

Report Number	Compound(s)	Method Matrix	LLOQ	Linear Range	Inter-Run Accuracy %Bias	Inter-Run Precision %CV	Long-Term Stability	ISR
(b) (4)	Elagolix (A-1278823)	LC-MS/MS plasma	0.101 ng/mL (range A) 1.57 ng/mL (range B)	0.101 to 196 ng/mL (range A) 1.57 to 2460 ng/mL (range B)	–12.3 to 5.1 (range A) –10.7 to 3.9 (range B)	2.1 to 4.4 (range A) 2.0 to 11.4 (range B)	1084 d (–20°C) 555 d (–70°C)	passed
	Elagolix (A-1278823)	LC-MS/MS plasma	0.100 ng/mL (low range) 1.50 ng/mL (high range)	0.100 to 200 ng/mL (low range) 1.50 to 2500 ng/mL (high range)	2.1 to 9.4 (low range) 0.8 to 8.5 (high range)	2.1 to 6.6 (low range) 3.2 to 4.6 (high range)	79 d (–20°C)	passed
	Norethindrone	LC-MS/MS plasma	0.101 ng/mL	0.101 to 58.3 ng/mL	–0.5 to 11.9	2.2 to 5.9	1018 d (–20°C) 148 d (–70°C)	passed
	Total Estrone	LC-MS/MS plasma	10.0 pg/mL	10.0 to 20000 pg/mL	–2.56 to 3.76[*] 0.56 to 2.28[£]	1.71 to 10.29[*] 1.94 to 3.51[£]	109 d[*£] (–20°C) 109 d[*£] (–80°C)	passed
	Estrone	LC-MS/MS plasma	5.00 pg/mL	5.00 to 1000 pg/mL	–5.07 to 0.30[§] –2.48 to –0.35[‡]	3.49 to 7.39[§] 1.85 to 3.08[‡]	224 d[§] (–20°C, –80°C) 218 d[‡] (–20°C, –80°C)	passed
	Estradiol	LC-MS/MS plasma	2.50 pg/mL	2.50 to 250 pg/mL	1.32 to 6.69[§] 2.34 to 3.28[‡]	1.55 to 10.63[§] 4.30 to 5.98[‡]	224 d[§] (–20°C, –80°C) 202 d[‡] (–20°C) 1992 d[‡] (–80°C)	passed
	β-Estradiol	LC-MS/MS serum	3.00 pg/mL 11.2 pg/mL[¥]	3.00 to 319 pg/mL 11.2 to 320 pg/mL[¥]	–2.6 to1.8[≠] –9.0 to 4.4[≠¥]	2.6 to 13.0[≠] 3.9 to 8.8[≠¥]	1016 d[≠] (–20°C) 102 d[≠] (–70°C) 1044 d[≠¥] (–20°C)	passed
	Progesterone	LC-MS/MS serum	0.116 ng/mL 0.121 ng/mL[¥]	0.116 to 58.2 ng/mL 0.121 to 60.4 ng/mL[¥]	–0.6 to 3.9[≠] –2.5 to 5.8[≠¥]	3.6 to 8.4[≠] 2.0 to 7.4[≠¥]	20 d[≠] (–70°C) 1044 d[≠¥] (–20°C)	passed
	Bupropion	LC-MS/MS plasma	0.500 ng/mL	0.500 to 250 ng/mL	–2.59 to 0.70	5.11 to 11.75	118 d (–20°C, –80°C)	passed
	Hydroxybupropion	LC-MS/MS plasma	5.00 ng/mL	5.00 to 800 ng/mL	–4.32 to –0.42	2.34 to 4.49	118 d (–20°C, –80°C)	passed
	Omeprazole	LC-MS/MS plasma	1.00 ng/mL	1.00 to 1000 ng/mL	–3.89 to 1.61	2.44 to 7.35	826 d (–20°C, –70°C)	passed
	Omeprazole Sulfone	LC-MS/MS plasma	1.00 ng/mL	1.00 to 1000 ng/mL	–1.74 to 5.75	3.69 to 13.0	826 d (–20°C, –70°C)	passed
	5-Hydroxyomeprazole	LC-MS/MS plasma	1.00 ng/mL	1.00 to 1000 ng/mL	0.282 to 5.99	4.14 to 10.9	826 d (–20°C, –70°C)	passed

LLOQ = lower limit of quantitation; ISR = incurred sample reanalysis; LC-MS/MS = liquid chromatography tandem mass spectrometry; d = days; *Surrogate = 5% bovine serum albumin in phosphate buffered saline; £Unstripped = regular human ethylenediaminetetraacetic acid (EDTA) dipotassium (K2) plasma; §Stripped = human ethylenediaminetetraacetic acid (EDTA) tripotassium (K3) plasma treated with activated charcoal to remove endogenous levels of estrone and estradiol prior to use; ‡Unstripped = regular human EDTA K3 plasma; ¥ = Method information from validation report c-da-rd170279-val-lcms-ser-estradiol-progesterone; ≠Stripped = 4x charcoal stripped human serum
Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 21.

The LC-MS/MS methods for the quantitative determination of elagolix in human plasma were reviewed in NDA 210450. Refer to Clinical Pharmacology Review for NDA 210450 dated 7/19/2018 in DARRTS for more information. The established frozen storage stability and run storage stability covered corresponding study period and sample analysis period.

One method validation report (Report #: R&D/11/994) and three stability update validation report (Report #: R&D/17/0278, R&D/17/0900, and R&D/19/0250) were submitted to support the bioanalysis of NETA in plasma samples. Six method validation reports were submitted for quantitation of E2, unconjugated estrone, and total estrone in plasma samples collected from pivotal BE and DDI studies. Method validation parameters are summarized in **Table 4.1-1**. The established frozen storage stability (1018 days for NETA and 109 -224 days for E2, unconjugated estrone, and total estrone) covered corresponding study period and sample analysis period.

PD Assays:
LC-MS/MS bioanalytical methods using liquid-liquid extraction were validated for quantitation of E2 and progesterone in human serum samples. Three method validation reports (Report #: R&D/11/124, R&D/17/0279, and R&D/17/0280) and three stability update validation report (Report #: R&D/17/0281, R&D/17/1027, and R&D/18/0967) were submitted to support the bioanalysis of E2 and progesterone in serum samples. The validation reports were reviewed in NDA 210450. Refer to Clinical Pharmacology Review for NDA 210450 dated 7/19/2018 in DARRTS for more information. The established frozen storage stability and run storage stability covered corresponding study period and sample analysis period.

Assays for DDI Studies:
LC-MS/MS methods were also developed and validated for the quantitative determination of bupropion, omeprazole, and their major metabolites (hydroxybupropion, omeprazole sulfone, and 5-hydroxyomeprazole) in drug interaction studies. The methods were validated for calibration curve linearity, specificity, carryover, limit of detection/limit of quantitation (LOD/LOQ), precision, accuracy, recovery, matrix effect, and stability (**Table 4.1-1**). The established frozen storage stability (118 – 826 days) covered corresponding study period and sample analysis period. The method validation reports (Report #: 175207 and P1009) were reviewed and found acceptable.

4.2 Clinical BA/BE Assessments

Three bioavailability/bioequivalence (BA/BE) studies were submitted in this NDA, including Studies M15-872, M16-856, and M19-648. The prototype FDC capsules tested in Study M15-872 were different from Phase 3 formulations and to-be-marketed (TBM) formulations. Therefore, Study M15-872 is not reviewed and only two pivotal BE studies (M16-856 and M19-648) are reviewed.

As shown in **Table 3.3.5-1**, Study M16-856 is a pivotal BE study which bridged the TBM morning dose formulation (FDC capsule) and Phase 3 formulations (elagolix 300 mg RC2 tablet and E2/NETA 1 mg/0.5 mg tablet). Study M19-648 is another pivotal BE study which bridged the TBM evening dose formulation (elagolix 300 mg EN03 capsule) and Phase 3 formulation (elagolix 300 mg RC2 tablet).

Study M16-856 was conducted at four sites: AbbVie Clinical Pharmacology Research Unit, Anaheim Clinical Trials LLC., [redacted] and the PK samples were analyzed at two facilities: Drug Analysis Department of AbbVie in North Chicago (elagolix and NETA) and [redacted] (E2, unconjugated estrone and total estrone). Study M19-648 was conducted at AbbVie Clinical Pharmacology Research Unit and the PK samples were analyzed at Drug Analysis Department of AbbVie.

The Division of Bone, Reproductive and Urologic Products (DBRUP) sent an on-site inspection request to the Office of Study Integrity and Surveillance (OSIS) to inspect the four clinical sites and two bioanalytical facilities involved in the two pivotal BE studies. On September 17, 2019, OSIS declined to conduct on-site inspections for the two bioanalytical facilities because the facilities were inspected in February and June of 2019 which fell within the surveillance interval. On November 12, 2019, OSIS declined to conduct on-site inspections for two clinical sites: [redacted] because the sites were inspected in [redacted]. Based on the inspection report dated January 30, 2020 in DARRTS, OSIS reviewer Dr. Xiaohan Cai concluded that the clinical data from Study M16-856 conducted at [redacted]. are reliable to support a regulatory decision. Based on the inspection report dated February 21, 2020 in DARRTS, OSIS reviewer Dr. Xiaohan Cai concluded that the clinical data from Studies M16-856 and M19-648 conducted at AbbVie Clinical Pharmacology Research Unit are reliable to support a regulatory decision.

4.2.1 Study M16-856 (Pivotal BE and food effects)

Title: *A Bioequivalence and Food Effect Study of Elagolix/Estradiol/Norethindrone Acetate Capsules in Healthy Postmenopausal Female Subjects*

Objectives:

- to assess the relative bioavailability of the test elagolix/E2/NETA (300 mg/1 mg/0.5 mg) fixed-dose combination capsule (Formulation FDC4) relative to co-administered elagolix 300 mg IR tablet (Formulation RC2) and E2/NETA (1 mg/0.5 mg) tablet.
- to assess the potential effects of food on the PK of the test elagolix/E2/NETA (300 mg/1 mg/0.5 mg) FDC4 capsule

Study Design:
This was a Phase 1, single-dose, open-label, multicenter study conducted according to a four-sequence, 2- or 3-period, randomized, crossover design. A total of 179 healthy postmenopausal women were randomly assigned to one of four sequences of Regimens A, B and C as outlined in **Table 4.2.1-1**.

Table 4.2.1-1. Sequence Groups in Study M16-856

Sequence	Number of Subjects	Regimens			Sites
		Period 1	Period 2	Period 3	
1	89[a]	A	B		4
2	90[b]	B	A		
3	6	A	B	C	1
4	6	B	A	C	

Regimen A: Single dose of one elagolix/E2/NETA (300 mg/1 mg/0.5 mg) hard gelatin capsule formulation (FDC4) administered under fasting conditions (test).

Regimen B: Single dose of one elagolix 300 mg IR tablet formulation (RC2) and 1 mg/0.5 mg E2/NETA tablet encapsulated administered under fasting conditions (reference).
Regimen C: Single dose of one elagolix/E2/NETA (300 mg/1 mg/0.5 mg) hard gelatin capsule formulation (FDC4) administered after a high high-fat meal.

A washout interval of 5 days separated the doses of the study periods. Blood samples for assay of elagolix were collected for up to 24 hours after dosing in each period. Blood samples for assay of norethindrone and total estrone (E1) were collected for up to 72 hours after dosing in each period. Blood samples for assay unconjugated E2 and unconjugated E1 were collected for up to 60 hours after dosing in each period.

PK Results:
Data of 165 subjects and 12 subjects were included in the BE and food effect analysis respectively. For the two one-sided test based on the analysis of log-transformed C_{max}, AUC_t, and AUC_∞, the point estimates and the corresponding 90% CIs of relative bioavailability calculated by the reviewer are presented in **Table 4.2.1-2**. The results show that the TBM FDC formulation and Phase 3 formulation (co-administered elagolix 300 mg RC2 tablet and E2/NETA 1 mg/0.5 mg tablet) are bioequivalent.

Figure 4.2.1-1. Mean Elagolix Plasma Concentration Time Profiles Under Fasting Conditions

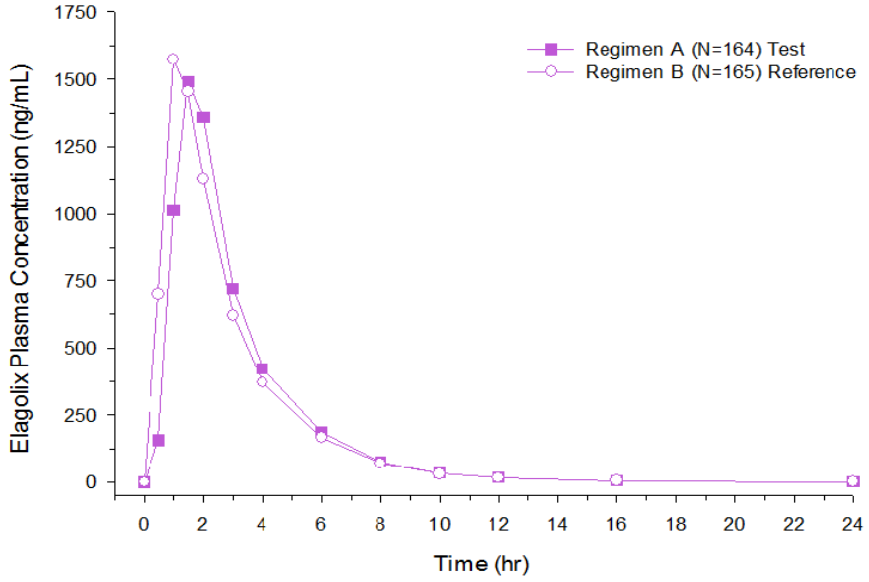


Figure 4.2.1-2. Mean Norethindrone Plasma Concentration Time Profiles Under Fasting Conditions

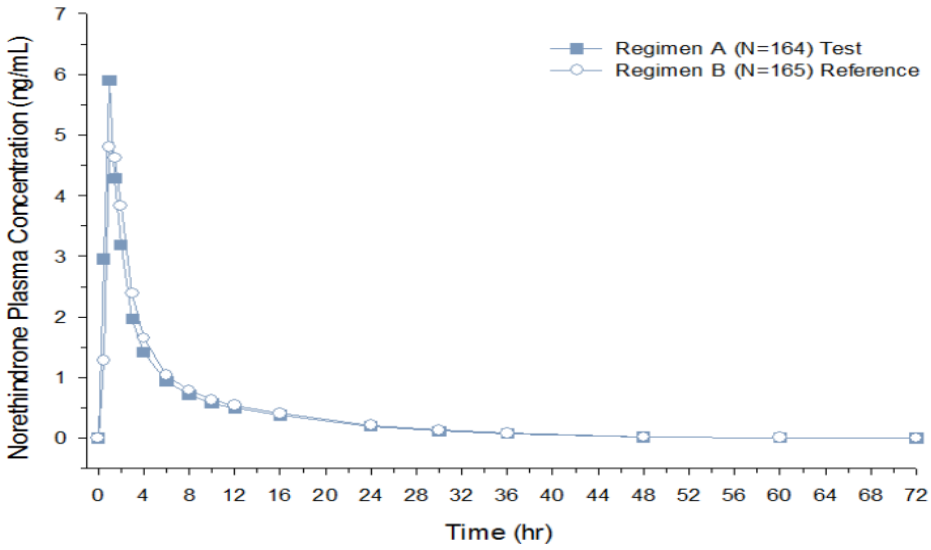


Figure 4.2.1-3. Mean Baseline-Adjusted E2 and Total Estrone Plasma Concentration Time Profiles Under Fasting Conditions

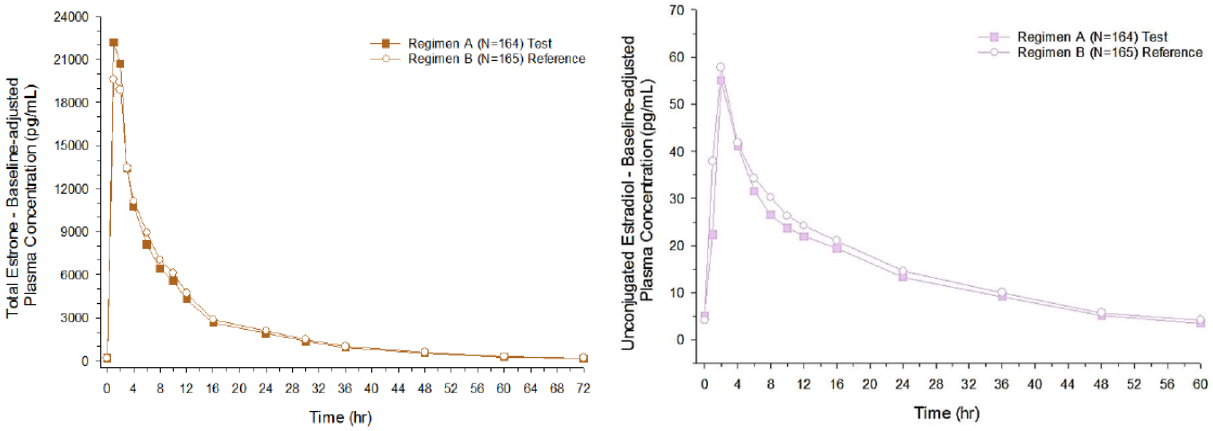


Table 4.2.1-2. Bioequivalence Assessment for Morning Dose To-Be-Marketed FDC Capsule (Study M16-856, N = 165)

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
	FDC [Test]	RC2 +E2/NETA [Reference]	
Baseline-corrected E2			
$AUC_{0\text{-}inf}$ (pg•h/mL)	878.3	963.4	91.2 (87.6 – 94.9)
$AUC_{0\text{-}t}$ (pg•h/mL)	786.2	867.3	90.7 (87.8 – 93.6)
C_{max} (pg/mL)	52.8	55.7	94.8 (91.3 – 98.5)
Baseline-corrected total Estrone			
$AUC_{0\text{-}inf}$ (ng•h/mL)	166.0	178.4	93.0 (86.7 – 99.8)
$AUC_{0\text{-}t}$ (ng•h/mL)	163.1	174.9	93.3 (86.8 – 100.2)
C_{max} (ng/mL)	21.7	21.2	102.0 (96.1 – 108.3)
Elagolix			

AUC_{0-inf} (ng•h/mL)	4297.9	4414.5	97.4 (94.7 – 100.1)
AUC_{0-t} (ng•h/mL)	4226.6	4333.5	97.5 (94.8 – 100.3)
C_{max} (ng/mL)	1642.1	1806.2	90.9 (86.6 – 95.5)
NETA			
AUC_{0-inf} (ng•h/mL)	22.03	22.93	96.1 (94.3 – 97.9)
AUC_{0-t} (ng•h/mL)	19.84	20.67	96.0 (94.1 – 97.8)
C_{max} (ng/mL)	5.49	4.91	111.8 (108.5 – 115.3)

Source: Reviewer's analysis

The effect of food on the PK of the TBM FDC capsule was shown in **Table 4.2.1-3**. When the FDC capsule was administered after a high-fat meal, elagolix C_{max} and AUC_{0-inf} were 36% and 25% lower, respectively when compared to exposures under fasting conditions. NETA C_{max} was 50% lower and AUC_{0-inf} was 23% higher, while baseline-adjusted total estrone C_{max} and AUC were 44% and 14% lower, respectively. A high-fat meal reduced C_{max} of baseline-adjusted E2 by 23% but did not affect AUC.

Table 4.2.1-3. The Effect of Food on the PK Parameters of To-Be-Marketed FDC Capsule (Study M16-856, N =12)

Parameters	**Least Squares Geometric Means**		**% Test/Ref Ratio (90% CIs)**
	Fed [Test]	**Fasting [Reference]**	
Baseline-corrected E2			
AUC_{0-inf} (pg•h/mL)	1081.2	1035.0	104.5 (95.5 – 114.3)
AUC_{0-t} (pg•h/mL)	912.7	914.8	99.8 (92.7 – 107.4)
C_{max} (pg/mL)	41.29	53.72	76.9 (65.1 – 90.7)
T_{max} (h)*	5.0 (2.0 – 6.0)	2.0 (1.0 – 4.0)	N.A.
Baseline-corrected total estrone			
AUC_{0-inf} (ng•h/mL)	163.3	189.1	86.4 (79.4 – 94.0)
AUC_{0-t} (ng•h/mL)	159.6	185.4	86.1 (79.3 – 93.4)
C_{max} (ng/mL)	13.0	23.3	55.7 (45.1 – 68.9)
T_{max} (h)*	3.5 (2.0 – 6.0)	1.5 (1.0 – 2.0)	N.A.
Elagolix			
AUC_{0-inf} (ng•h/mL)	3390.4	4536.5	74.7 (66.2 – 84.4)
AUC_{0-t} (ng•h/mL)	3377.7	4524.0	74.7 (66.1 – 84.3)
C_{max} (ng/mL)	1078.5	1681.3	64.1 (50.7 – 81.1)
T_{max} (h)*	3.0 (2.0 – 6.0)	1.5 (1.0 – 2.0)	N.A.
NETA			
AUC_{0-inf} (ng•h/mL)	26.38	21.53	122.5 (114.2 – 131.5)
AUC_{0-t} (ng•h/mL)	24.20	19.51	124.1 (114.4 – 134.5)
C_{max} (ng/mL)	2.72	5.44	49.9 (42.6 – 58.5)
T_{max} (h)*	4.0 (1.0 – 6.0)	1.0 (1.0 – 1.0)	N.A.

*Median (minimum – maximum).
Source: Reviewer's analysis

Reviewer's Comments:

- *The reviewer's BE and food effect analyses are consistent with the Applicant's results.*
- *Based on elagolix exposure-response relationship for efficacy, 25% decrease in elagolix AUC and 36% decrease in elagolix Cmax under fed conditions are not expected to have a clinically meaningful impact on responder rates. In addition, both morning and evening doses were administered without regards to meals in Phase 3 trials. The review team concurs with the Applicant that Oriahnn can be orally administered without regard to meals and no dose adjustment was recommended under fed conditions.*
- *The PK data for BE analysis (N = 165) were collected from four clinical sites. Quantitation of plasma elagolix and NETA was conducted in the Applicant's lab while quantitation of plasma E2, unconjugated estrone and total estrone was performed at* (b) (4)*. This reviewer assessed the effects of clinical study site on the PK parameters of elagolix, E2 and NETA. As shown in* ***Table 4.2.1-4****, study sites had no obvious impact on the C_{max} or T_{max} of elagolix, E2 or NETA.*

Table 4.2.1-4. The Effect of Clinical Site on the Pharmacokinetics of Elagolix, E2, and NETA (Study M16-856)

Analytes	**Formulations**	**PK parameters**	**Study Sites (Mean ± SD)**			
			AbbVie (13972) (N = 39)	(b) (4) (945791) (N = 28)	(53505) (N =40)	(11516) (N = 58)
Elagolix	FDC (Test)	$AUC_{0\text{-}inf}$ (ng•h/mL)	4455 ± 1898	4122 ± 1453	4954 ± 2640	4177 ± 1492
		C_{max} (ng/mL)	1589 ± 757	1582 ± 586	1762 ± 945	1605 ± 586
	RC2+ E2/NETA (Ref)	$AUC_{0\text{-}inf}$ (ng•h/mL)	4590 ± 1911	4353 ± 1309	4850 ± 2272	4394 ± 2292
		C_{max} (ng/mL)	1795 ± 785	1790 ± 643	1776 ± 851	1833 ± 893
Baseline-adjusted E2	FDC (Test)	$AUC_{0\text{-}inf}$ (ng•h/mL)	991 ± 420	1011 ± 297	968 ± 323	971 ± 499
		C_{max} (ng/mL)	59.9 ± 28.3	63.1 ± 31.5	54.3 ± 23.3	56.5 ± 34.8
	RC2+ E2/NETA (Ref)	$AUC_{0\text{-}inf}$ (ng•h/mL)	1077 ± 411	1052 ± 334	1078 ± 441	1079 ± 620
		C_{max} (ng/mL)	73.9 ± 48.6	58.6 ± 24.7	57.1 ± 24.8	59.0 ± 36.9
NETA	FDC (Test)	$AUC_{0\text{-}inf}$ (ng•h/mL)	27.4 ± 14.1	23.4 ± 11.1	27.2 ± 10.3	24.9 ± 10.9
		C_{max} (ng/mL)	6.55 ± 2.35	5.38 ± 2.25	6.49 ± 1.70	5.77 ± 2.11
	RC2+ E2/NETA (Ref)	$AUC_{0\text{-}inf}$ (ng•h/mL)	28.9 ± 14.8	23.9 ± 11.7	27.6 ± 10.4	26.3 ± 11.7
		C_{max} (ng/mL)	5.98 ± 2.34	5.02 ± 2.14	5.49 ± 1.62	5.26 ± 1.70

Source: Reviewer's analysis

Safety Results:

No clinically significant abnormalities in vital signs or laboratory measurements were observed during the course of the study. Three subjects were discontinued from the study due to mild adverse events of oropharyngeal pain, upper respiratory tract infection and constipation.The proportions of subjects who reported at least one treatment-emergent adverse were similar among the regimens (**Table 4.2.1-5)**.

