

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210450Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation {NDA 210450}
{Orilissa and elagolix sodium}

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210450
Priority or Standard	Priority
Submit Date(s)	August 23, 2017
Received Date(s)	August 23, 2017
PDUFA Goal Date	July 23, 2018
Division/Office	DBRUP/ODE3
Review Completion Date	(electronic stamp)
Established Name	Elagolix Sodium
(Proposed) Trade Name	Orilissa
Pharmacologic Class	Gonadotropin-releasing hormone (GnRH) receptor antagonist
Applicant	Abbvie, Inc.
Formulation(s)	Oral Tablets
Dosing Regimen	150 mg once daily or 200 mg twice daily, with or without food
Applicant Proposed Indication(s)/Population(s)	For the management of endometriosis with associated pain
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the management of moderate to severe pain associated with endometriosis

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Reviewers of Multi-Disciplinary Review and Evaluation

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED
Drug Product Reviewer	Mark Seggel, PhD	OPQ/ONDP/DNDP2	Approved: Section 4.2, 11
	Signature: Mark R. Seggel -S Digitally signed by Mark R. Seggel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R. Seggel -S, 0.9.2342.19200300.100.1.1=1300071539 Date: 2018.07.17 15:08:30 -04'00'		
Pharmacology/ Toxicology Reviewer	Leslie McKinney, PhD	DBRUP	Authored: Section 5
	Signature: Leslie C. Mckinney -S Digitally signed by Leslie C. Mckinney -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300373366, cn=Leslie C. Mckinney -S Date: 2018.07.12 14:14:24 -04'00'		
Pharmacology/ Toxicology Supervisor	Mukesh Summan, PhD, DABT	DBRUP	Approved: Section 5
	Signature: Mukesh Summan -S Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9.2342.19200300.100.1.1=2000337340 Date: 2018.07.12 15:41:42 -04'00'		
ODE Associate Director for Pharmacology and Toxicology (Acting)	Ronald Wange, PhD	OND	Approved: Section 5
	Signature: Ronald L. Wange -S Digitally signed by Ronald L. Wange -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300236480, cn=Ronald L. Wange -S Date: 2018.07.12 15:45:03 -04'00'		
Clinical Pharmacology and PBPK Reviewer	Peng Zou, PhD	OCP/DCP3	Authored: Section 6, 14.3
	Signature: Peng Zou -S Digitally signed by Peng Zou -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peng Zou -S, 0.9.2342.19200300.100.1.1=2000783342 Date: 2018.07.16 12:55:41 -04'00'		
Clinical Pharmacology Reviewer	Da Zhang, PhD	OCP/DCP3	Authored: Section 6
	Signature: Da Zhang -S Digitally signed by Da Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Da Zhang -S, 0.9.2342.19200300.100.1.1=0012242580 Date: 2018.07.13 18:09:19 -04'00'		
PBPK Secondary Reviewer	Nan Zheng, PhD	OCP/DPM	Approved: Section 6
	Signature: Nan Zheng -S Digitally signed by Nan Zheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nan Zheng -S, 0.9.2342.19200300.100.1.1=2000849162 Date: 2018.07.13 18:14:15 -04'00'		
Clinical Pharmacology Team Leader	Doanh Tran, PhD	OCP/DCP3	Approved: Section 6, 14.3
	Signature: Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2018.07.16 13:03:34 -04'00'		