Table 4.2.1-5. The Proportions of Subjects Who Reported Adverse Events in Study M15-817

	Treatment		
	Regimen A	**Regimen B**	**Regimen C**
Frequency of adverse events	32/183 (18%)	39/185 (21%)	1/12 (8%)

4.2.2 Study M19-648 (Pivotal BE and food effects)

Title: *A Bioequivalence and Food Effect Study of Elagolix Capsules in Healthy Premenopausal Female Subjects*

Objectives:

- To assess the BE of a single dose of elagolix 300 mg capsule (EN03 capsule; test) relative to that of a single dose of a 300 mg elagolix IR tablet (RC2; reference) under fasting conditions.
- To assess the potential effects of high-fat meals on the PK of the test capsule formulation.

Study Design:
This was a Phase 1, single-dose, open-label, randomized, four-sequence, two or three-period, complete crossover study designed to evaluate bioequivalence and effect of a high-fat meal on the PK of the test elagolix 300 mg EN03 capsule formulation. A total of 57 subjects were randomly assigned to one of four seuqneces of Regimens A, B and C as outlined in **Table 4.2.2-1**.

Table 4.2.2-1. Sequence Groups in Study M19-648

		Regimens		
Sequence Group	**N**	**Period 1**	**Period 2**	**Period 3**
1	23	A	B	
2	22	B	A[a]	
3	6	A	B	C
4	6	B	A	C

Regimen A: Single dose of one elagolix 300 mg capsule formulation (EN03) administered under fasting conditions (test).
Regimen B: Single dose of one elagolix 300 mg IR film-coated tablet formulation (RC2) administered under fasting conditions (reference).
Regimen C: Single dose of one elagolix 300 mg capsule formulation (EN03) administered after a high-fat meal.

A washout interval of 4 days separated the doses between study periods. Blood samples for assay of elagolix were collected for up to 36 hours after dosing in each period. On the dosing day (Day 1) in each period, subjects in Regimens A and B were not served breakfast, and subjects in Regimen C received a high-fat breakfast at approximately 30 minutes prior to dosing.

PK Results:
Forty-four (44/45) subjects each received a single dose of the EN03 test capsule and a single dose of the RC2 reference IR tablet. One subject (1/45), who discontinued study drug, received a single dose of the RC2 reference IR tablet. Twelve subjects (12/12) received two doses of the EN03 test capsule and a single dose of the RC2 reference IR tablet. For the analysis of log-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf},

the 90% CIs and corresponding point estimates are shown in **Table 4.2.2-2**. Both the Applicant's and this reviewer's calculations showed that the 90% CIs with respect to elagolix C_{max} and AUCs were within the 80 - 125% range following administration of one 300 mg elagolix EN03 capsule (Regimen A, test) relative to one 300 mg elagolix IR tablet (Regimen B, reference) under fasting conditions. The TBM evening dose formulation and Phase 3 formulation RC2 tablet are bioequivalent.

Figure 4.2.2-1. Mean Elagolix Plasma Concentration-Time Profiles for the EN03 Capsule vs. RC2 Tablet Under Fasting Conditions

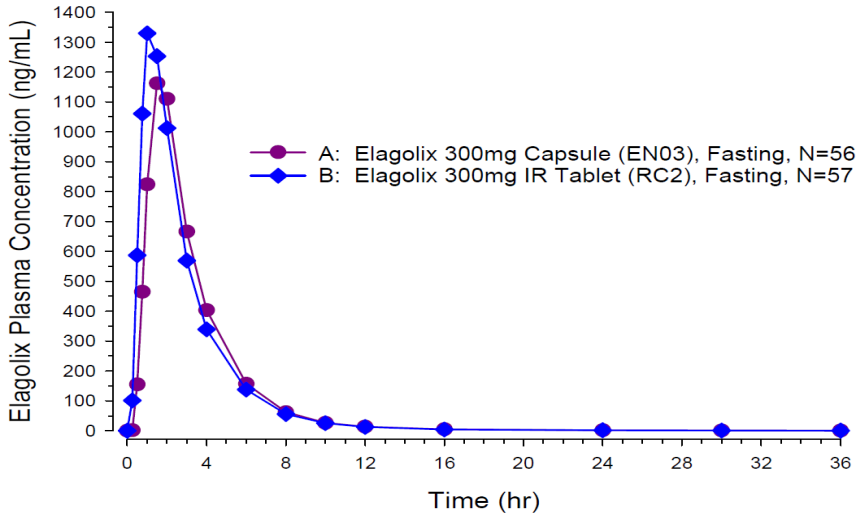


Table 4.2.2-2. Bioequivalence Assessment for Elagolix in EN03 Capsule and RC2 Tablet (Study M19-648, N = 45)

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
	EN03 [Test]	RC2 [Reference]	
$AUC_{0\text{-}inf}$ (ng•h/mL)	3746	3875	96.7 (92.7 – 100.8)
$AUC_{0\text{-}t}$ (ng•h/mL)	3740	3869	96.7 (92.7 – 100.8)
C_{max} (ng/mL)	1313	1504	87.3 (80.7 – 94.6)

Source: Reviewer's analysis

The effect of food on the PK of the TBM EN03 capsule was shown in **Table 4.2.2-3**. When the EN03 capsule was administered after a high-fat meal, elagolix C_{max} and $AUC_{0\text{-}inf}$ were 40% and 28% lower, respectively, when compared to exposures under fasting conditions.

Figure 4.2.2-2. Mean Elagolix Plasma Concentration-Time Profiles for the EN03 Capsule Under Fasting and Non-Fasting Conditions

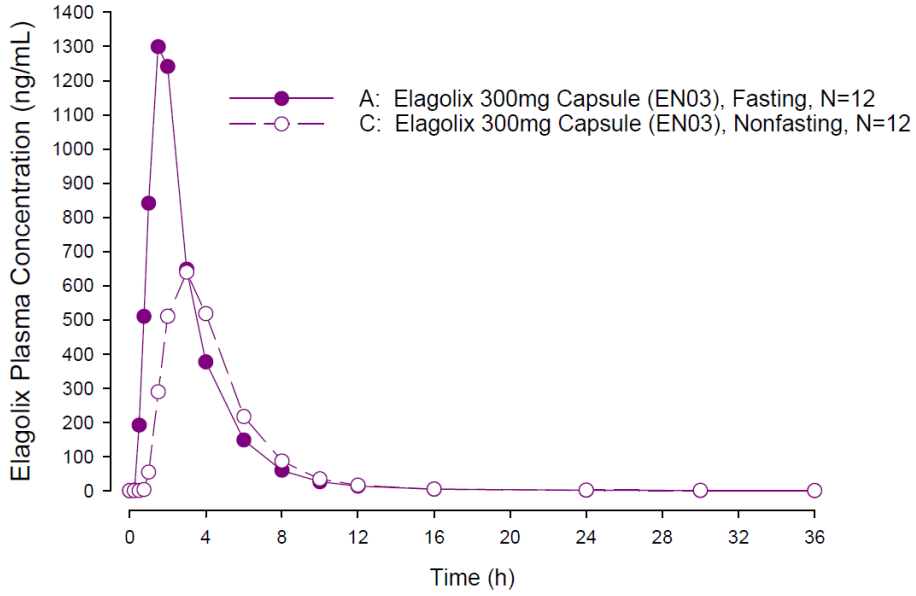


Table 4.2.2-3. The Effect of Food on the PK Parameters of Evening Dose Capsule (Study M19-648, N =12)

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
	Fed [Test]	Fasting [Reference]	
$AUC_{0\text{-}inf}$ (ng•h/mL)	2618	3634	72.03 (65.68 – 78.99)
$AUC_{0\text{-}t}$ (ng•h/mL)	2609	3630	71.88 (65.53 – 78.84)
C_{max} (ng/mL)	755	1262	59.79 (48.22 – 74.15)
T_{max} (h)*	3.0 (2.0 – 6.0)	1.75 (1.5 – 2.0)	N.A.

*Median (minimum – maximum).
Source: Reviewer's analysis

Reviewer's Comments:

- *The reviewer's BE and food effect analyses are consistent with the Applicant's results.*
- *Based on elagolix exposure-response relationship for efficacy, 28% decrease in elagolix AUC and 40% decrease in elagolix C_{max} under fed conditions are not expected to have a clinically meaningful impact on responder rates. In addition, both morning and evening doses were administered without regards to meals in Phase 3 trials. The review team concurs with the Applicant that Oriahnn can be orally administered without regard to meals and no dose adjustment was recommended under fed conditions.*

Safety Results:
No clinically significant abnormalities in vital signs, ECG, physical examinations or laboratory measurements were observed during the course of the study. No deaths, serious adverse events or other significant adverse events were reported during the study. The proportion of subjects reporting at least one treatment-emergent adverse event were 9/56 (16%) in Regimen A, 10/57 (18%) in Regimen B, and 1/12 (8%) in the Regimen C.

4.3 Clinical Drug Interaction Assessments

In the current NDA, the Applicant conducted 4 Phase 1 clinical studies (M13-757, M14-708, M16-850 and M16-855) and one PBPK modeling report to assess potential DDI between Oriahnn and other drugs.

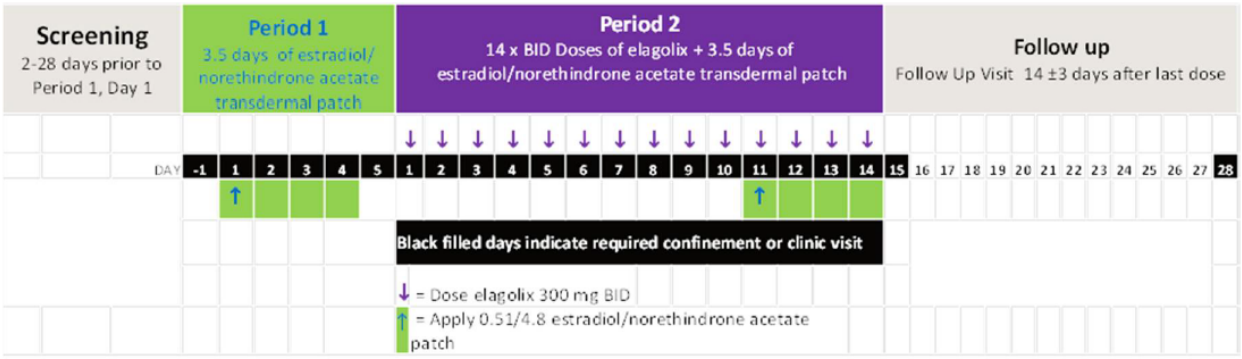
4.3.1 Study M13-757

Title: A Phase 1 Study to Evaluate the Effect of Multiple Doses of Elagolix on the Pharmacokinetics of CombiPatch® in Healthy Postmenopausal Female Subjects

Objectives:
To evaluate the effect of multiple doses of elagolix on the pharmacokinetics of estrone (E1), E2, and norethindrone from CombiPatch® in healthy postmenopausal female subjects.

Study Design:

Figure 4.3.1-1 Study Design Schematic (Study M13-757)



This was a Phase 1, single-center, multiple-dose, open-label, two-period, sequential design study. A total of 36 healthy postmenopausal women were enrolled and administered study drugs as presented in (**Figure 4.3.1-1)**. Blood samples for assay of total E1, unconjugated E2, and norethindrone were collected for up to 96 hours after transdermal application on Day 1 of Period 1 and Day 11 of Period 2. Blood samples for assay of elagolix were collected for up to 1 hour after the morning dose on Days 11 through 14 of Period 2.

Results:
Among 36 enrolled subjects, 34 subjects completed the study. Subject (b) (6) dropped out due to an adverse event of dehydrationon Day 10 of Period 2 and Subject (b) (6) dropped out after Day 13 of Period 2. The PK data of these two subjects was not included in the relative bioavailability calculation. The point estimates and 90% confidence intervals for the relative bioavailability assessments from the analysis of the log-transformed C_{max} and AUC_{0-t} are presented in **Table 4.3.1-1**. Both the Applicant's and the reviewer's analyses showed that no significant change was observed in the C_{max} and AUC of NETA, and baseline-adjusted E2 between test (with elagolix) and reference (without elagolix) group. Co-administration of elagolix 300 mg BID did not affect the PK of transdermally delivered E2 and NETA. Elagolix 300 mg BID slightly decreased the AUC and C_{max} of baseline-corrected total E1 by 9% and 14%, respectively, which is not considered clinically meaningful. No clinically significant vital signs, ECG or laboratory measurements were observed during the study.

Table 4.3.1-1. Relative Bioavailability and 90% Confidence Intervals for Norethindrone, Unconjugated Estradiol and Total Estrone (N =34)

	PK Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
		Day 11 [Test]	Day 1 [Reference]	
		Baseline-corrected E2		
Reviewer's analysis	AUC_{0-t} (pg•h/mL)	4288	3990	107.5 (94.5 – 122.3)
	C_{max} (pg/mL)	70.2	63.7	110.3 (99.1 –122.7)
	T_{max} (h)*	24 (12 – 84)	36 (12 – 84)	N.A.
Applicant's analysis	AUC_{0-t} (pg•h/mL)	4510	3990	113.1 (102.0 – 125.4)
	C_{max} (pg/mL)	71.7	63.7	112.6 (101.3 – 125.1)
		Baseline-corrected total E1		
Reviewer's analysis	AUC_{0-t} (pg•h/mL)	29403	32162	91.4 (78.1 – 107.0)
	C_{max} (pg/mL)	488	565	86.4 (75.0 – 99.5)
	T_{max} (h)*	48 (24 – 84)	48 (24 – 96)	N.A.
Applicant's analysis	AUC_{0-t} (pg•h/mL)	31000	32200	96.3 (84.0 – 110.4)
	C_{max} (pg/mL)	506	565	89.5 (78.4 – 102.2)
		NETA		
Reviewer's analysis	AUC_{0-t} (ng•h/mL)	70.9	72.0	98.3 (88.2 – 109.7)
	C_{max} (ng/mL)	1.03	1.02	101.3 (93.5 – 109.6)
	T_{max} (h)*	48 (12 – 84)	36 (24 – 84)	N.A.
Applicant's analysis	AUC_{0-t} (ng•h/mL)	74.5	72.0	103.4 (96.2 – 111.1)
	C_{max} (ng/mL)	1.05	1.02	103.1 (95.6 – 111.2)

*Median (minimum – maximum)
Source: Reviewer's analysis

Reviewer's Comments:

- *The reviewer's relative bioavailability analysis results are slightly different from the Applicant's results but the differences do not affect the conclusion. Co-administration of elagolix 300 mg BID did not affect the PK of transdermally delivered E2 and NETA.*

4.3.2 Study M14-708

Title: A Phase 1 Study to Evaluate the Effect of Multiple Doses of Elagolix on the Pharmacokinetics of Activella® in Healthy Postmenopausal Female Subjects

Objectives:
To evaluate the effect of multiple doses of elagolix on the PK of Activella® in healthy postmenopausal female subjects.

Study Design:
This was a Phase 1, single-center, multiple-dose, open-label study. A total of 24 healthy postmenopausal women were enrolled and administered study drugs as presented in (**Table 4.3.2-1)**. Each dose of study drug administered in the morning was taken orally with approximately 240 mL of water after a 10-hour fast and either 4 hours (Days 1 and 11) or 2.5 hours (Days 4 – 10) before lunch. The evening dose of elagolix was administered with approximately 240 mL of water on an empty stomach. Blood samples for

assay of total E1, unconjugated E1 and unconjugated E2 were collected for up to 72 hours after dosing on Day 1 and Day 11. Blood samples for assay of NETA were collected for up to 60 hours after dosing on Day 1 and Day 11. Blood samples for assay of elagolix were collected immediately prior to dosing (0-hour), and at 1 hour after dosing for the morning on Day 11.

Table 4.3.2-1 Study Dosing (Study M14-708)

Drug	Study Day 1	Study Days 2 – 3	Study Days 4 – 10	Study Day 11	Study Day 12[a]
Elagolix (300 mg BID)			x	x	x
Activella® (1 mg/0.5 mg)	x			x	

BID = Twice Daily

a. Only a single morning dose of elagolix was administered on Day 12.

Results:

All the 24 enrolled subjects completed the study. The point estimates and 90% confidence intervals for the relative bioavailability assessments from the analysis of the log-transformed C_{max}, and AUC are presented in **Table 4.3.2-2**. Both the Applicant's and the reviewer's analyses showed that no significant change was observed in the C_{max} and AUC of NETA between test (with elagolix) and reference (without elagolix) group. However, co-administration of elagolix 300 mg BID increased the C_{max} and $AUC_{0\text{-inf}}$ of baseline-corrected E2 by 128% and 34%, respectively compared to Activella alone treatment. The C_{max} of baseline-corrected total E1 increased by 69% but AUC did not change. No clinically significant vital signs, ECG or laboratory measurements were observed during the study.

Figure 4.3.2-1. Mean Baseline-Adjusted Unconjugated Estradiol Plasma Concentration-Time Profiles

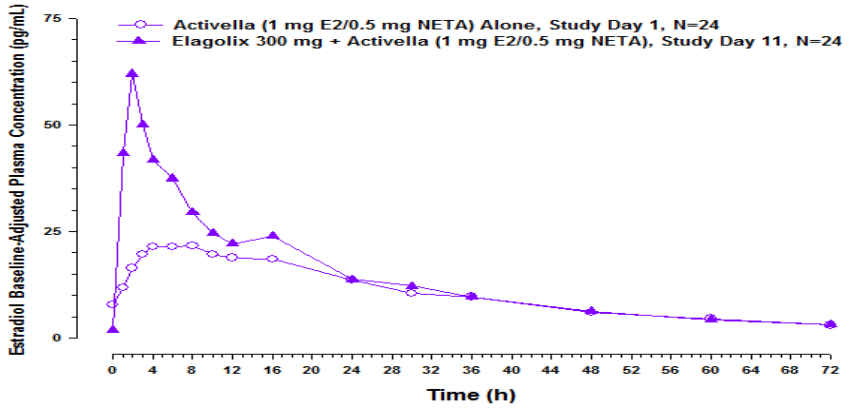


Figure 4.3.2-2. Mean Baseline-Adjusted Total Estrone Plasma Concentration-Time Profiles

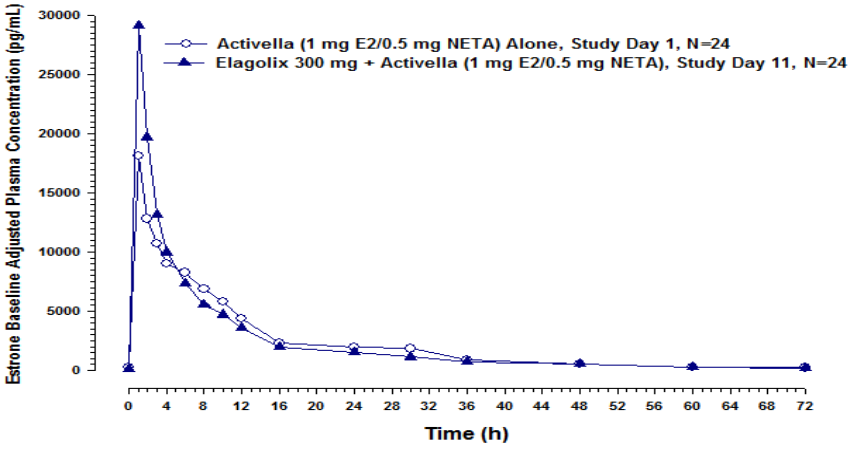


Table 4.3.2-2. Relative Bioavailability and 90% Confidence Intervals for Norethindrone, Unconjugated Estradiol and Total Estrone (N =24)

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
	Day 11 [Test]	Day 1 [Reference]	
Baseline-corrected E2			
AUC_{0-inf} (pg•h/mL)	1062.5	791.1	134.3 (119.7 – 150.7)
AUC_{0-t} (pg•h/mL)	951.8	694.6	137.0 (122.2 – 153.7)
C_{max} (pg/mL)	58.5	25.7	227.8 (197.9 – 262.2)
T_{max} (h)*	2 (1 – 4)	6 (0 – 16)	N.A.
Baseline-corrected total E1			
AUC_{0-inf} (ng•h/mL)	166.2	162.1	102.5 (96.7 – 108.8)
AUC_{0-t} (ng•h/mL)	161.1	157.4	102.3 (96.1 – 108.9)
C_{max} (ng/mL)	28.9	17.1	168.9 (150.9 – 189.0)
T_{max} (h)*	1 (1 – 2)	1 (1 – 2)	N.A.
NETA			
AUC_{0-inf} (ng•h/mL)	22.6	22.1	102.6 (95.7 – 110.0)
AUC_{0-t} (ng•h/mL)	20.7	19.9	103.8 (96.5 – 111.7)
C_{max} (ng/mL)	5.68	5.82	97.5 (91.2 – 104.2)
T_{max} (h)*	1 (0.5 – 1)	1 (0.5 – 1.5)	N.A.

*Median (minimum – maximum)

Source: Reviewer's analysis

Reviewer's Comments:

- *Studies M14-708 and M13-757 showed that concomitant use of elagolix 300 mg BID increased the AUC and Cmax of orally administered E2 but did not affect the PK of transdermally delivered E2, indicating elagolix 300 mg BID might increase oral absorption of E2 in gastrointestinal (GI) tract.*
- *As shown in Figure 4.3.2-1, co-administration of elagolix increased the oral absorption of E2 but did not affect the terminal half-life or elimination rate. This may indicate that elagolix inhibited CYP3A in small intestine but did not significantly affect CYP3A in liver. The first-pass metabolism of E2 was reduced.*
- *Estrogens are metabolized by CYP3A, CYP1A2, UGTs, and SULTs in liver and metabolized by CYP1A1, CYP1B1, CYP3A, UGTs, and SULTs in extrahepatic tissues. In vitro DDI studies showed that elagolix is a time-dependent inhibitor of CYP3A4/5 (Ki 74 μM), CYP2C8 (Ki 82 μM) and CYP2C19 (Ki 34 μM). Clinical DDI studies showed that elagolix is an inhibitor of OATPs/BCRP and P-gp and an inducer of CYP3A.*
- *Following oral administration of 300 mg elagolix, the concentration of elagolix in GI tract is approximately 1.2 mg/mL or 1.9 mM if elagolix is completely dissolved. The lowest aqueous solubility of elagolix is 0.89 mg/mL or 1.41 mM between pH 5 and pH 9. Thus, $R_{1,gut}$ = 1 + (1410 μM/74 μM) = 20. It is reasonable to expect CYP3A inhibition in GI tract after oral administration of 300 mg elagolix.*
- *Phase 3 trials showed that the steady-state average concentrations of E2 in patientis treated with Oriahnn were approximately 50-60 pg/mL(Figure 3.3.1-4), which was slightly lower than the*

normal serum E2 level in healthy pre-menopausal women (65 ± 34 pg/mL)[1]. In addition, the Applicant's population PK simulation showed that the addition of 1 mg E2/0.5 mg NETA did not affect the PK of elagolix. Therefore, the DDI between elagolix 300 mg BID and add-back E2 is not expected to have clinically meaningful impact on the efficacy and safety of Oriahnn.