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Pharmacometrics Reviewer	Fang Li, PhD	OCP/DPM	Authored: Section 6
	Signature: Fang Li -S Digitally signed by Fang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fang Li -S, 0.9.2342.19200300.100.1.1=1300430137 Date: 2018.07.12 19:31:47 -04'00'		
Pharmacometrics Team Leader	Jingyu (Jerry) Yu, PhD	OCP/DPM	Approved: Section 6
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2018.07.12 19:59:20 -04'00'		
Pharmacogenomics Reviewer	Oluseyi Adeniyi, PhD	OCP/GTT	Authored: Section 6
	Signature: Oluseyi Adeniyi -S Digitally signed by Oluseyi Adeniyi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001901490, cn=Oluseyi Adeniyi -S Date: 2018.07.12 16:31:14 -04'00'		
Pharmacogenomics Team Leader	Christian Grimstein, PhD	OCP/GTT	Approved: Section 6
	Signature: Christian Grimstein -S Digitally signed by Christian Grimstein -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000357917, cn=Christian Grimstein -S Date: 2018.07.12 16:39:56 -04'00'		
Clinical Pharmacology Division Director (Acting)	Gilbert J Burckart, PharmD	OCP/DCP3	Approved: Section 6, 14.3
	Signature: Gilbert J. Burckart -S Digitally signed by Gilbert J. Burckart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300382447, cn=Gilbert J. Burckart -S Date: 2018.07.16 14:09:23 -04'00'		
Biostatistics	Jia Guo, PhD	OB/DB3	Authored: Sections 7, 8
	Signature: Jia Guo -S Digitally signed by Jia Guo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jia Guo -S, 0.9.2342.19200300.100.1.1=2000520093 Date: 2018.07.17 15:48:34 -04'00'		
Biostatistics Team Leader (Acting)	Mahboob Sobhan, PhD	OB/DB3	Approved: Sections 7, 8
	Signature: Mahboob Sobhan -S Digitally signed by Mahboob Sobhan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mahboob Sobhan -S, 0.9.2342.19200300.100.1.1=1300084769 Date: 2018.07.17 15:50:33 -04'00'		
Biostatistics Division Director (Acting)	Laura Lee Johnson, PhD	OB/DB3	Approved: Sections 7, 8
	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2018.07.17 20:23:40 -04'00'		
Clinical	Abby Anderson, MD	OND/DBRUP	Authored: Sections 2.1, 8.1, 14.1
	Signature: Abby Anderson -S Digitally signed by Abby Anderson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Abby Anderson -S, 0.9.2342.19200300.100.1.1=2002091441 Date: 2018.07.18 09:16:06 -04'00'		
Clinical	Gerald Willett, MD	OND/DBRUP	Authored: Sections 8.2
	Signature: Gerald D. Willett -S Digitally signed by Gerald D. Willett -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144046, cn=Gerald D. Willett -S Date: 2018.07.18 11:01:36 -04'00'		

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Clinical	Linda Jaffe, MD	OND/DBRUP	Authored: Sections 8.2.7
	Signature: Linda S. Jaffe -S Digitally signed by Linda S. Jaffe -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Linda S. Jaffe -S, 0.9.2342.19200300.100.1.1=2002157496 Date: 2018.07.18 10:20:37 -0400		
Clinical	Theresa Kehoe, MD	OND/DBRUP	Approved: Sections 8.2.7
	Signature: Theresa E. Kehoe -S Digitally signed by Theresa E. Kehoe -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300186604, cn=Theresa E. Kehoe -S Date: 2018.07.18 10:28:05 -0400		
CDTL	Christina Chang, MD, MPH	OND/DBRUP	Authored: Sections 1, 2, 3, 4, 9, 10, 12, 13 Approved: All Sections
	Signature: see DARRTS signature page		
DBRUP	Hylton Joffe, MD, MMSc	OND/DBRUP	Approved: All Sections
	Signature: see DARRTS signature page		
ODE 3	Victor Crentsil, MD, MHS, FCP	OND/ODE3	Approved: All Sections
	Signature: see DARRTS signature page		

Additional Reviewers of Application

COA	Nikunj Patel, Selena Daniels, Elektra Papadopoulos
DAAAP	Robert Shibuya, Ellen Fields, Sharon Hertz
DGIEP	Erica Lyons, Kathleen Donohue, Lisa Soule
OMP/OPDP	Lynn Panholzer
OMP/DMPP	Sharon Williams, Marcia Britt-Williams
OSI	Roy Blay, Yolanda Patague, Jenn Sellers,
OSE	Mark Avigan
OSE/DEPI	Wei Liu, Jie Li, David Moeny
OSE/DMEPA	Walter Fava, Briana Rider, Lolita White
OSE/DPV	Emeri Potter, Lynda McCulley
OSE/DRISK	Courtney Cunningham, Leah Hart, Laura Zendel
DPMH	Leyla Sahin, Lynne Yao
CSS	Katherine Bonson, Silvia Calderon, Dominic Chiapperino
QT-IRT	Dhananjay Marathe, Christine Garnett

COA = Clinical Outcome Assessment
 DAAAP = Division of Anesthesia, Analgesia, and Addiction Products
 DGIEP = Division of Gastroenterology and Inborn Errors Products
 OMP = Office of Medical Policy
 OPDP = Office of Prescription Drug Promotion
 DMPP = Division of Medical Policy Programs
 OSI = Office of Scientific Investigations
 OSE = Office of Surveillance and Epidemiology
 DEPI = Division of Epidemiology
 DMEPA = Division of Medication Error Prevention and Analysis
 DPV = Division of Pharmacovigilance
 DRISK = Division of Risk Management
 DPMH = Division of Pediatric and Maternal Health
 CSS = Controlled Substance Staff
 QT-IRT = QT Interdisciplinary Review Team

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
B&B	Biberoglu and Behrman scale
BCRP	breast cancer resistance protein
BID	twice daily
BLA	biologics license application
BMD	bone mineral density
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDF	cumulative distribution function
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMQ	customized MedDRA queries
CPSSS	Composite Pelvic Signs and Symptoms Score
CSR	clinical study report
CSS	Controlled Substance Staff
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DDI	drug-drug interaction
DGIEP	Division of Gastroenterology and Inborn Errors Products
DXA	dual-energy X-ray absorptiometry
DYS	dysmenorrhea
DYSP	dyspareunia
EAP	endometriosis-associated pain
ECG	electrocardiogram
EFD	embryofetal development
Ela	elagolix
ESRD	end-stage renal disease
ET	extensive transporter
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FSH	follicle-stimulating hormone
GD	gestation day
GnRH	gonadotropin-releasing hormone
hCG	β -human chorionic gonadotropin

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HDL-C	high density lipoprotein cholesterol
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IT	intermediate transporter
ITT	intent-to-treat
LD	lactation day
LDL-C	low density lipoprotein cholesterol
LOCF	last observation carried forward
LS	least squares
LH	leutinizing hormone
M3	an O-demethyl metabolite of elagolix
M6x	an N-dealkyl metabolite of elagolix
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MOE	multiple of exposure
MRHD	maximum recommended human dose
NBI	Neurocrine Biosciences, Inc.
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NMPP	nonmenstrual pelvic pain
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRS	numeric rating score
NSAID	non-steroidal anti-inflammatory drug
OATP	organic-anion-transporting polypeptide
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
P1NP	procollagen type 1 N-terminal propeptide
PD	pharmacodynamics
PGIC	Patient Global Impression of Change
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PND	post-natal day
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
PT	poor transporter
PTFU	post-treatment follow-up
QD	once daily

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REMS	risk evaluation and mitigation strategy
ROC	receiver operating characteristic
SAB	spontaneous abortion
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous (injection)
SD	standard deviation
SE	standard error
SMQ	standardised MedDRA query
SOC	System Organ Class
TEAE	treatment emergent adverse event
TVU	transvaginal ultrasound
TK	toxicokinetic
ULN	upper limit of normal

1. Executive Summary

1.1. Product Introduction

AbbVie, Inc. has submitted this New Drug Application (NDA) under section 505(b)(1) of the Food, Drug, and Cosmetic Act for elagolix sodium (hereafter referred to as elagolix, proprietary name Orilissa) for the management of endometriosis with associated pain. Elagolix, a new molecular entity, is a nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist that reduces pituitary secretion of the gonadotropins (leutinizing hormone (LH) and follicle-stimulating hormone (FSH)) resulting in dose-dependent decreases in ovarian production of estradiol and progesterone. If approved, elagolix will be the only marketed oral treatment and the first GnRH receptor antagonist indicated for endometriosis. Unlike GnRH agonists, which cause an initial stimulation of the hypothalamic–pituitary–gonadal axis (HPG axis) and a surge in estrogen levels, GnRH antagonists reduce sex hormones without an initial surge.