- *In the Phase 3 trials, the add-back of E2 reduced the efficacy of elagolix 300 mg alone treatment. The review team recommends that concomitant use of hormonal contraceptives be prohibited during Oriahnn treatment.*

4.3.3 Study M16-850

Title: A Phase 1 Study to Evaluate the Effect of Multiple Doses of Elagolix on the Pharmacokinetics of Bupropion in Healthy Premenopausal Female Subjects

Objectives:
To evaluate the effect of multiple doses of elagolix on the pharmacokinetics of a CYP2B6 substrate, bupropion, and its major metabolite, hydroxybupropion (OH-bupropion), in healthy premenopausal female subjects.

Study Design:
This was a Phase 1 single-center, multiple-dose, open-label, two-period, sequential study design. A total of 24 healthy premenopausal women were enrolled and administered study drugs as presented in (**Table 4.3.3-1)**. The doses of bupropion were taken orally in the morning after at least an 8-hour fast with approximately 240 mL of water. Each dose of elagolix was taken orally under fasting conditions with approximately 240 mL of water. Blood samples for assay of bupropion and its metabolite (OH-bupropion) were collected for up to 120 hours after dosing on Study Day 1 of Period 1 and Study Day 11 of Period 2. Blood samples for assay of elagolix were collected up to 1 hour after the morning dose on Study Day 11 of Period 2.

Table 4.3.3-1 Study Dosing (Study M16-850)

	Period 1	Period 2		
Drug	**Study Day 1**	**Study Days 1 – 10**	**Study Day 11**	**Study Days 12 – 14**
Elagolix (300 mg BID)		X	X	X
Bupropion (150 mg)	X		X	

BID = Twice Daily

Results:
A total of 23 subjects completed the study. One subject was lost to follow-up during the Follow-up period of the study. Data from all subjects (N = 24) were included in the safety analyses and PK analyses. The point estimates and 90% confidence intervals for the relative bioavailability assessments from the analysis of the log-transformed C_{max}, and AUC are presented in **Table 4.3.3-2**. Both the Applicant's and the reviewer's analyses showed that no significant change was observed in the AUC of bupropion or hydroxybupropion between test (with elagolix) and reference (without elagolix) group. The C_{max} values of

[1] Hassan LS et. al., 2017 Diabetes Metab Res Rev. Feb; 33(2). doi: 10.1002/dmrr.2829

buproprion and hydroxybupropion were increased by 25% and 32%, respectively, as compared to the bupropion alone group. The DDI between elagolix 300 mg BID and bupropion is not considered clinically relevant, and hence no dose adjustment is required for buproprion when co-administered with Oriahnn. No clinically significant vital signs, ECG, physical examinations or laboratory measurements were observed during the study.

Table 4.3.3-2. Relative Bioavailability and 90% Confidence Intervals for Bupropion and Hydroxybupropion (N =24)

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
	Day 11 [Test]	Day 1 [Reference]	
Bupropion			
$AUC_{0\text{-}inf}$ (pg•h/mL)	1054	1092	96.5 (91.0 – 102.3)
$AUC_{0\text{-}t}$ (pg•h/mL)	1024	1051	97.4 (92.0 – 103.2)
C_{max} (pg/mL)	108.3	86.9	124.6 (110.4 – 140.7)
T_{max} (h)*	3 (3 – 5)	4 (3 – 8)	N.A.
Hydroxybupropion			
$AUC_{0\text{-}inf}$ (ng•h/mL)	16648	15663	106.3 (99.3 – 113.7)
$AUC_{0\text{-}t}$ (ng•h/mL)	16181	14808	109.3 (102.1 – 117.0)
C_{max} (ng/mL)	406.0	308.2	131.7 (121.6 – 142.7)
T_{max} (h)*	6 (5 – 12)	10 (6 – 24)	N.A.

*Median (minimum – maximum)
Source: Reviewer's analysis

Reviewer's Comments:

- *The reviewer's relative bioavailability analysis results are consistent with the Applicant's results.*
- *No dose adjustment is required for buproprion when co-administered with Oriahnn.*
- *Co-administration of Oriahnn is unlikely to affect the PK of CYP2B6 substrates.*

4.3.4 Study M16-855

Title: A Phase 1 Study to Evaluate the Effect of Multiple Doses of Elagolix on the Pharmacokinetics of Omeprazole in Healthy Premenopausal Females

Objectives:
To evaluate the effect of repeated doses of elagolix on the pharmacokinetics of omeprazole and its metabolites in healthy premenopausal female subjects.

Study Design:
This was a Phase 1 single-center, multiple-dose, open-label, single-arm study design. Healthy adult premenopausal women (N = 20) were enrolled.

Study drugs were administered as follows:
Study Day 1 – A single dose of omeprazole delayed release capsule 40 mg was administered under fasting conditions.
Study Days 3 – 10 Elagolix 300 mg BID was administered under fasting conditions.

Study Day 11 – Elagolix 300 mg BID and a single dose of omeprazole delayed release capsule 40 mg were administered under fasting conditions.

Pharmacokinetic (PK) blood samples for omeprazole and its metabolites (5-hydroxyomeprazole, a metabolite formed primarily by CYP2C19, and omeprazole sulfone, a metabolite formed primarily by CYP3A4) were collected prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after dosing on Study Days 1 and 11. PK blood samples for elagolix were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, and 2 hours after the morning dose on Study Day 11.

Results:
All 20 subjects completed the study. The PK profiles of omeprazole and its metabolites, 5-hydroxyomeprazole and omeprazole sulfone, are shown in **Figure 4.3.4-1**, **Figure 4.3.4-2** and **Figure 4.3.4-3**.

Figure 4.3.4-1. Mean Omeprazole Plasma Concentration-Time Profiles

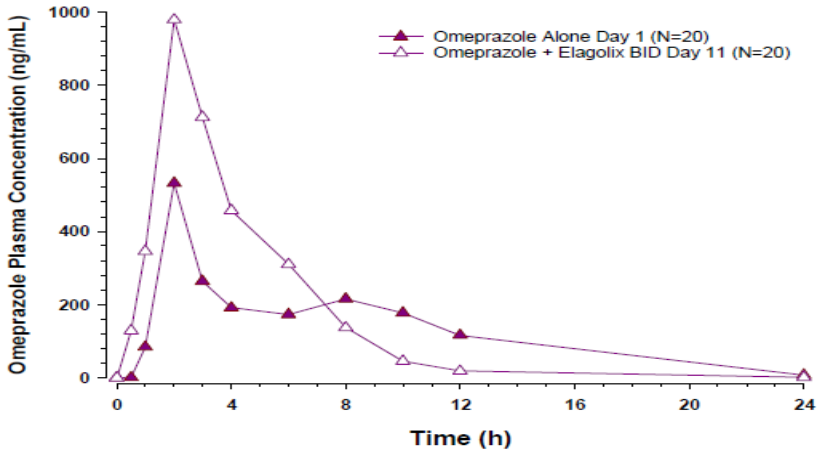


Figure 4.3.4-2. Mean 5-Hydroxyomeprazole Plasma Concentration-Time Profiles

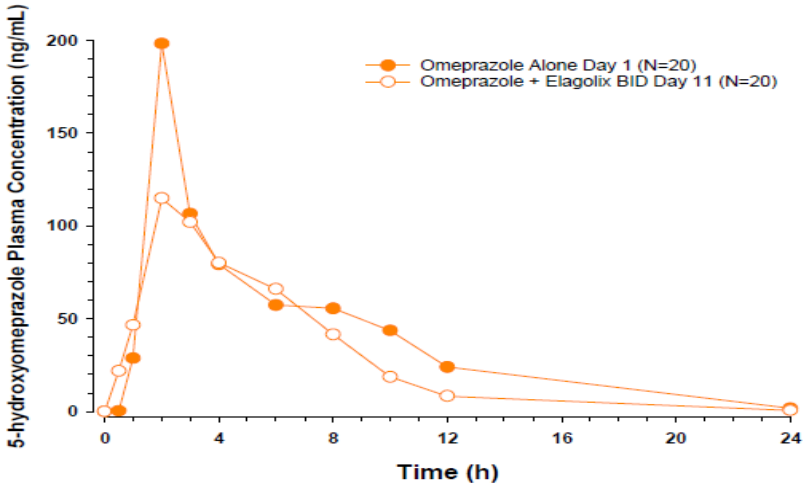
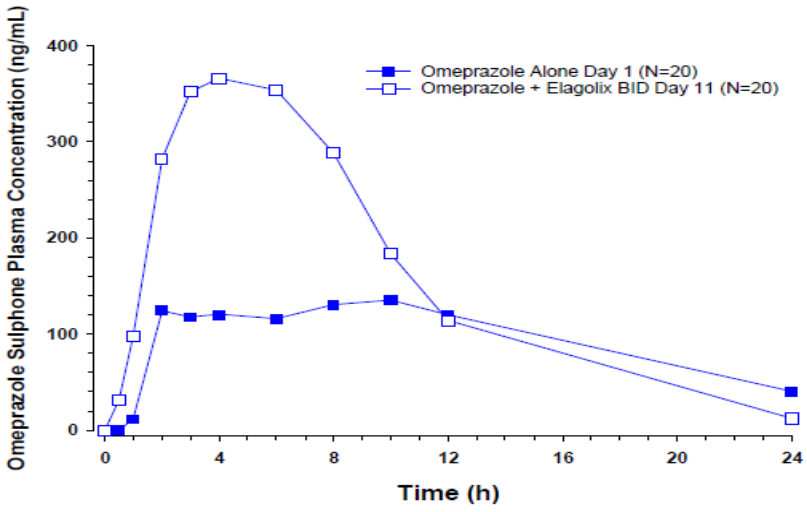


Figure 4.3.4-3. Mean Omeprazole Sulfone Plasma Concentration-Time Profiles



Following oral administration of elagolix 300 mg BID for 9 days, omeprazole exposure (C_{max} and AUC) increased by 1.8- to 1.9-fold (**Table 4.3.3-1**). The conversion of omeprazole into 5-hydroxyomeprazole is catalyzed by CYP2C19 and the formation of omeprazole sulfone is catalyzed by CYP3A. The metabolite-to-parent $AUC_{0\text{-}inf}$ ratios for 5-hydroxyomeprazole decreased from 0.46 to 0.20, suggesting an inhibitory effect on the CYP2C19 metabolic pathway of omeprazole by elagolix 300 mg BID. In contrast, there was a slight increase in the metabolite-to-parent $AUC_{0\text{-}inf}$ ratios for omeprazole sulfone from 0.83 to 1.03, suggesting some induction on the CYP3A metabolic pathway of omeprazole by elagolix 300 mg BID.

Table 4.3.3-1. Relative Bioavailability and 90% Confidence Intervals for Omeprazole, 5-Hydroxyomeprazole, and Omeprazole Sulfone

Regimens Test vs. Reference	Pharmacokinetic Parameters	Central Value		Relative Bioavailability	
		Test	Reference	Point of Estimate	90% CIs
		Omeprazole			
Day 11 vs Day 1	C_{max} (ng/mL)	956	491	1.94	123.2 – 308.0
	$AUC_{0\text{-}t}$ (ng*h/mL)	3319	1821	1.82	115.2 – 288.4
	$AUC_{0\text{-}inf}$ (ng*h/mL)	3321	1875	1.77	109.4 – 286.6
	T_{max} (h)*	2 (1 – 8)	2 (2 – 8)	N.A.	N.A.
		5-Hydroxomeprazole			
Day 11 vs Day 1	C_{max} (ng/mL)	134	195	0.68	51.2 – 91.4
	$AUC_{0\text{-}t}$ (ng*h/mL)	643	857	0.75	63.8 – 88.4
	$AUC_{0\text{-}inf}$ (ng*h/mL)	664	883	0.75	64.5 – 87.8
	T_{max} (h)*	3 (1 – 8)	2 (2 – 10)	N.A.	N.A.
	$RAUC_{0\text{-}t}$	0.194	0.471	0.412	32.6 – 52.0
	$RAUC_{0\text{-}inf}$	0.198	0.458	0.432	34.3 – 54.4
		Omeprazole Sulfone			
Day 11 vs Day 1	C_{max} (ng/mL)	411	152	2.70	172.5 – 420.9
	$AUC_{0\text{-}t}$ (ng*h/mL)	3375	1237	2.73	157.7 – 472.0
	$AUC_{0\text{-}inf}$ (ng*h/mL)	3450	1402	2.46	162.0 – 373.8
	T_{max} (h)*	4 (3 – 8)	3.5 (2 – 12)	N.A.	N.A.
	$RAUC_{0\text{-}t}$	1.017	0.679	1.497	127.2 – 176.1
	$RAUC_{0\text{-}inf}$	1.028	0.825	1.246	109.2 – 142.2

*Median (minimum – maximum)

Note: The apparent terminal phase elimination rate constant and $AUC_{0\text{-}inf}$ could not be calculated for omeprazole for Subject (b) (6) on Day 1, and for omeprazole sulfone for Subjects (b) (6) on Day 1. RAUC stands for metabolite-to-parent AUC ratio.
Source: Reviewer's analysis

The regimens tested were generally well tolerated by the subjects in this study. No clinically significant vital signs, ECGs, physical examinations or laboratory measurements were observed during the course of the study.

Reviewer's Comments:

- *This reviewer's relative bioavailability analysis for the test /reference ratios was comparable to the Applicant's analysis but the Applicant's 90% confidence intervals were narrower than that of the reviewer's calculations. Since the point of estimate values were similar between the reviewer's and Applicant's analyses, the difference in the confidence interval would not affect our recommendation of labeling language for clinical management.*
- *Following administration of elagolix 300 mg BID for 9 days, omeprazole exposure increased by 1.8- to 1.9-fold. Based on the criteria for categorization of clinical CYP enzyme inhibitors stated in the current draft guidance for industry: Clinical Drug Interaction Studies-Study Design, Data Analysis, and Clinical Implications (October 2017), elagolix administered with 300 mg BID dosing regimen can be assigned as a weak CYP2C19 inhibitor. Co-administration with Oriahnn may increase plasma concentrations of drugs that are substrates of CYP2C19.*
- *It should be noted that since elagolix is also an inducer of CYP3A and omeprazole is a substrate of CYP3A, the 1.8- to 1.9-fold increase in omeprazole exposure is a net effect of CYP2C19 inhibition and CYP3A induction caused by elagolix.*
- *Per the label of PRILOSEC (omeprazole delayed-release oral suspension and capsules), when voriconazole (400 mg Q12h x 1 day, then 200 mg x 6 days), an inhibitor of CYP2C19 and CYP3A4, was given with omeprazole (40 mg once daily x 7 days) to healthy subjects, the steady-state C_{max} and $AUC_{0\text{-}24}$ of omeprazole were increased by an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole was given without voriconazole. In Section 7 of PRILOSEC label, for concomitant use of voriconazole, it is recommended that "Dose adjustment of PRILOSEC is not normally required. However, in patients with Zollinger-Ellison syndrome, who may require higher doses, dose adjustment may be considered". This reviewer recommends that when Oriahnn is used concomitantly with higher doses of omeprazole, e.g. in patients with Zollinger-Ellison syndrome, dosage reduction of omeprazole be considered.*

4.3.5 PBPK Modeling and Simulation

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to predict the effect of elagolix on the PK of digoxin.

The Division of Pharmacometrics has reviewed the report, supporting modeling files, and response to our information requests submitted on January 15, 2020, and January 22, 2020, and concludes that the Applicant's PBPK analyses are adequate to evaluate the effect of elagolix (300 mg twice daily (BID)) on the PK of digoxin. The effect of elagolix at 300 mg BID dose level on the PK of digoxin is expected to be similar to that at 200 mg BID where the Cmax of digoxin was increased by about 70% and AUC was increased by about 30%.

Regulatory history

Elagolix sodium (Orilissa™) was approved on 07/23/2018 under NDA 210450. PBPK analyses were conducted in the Orilissa™ program as summarized in Table 4.3.5-1. PBPK analyses report R&D/17/0098 was reviewed previously by the Office of Clinical Pharmacology and was deemed acceptable for the intended uses. In this submission, the Applicant submitted PBPK analysis report R&D/18/1239 to update the elagolix PBPK model and to evaluate the DDI between elagolix 300 mg BID and a single dose (SD) of digoxin 0.5 mg.

Table 4.3.5-1 Summary of PBPK analyses in elagolix programs

Application #	Report #	Title	Intended uses
NDA 210450	R&D/17/0098	Assessment of Elagolix Drug-Drug Interaction Potential Using Physiologically-Based Pharmacokinetic Modeling and Simulations	• To predict the DDI potential of elagolix as a CYP3A inducer at a dose of 200 mg BID. • To predict the DDI potential of elagolix as a P-gp inhibitor at a dose of 150 mg QD.
NDA 210450	R&D/17/1371	Prediction of Elagolix Exposures from In Vitro Drug Dissolution Rates Using PBPK Absorption Modeling	• To evaluate the predictive ability of a PBPK model of elagolix that incorporates in vitro dissolution data to predict the exposures of elagolix after administration of commercial 200 mg IR elagolix tablets. • To determine the impact of changing the in vitro dissolution profile on the exposures of elagolix using a PBPK modeling approach.
NDA 213388	R&D/18/1239	Assessment of Elagolix Drug-Drug Interaction Potential Using Physiologically-Based Pharmacokinetic Modeling and Simulations	• To evaluate DDI potential of elagolix at a dose of 300 mg BID with SD of digoxin.

Source: Reviewer's summary, NDA210450 Multi-Discipline Review/Summary, Clinical, Non-Clinical: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210450Orig1s000MultiD.pdf

Background

The mass balance study (NBI-56418-0601) suggested that following a single dose of 150 mg [^{14}C] elagolix, 90% of radioactivity excreted in feces with urinary excretion accounting for less than 3%. In feces, 26.3% was unchanged elagolix.

Elagolix is approximately 80% bound to human plasma proteins (R&D/10/1243) and blood-to-plasma ratio was approximately 0.6 (Study NBI-56418-0601).

Elagolix shows dose proportional increase in exposures (Cmax and AUC) up to 400 mg BID (Study M12-790) and a more than dose proportional increase from 600 mg to 1200 mg (Study M13-784 and Study M12-661). A high-fat meal decreased the elagolix AUC only by 24% (Study M15-817). Elagolix has high solubility and low permeability.

In vitro study suggested that elagolix is metabolized by multiple CYP enzymes with major contributions from CYP3A and to a lesser extent from CYP2C8. In vitro, elagolix is a weak to moderate inducer of CYP3A, a time-dependent inhibitor of CYP3A, CYP2C8 and CYP2C19. In vitro study suggested that elagolix is a substrate of P-pg and OATP1B1, and an inhibitor of OATP1B1, P-gp, and BCRP.

Multiple clinical DDI studies were conducted to evaluate the effects of ketoconazole, rifampin (single dose and multiple dose), and fluconazole on the PK of elagolix; the effects of elagolix on the PK of digoxin, rosuvastatin, midazolam, sertraline, fluconazole, bupropion, omeprazole, and oral contraceptives. The DDI study that is relevant to the PBPK analysis was the digoxin DDI study (M12-652) where the effect of elagolix 200 mg BID on digoxin (0.5 mg) PK was evaluated. In this submission, the Applicant applied PBPK modeling and simulation to evaluate the effect of elagolix on digoxin (a P-gp substrate) PK at the proposed dose level (300 mg BID).

Methods

Software

Simcyp® Version 17.1 (Certara) was used for PBPK analyses by the Applicant and the reviewer.

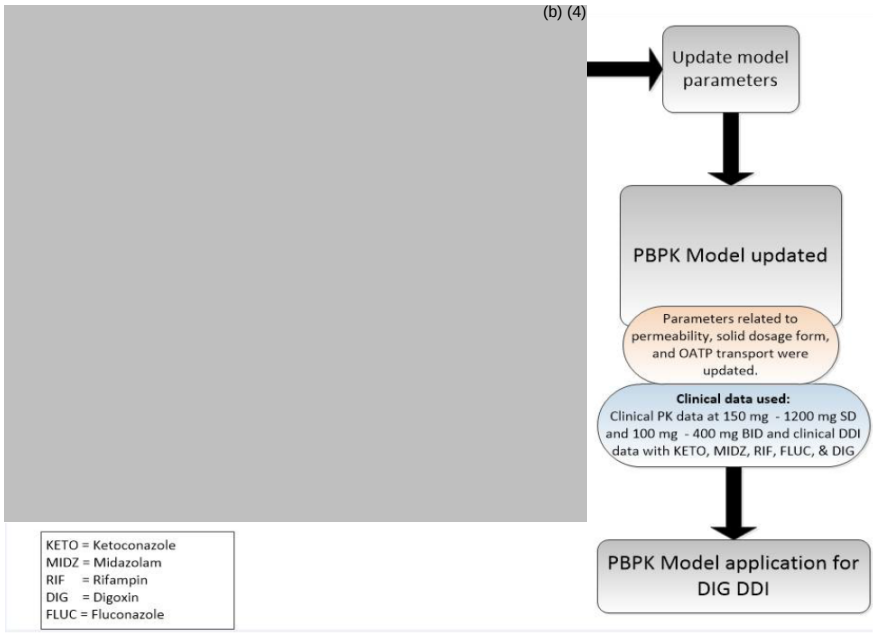
PBPK model development and validation

The PBPK modeling workflow is shown in Figure 4.3.5-1. Briefly, elagolix PBPK model consists of an ADAM (advanced dissolution and absorption model) for absorption and a full body PBPK model for distribution. The permeability of elagolix was modeled within Simcyp using the MechPeff (mechanistic effective permeability) model. Clearance consists of mean values of 36% via CYP3A, 15% via CYP2D6, 1% via CYP2C8, 41% via additional systemic clearance, and 7% via renal clearance. The elagolix PBPK model incorporated P-gp in the GI tract and liver, and the OATP1B1 transporter in the liver.

The model input parameters can be found in NDA 210450 Multi-Discipline Review/Summary, Clinical, Non-Clinical[2]. The updated parameters can be found in Table 4.3.5-2.

Figure 4.3.5-1 PBPK modeling workflow

[2]NDA 210450 Multi-Discipline Review/Summary, Clinical, Non-Clinical: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210450Orig1s000MultiD.pdf



Source: Figure 1 in report R&D/18/1239

Table 4.3.5-2 Updated parameters for elagolix PBPK model

Parameter	Original Parameter Values Used in PBPK Model	Final Parameter Values Used in Updated PBPK Model	Rationale
Absorption			
Absorption Model	(b) (4)	ADAM	
Permeability Model		MechPeff (based on transcellular permeability, P_{trans} of 0.3 cm/s)	Permeability was measured in vitro;[a] In the updated PBPK model, regional permeabilities were predicted by the Simcyp mechanistic P_{eff} (MechPeff) model using the value of transcellular permeability (P_{trans}) of 0.3 cm/s, optimized to capture the clinically observed PK profile. This helps capture population variability on regional permeability in the gut.
Peff,man Duodenum (10^{-4}cm/s)		1.11 (Simcyp estimated)	
Peff,man Jejunum I (10^{-4} cm/s)		2.38 (Simcyp estimated)	
Peff,man Jejunum II (10^{-4} cm/s)		1.67 (Simcyp estimated)	
Peff,man Ileum I (10^{-4} cm/s)		0.67 (Simcyp estimated)	
Peff,man Ileum II (10^{-4} cm/s)		0.67 (Simcyp estimated)	
Peff,man Ileum III (10^{-4}cm/s)		0.66 (Simcyp estimated)	
Peff,man Ileum IV (10^{-4} cm/s)		0.63 (Simcyp estimated)	
Peff,man Colon (10^{-4} cm/s)		0.41 (Simcyp estimated)	
Formulation type		Solid	Based on in vitro evaluation of elagolix API[b]
Aqueous solubility (mg/mL)		0.89	
Transport			
Transporter		SLCO1B1 (OATP1B1)	
J_{max} (pmol/min/million cells)	(b) (4)	323	Parameter updated to reconcile change to rifampin compound model in Simcyp V17 compared to V15. Calibrated and updated based on DDI with single and multiple doses of rifampin based on Study M12-659.[c]
K_m (µM)		0.66	No change from original model.