The immediate-release tablets contain 150 mg or 200 mg of elagolix. The proposed dosing regimen is either 150 mg once daily or 200 mg twice daily. Each dosage strength is presented in cartons for monthly supply with each carton containing 4-weekly blister packs.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant conducted two adequate and well-controlled trials. The design of these trials and their results meet the statutory requirement for establishing substantial evidence of effectiveness. In both trials, 3 months of treatment with elagolix 150 mg once daily and 200 mg twice daily significantly reduced dysmenorrhea and non-menstrual pelvic pain (co-primary efficacy endpoints) compared to placebo in women with endometriosis-associated pain. Based on secondary endpoints controlled for type I error, both treatment regimens also reduced dysmenorrhea and non-menstrual pelvic pain compared to placebo with 6 months of treatment, and the 200 mg twice daily regimen reduced dyspareunia compared to placebo with 3 months of treatment. Results were similar across both trials without inconsistencies in the data.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Endometriosis refers to endometrial tissue outside of the uterus. The hallmark symptoms are chronic pain and infertility. The pain may occur with menses (dysmenorrhea), between menses (non-menstrual pelvic pain) or with sexual intercourse (dyspareunia). Because estrogen promotes the growth of endometriosis tissue and contributes to local inflammation and pain, most medical therapies for endometriosis reduce estrogen concentrations. Treatment options include gonadotropin releasing hormone (GnRH) agonists, subcutaneously administered medroxyprogesterone acetate, and surgery. There are currently no marketed oral treatments for endometriosis. A safe and effective oral therapy would provide another treatment option for endometriosis.

Orilissa (elagolix), a GnRH antagonist, is an oral treatment for moderate to severe pain associated with endometriosis. The proposed dose is 150 mg once daily or 200 mg twice daily.

The Applicant evaluated the efficacy of Orilissa in two Phase 3 trials (Studies 665 and 671) that randomized a total of 1686 premenopausal women with moderate to severe pain associated with endometriosis to Orilissa (475 received 150 mg once daily and 477 received 200 mg twice daily) or placebo.

The co-primary efficacy endpoints in both trials assessed the proportion of subjects whose dysmenorrhea responded to treatment at Month 3 and the proportion of subjects whose non-menstrual pelvic pain responded to treatment at Month 3. In both trials, the 150 mg once daily dose and 200 mg twice daily dose were superior to placebo on both co-primary endpoints. For example, in Study 665, the proportion of responders for dysmenorrhea at Month 3 was 46% with Orilissa 150 mg once daily, 76% with Orilissa 200 mg twice daily and 20% with placebo ($p \leq 0.001$ for each comparison to placebo). In this trial, the proportion of responders for non-menstrual pelvic pain at Month 3 was 50% with Orilissa 150 mg once daily, 55% with Orilissa 200 mg twice daily and 36% with placebo ($p \leq 0.001$ for each comparison to placebo). The results for the other Phase 3 trial were similar.

Both trials included several secondary efficacy endpoints that were controlled for type 1 error. Results for these endpoints showed that, compared to placebo, both Orilissa doses in both trials reduced dysmenorrhea and non-menstrual pelvic pain at Month 6 and that only the 200 mg twice daily dose reduced dyspareunia at Month 3. In both trials, there was a statistically significant reduction in opioid use at Month 6 for the 200 mg twice daily dose only, but the Applicant did not show that the mean reduction in opioid pill

counts of 0.12 is clinically meaningful.

The highly consistent results from these two adequate and well-controlled trials clearly establish the efficacy of both the 150 mg once daily and 200 mg twice daily regimens for the treatment of moderate to severe pain associated with endometriosis.

The endometriosis safety database includes 2966 subjects who received at least one dose of Orilissa, 1283 of whom received Orilissa for at least 6 months and 425 of whom received Orilissa for at least 12 months. A total of 279 women received the maximum recommended dose of 200 mg twice daily for 12 months.