Source: Table 1 of study report R&D/18/1239; Peff = Effective permeability; Jmax = Kinetic parameter representing maximal rate of transport; Km = Michaelis – Menten parameter (corresponding to half-maximal rate); NA = Not applicable; a. R&D/10/1204, NDA 210450, Module 4, Section 4.2.2.2.;
b. Pharmaceutics Technical Report (PTR)-16-0001, NDA 210450, Module 4 Section 4.3.; c. Study M12-659, NDA 210450, Module 5, Section 5.3.3.4

Data from a multiple ascending dose study (M12-790, 150 mg QD and 100 mg – 400 mg BID) was used for model calibration. PK measured following single dose administration (M12-662/150 mg, M12-655/200 mg, M12-661, M13-756, M15-973, M15-872/300 mg, M13-784/600 mg and 900 mg, M12-661/1200 mg), or multiple dose administration (M15-974, M15-629/300 mg BID) were used for model validation with regard to PK prediction.

Data from a DDI study with rifampin SD and MD (M12-659) were used for model calibration regarding CYP3A4, OATP1B1, and P-gp contributions. Results from DDI studies with ketoconazole (M12-660) and fluconazole (M15-974) were used for model validation for CYP3A contribution.

A DDI study with midazolam using elagolix at the dose of 150 mg QD (NBI-56418-0502) was used to calibrate the effects on CYP3A substrates. A DDI study with midazolam using elagolix at 300 mg BID (M15-629) was used for model validation with regards to the effects on CYP3A substrates.

A DDI study with digoxin (elagolix 200 mg BID, M12-652) was used to calibrate the effects on P-gp substrates.

Reviewer's comments: *The Applicant used the prediction errors (% PE) ([predicted mean – observed mean]/ observed mean *100%) to evaluate the ability of the PBPK model to predict the observed clinical PK data. The Applicant pre-specified an acceptable limit of prediction ≤ 50% for pharmacokinetic parameters such as Cmax and AUC (Section 7.4, PBPK report R&D/18/1239). The reviewer considered this criterion acceptable when the simulated results were compared with various clinical PK datasets across different dosing levels and/or exposure scenarios. A different acceptance criterion could be applied for a different drug considering factors such as therapeutic windows, and variability in the PK parameters.*

PBPK model application

The purpose of this PBPK analysis is to evaluate the effects of elagolix on the PK of digoxin (a P-gp substrate) at the proposed dose level of elagolix (300 mg BID).

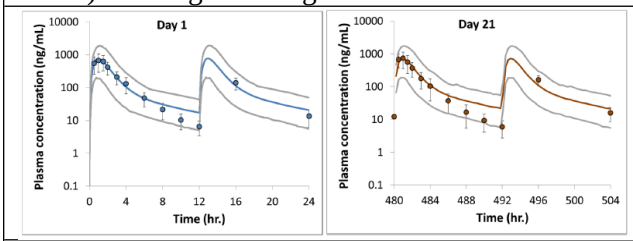
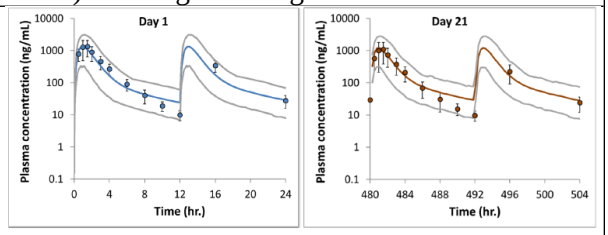
Reviewer's comments: *The digoxin default model in Simcyp V17 was used as the substrate model. The default digoxin model was built to evaluate the effect of a perpetrator on gut P-gp interaction as P-gp is not incorporated in the kidney compartment of the digoxin model. An information request was sent and the Applicant was asked to evaluate the impact of allocating all observed DDI to the gut P-gp mediated interaction on the evaluation of elagolix-digoxin DDI. In response to the FDA's information request, the Applicant conducted additional modeling by incorporating a mechanistic kidney model (MechKiM) in the digoxin model and conducted additional sensitivity analysis on the elagolix P-gp Ki (concentration that supports half maximal inhibition) value. Refer to the 'Results' for details.*

Results

1. **Can the elagolix PBPK model describe the elagolix PK?**

Yes. The predicted elagolix PK parameters (Cmax, AUCt, or AUCtau) were compared to the observed PK parameters from single dose and multiple dose PK studies (Tables 3 and 5 of report R&D/18/1239). For majority of the simulations, the prediction errors ([predicted mean – observed mean]/ observed mean *100%) for Cmax and AUC were within the pre-specified ±50% limits except for the AUC following single dose administration of 900 mg and 1200 mg elagolix, which were -50% and -55%, respectively. **Figure 4.3.5-2** showed the comparison of simulated and observed plasma-time PK profile of elagolix following 200 mg and 300 mg BID.

Figure 4.3.5-2 Comparison of predicted and observed PK profiles of elagolix

A) 200 mg BID elagolix	B) 300 mg BID elagolix
	
Reference: Figure 4, PBPK report R&D/18/1239	Reference: Figure 5, PBPK report R&D/18/1239.
Line represent the predicted mean and [5%, 95%] confidence limits.	

It was noticed that the elagolix model tends to over-predict the elimination phase which could be related to the elimination model setting but not expected to impact the evaluation of DDI between elagolix and digoxin. In addition, the reviewer compared the simulated accumulated elagolix amount in feces following a single dose administration of 150 mg elagolix. The predicted fecal excretion of 27% was similar to the 26.3% of unchanged elagolix observed in the mass balance study.

2. **Can the elagolix PBPK model predict the effect of elagolix on the PK of digoxin (a P-gp substrate) at the proposed dose level (300 mg BID)?**

Yes. In order to evaluate the effect of elagolix (300 mg BID) on the PK of digoxin, the Applicant developed DDI PBPK simulations based on an in vivo study that evaluated the DDI between elagolix (200 mg BID) and digoxin.

The Applicant utilized the digoxin default model which does not include P-gp in the kidney compartment. The observed DDI effect between elagolix and digoxin then was all allocated to the inhibition effect on gut and liver P-gp, and therefore the optimized elagolix P-gp Ki value could be lower compared to that obtained by optimizing using a digoxin model that includes P-gp in the kidney compartment. The Applicant revised the default digoxin model by incorporating a mechanistic kidney model (MechKiM) in response to the FDA's information request. The updated digoxin PBPK model was verified by comparing its PK prediction with the simulated PK by the original digoxin model, and theobserved data from a DDI study between quinidine and oral digoxin. Ideally, the role of kidney P-gp in digoxin clearance should be

assessed by comparing the renal clearance of digoxin following intravenous administration in the presence and absence of a P-gp inhibitor.

The elagolix P-gp inhibition potential, Ki, was optimized against the elagolix (200 mg BID) and digoxin (0.5 mg) DDI study (M12-652). The optimized Ki value of 0.5 µM was about 100-fold lower than the in vitro IC50 value (54 µM, R&D/16/1157).

Elagolix has high solubility across the GI tract. The simulated Cmax values or solubility, whichever is lower, in GI luminal compartments are in the range of 10^3 µM which are over 1000-fold higher than the Ki value of 0.5 µM. Increasing the dose from 200 mg BID to 300 mg BID is not expected to increase the effect of elagolix on digoxin PK because the effective concentrations are much higher than the estimated Ki value. Nevertheless, the predicted CmaxR and AUCR (Cmax or AUC ratios in the presence vs. absences of a perpetrator) of digoxin using the default digoxin model or the MechKiM digoxin model were similar (**Table 4.3.5-3**).

Table 4.3.5-3 Summary of observed and predicted effect of elagolix on the PK of digoxin

Digoxin dose	Elagolix dose	Observed		Predicted with default digoxin model		Predicted with MechKiM digoxin model	
		CmaxR	AUCinfR	CmaxR	AUCinfR	CmaxR	AUCinfR
0.5mg day1	200 mg BID	1.73	1.32	1.70	1.25	1.74	1.31
0.5mg day10		1.71	1.26	1.69	1.26	1.69	1.26
0.5mg day1	300 mg BID	NA	NA	1.78	1.28	1.78	1.29
0.5mg day10		NA	NA	1.76	1.29	1.77	1.30

Source: Tables 4 and 6 of report R&D/18/1239, Table 9 of response to FDA's information request submitted on January 15, 2020; NA: not available

Conclusions

The PBPK analyses are adequate to evaluate the effect of elagolix at 300 mg BID dose level on the PK of digoxin. The effect of elagolix at 300 mg BID dose level on the PK of digoxin is expected to be similar to that at 200 mg BID where the Cmax of digoxin was increased by about 70% and AUC was increased by about 30%.

4.4 Dose Finding Studies

The Applicant conducted two Phase 2 dose-finding studies (M12-663 and M12-813) in patients with uterine fibroids to support dose selection. Study M12-663 was a Phase 2a, dose-finding, proof-of-concept study that evaluated different doses of elagolix at total daily doses (TDD) of 200, 400, and 600 mg along with two hormonal add-back regimens: elagolix 200 mg BID + low-dose (LD) Activella (E2/NETA 0.5 mg/0.1 mg) QD and elagolix 300 mg BID + oral Estrace® 1 mg QD and cyclical Prometrium® 200 mg QD, in premenopausal women with HMB. A TDD of 600 mg provided a robust response (responder rates of > 80% for the composite bleeding assessment) and an acceptable safety and bleeding profile for the majority of women. Based on the efficacy and safety results from Study M12-663, a TDD of elagolix 600 mg was chosen for Phase 2b Study M12-813 which evaluated the efficacy, safety, and tolerability of two dosing regimens, elagolix 300 mg BID and 600 mg QD, without or with one of two strengths of E2/NETA (0.5 mg/0.1 mg or 1 mg/0.5 mg) for up to 6 months of treatment. Study M12-813 demonstrated

that E2/NETA (1.0 mg/ 0.5 mg) attenuated the hypoestrogenic effects (e.g., BMD decrease and hot flush) and slightly reducedthe efficacy of elagolix. Based on the totality of safety/efficacy data and exposure-response analyses, elagolix 300 mg BID + E2/NETA 1.0 mg/0.5 mg QD was selected for further evaluation in Phase 3 uterine fibroid trials.

4.4.1 Study M12-663

Title: A Phase 2a Proof of Concept Study to Evaluate the Safety and Efficacy of Elagolix in Pre-Menopausal Women with Heavy Uterine Bleeding and Uterine Fibroids

Objectives:

- To assess the safety and effectiveness of elagolix versus placebo to reduce uterine bleeding associated with uterine fibroids, and to reduce fibroid volume and uterine volume in premenopausal women 20 to 49 years of age with heavy uterine bleeding (> 80 mL blood loss per menstrual cycle).
- To explore the effects of add-back therapy with continuous combined estrogen + progestin (EP) regimens (LD Activella + NETA) and with cyclical EP regimens (Estrace + cyclical Prometrium) on efficacy, safety, and tolerability when used with elagolix.
- To evaluate the effect of elagolix with or without add-back therapy on bone as measured by exploratory bone turnover biomarkers and dual energy x-ray absorptiometry (DEXA), and also assess quality of life measures.

Study Endpoints:
Primary Efficacy Endpoint:
The mean change in MBL, measured by the alkaline hematin method, from Baseline to the last complete menstrual cycle (last 28 days) during treatment

Selected Secondary Efficacy Endpoints:

- Percentage of subjects with uterine blood loss volume < 80 mL as assessed by alkaline hematin method for the last month of treatment.
- Percentage of subjects with 50% or greater reduction in uterine blood loss volume from Baseline as assessed by alkaline hematin method for the last month of treatment.
- Percentage of subjects with uterine blood loss volume < 80 mL and 50% or greater reduction in bleeding from Baseline as assessed by alkaline hematin method for the last month during treatment (composite bleeding endpoint).

Safety Endpoints: Safety endpoints included AEs, clinical safety laboratory parameters (including lipid profiles), and vital signs; bone biomarkers and bone mineral density (BMD) were monitored as exploratory safety endpoints.

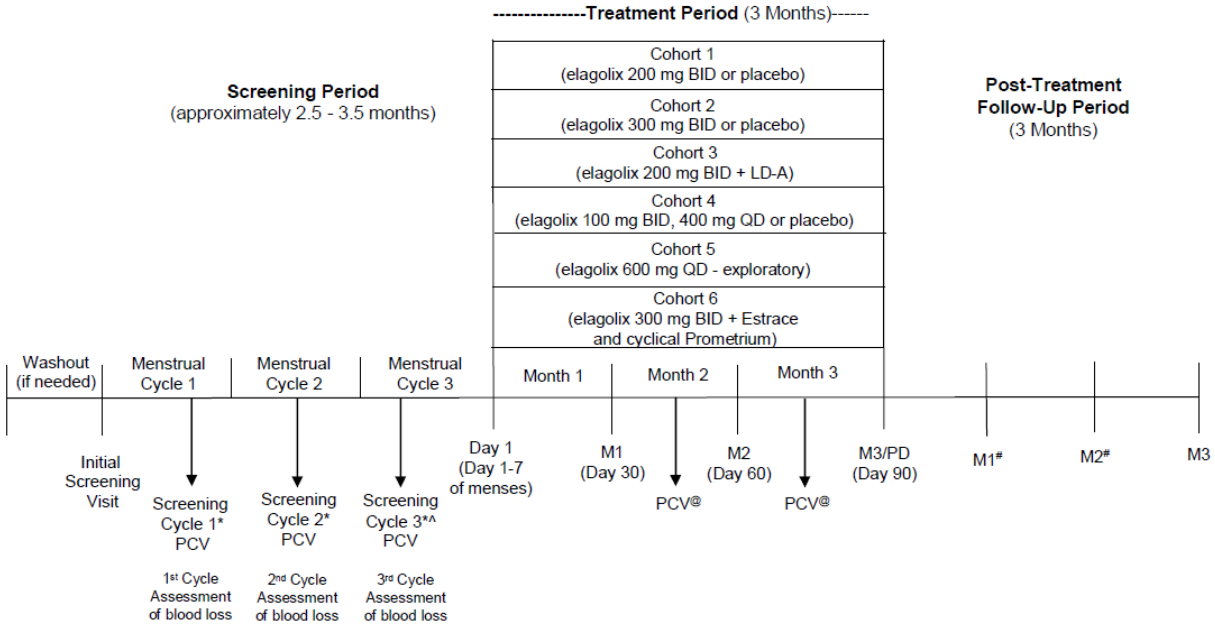
Study Design:
Study M12-663 was a Phase 2a, cohort-design, proof-of-concept study. This study was conducted in premenopausal women 20 to 49 years of age with HMB (> 80 mL blood loss per menstrual cycle) associated with uterine fibroids. A total of 271 pre-menopausal women with heavy uterine bleeding and uterine fibroids were enrolled across 6 cohorts (**Table 4.4.1-1**). Study design is shown in **Figure 4.4.1-1**.

Table 4.4.1-1. Study M12-663 Cohort Design

Cohort	Approximate No. of Subjects	Treatment	Design
1	45	Elagolix 200 mg BID Placebo	Randomized, double-blind, placebo-controlled
2	45	Elagolix 300 mg BID Placebo	Randomized, double-blind, placebo-controlled
3	30	Elagolix 200 mg BID + low-dose Activella	Open-label
4	75	Elagolix 100 mg BID Elagolix 400 mg QD Placebo	Randomized, double-blind, placebo-controlled
5	30	Elagolix 600 mg QD	Open-label
6	30	Elagolix 300 mg BID + cyclical EP	Open-label

Note: Cyclical EP stands for Estrace 1 mg and cyclical Prometrium 200 mg, once daily. Low-dose Activella stands for E2 0.5 mg/NETA 0.1 mg, once daily.

Figure 4.4.1-1. Study M12-663 Design Schematic



PCV = Product Collection Visit

* Approximately 5 days after cessation of menses

@ PCV only required if bleeding or spotting does not stop within approximately 5 days of a scheduled monthly visit

Phone Visit

^ Only if a subject requires a 3rd cycle per Table 7 Menstrual Blood Loss Volume Eligibility

Study drug was to be taken with approximately 8 ounces (240 mL) of water under fasting conditions on an empty stomach (at least 1 hour before or 2 hours after a meal) and no food was to be consumed for 1 hour after study drug administration. Sparse plasma PK samples were collected during the visits on Day 1, Day 30, Day 60, and Day 90. PK sample was collected approximately 1 hour after study drug dosing during Day 1 visit. PK samples were collected at any time during other visits. Serum E2 and progesterone samples were collected during Screening visit, Day 1, Day 30, Day 60, and Day 90 visits. Serum E2 and progesterone samples were collected prior to and approximately 1 hour after study drug administration during Day 1 visit.

Results:

PK/PD:
Plasma concentrations of elagolix determined for population PK and exposure-response. As shown in **Table 4.4.1-2, Figure 4.4.1-2** and **Figure 4.4.1-3**, E2 and progesterone plasma concentrations were decreased from Baseline to the Final Visit of the treatment period at all doses of elagolix compared with placebo, with the largest decrease noted with the elagolix 300 mg BID dosing regimen (mean decreases of 66% for estradiol 88% for progesterone at Month 3). When the same total daily dosing of elagolix was administered, BID dosing appeared to have slightly greater mean E2 and progesterone suppression than QD dosing (200 mg BID versus 400 mg QD and 300 mg BID versus 600 mg QD).

Table 4.4.1-2. Mean ± SD Estradiol Serum Concentrations by Treatment Group (Study M12-663)

	Estradiol Concentration (pg/mL) Mean ± SD					Month 3 Mean % Decrease from Screening
Treatment	**Screening**	**Day 1 (Predose)**	**Month 1**	**Month 2**	**Month 3**	
100 mg BID	154.11 ± 108.40	29.17 ± 29.85	24.39 ± 34.83	26.72 ± 35.09	35.86 ± 40.46	77%
200 mg BID	138.76 ± 101.30	42.91 ± 40.24	5.01 ± 13.52	22.16 ± 50.75	9.42 ± 14.86	93%
400 mg QD	130.62 ± 109.59	47.24 ± 69.44	18.50 ± 46.20	43.80 ± 93.38	39.17 ± 85.20	70%
200 mg BID + LDA	113.84 ± 62.04	31.07 ± 18.30	25.33 ± 20.15	32.64 ± 39.68	45.85 ± 52.36	60%
300 mg BID	128.05 ± 103.99	72.46 ± 143.43	3.93 ± 12.76	5.60 ± 15.59	43.56 ± 77.12	66%
600 mg QD	128.98 ± 114.76	90.55 ± 90.06	9.61 ± 35.62	18.22 ± 40.16	31.39 ± 51.38	76%
300 mg BID + CEP	124.32 ± 82.63	72.14 ± 56.68	52.90 ± 45.11	54.92 ± 45.35	49.49 ± 29.13	60%
Placebo	133.69 ± 98.04	38.78 ± 31.21	72.28 ± 63.38	110.17 ± 78.69	128.62 ± 83.76	4%

LDA = low-dose Activella; CEP = cyclical EP; ND = no decrease from Screening

Figure 4.4.1-2. Mean (+SD) Estradiol Concentration – Time Profiles by Treatment Group (Study M12-663)

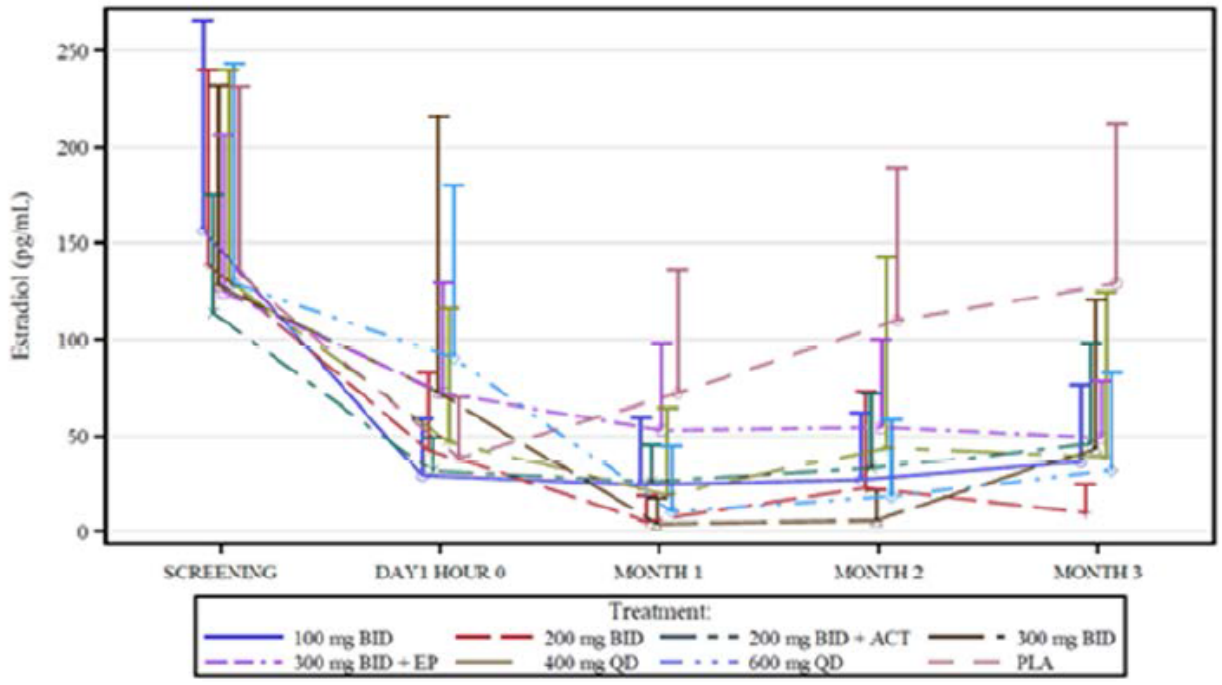
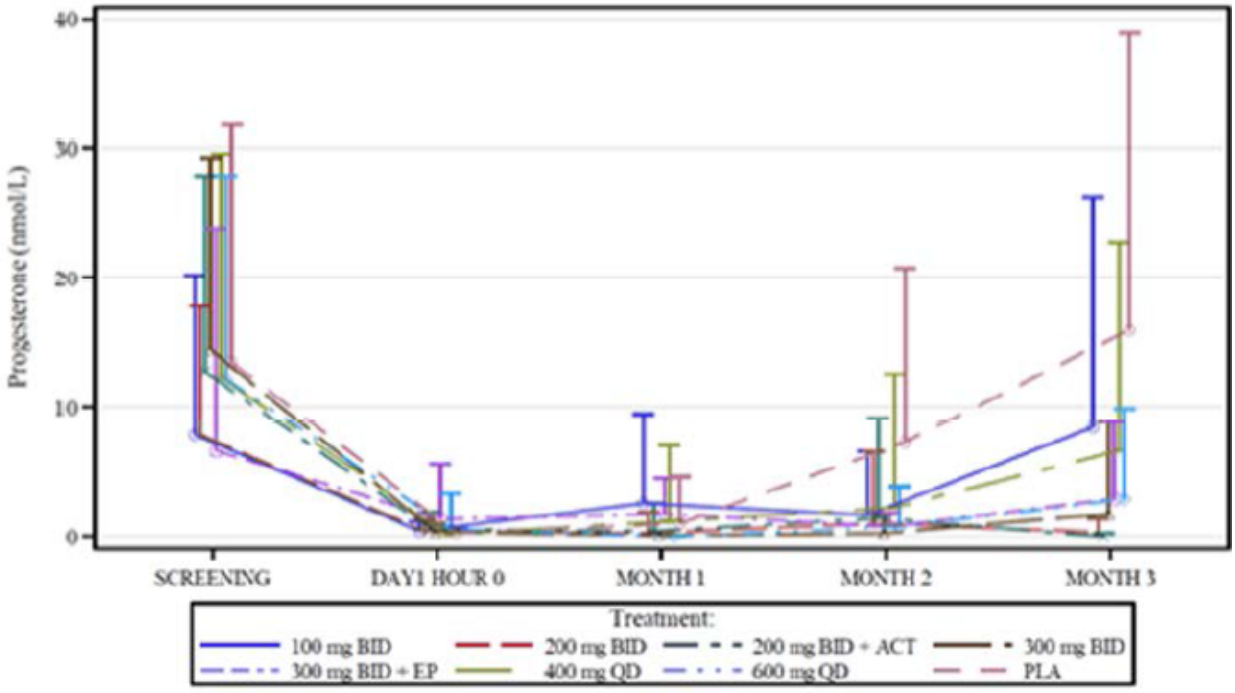


Figure 4.4.1-3. Mean (+SD) Progesterone Concentration – Time Profiles by Treatment Group (Study M12-663)



Efficacy:
In Cohorts 1, 2, and 4, all of the doses of elagolix (100 mg BID, 200 mg BID, 400 mg QD, and 300 mg BID) showed statistically significantly greater reductions in LS mean MBL volume from Baseline to the last 28 days of treatment compared with placebo ($P \leq 0.001$) (**Figure 4.4..1-4**). At an elagolix TDD of 600

mg, the 300 mg BID regimen resulted in a greater reduction in MBL than the 600 mg QD regimen (–203 mL and –189 mL, respectively. At an elagolix TDD of 400 mg, the 200 mg BID regimen resulted in a greater reduction in MBL than the 400 mg QD regimen (–273 mL and –184 mL, respectively). The arithmetic mean changes in MBL during the last 28 days of treatment were comparable with coadministration of elagolix 300 mg BID + cyclical EP relative to elagolix 300 mg BID administration alone (–216 mL and –203 mL, respectively). A smaller reduction in MBL was observed with coadministration of elagolix 200 mg BID + LD Activella than with elagolix alone (–192 mL and –273 mL, respectively).

As an exploratory analysis, the placebo groups in Cohorts 1, 2, and 4 were combined and compared with active treatment (**Figure 4.4..1-5**). In this exploratory analysis, all of the active treatment groups (independent of use of add-back therapy or dosing frequency) were statistically significantly higher in the percentage of subjects who met the composite endpoint during the last 28 days of treatment relative to placebo. The response was dose-dependent and ranged from 74% for elagolix TDD of 200 mg, 84% to 85% for elagolix TDD of 400 mg, and 85% to 97% for elagolix TDD of 600 mg compared with 21% for the combined placebo group.

Figure 4.4.1-4. Mean Change from Baseline to the Last 28 Days of Treatment in MBL Measured by the Alkaline Hematin Method (Primary Efficacy Endpoint)

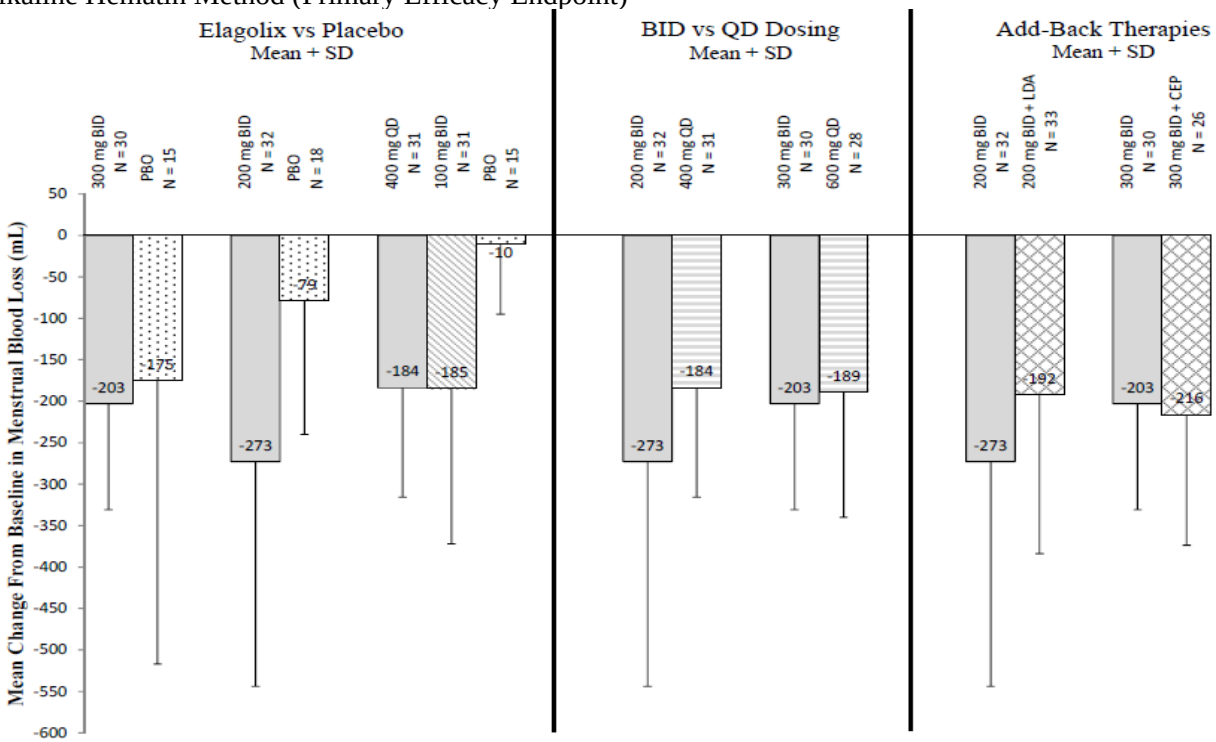
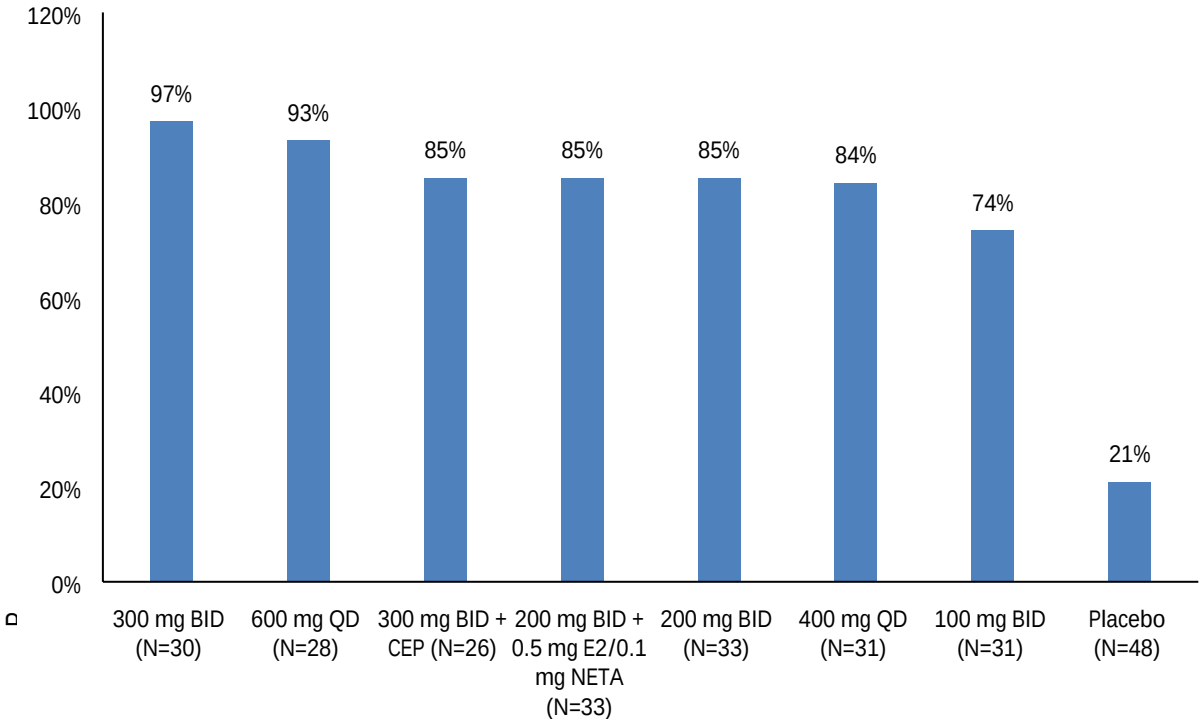


Figure 4.4.1-5. Exploratory Analysis: Analysis of Composite Endpoint for the Last 28 Days of Treatment Using Combined Placebo Group



Note: Efficacy endpoint: the percentage of subjects who have MBL < 80 mL during the last 28 days of treatment and ≥ 50% reduction in MBL volume from baseline to the final month. CEP: 1 mg E2 and 200 mg cyclical progesterone QD.
Source: Study M12-663 report, Table 20.

Safety:

Bone mineral density was determined for the lumbar spine, total hip, and femoral neck at Month 3 and the Final Visit (for subjects who prematurely discontinued from the study) during treatment as well as Month 1 and the Final Visit during Post-treatment Follow-up. Due to the short treatment duration (3 months), the BMD data might not be reliable to support dose selection. Therefore, BMD data from Study M12-663 was not reviewed.

The most commonly reported AEs across all treatment groups were hot flush, headache, and nausea. The addition of add-back therapy reduced hot flush incidence to 27% (LD Activella) and 19% (cyclical EP) compared with 46% to 63% with elagolix alone. The overall incidence of AEs was not affected by the frequency of dosing, as similar incidences were observed with the same total daily exposure (e.g., approximately 80% for 200 mg BID and 400 mg QD, and approximately 70% for 300 mg BID and 600 mg QD)

4.4.2 Study M12-813

Title: A Phase 2b Study to Evaluate the Safety and Efficacy of Elagolix in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Objectives:

- To assess the safety and efficacy of elagolix alone and in combination with 2 different strengths of add-back therapy (E2/NETA) versus placebo to reduce HMB associated with uterine fibroids, and to reduce fibroid volume and uterine volume in premenopausal women 18 to 51 years of age.

- To Assess the impact of add-back therapy with E2/NETA (both strengths) on the efficacy, safety, and tolerability of elagolix, including hypoestrogenic side effects such as BMD decrease, and vasomotor symptoms such as hot flush.
- To evaluate the effects of elagolix (with and without E2/NETA) on non-bleeding uterine fibroid symptoms and quality of life (QoL) measures.

Study Endpoints:
Primary Efficacy Endpoint:
the percentage of subjects meeting a composite endpoint consisting of these 2 bleeding assessments:

- MBL volume of < 80 mL at the Final Month (last 28 days of treatment), and
- 0% or greater reduction in MBL volume from Baseline to the Final Month (last 28 days of treatment)

Safety Endpoints: Safety endpoints included AEs, clinical safety laboratory parameters (including lipid profiles), and vital signs; bone biomarkers and BMD were monitored as exploratory safety endpoints.

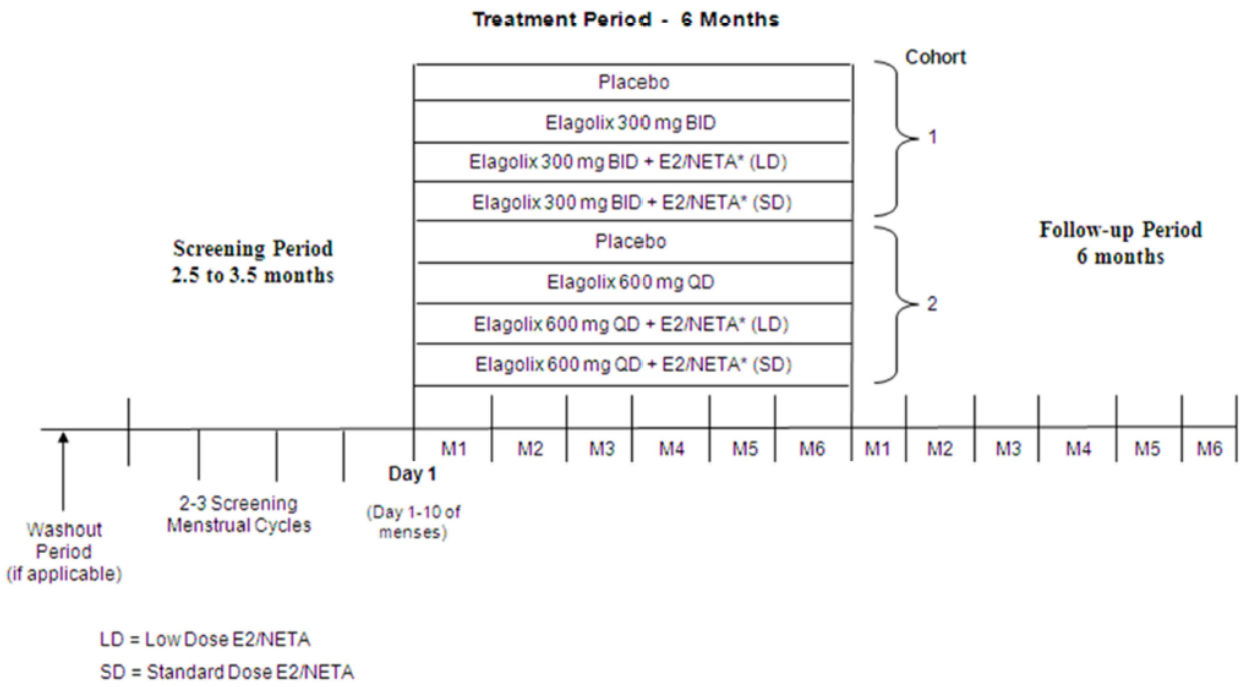
Study Design:
Study M12-663 was a Phase 2b, randomized, double-blind, multicenter, placebo-controlled, 2-cohort study with a 6-month treatment duration and a 6-month off-treatment follow-up period in premenopausal women 18 to 51 years of age with HMB (defined as > 80 mL blood loss per menstrual cycle) associated with uterine fibroids. This study was conducted in premenopausal women 20 to 49 years of age with HMB (> 80 mL blood loss per menstrual cycle) associated with uterine fibroids. The study was designed to enroll approximately 520 subjects (260 subjects in each cohort) (**Table 4.4.2-1**). Study design is shown in **Figure 4.4.2-1**.

Table 4.4.2-1. Study M12-813 Cohort Design

Cohort	N	Treatment
1	65	Placebo
	65	Elagolix 300 mg BID alone
	65	Elagolix 300 mg BID plus LD E2/NETA QD[a]
	65	Elagolix 300 mg BID plus SD E2/NETA QD[b]
2	65	Placebo
	65	Elagolix 600 mg QD alone
	65	Elagolix 600 mg QD plus LD E2/NETA QD[a]
	65	Elagolix 600 mg QD plus SD E2/NETA QD[b]

a. LD E2/NETA = estradiol 0.5 mg/norethindrone acetate 0.1 mg.
b. SD E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg.

Figure 4.4.2-1. Study M12-813 Design Schematic



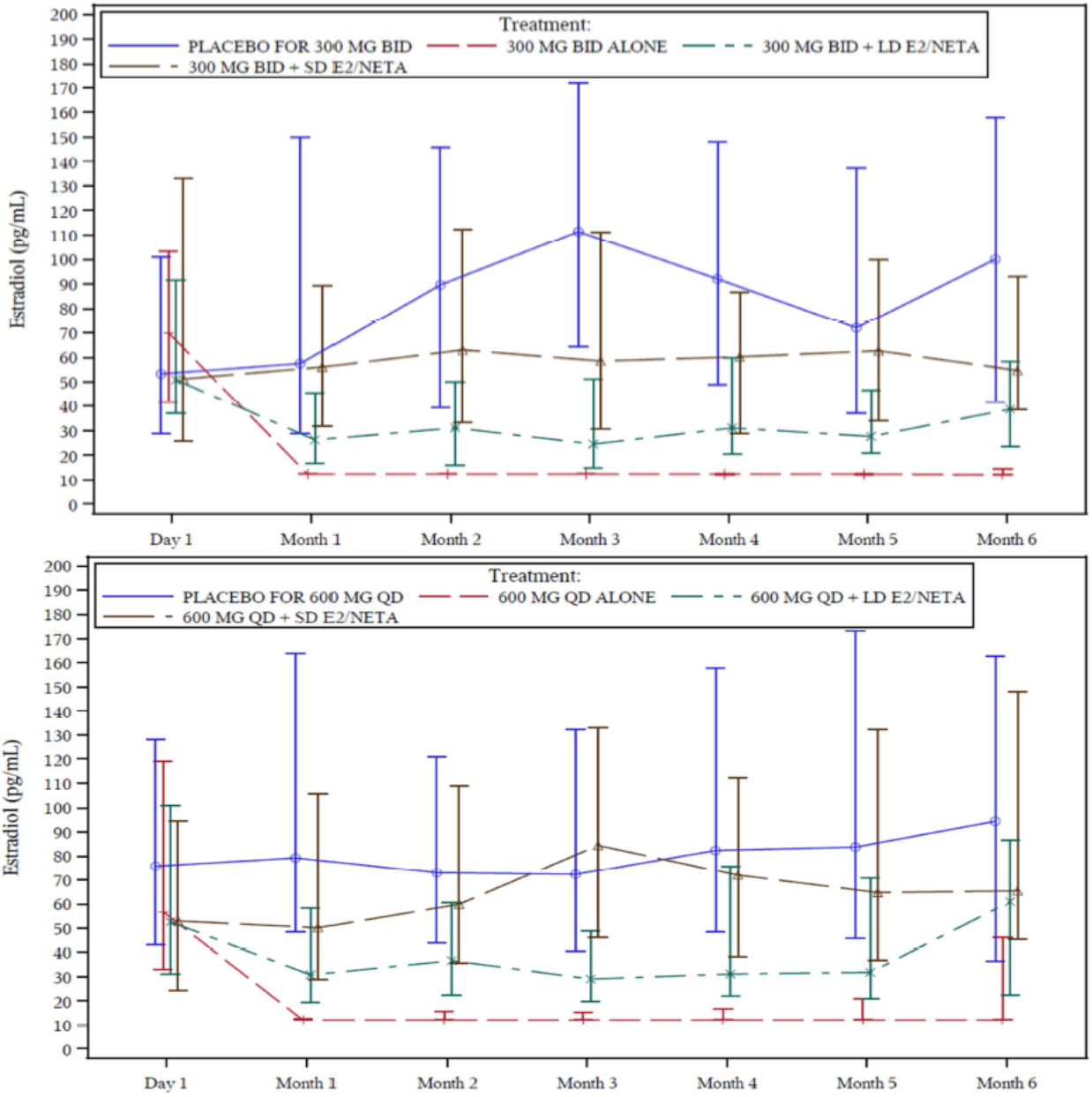
Study drug was to be taken with approximately 8 ounces (240 mL) of water under fasting conditions on an empty stomach (at least 1 hour before or 2 hours after a meal) and no food was to be consumed for 1 hour after study drug administration. Sparse plasma PK samples and PD samples [E2, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH)] were collected during the visits on Day 1, and at Months 1, 2, 3, 4, 5 and 6. PD samples at Day 1 were collected prior to dose and PK samples at Day 1 were collected approximately 1 hour after study drug dosing. PK and PD samples were collected at any time during other visits.

Results:

PK/PD:

Plasma concentrations of elagolix determined for population PK and exposure-response. As shown in **Figure 4.4.2-2**, for both cohorts, suppression of E2 was observed in the elagolix groups, compared with that of placebo. Coadministration of E2/NETA with elagolix results in higher E2 values than in the elagolix alone group. Suppression of progesterone, LH, and FSH was observed in the elagolix groups for both cohorts.

Figure 4.4.2-2. Median Estradiol Concentration – Time Profiles by Treatment Group (Study M12-813)



Note: Figure shows the median and interquartile range (bars) for E2 concentrations.

In Cohort 1, for the placebo group, median E2 levels (i.e., median of each subject's hormone value over the 6 monthly study visits) were approximately 94 pg/mL. Approximately, 8% to 16% of women had E2 concentrations < 20 pg/mL. For the 300 mg BID alone and 300 mg BID + SD E2/NETA groups, median E2 levels were 12 and 61 pg/mL, respectively; 80% to 95% and 10% to 15% of women had E2 concentrations < 20 pg/mL.

In Cohort 2, for the placebo group, median E2 levels (i.e., median of each subject's hormone value over the 6 monthly study visits) were approximately 82 pg/mL. Approximately 4% to 13% of women had E2 concentrations < 20 pg/mL. For the 600 mg QD alone and 600 mg QD + SD E2/NETA group, median E2 levels were 12 and 66 pg/mL, respectively; 67% to 87% and 2% to 13% of women had E2 concentrations < 20 pg/mL.

Efficacy:
All elagolix treatment groups in both cohorts met the primary efficacy endpoint (proportion of responders who achieved MBL volume of < 80 mL at the Final Month and 50% or greater reduction in MBL volume from Baseline to the Final Month), with a statistically significantly greater proportion of responders compared to that of placebo (**Table 4.4.2-2**). In Cohort 1, the largest effect was seen with elagolix 300 mg BID. Responder rates were 92% for elagolix 300 mg BID, 85% for elagolix 300 mg BID + LD E2/NETA, and 79% for elagolix 300 mg BID + SD E2/NETA compared with 27% for placebo. For Cohort 2, results were comparable to Cohort 1. Responder rates in Cohort 2 were 90% for elagolix 600 mg QD, 73% for elagolix 600 mg QD + LD E2/NETA, and 82% for elagolix 600 mg QD + SD E2/NETA compared with 32% for placebo.

Table 4.4.2-2. Percentage of Subjects Who Met the Primary Endpoint (Modified ITT Analysis Set)

Cohort/Treatment Group	n/N (%)	Between-Group Difference	Odds Ratio (95% CI)	*P* value[a]	*P* value[b]
Cohort 1					
Placebo	17/64 (26.56)	--	--	--	--
Elagolix 300 mg BID	57/62 (91.94)	65.37	32.51 (11.12, 95.05)	< 0.001	< 0.001
Elagolix 300 mg BID + LD E2/NETA	52/61 (85.25)	58.68	16.66 (6.72, 41.30)	< 0.001	< 0.001
Elagolix 300 mg BID + SD E2/NETA	49/62 (79.03)	52.47	11.13 (4.79, 25.84)	< 0.001	< 0.001
Cohort 2					
Placebo	24/76 (31.58)	--	--	--	--
Elagolix 600 mg QD	64/71 (90.14)	58.56	19.62 (7.81, 49.27)	< 0.001	< 0.001
Elagolix 600 mg QD + LD E2/NETA	53/73 (72.60)	41.02	6.02 (2.95, 12.30)	< 0.001	< 0.001
Elagolix 600 mg QD + SD E2/NETA	62/76 (81.58)	50.00	10.34 (4.79, 22.34)	< 0.001	< 0.001

a. *P* value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

b. *P* value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Safety:
Treatment-emergent AEs were reported by the majority of subjects, and the proportion of subjects who experienced an AE was highest in the elagolix alone (300 mg BID or 600 mg QD) group in each cohort. In the elagolix 300 mg BID alone or 600 mg QD alone groups, hot flush (44.6% or 49.4% of subjects, respectively) and insomnia were the 2 most frequently reported AEs, and the frequencies of these AEs were partially attenuated in a dose-dependent fashion by add-back therapy with E2/NETA (hot flush, 10.8% of subjects with elagolix 300 mg BID + SD E2/NETA and 14.3% of subjects with elagolix 600 mg QD + SD E2/NETA).