The most important safety concerns are bone loss and depression-related adverse reactions.

Orilissa causes a dose- and duration-dependent decline in bone mineral density (BMD). Compared to placebo, the mean change in lumbar spine BMD was about 1% after 6 months with 150 mg once daily and approximately 3% after 6 months with elagolix 200 mg twice daily. Partial recovery was seen in subjects who received Orilissa for up to 12 months and who were followed for 12 months after stopping treatment. The impact of these BMD declines on long-term bone health and future fracture risk is unknown. The concerns with bone loss will be mitigated with labeling (Warning and medication guide) that includes a contraindication for women with known osteoporosis, a recommendation to assess BMD in women with additional risk factors for bone loss, and a limitation on duration of use. Because the bone loss did not plateau, the maximum recommended duration of use will be 24 months for the 150 mg once daily dose and 6 months for the 200 mg twice daily dose. Although endometriosis is chronic, treatment for 6 to 24 months can be useful for some women who are close to menopause (endometriosis improves during menopause) and for those who wish to delay surgical therapy.

Compared to placebo, Orilissa-treated subjects in the Phase 3 trials had a higher incidence of depression-related adverse reactions (2.7% with 150 mg once daily, 6.1% with 200 mg twice daily, and 2.3% with placebo). In addition, suicidal ideation and behavior, including one completed suicide, occurred in Orilissa-treated subjects. These risks will also be mitigated with labeling (Warning and medication guide), recommending immediate medical attention for suicidal ideation and behavior, prompt evaluation if depressive symptoms occur and for the prescriber to determine whether the risk of continuing treatment in these patients outweighs the benefits.

Other safety concerns include the potential for early pregnancy loss (Orilissa will be contraindicated in pregnant women, pregnancy is to be excluded before treatment, and women are to use contraception), increased systemic exposures to elagolix (the active ingredient in Orilissa) in women with moderate or severe hepatic impairment and in the setting of certain drug-drug interactions, a dose-dependent elevation in serum alanine aminotransferase to at least three times the upper limit of the reference range without evidence of severe drug-

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induced hepatotoxicity in the clinical program, and increases in low density lipoprotein cholesterol and serum triglycerides. These safety concerns as well as the common adverse reactions (e.g., hot flushes or night sweats, headache, nausea, insomnia, amenorrhea, anxiety and arthralgia) can also be handled with labeling.

Based on the above findings, we conclude that the benefits of Orilissa, when used according to labeling, outweigh its risks for the treatment of moderate to severe pain associated with endometriosis. The benefits of Orilissa do not outweigh its risks for mild pain associated with endometriosis.

In addition to routine pharmacovigilance, postmarketing activities will include enhanced pharmacovigilance for liver adverse events (because of the elevated alanine aminotransferase in the clinical trials), two required postmarketing studies to assess pregnancy outcomes in women who inadvertently become pregnant while on treatment, a required postmarketing drug-drug interaction trial with Orilissa and a combined oral contraceptive, and a postmarketing commitment to assess the effects of hormonal contraception on the efficacy of Orilissa. Until results from the latter two trials are known, labeling will recommend non-hormonal contraception because hormonal contraception may reduce the efficacy of Orilissa.