Elagolix 300 mg BID groups were generally more tolerable than elagolix 600 mg QD groups. AEs such as hot flush and hypertension; gastrointestinal AEs, such as abdominal distension, diarrhoea, nausea, and

vomiting; and AEs of headache occurred less frequently in the elagolix 300 mg BID groups combined compared to the elagolix 600 mg QD groups combined.

BMD of the lumbar spine, total hip, and femoral neck was measured at Screening, Month 6 of Treatment Period and Month 6 of the Post-Treatment Period. As shown in **Table 4.4.2-3**, in both cohorts, elagolix treatment was associated with statistically significant mean percentage decreases from Baseline in BMD relative to placebo at Month 6 at lumbar spine, total hip, and femoral neck, with the largest effect at the lumbar spine. Mean percentage decreases in BMD were greatest in the elagolix alone (300 mg BID and 600 mg QD) groups and were partially attenuated in a dose-dependent fashion by addback therapy with E2/NETA.

Table 4.4.2-3. Mean Percentage Changes in Lumbar Spine Bone Mineral Density from Baseline to Month 6 During the Treatment Period in Cohort 1 and Cohort 2 (Safety Analysis Set)

Variable/ Treatment Group	Visit N	Baseline Mean, g/cm^2	Month 6 Mean, g/cm^2	Mean % Change	95% CI
			Cohort 1		
Placebo	44	1.232	1.243	0.913	(0.1028, 1.7226)
Elagolix 300 mg BID	48	1.246	1.199	–3.797	(–4.5720, –3.0212)
Elagolix 300 mg BID + LD E2/NETA	48	1.275	1.254	–1.623	(–2.3984, –0.8476)
Elagolix 300 mg BID + SD E2/NETA	48	1.250	1.247	–0.141	(–0.9161, 0.6348)
			Cohort 2		
Placebo	58	1.282	1.281	–0.125	(–0.8242, 0.5748)
Elagolix 600 mg QD	57	1.290	1.248	–3.403	(–4.1088, –2.6976)
Elagolix 600 mg QD + LD E2/NETA	46	1.233	1.217	–1.235	(–2.0206, –0.4497)
Elagolix 600 mg QD + SD E2/NETA	52	1.326	1.312	–1.111	(–1.8493, –0.3718)

Reviewer's comments: *Study M12-663 showed dose-dependent efficacy of elagolix. A daily dose of 600 mg elagolix (300 mg BID or 600 mg QD) resulted in robust efficacy response (responder rates of > 80% for the composite bleeding assessment. Thereofore, elagolix 300 mg BID and 600 mg QD with or without add back therapy were investigated in Phase 2b Study M12-813. Study M12-813 demonstrated that E2/NETA (1.0 mg/ 0.5 mg) attenuated the hypoestrogenic effects (e.g., BMD decrease and hot flush) and slightly reduced efficacy of elagolix. Elagolix 300 BID + E2/NETA 1 mg/0.5 mg and elagolix 600 mf QD + E2/NETA 1 mg/0.5 mg demonstrated similar efficacy response (percentage of subjects who met primary efficacy endpoint) and BMD loss in Study M12-813. However, the elagolix 300 BID + E2/NETA 1 mg/0.5 mg dose was more tolerable and showed less adverse events than the elagolix 600 QD + E2/NETA 1 mg/0.5 mg dose. Based on the safety/efficacy data observed in Studies M12-663/M12-813 and exposure-response analyses, it appears reasonable to select elagolix 300 mg BID + E2/NETA 1.0 mg/0.5 mg QD for further evaluation in Phase 3 uterine fibroid trials.*

4.5 Population PK Analyses

The Applicant submitted a population PK report entitled "Population Pharmacokinetics of Elagolix in Healthy Subjects and Subjects with Heavy Menstrual Bleeding Associated with Uterine Fibroids". The analysis in this report is an extension of the population PK analysis previously submitted in the NDA for management of moderate to severe pain associated with endometriosis (NDA 210450 R&D/17/0088))

Objectives: The objectives of this report were to describe elagolix population pharmacokinetics and factors affecting elagolix exposure in healthy women, women with heavy menstrual bleeding associated with uterine fibroids, and women with moderate to severe endometriosis-associated pain.

Data: The population pharmacokinetic analysis included data from adult premenopausal female subjects (N = 2168) enrolled in six Phase 1 studies (Studies M12-790,M12-653, M13-995, M15-817, M15-973, and M15-974) and seven Phase 3 UF and Endometriosis studies (Studies M12-815, M12-816, M12-817, M12-665, M12-667, M12-671, and M12-821). The demographic data for subjects included in the final population PK dataset is summarized in **Table 4.5-1** and **Table 4.5-2**.

Table 4.5-1. Summary of Continuous Covariates at Baseline

All Subjects (N=2168)	Mean (SD)	Range
Age (year)	35.8(7.8)	18-53
Body Weight (kg)	79.4(20.3)	40-160
Body Mass Index (kg/m2)	29.4(7.3)	16.2-61.5
Albumin (g/L)	43.8(3.2)	33-54
Bilirubin (mcmol/L)	7.3(3.5)	1.7-32.5
Creatinine(mcmol/L)	63.8(10.6)	29.2-248
Aspartate Amino Transferase (IU/L)	18.1(9.9)	7-275
Alanine Amino Transferase (IU/L)	15.5(13.9)	3-367
Creatinine(mcmol/L)	63.8(10.6)	29.2-248
Creatinine Clearance (mL/min)	137(38.2)	35.6-347

Table 4.5-2. Summary of Categorical Covariates

All Subjects (N=2168)	Level	N(%)
Race	Black	194(11.9)
	White and Others	1430(88.1)
Ethnicity	Hispanic/Latino	272(16.7)
	Others	1352(83.3)
Tobacco Use	Never used, Ex-User	1747(80.6)
	User	420(19.4)
	Missing	1(0.05)
Alcohol Use	Never Used	718(33.1)
	User	1442(66.5)
	Missing	8(0.4)
OATP Transporter Status	ET	1256(57.9)
	IT	335(15.5)
	PT	32(1.5)
	Missing	545(25.1)
Co-Administration with E2/NETA	No	1732(79.9)
	Yes	436(20.1)

Population PK Model Development

Base Model: The base model (PK_run002) was a two-compartment model with lag time, combined residual error model with different estimates for Phase 1 and 3, and inter-individual variability on CL/F

and V2/F). The estimated pharmacokinetic parameter values and their associated variability for the elagolix pharmacokinetic base model are summarized in **Table 4.5-3**.

Table 4.5-3: Summary of Fixed and Random Effects Parameter Estimates for Elagolix Population Pharmacokinetic Base Model (PK_run002)

Parameter	Population Estimate (SEE)[a]	%RSE[b]	95% Confidence Interval
Pharmacokinetic Parameters			
CL/F (L/hr)	115 (1.42)	1.24	112 – 117
V_2/F (L)	257 (4.03)	1.57	249 – 265
K_A (1/hr)	2.43 (0.0600)	2.47	2.31 – 2.55
Q/F (L/hr)	5.17 (0.200)	3.86	4.78 – 5.56
V_3/F (L)	47.1 (1.27)	2.70	44.6 – 49.6
Lag-time (hr)	0.207 (0.00109)	0.524	0.205 – 0.209
F1	1.00 (fix)	-	-
Inter-Individual and Residual Variability			
Inter-Individual Variability on CL/F (%CV)[c]	0.218 (49.4)	4.17	0.200 – 0.236
Inter-Individual Variability on V_2/F (%CV)[c]	0.227 (50.5)	5.29	0.203 – 0.251
Proportional Error (Phase 1 Studies)	0.148 (0.00391)	2.64	0.140 – 0.156
Additive Error (Phase 1 Studies)	5.99×10^{-05} (8.02×10^{-06})	13.4	4.42×10^{-05} – 7.56×10^{-05}
Proportional Error (Phase 3 Studies)	0.283 (0.00564)	1.99	0.272 – 0.294
Additive Error (Phase 3 Studies)	0.269 (0.00651)	2.42	0.256 – 0.282

CL/F = apparent clearance; V_2/F = apparent volume of distribution in the central compartment; K_A = first-order absorption rate constant; Q/F = apparent inter-compartmental clearance; V_3/F = apparent volume of distribution in the peripheral compartment; F1 = relative bioavailability

a. SEE = Standard error of estimate.

b. % Relative standard error (%RSE) was estimated as the SEE divided by the population estimate multiplied by 100.

c. $\%CV = 100 * (\sqrt{e^{\omega^2} - 1})$.

Source: Table 5 on page 45 of Applicant's population PK report

Final Model: The covariates investigated for influence on each of the elagolix pharmacokinetic parameters, apparent clearance (CL/F) and apparent volume of distribution (V2/F), included age, body weight, body mass index, race, ethnicity, tobacco use, alcohol use, albumin, bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT), organic anion-transporting polypeptide (OATP) phenotype status, and adenomyosis. Creatinine, creatinine clearance, and addition of estradiol/norethindrone (E2/NETA at 1/0.5 mg QD) were tested on CL/F. OATP1B1 phenotype status was also tested on relative bioavailability (F1). The estimated pharmacokinetic parameter values from the final model including covariates and their associated variability for the selected final pharmacokinetic model (PK_run003) are summarized in **Table 4.5-4**.

Table 4.5-4: Parameter Estimates and Covariate Effects for Elagolix Population Pharmacokinetic Final Model (PK_run003)

Parameter	Population Estimate (SEE)[a]	%RSE[b]	95% Confidence Interval
Pharmacokinetic Parameters			
CL/F (L/hr)	125 (1.76)	1.41	121 – 128
V_2/F (L)	279 (4.75)	1.70	270 – 288
K_A (1/hr)	2.46 (0.0592)	2.41	2.34 – 2.57
Q/F (L/hr)	5.63 (0.209)	3.72	5.22 – 6.03
V_3/F (L)	51.7 (1.37)	2.65	49.0 – 54.4
Lag-time (hr)	0.207 (0.00105)	0.507	0.205 – 0.209
F1	1.00 (fix)	-	-
OATP on F1 (IT)	0.421 (0.0386)	9.17	0.345 – 0.497
OATP on F1 (PT)	0.963 (0.161)	16.7	0.647 – 1.28
OATP on F1 (Missing)	0.101 (0.0207)	20.5	0.0604 – 0.142
WTKG on V_2/F	0.160 (0.0454)	28.4	0.0710 – 0.249
Inter-Individual and Residual Variability			
Inter-Individual Variability on CL/F (%CV)[c]	0.198 (46.8)	4.28	0.181 – 0.215
Inter-Individual Variability on V_2/F (%CV)[c]	0.208 (48.1)	5.53	0.185 – 0.231
Proportional Error (Phase 1 Studies)	0.145 (0.00382)	2.63	0.138 - 0.152
Additive Error (Phase 1 Studies)	5.26×10^{-05} (7.05×10^{-06})	13.4	3.88×10^{-05} – 6.64×10^{-05}
Proportional Error (Phase 3 Studies)	0.284 (0.00565)	1.99	0.273 – 0.295
Additive Error (Phase 3 Studies)	0.266 (0.00651)	2.45	0.253 – 0.279

CL/F = apparent clearance; V_2/F = apparent volume of distribution in the central compartment; K_A = first-order absorption rate constant; Q/F = apparent inter-compartmental clearance; V_3/F = apparent volume of distribution in the peripheral compartment; F1 = relative bioavailability; OATP = Organic Anion Transporting polypeptide; WTKG = body weight; IT = intermediate transporter; PT = poor transporter

a SEE = Standard error of estimate.

b %RSE was estimated as the SEE divided by the population estimate multiplied by 100.

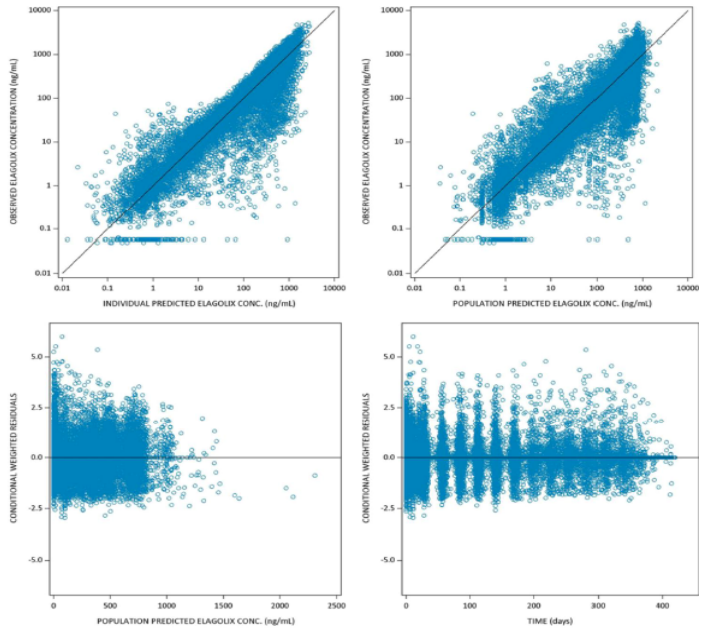
c $\%CV = 100 * (\sqrt{e^{\omega^2} - 1})$.

Cross reference: Table 13.3__2.5, Table 13.3__2.6

Source: Table 7 on page 49 of Applicant's population PK report

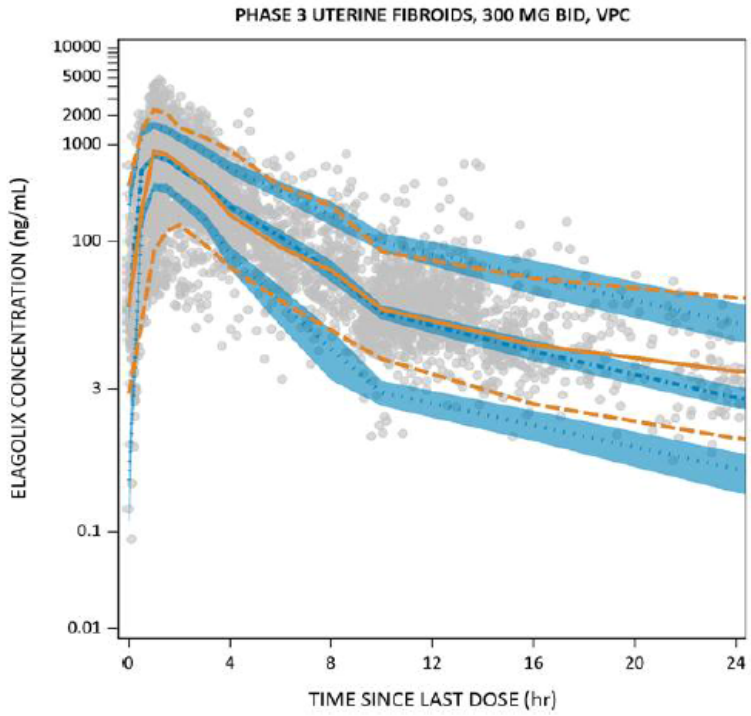
Model Evaluation: The final model was evaluated graphically by goodness-of-fit plots, visual predictive checks (VPCs) as well as bootstrap evaluation. The goodness-of-fit plots for the final model are displayed in **Figure 4.5-1** and the VPCs plots are demonstrated in **Figure 4.5-2**.

Figure 4.5-1: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figure 2 on page 51 of Applicant's population PK report rd190028

Figure 4.5-2: Visual Predictive Checks for Phase 3 Studies in Subjects with HMB Associated with Uterine Fibroids Who Received Elagolix 300 mg BID Dose Using the Final Population Pharmacokinetic Model



The gray dots represent observed data, the lines represent observed median (solid orange) and observed 5%/95% percentiles (dashed orange), and the shaded regions represent the 95% confidence intervals for the simulated median (blue dashed-dotted) and simulated 5%/95% percentiles (blue dotted).*Source: Adapted from Figure 3 on page 52 of Applicant's population PK report rd190028*

Bootstrap evaluation was used to estimate confidence intervals of the model parameters. A total of 880 out of 1000 bootstrap replicates plus the original dataset converged successfully. The bootstrap results are summarized in **Table 4.5-5**.

Table 4.5-5: Summary of Elagolix Pharmacokinetic Parameters Estimated from Bootstrap Evaluation

		Bootstrap Results (N = 880)	
Parameter	**Model Result**	**Median**	**95% Confidence Interval**
Pharmacokinetic Parameters			
CL/F (L/hr)	125	126	119 – 131
V_2/F (L)	279	281	82.3 – 294
K_A (1/hr)	2.46	2.45	0.575 – 2.73
Q/F (L/hr)	5.63	5.85	4.91 – 9.19
V_3/F (L)	51.7	53.6	46.4 – 75.9
Lag-time (hr)	0.207	0.209	0.133 – 0.219
OATP on F1 (IT)	0.421	0.484	0.353 – 0.635
OATP on F1 (PT)	0.963	1.25	0.935 – 1.65
OATP on F1 (Missing)	0.101	0.0982	0.0350 – 0.164
WTKG on V_2/F	0.160	0.130	0.0315 – 0.276
Inter-Individual and Residual Variability			
Inter-Individual Variability on CL/F	0.198	0.200	0.179 – 0.223
Inter-Individual Variability on V_2/F	0.208	0.223	0.188 – 0.599
Proportional Error (Phase 1 Studies)	0.145	0.146	0.132 – 0.162
Additive Error (Phase 1 Studies)	5.26×10^{-05}	5.07×10^{-05}	1.99×10^{-05} – 9.76×10^{-05}
Proportional Error (Phase 3 Studies)	0.284	0.278	0.260 – 0.300
Additive Error (Phase 3 Studies)	0.266	0.242	0.00361 – 0.593

CL/F = apparent clearance; V_2/F = apparent volume of distribution in the central compartment; K_A = first-order absorption rate constant; Q/F = apparent inter-compartmental clearance; V_3/F = apparent volume of distribution in the peripheral compartment; F1 = relative bioavailability; OATP = Organic Anion Transporting polypeptide; WTKG = body weight; IT = intermediate transporter; PT = poor transporter

Source: Table 8 on page 54 of Applicant's population PK report

Posthoc PK Parameter Estimation: Model-predicted elagolix exposures in women with heavy menstrual bleeding associated with uterine fibroids at the proposed clinical regimen of elagolix 300 mg BID are summarized below using the final model (Table 4.5-6).

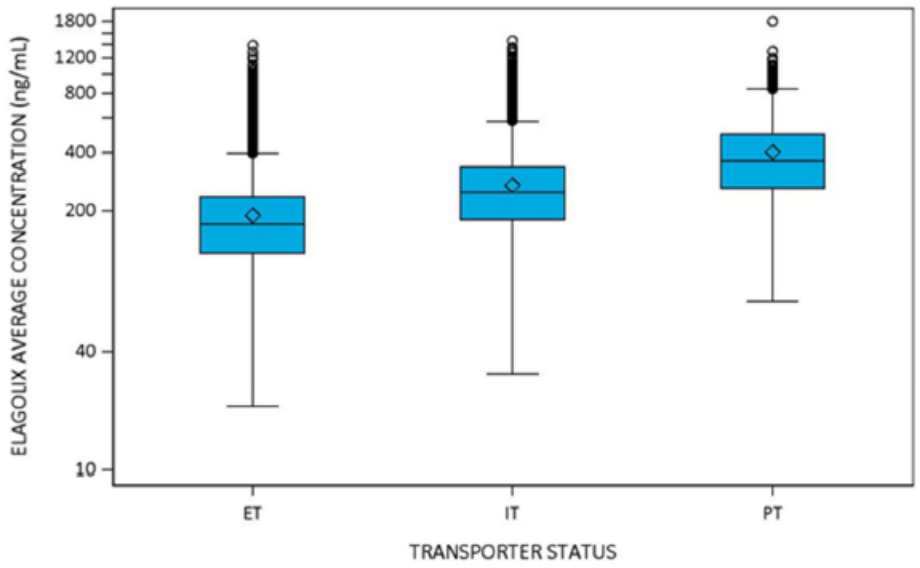
Table 4.5-6: Predicted Elagolix Exposures for Elagolix 300 mg BID Using the Final Model

Parameter	Mean	Median	5th Percentile	95th Percentile
C_{avg} (ng/mL)	211	189	97.2	391
C_{trough} (ng/mL)	3.90	2.18	0.654	11.4
C_{max} (ng/mL)	752	688	360	1393

C_{avg} = average plasma concentration; C_{trough} = trough plasma concentration; C_{max} = maximum plasma concentration

Effect of OATP Phenotype Status on Elagolix Average Concentration: For the effect of OATP1B1 transporter status on the PK of elagolix, subjects with IT phenotype had elagolix average concentration 1.45-fold higher compared to subjects with the reference ET phenotype; while subjects with PT phenotype had elagolix exposures 2.09-fold higher compared to the reference ET phenotype (Figure 4.5-3).

Figure 4.5-3. Effects of OATP1B1 and Body Weight on Elagolix Average Concentration



Source: Figure 4 on page 55 of Applicant's population PK report

Reviewer's comments: *we generally agreed with the conclusions of the population pharmacokinetics analysis by the Applicant.*

Subjects with OATP1B1 PT phenotype had elagolix exposures 2.09-fold higher compared to the reference ET phenotype. The Applicant stated that, despite the difference in elagolix Cavg across OATP1B1 phenotypes, the exposures greatly overlapped. In addition, based on the safety data across Phase 3 studies as summarized in Summary of Clinical Safety and exposure-response analysis for safety (R&D/19/0282), this exposure difference is not considered to be clinically relevant. The reviewer agrees with this conclusion.
Overall, the final population PK model appeared to be able to characterize the PK profile of elagolix as indicated in the Applicant's goodness-of-fit plots and VPC plots. This reviewer was able to repeat and verify the Applicant's analysis with no discoordance identified.

4.6 Exposure-Response Analyses

4.6.1 Exposure-Response for Primary Efficacy Endpoints

The Applicant submitted an exposure-response (ER) analysis report entitled *Exposure-Efficacy Analyses of Elagolix in Subjects with Heavy Menstrual Bleeding Associated with Uterine Fibroids Based on Data from Two Phase 3 Studies*. The ER model was able to describe the relationship between elagolix exposure and the primary efficacy endpoint.

Objective: The objective of this report was to describe the relationship between elagolix exposure and the primary efficacy point of MBL < 80 mL using data from two Phase 3 clinical studies (M12-815, M12-817) and to identify the influence of subject-specific covariates on the exposure response relationship of clinical efficacy response variables.

Data: In the exposure-efficacy analyses between elagolix exposure and primary clinical response, data from N = 734 premenopausal female subjects with HMB associated with UF in two Phase 3 studies

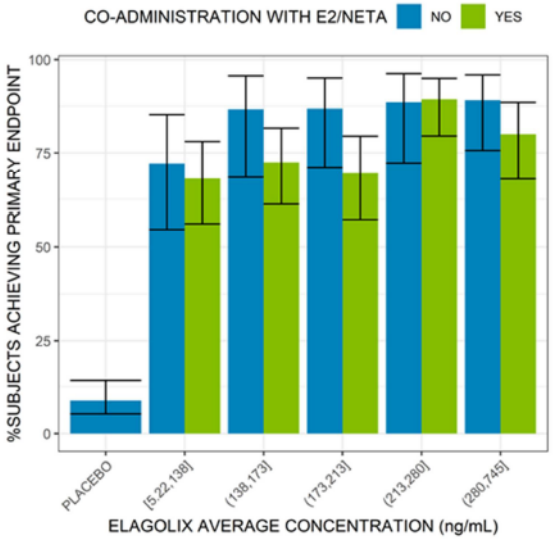
(Studies M12-815 and M12-817) were included. The analysis of the secondary clinical response amenorrhea and suppression of bleeding included data from N = 706 premenopausal female subjects with HMB associated with UF in the Phase 3 studies M12-815 and M12-817. Summaries of demographic data for the subjects included in the exposure-efficacy analysis for the primary and secondary endpoints are presented in Table 4.6-1. The proportion of subjects for each model-predicted elagolix average concentration quintile that achieved the primary endpoint at final visit is shown in **Figure 4.6-1**.

Table 4.6-1: Summary of Demographic Characteristics for Efficacy Primary Response Dataset

		Subjects Included in Population Analysis
Characteristics		**Total**
Adenomyosis	Yes	118 (16.1%)
	No	587 (80.0%)
	Missing	29 (4.0%)
MBL at Baseline (mL)	N	734
	Mean (SD)	238.9 (157.0)
	Median	187.20
	Min – Max	83.8 - 1207.1
Treatment	Placebo	182 (24.8%)
	300 mg BID	185 (25.2%)
	300 mg BID + E2/NETA	367 (50.0%)

BID = Twice daily; E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg; Min = Minimum; Max = Maximum; SD = standard deviation

Figure 4.6-1: Elagolix Exposure Quintile Plot for Proportion of Subjects that Achieved the Primary Endpoint at Final Visit in Subjects with HMB Associated with UF



Note: Bars plots represents observed proportions and error bars represents 95% binomial confidence interval of the observed proportions versus the model-predicted average elagolix concentration quintile.

Exposure-Response for Primary Efficacy Endpoints: The exposure metrics used for the exposure-response analyses were derived using the subject-specific empirical Bayes estimates (post-hoc estimates) from the final population pharmacokinetic model. The parameters used included the average plasma concentration (C_{avg}), the maximum plasma concentration (Cmax) or the plasma concentrations at the end of the dosing interval (C_{trough}).

Exposure-response modeling of primary endpoint was conducted using logistic regression analysis with R 3.5.1 using the glm function for fitting generalized linear models (with binomial family and logit link) to characterize the relationship between elagolix C_{avg} at steady state as the predictor variable and the binary efficacy. The estimated parameter values from the final linear logistic regression model are summarized in Table 4.6-2. The observed and model-predicted percentage of subjects achieving the primary endpoint with increasing elagolix C_{avg} based on the final model are presented in Figure 4.6-2. The effect of covariate on the probability of achieving the primary endpoint is demonstrated in Figure 4.6-3.

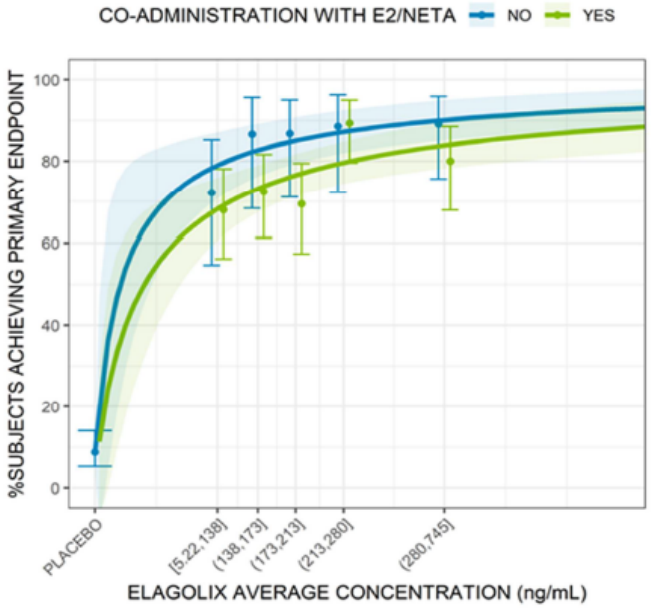
Table 4.6-2: Parameter Estimates of the Primary Endpoint Logistic Regression: Final Model (PE_run4)

Parameter	Estimate (SEE)	95% Confidence Interval	p-value
(Intercept)	2.07 (0.264)	1.56, 2.59	3.78×10^{-15}
logCAVG	1.96 (0.576)	0.831, 3.09	0.000669
TRTPLACEBO	–4.10 (0.336)	–4.75, –3.44	3.25×10^{-34}
Co-administration with E2/NETA on Intercept	–0.579 (0.242)	–1.05, –0.104	0.0169
MBL at baseline on Intercept	–0.00131 (0.000623)	–0.00253, -8.83×10^{-5}	0.0356

SEE = Standard error of estimate

Source: Table 8 on page 29 of Applicant's clinical study report rd190059

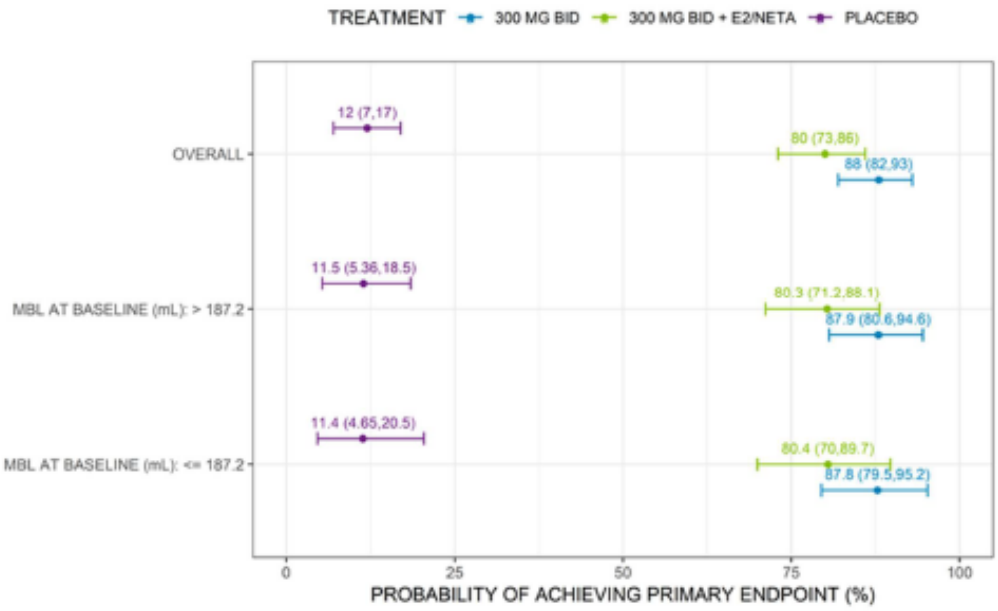
Figure 4.6-2: Observed and Model-Predicted Probability of Achieving Primary Endpoint vs. Elagolix Cavg in Subjects with HMB Associated with UF: Final Model



Note: Dots represent observed proportions, error bars represent 95% binomial confidence interval of the observed proportions, lines represent the predicted probability and shaded regions represent the 95% confidence intervals of the model-predicted rates versus the model-predicted average elagolix concentration quintile

Source: Figure 5 on page 30 of Applicant's clinical study report rd190059

Figure 4.6-3: Model-Predicted Probability of Achieving the Primary Endpoint at Final Visit for Placebo, Elagolix 300 mg BID, and Elagolix 300 mg BID + E2/NETA Stratified by Covariate Subgroups



Note: Dots represent simulated probability and error bars represent 95% confidence intervals of the model-simulated predicted stratified by covariate subgroups

Source: Figure 6 on page 31 of Applicant's clinical study report rd190059

Reviewer's Comment: *The Applicant's exposure-resposne analysis for the primary efficacy endpoints is reasonable and acceptable. Overall, the exposure-efficacy analysis indicated that the addition of E2/NETA compared with elagolix 300 mg BID alone causes a small decrease (< 10%) in the probability of achieving the primary endpoint with improved safety as described below. The benefit-risk profile supports the proposed clinical regimen of elagolix 300 mg BID with E2/NETA 1 mg/0.5 mg QD for treatment for HMB in women with UF.*

4.6.2 Exposure-Response Analyses for Safety

The applicant submitted an exposure-response analyses report for safety entitled *Exposure-Safety Analyses of Elagolix Effects on Changes in Bone Mineral Density and Incidence of Hot Flush in Subjects with Heavy Menstrual Bleeding Associated with Uterine Fibroids Based on Data from Three Phase 3 Studies* to characterize the relationship between elagolix average plasma concentrations (C_{avg}) and changes in lumbar spine or femoral neck BMD, and incidence of hot flush.

Objectives: The objectives of this report are:

- To characterize the relationship between elagolix average plasma concentrations (C_{avg}) and changes in lumbar spine or femoral neck BMD, and incidence of hot flush.
- To identify the influence of subject-specific covariates on the exposure-response relationship of clinical safety variables
- Predict BMD changes following continuous duration of elagolix treatment or placebo

Data: The relationship between elagolix exposure and safety outcomes was evaluated using data from clinical studies as shown in Table 4.6-3.

Table 4.6-3: Clinical Studies and Data Source Used in Exposure-Safety Analyses

Safety Endpoint	Studies Used in Analysis
Changes in lumbar spine BMD	M12-815, M12-816, M12-817, NHANES
Changes in femoral neck BMD	M12-665, M12-667, M12-671, M12-821, M12-815, M12-816, M12-817, NHANES
Occurrence of hot flush	M12-815, M12-817

BMD = Bone mineral density; NHANES = National Health and Nutrition Examination Survey

For the exposure-safety analysis relating elagolix exposure and lumbar spine BMD, data from N = 790 premenopausal female subjects with HMB associated with UF from the Phase 3 Studies M12-815, M12-816 (a Phase 3 extenstion Study), and M12-817. For the exposure-safety analysis of femoral neck BMD, additional data from N = 1684 premenopausal female subjects with moderate to severe endometriosis-associated pain from the Phase 3 Studies M12-665, M12-667, M12-671 and M12-821 were added (NDA 210450, R&D/17/0090). In the exposure-safety analysis relating elagolix exposure and hot flush, data from N = 790 premenopausal female subjects with HMB associated with UF in the Phase 3 Studies M12-815 and M12-817 were included.

Exposure-BMD Modeling: For modeling the exposure/change in lumbar spine BMD relationship in premenopausal women with UF, a previously established indirect response model in subjects with moderate to severe endometriosis-associated pain based on data from four Phase 3 Studies (Studies M12-665, M12-667, M12-671, and M12-821) (NDA 210450, R&D/17/0090) was used and accounted for demographics and patient characteristics from subjects with HMB associated with UF. The exposure-BMD models were built in a step-wise manner, first developing appropriate placebo models, followed by adding the response to elagolix treatment via indirect response models.

Placebo Model: In order to extend the understanding of the natural time course of BMD changes in premenopausal women on placebo, lumbar spine BMD data over a wide range of age (≥ 8 years old up to postmenopausal age) was used from real-world National Health and Nutrition Examination Survey (NHANES) data. A bi-exponential model was developed (Section 13.4.2.2.2) and the population parameter estimates and the variance-covariance matrix of the fixed effects was used as a prior to inform the placebo model. The equation for the placebo model is as followed:

$$\mathrm{PLAC}(t)=PLAC_{max}\cdot\frac{k_{form}}{k_{form}-k_{res}}\cdot\left(e^{-k_{res}\cdot(AGE+t/365)}-e^{-k_{form}\cdot(AGE+t/365)}\right) \qquad \text{Equation 1}$$

where PLAC(t) is the BMD in subjects on placebo at time after baseline t in days, $PLAC_{max}$ is the parameter describing the maximum BMD, k_{form} and k_{res} are the parameters describing the formation and resorption rate constants in BMD over age, respectively, and t/365 is the time since baseline observation time in years.

BMD over time in subjects on placebo accounting for each type of DXA scan machine (Hologic and Lunar) as well as for the inclusion and exclusion criteria of the Phase 3 studies is described by the following equation

$$BMD(t) = PLAC(t)\cdot(1+\mathrm{fac}_{\mathrm{Lunar}})\cdot(1+\mathrm{fac}_{\mathrm{Ph3}}) \qquad \text{Equation 2}$$

where BMD(t) is the BMD at time (t), PLAC(t) is the BMD in subjects on placebo at time

t, fac_{Lunar} is the factor to account for differences in BMD measured with Hologic and Lunar machine types, and fac_{Ph3} is the factor to account for differences between NHANES and Phase 3 population.

Parameter Estimates for the Final Placebo Lumbar Spine BMD Model are shown in Table 4.6-4.

Table 4.6-4: Parameter Estimates for the Final Placebo Lumbar Spine BMD Model (BMD_run006)

Parameter	Population Estimate (SEE)	%RSE[a]	95% Confidence Interval
$PLAC_{max}$ (g/cm^2)	1.54 (0.0267)	1.73	1.49, 1.59
k_{form} (1/year)	0.0590 (0.00371)	6.29	0.0517, 0.0663
k_{res} (1/year)	0.0110 (0.000579)	5.26	0.00987, 0.0121
Race black on k_{res}	0.135 (0.0378)	28.0	0.0609, 0.209
Race black on k_{form}	–0.191 (0.0236)	12.4	–0.237, –0.145
Factor for inclusion/exclusion criteria	0.0847 (0.0139)	16.4	0.0575, 0.112
Machine type Lunar on placebo response	0.133 (0.00293)	2.20	0.127, 0.139
Baseline Z-score on k_{res}	–0.240 (0.0166)	6.92	–0.273, –0.207
Baseline Z-score on k_{form}	0.169 (0.0128)	7.57	0.144, 0.194
Inter-Individual Variability on k_{form} (%CV)[b]	0.00286 (5.35)	84.3	–0.00186, 0.00758
Inter-Individual Variability on k_{res} (%CV)[b]	0.00264 (5.14)	49.6	7.24×10^{-05}, 0.00521
Proportional Error	0.000263 (2.46×10^{-05})	9.35	0.000215, 0.000311

BMI = body mass index; RSE = relative standard error; SEE = standard error of the estimate; k_{form} = placebo response formation rate constant; k_{res} = placebo response resorption rate constant; $PLAC_{max}$ = maximum lumbar spine BMD

a. %RSE = Relative standard error; estimated as the standard error of the estimate divided by the population estimate multiplied by 100.

b. $\%CV = 100 * (\sqrt{e^{\omega^2} - 1})$.

Source: Table 6 on page 55 of Applicant's clinical report rd190280

Exposure-Response Model for BMD: Once the placebo model that best described observed BMD changes in the placebo arm was selected, the combined placebo and exposure-response model for BMD changes was built.

The model was an indirect response model described the change from placebo response (PLAC) and assumed a baseline steady state between bone formation and resorption described by the following equations:

$$\frac{dR(t)}{dt} = k_{in} - k_{out} \cdot R(t) \qquad \text{Equation 6}$$

$$BMD(t) = PLAC(t) \cdot R(t) \qquad \text{Equation 7}$$

And at the baseline

$$R(0) = 1 \text{ and } k_{out} = k_{in}/1 \qquad \text{Equation 8}$$

where dR(t)/dt is the change in BMD over time, k_{in} is a zero-order rate constant reflecting bone formation, k_{out} is a first-order rate constant reflecting bone resorption, BMD(t) is the BMD at time t, and R(t) is the change in BMD from placebo response (PLAC) at time t.

The effects of elagolix on BMD were modeled using a stimulatory Emax function on the bone resorption (k_{out}), as follows:

$$\frac{dR(t)}{dt} = k_{in} - k_{out} \cdot \left(1 + \frac{E_{max} \cdot C_{avg}{}^{HILL}}{EC_{50}{}^{HILL} + C_{avg}{}^{HILL}}\right) \cdot R(t) \qquad \text{Equation 9}$$

where E_{max} is the elagolix maximum stimulatory effect on k_{out}, EC_{50} is the elagolix average concentration at which half of the maximal effect is achieved, and HILL is the stimulatory E_{max} curve shape factor. Due to the strong influence of co-administration with E2/NETA on the change in BMD, different population estimates for E_{max} were incorporated into the model.

Parameter estimates for the final exposure-lumbar spine BMD model are summarized in Table 4.6-5. The goodness-of-fit plots are shown in Figure 4.6-4. The VPC plots are shown in Figure 4.6-5 and Figure 4.6-6.

Table 4.6-5: Parameter Estimates for the Final Exposure-Lumbar Spine BMD Model (BMD_run100)

Parameter	Population Estimate (SEE)	%RSE[a]	95% Confidence Interval
$PLAC_{max}$ (g/cm^2)	1.60 (0.0151)	0.944	1.57, 1.63
k_{form} (1/year)	0.0542 (0.00126)	2.32	0.0517, 0.0567
k_{res} (1/year)	0.0129 (0.000258)	2.00	0.0124, 0.0134
Race black on k_{res}	0.0674 (0.0211)	31.3	0.0260, 0.109
Race black on k_{form}	–0.185 (0.00928)	5.02	–0.203, –0.167
Factor for inclusion/exclusion criteria	0.107 (0.00977)	9.13	0.0879, 0.126
Machine type Lunar on placebo response	0.137 (0.00187)	1.36	0.133, 0.141
Baseline Z-score on k_{res}	–0.194 (0.00485)	2.50	–0.204, –0.184
Baseline Z-score on k_{form}	0.155 (0.00571)	3.68	0.144, 0.166
k_{in} (1/day)	0.00164 (8.03×10^{-05})	4.90	0.00148, 0.00180
E_{max}	0.181 (0.0233)	12.9	0.135, 0.227
EC_{50} (ng/mL)	134 (31.4)	23.4	72.5, 196
BMI on k_{in}	–0.518 (0.141)	27.2	–0.794, –0.242
E2/NETA on E_{max}	0.0399 (0.00724)	18.1	0.0257, 0.0541
Inter-Individual Variability on k_{form} (%CV)[b]	0.00887 (9.44)	75.6	–0.00428, 0.0220
Inter-Individual Variability on k_{res} (%CV)[b]	0.00430 (6.56)	59.8	–0.000737, 0.00934
Inter-Individual Variability on EC_{50} (%CV)[b]	2.24 (290)	32.4	0.817, 3.66
Proportional Error	0.000392 (1.61×10^{-05})	4.11	0.000360, 0.000424

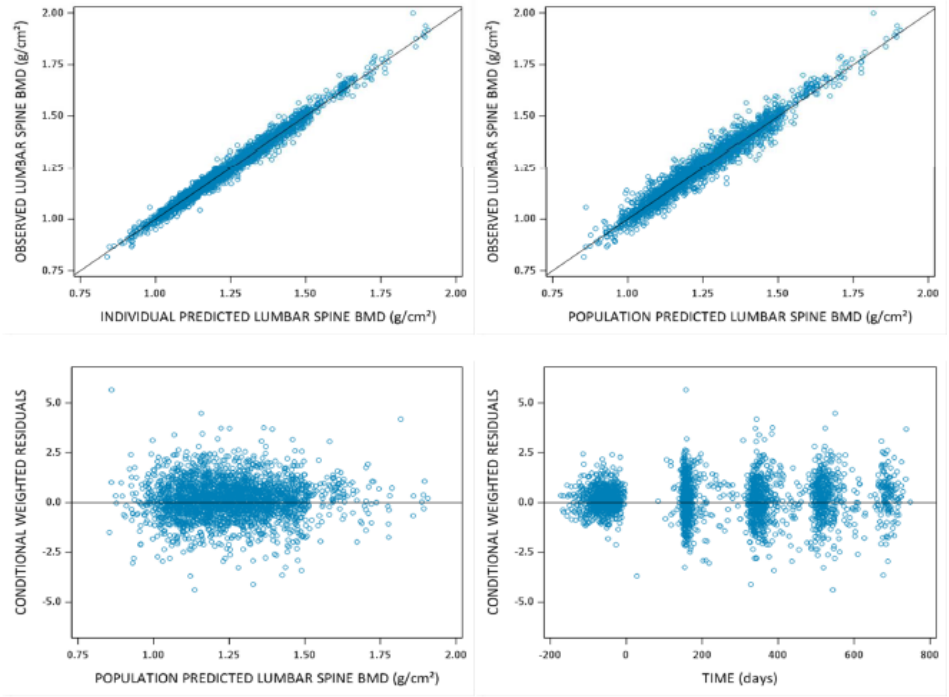
BMI = body mass index; EC_{50} = average concentration at which half of the maximal effect is achieved; E_{max} = maximal effect; k_{form} = placebo response formation rate constant; k_{in} = zero-order rate constant reflecting bone formation; k_{res} = placebo response resorption rate constant; $PLAC_{max}$ = maximum lumbar spine BMD; RSE = relative standard error; SEE = standard error of the estimate; E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg

a. %RSE = Relative standard error; estimated as the standard error of the estimate divided by the population estimate multiplied by 100.

b. $\%CV = 100 * (\sqrt{e^{\omega^2} - 1})$.

Source: Table 7 on page 57 of Applicant's clinial report rd190282

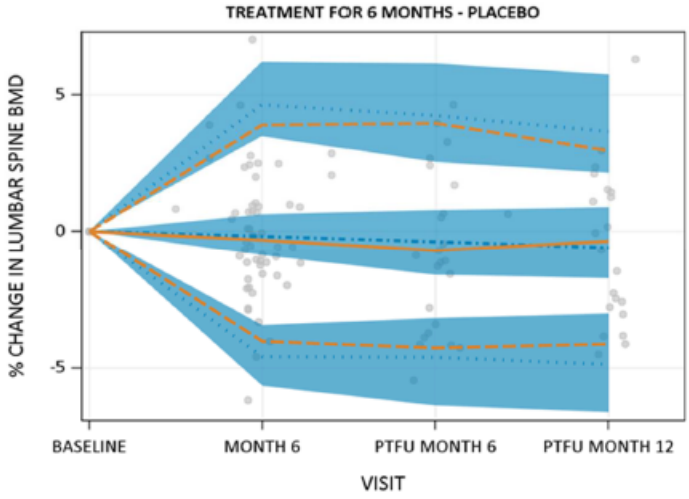
Figure 4.6-4: Goodness-of-Fit Plots for the Final Exposure-Lumbar Spine BMD Model



Note: Individual (Upper Left) and Population Predicted (Upper Right) versus Observed Lumbar Spine and Conditional Weighted Residuals versus Population Predicted Lumbar Spine (Lower Left) and versus Time (Lower Right).

Source: Table 7 on page 57 of Applicant's clinial report rd190282

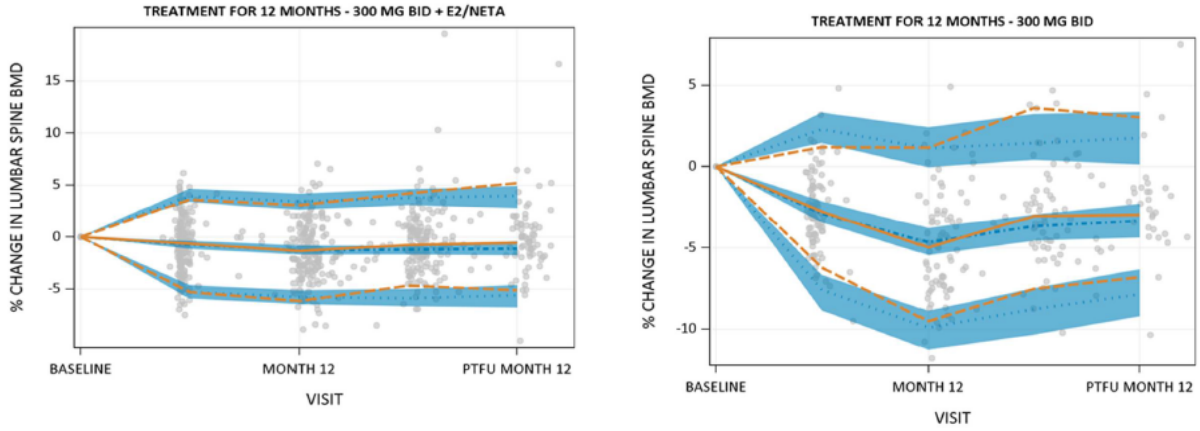
Figure 4.6-5: Visual Predictive Check Plots for the Final Exposure-Lumbar Spine BMD Model - Treatment with Placebo for 6 months



Note: Median (solid line), 5th and 95th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals of the median, 5th and 95th percentiles of the simulated data (shaded regions).

Source: Table 7 on page 57 of Applicant's clinial report rd190282

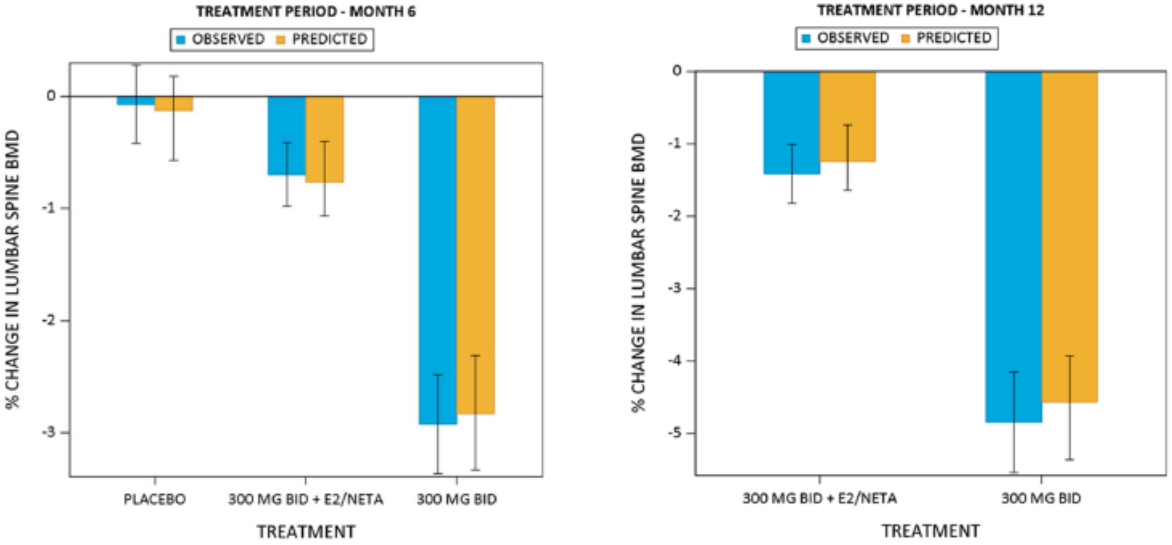
Figure 4.6-6: Visual Predictive Check Plots for the Final Exposure-Lumbar Spine BMD Model - Treatment with 300 mg Elagolix BID + E2/NETA or 300 mg Elagolix BID for 12 months



Note: Median (solid line), 5th and 95th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals of the median, 5th and 95th percentiles of the simulated data (shaded regions).

Source: Adapted from Figure 10 on page 62 of Applicant's clinial report rd190282

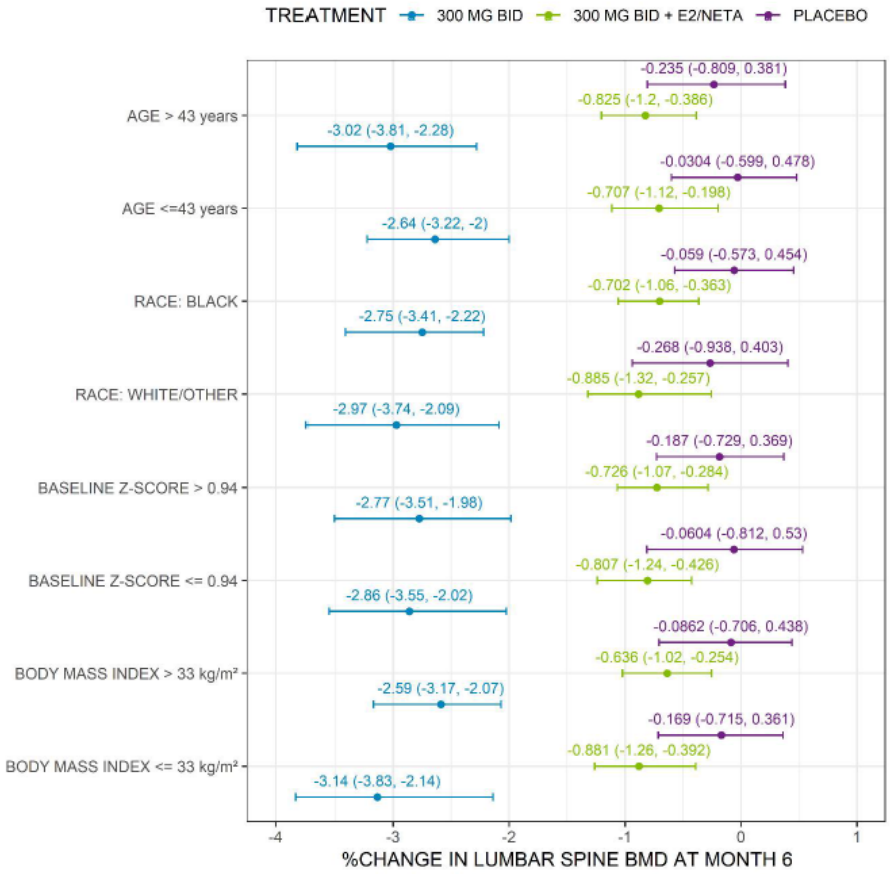
Figure 4.6-7: Observed and Model-Predicted % Change in Lumbar Spine BMD for the Final Exposure-BMD Model at Month 6 and Month 12



Source: Adapted from Figure 11 on page 64 of Applicant's clinial report rd190282

Effect of Covariates: Figure 4.6-8 summarized the model-simulated % change in lumbar spine BMD at Month 6 for placebo, elagolix 300 mg BID, and elagolix 300 mg BID + E2/NETA stratified by the significant covariates in the final exposure-BMD model

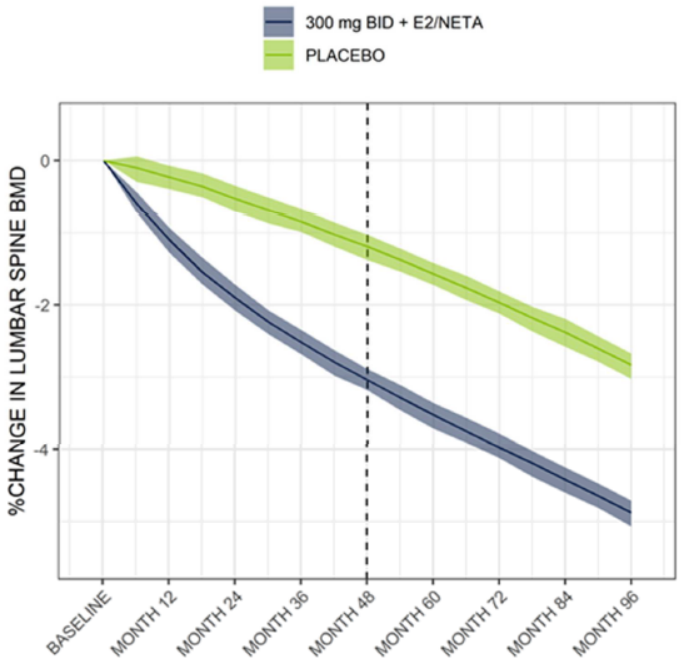
Figure 4.6-8: Model-Predicted % Change in Lumbar Spine BMD at Month 6 for Placebo, Elagolix 300 mg BID, and Elagolix 300 mg BID + E2/NETA Stratified by Covariate Subgroups



Note: Dots and error bars represent simulated mean % change in lumbar spine BMD at Month 6 and 95% confidence intervals stratified by covariate subgroups.

Simulations of BMD Changes Beyond 12 months: Parameter distributions for demographics and baseline characteristics of subjects in women with UF (Studies M12-815, M12-817) and endometriosis (Studies M12-665 and M12-671) were used as inputs for the lumbar spine BMD simulations to predict BMD changes following treatment with elagolix beyond 12 months and up to 96 months. In this scenario each simulated subject was treated with elagolix 300 mg BID + E2/NETA or placebo for 96 months and the % change from baseline BMD was predicted over the treatment period. Simulated mean % change in Lumbar Spine BMD over time is demonstrated in Figure 4.6-9 and summarized in Table 4.6-6. The Applicant proposed a duration of continuous use of elagolix 300 mg BID + E2/NETA for (b) (4) months at which the BMD loss from baseline was predicted to be approximately (b) (4)%, a threshold established for limiting the duration of use with Lupron based on BMD loss.

Figure 4.6-9: Simulated Mean % Change in Lumbar Spine BMD Over Time for Placebo and Treatment with Elagolix 300 mg BID + E2/NETA for 96 Months



Note: Lines and shaded regions represent mean % change in lumbar spine BMD and 95% confidence interval of the mean.

Table 4.6-6: Summary Statistics of Predicted Mean % Change in Lumbar Spine BMD for Placebo and Treatment with Elagolix 300 mg BID + E2/NETA for 96 Months

	Placebo		300 mg BID + E2/NETA		Placebo-Corrected 300 mg BID + E2/NETA	
Month	Mean % Change in BMD	95% CI of Mean % Change in BMD	Mean % Change in BMD	95% CI of Mean % Change in BMD	Mean % Change in BMD	95% CI of Mean % Change in BMD
Month 6	–0.102	–0.293, 0.0578	–0.599	–0.722, –0.438	–0.498	–0.699, –0.293
Month 12	–0.230	–0.397, –0.0722	–1.10	–1.28, –0.938	–0.873	–1.11, –0.612
Month 18	–0.360	–0.509, –0.177	–1.55	–1.72, –1.35	–1.19	–1.42, –0.928
Month 24	–0.531	–0.705, –0.352	–1.91	–2.08, –1.73	–1.37	–1.62, –1.13
Month 30	–0.689	–0.870, –0.514	–2.24	–2.41, –2.08	–1.55	–1.77, –1.33
Month 36	–0.850	–0.992, –0.671	–2.52	–2.68, –2.35	–1.67	–1.86, –1.43
Month 42	–1.03	–1.19, –0.860	–2.79	–2.98, –2.63	–1.77	–2.00, –1.55
Month 48	–1.19	–1.38, –1.03	–3.04	–3.18, –2.89	–1.85	–2.07, –1.64
Month 54	–1.38	–1.54, –1.22	–3.29	–3.46, –3.11	–1.91	–2.18, –1.67
Month 60	–1.57	–1.72, –1.42	–3.52	–3.71, –3.36	–1.95	–2.20, –1.73
Month 66	–1.77	–1.93, –1.60	–3.75	–3.91, –3.56	–1.98	–2.18, –1.77
Month 72	–1.97	–2.12, –1.81	–3.97	–4.12, –3.78	–2.00	–2.21, –1.77
Month 78	–2.18	–2.37, –2.03	–4.19	–4.38, –4.02	–2.01	–2.23, –1.79
Month 84	–2.38	–2.58, –2.19	–4.42	–4.60, –4.25	–2.04	–2.32, –1.85
Month 90	–2.61	–2.79, –2.43	–4.65	–4.81, –4.47	–2.04	–2.33, –1.77
Month 96	–2.83	–3.03, –2.67	–4.88	–5.06, –4.71	–2.04	–2.36, –1.82

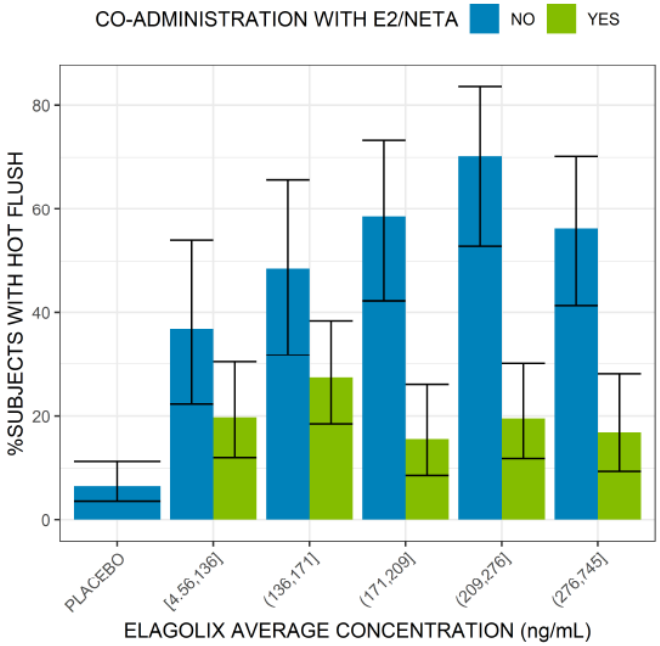
BMD = bone mineral density; E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg; CI = confidence interval

Source: Table 9 on page 74 of Applicant's clinical study report rd190282

Exposure-Response Model for Hot Flush: The proportion of subjects for each model-predicted elagolix C_{avg} quintile experiencing hot flush was demonstrated in Figure 4.6-10. An increasing trend of incidence of hot flush was observed with increasing elagolix average concentrations for 300 mg BID. For 300 mg

BID + E2/NETA, no clear exposure-response relationship was identified between elagolix exposure and incidence of hot flush.

Figure 4.6-10: Quintile Plot for Hot Flush



Note: Bars plots represents observed proportions and error bars represents 95% binomial confidence interval of the observed proportions at the model-predicted average concentration quintile

Source: Figure 19 on page 88 of Applicant's clinical study report rd190282

Exposure-response modeling of hot flush was conducted using logistic regression analysis with R (Version 3.5.1) using the glm function for fitting generalized linear models (with binomial family and logit link) to characterize the relationship between elagolix exposure and the binary safety endpoint. Logistic regression models were evaluated graphically by plotting the predicted probability of occurrence of hot flush versus elagolix exposure overlaid with the percent of subjects experiencing hot flush by exposure quintiles. Parameter estimates of the hot flush logistic regression are summarized in Table 3.6-7. Observed and model predicted probability of hot flush vs. elagolix C_{avg} is shown in Figure 4.6-11. Effect of covariates on the probability of hot flush is demonstrated in Figure 4.6-12.

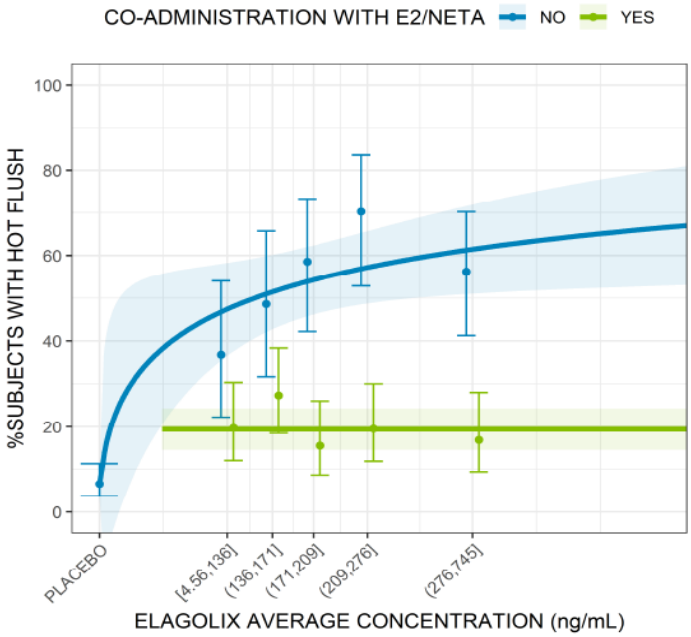
Table 4.6-7: Parameter Estimates of the Hot Flush Logistic Regression: Final Model (HF_run5)

Parameter	Estimate (SEE)	95% Confidence Interval	p-value
(Intercept)	0.0483 (0.148)	–0.242, 0.339	0.745
logCAVG	1.24 (0.638)	–0.00524, 2.49	0.0510
TRTPLACEBO	–2.86 (0.325)	–3.50, –2.23	< 0.001
ADDBACKYES	–1.59 (0.194)	–1.97, –1.21	< 0.001
TOBACURRENT	0.697 (0.256)	0.195, 1.20	0.00652
BLPRG	0.103 (0.0484)	0.00783, 0.198	0.0339

SEE = Standard error of estimate; TOBA = Tobacco use; BLPRG = Progesterone at baseline

Source: Table 15 on page 91 of Applicant's clinical study report rd190282

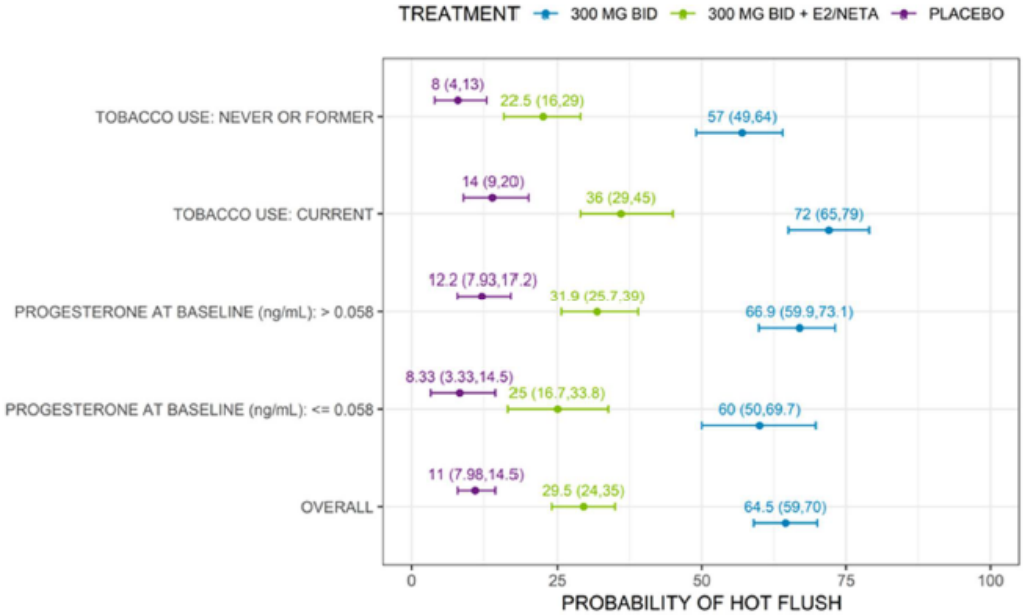
Figure 4.6-11: Observed and Model-Predicted Probability of Hot Flush vs. Elagolix Cavg: Final Model



Note: Dots represent observed proportions, error bars represent 95% binomial confidence interval of the observed proportions, lines represent the predicted probability and shaded regions represent the 95% confidence intervals of the model-predicted rates versus the model-predicted average elagolix concentration quintile

Source: Figure 20 on page 92 of Applicant's clinical study report rd190282

Figure 4.6-12: Model-Predicted Probability of Occurrence of Hot Flush for Placebo, Elagolix 300 mg BID, and Elagolix 300 mg BID + E2/NETA Stratified by Covariate Subgroups



Note: Dots represent simulated probability and error bars represent 95% confidence intervals of the model-simulated probability stratified by covariate subgroups.

Source: Figure 21 on page 93 of Applicant's clinical study report rd190282

***Reviewer's Comment**: The Applicant's exposure-resposne analysis for lumbar BMD was adequate to capture the observed change in BMD after treatment with elagolix 300 mg BID and elagolix 300 BID+E2/NETA up to 12 months.*

As no BMD data was available after administration of drug for more than 12 months, simulations based on the BMD model were used to support the proposed treatment duration of (b)(4) months. Although the reviewer agrees that the model may provide an conservative estimate of BMD loss (i.e., overestimation of the BMD loss), uncertainty still exists when a model based on 12 months BMD data is used to predict the BMD loss up to (b)(4) months considering that the trajectory of long term BMD loss effect of this product is still unknown. However, we consider the model is adequate to predict the mean BMD loss up to 24 months. The model predicted mean BMD loss up to 24 months is less than 2%, which supports an extended treatment of 12 months beyond the observed 12 month-data for a total of up to 24 months.

4.7 Enrichment, Stratification, and/or Biomarker-based Assessment

The Applicant determined SLCO1B1 genotype for the reference single nucleotide polymorphism (SNP), rs1419056, 521T > C allele (*5). Whole blood samples from twenty phase 1 studies, one Phase 2 study, two Phase 3 studies in subjects with uterine fibroids, and two Phase 3 studies in subjects with endometriosis were analyzed via pyrosequencing. SLCO1B1*5 genotype was assayed, and subjects were assigned into OATP1B1 phenotypes as follows:
Homozygous variant 521T > C (*5) → Poor transporter (PT)
Heterozygous for 521T > C (*5) → Intermediate transporter (IT)
Homozygous wild-type 521T > C (*5) → Extensive transporter (ET)

The Applicant evaluated data from six new Phase 1 clinical studies (M12-653, M12-790, M13-995, M15-817, M15-973, and M15-974), two Phase 3 studies in premenopausal women with uterine fibroids (M12-815 and M12-817), and two Phase 3 studies in premenopausal women with endometriosis (M12-665 and M12-671) to compare elagolix exposures across OATP1B1 phenotypes in the population pharmacokinetic analysis (**Table 4.7-1**). Genotype results from other studies were previously submitted under the cross-referenced NDA 210450, and included in the pharmacogenetics report (Study R&D/18/1201).

Table 4.7-1: Distribution of *SLCO1B1* Genotypes (OATP1B1 Phenotypes) across Elagolix Studies in Subjects with Endometriosis Associated Pain and Women with Uterine Fibroids.

Study ID	Number of Samples Available and Analyzed by Phenotypes				
Phase 1	T/T (ET)	T/C (IT)	C/C (PT)	Missing Data	Total
M12-653	22	2	0	0	24
M12-790	38	6	0	0	44
M13-995	17	6	0	0	23
M15-817	41	12	1	0	54
M15-973	16	4	0	0	20
M15-974	17[a]	2	0	0	19
Phase 2 and 3					
M12-815	273	39	1	0	313
M12-817	227	35	4	0	266
M12-665	513	179	12	2	706
M12-671	432	154	21	1	608

Total N (%)	1596 (76.8)	439 (21.1)	39 (1.9)	3 (0.1)	2077

Source: Adapted from Applicant's Table 3 of Pharmacogenetics Report (Study R&D/18/1201). ET: extensive transporter; IT: intermediate transporter; PT: poor transporter; Missing Data = Unable to analyze/genotype the sample. One subject was excluded (Clinical Study Report M15-974) from study data analysis.
Note: All available samples were analyzed there was no missing data from the Phase 1 studies.

The Applicant found that elagolix exposures in subjects with IT and PT phenotypes were 1.45-fold and 2.09-fold higher, respectively, when compared to exposure in subjects with ET phenotypes. However, the exposures greatly overlapped across OATP1B1 phenotype status (See Figure **3.3.3-1**).

Proposed Labelling Recommendations
Hepatic uptake of elagolix involves the OATP 1B1 transporter protein. Higher plasma concentrations of elagolix have been observed in patients who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C) (these patients are likely to have reduced hepatic uptake of elagolix; and thus, higher plasma elagolix concentrations). The frequency of this SLCO1B1 521 C/C genotype is generally less than 5% in most racial/ethnic groups. Women with this genotype are expected to have approximately 2-fold higher elagolix mean concentrations compared to women with normal transporter function (i.e., SLCO1B1 521T/T genotype). Adverse effects of elagolix have not been fully evaluated in subjects who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C).

Reviewer's comment: *The variability in exposure exhibited across OATP1B1 phenotypes suggests no clinically-meaningful differences of elagolix exposures across different OATP1B1 phenotypes. The lack of significant bone loss in the limited number of patients with uterine fibroids who received elagolix +E2/NETA and exhibited OATP1B1 poor transporter phenotypes (Figure 3.3.3-2) does not support requiring SLCO1B1 genotyping before treatment with elagolix. The Applicant's proposed labeling description with respect to SLCO1B1 genotype is acceptable.*

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/s/

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