Table 1. Dimensions of Risk and Benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	• Endometriosis is a chronic condition that affects up to 11% of premenopausal women. The hallmark symptoms of endometriosis are pain (which may occur during menses or between menses, or with sexual intercourse) and infertility. • Estrogen promotes the growth of endometriosis implants (endometrium-like tissues) outside the uterine cavity and enhances a local inflammatory response that contributes to the occurrence of pain. Therefore, the aim of most medical therapies is to reduce estrogen concentrations or to inhibit the effects of estrogen on endometrium-like tissues.	Endometriosis can be a serious and disabling disease that can cause chronic pain and infertility.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Current Treatment Options</u>	• Gonadotropin releasing hormone (GnRH) agonists (leuprolide acetate intramuscular injection, nafarelin acetate nasal spray, goserelin acetate implants) • Depo medroxyprogesterone acetate subcutaneous injection • Conservative surgery, including laparoscopic resection/laser ablation, drainage or resection of endometriomas, resection of rectovaginal nodules, lysis of adhesions, or interruption of nerve pathways (e.g., uterosacral nerves) • Definitive surgery, such as hysterectomy and bilateral oophorectomy for refractory disease	• There are no marketed oral therapies indicated for the treatment of endometriosis. A safe and effective oral therapy would provide another treatment option for women with endometriosis. • Disadvantages of GnRH agonists include (1) an initial stimulatory phase that results in “flare” effects before inhibition of pituitary and ovarian hormone production; (2) health care provider administration (for intramuscular injections or implants); and (3) bone loss, limiting treatment duration. • Symptoms can recur when treatment is discontinued or after conservative surgery. • Definitive surgery causes surgical menopause.
<u>Benefit (continued next page)</u>	• In two Phase 3 placebo-controlled trials (Studies 665 and 671) that enrolled adult women with endometriosis-associated moderate to severe pain, Orilissa 150 mg once daily and 200 mg twice daily successfully met the pre-specified co-primary efficacy endpoints: A significantly greater proportion of Orilissa-treated subjects met the thresholds for reduction in dysmenorrhea and non-menstrual pelvic pain scores compared to placebo after 3 months of treatment. • In one trial (M12-665), the proportion of responders for dysmenorrhea at Month 3 was 46% with Orilissa 150 mg once daily, 76% with Orilissa 200 mg twice daily and 20% with placebo. In this trial, the proportion of responders for non-menstrual pelvic pain at Month 3 was 50% with Orilissa 150 mg once daily, 55% with Orilissa 200 mg twice daily and 36% with placebo. Results for the other Phase 3 trial were similar.	• The Applicant established substantial evidence of effectiveness for Orilissa 150 mg once daily and 200 mg twice daily for the treatment of moderate to severe pain associated with endometriosis based on data from two adequate and well-controlled trials. • These trials also showed that three months of treatment with Orilissa 200 mg twice daily improved dyspareunia. • The Applicant has not demonstrated that any effects on opioid use are clinically relevant.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u> <u>(continued)</u>	- For both doses, there was a statistically significant reduction from baseline in mean dysmenorrhea and non-menstrual pelvic pain scores compared to placebo after 6 months of treatment. - Three months of treatment with Orilissa 200 mg twice daily also reduced dyspareunia compared to placebo. - In both trials, Orilissa 200 mg twice daily showed a statistically significant decrease from baseline in analgesic pill use compared to placebo. The mean difference from placebo was about 0.1 pills at Month 3. The Applicant did not show that the changes in opioid use were clinically relevant.	Orilissa will not be indicated for treating mild pain associated with endometriosis. The Phase 3 trials did not enroll women with mild pain and the risks of Orilissa, such as bone loss, outweigh any potential benefit for those with only mild pain.
<u>Risk and Risk Management</u> <u>(continued next page)</u>	- Because elagolix suppresses ovarian production of estrogen and progesterone, women who are exposed to elagolix during early pregnancy may be at risk for pregnancy loss. - Elagolix causes dose- and duration-dependent decreases in bone mineral density (BMD). For example, in Study M12-665, compared to placebo, the mean change in lumbar spine BMD at 6 months was -0.8% (95% confidence interval (CI): -1.3 to -0.4) with 150 mg once daily and -3.1% (95% CI: -3.6 to -2.6) with 200 mg twice daily. Similar findings were seen in Study M12-671. Partial recovery was seen in subjects who received Orilissa for up to 12 months and who were then followed for an additional 12 months after stopping treatment. The impact of these BMD decreases on long-term bone health and future fracture risk is unknown. - Elagolix exposures in women with severe hepatic impairment are approximately 7-fold higher than in women with normal hepatic function. Elagolix exposures are more than 5-fold higher when co-administered with strong organic anion transporting polypeptide (OATP) 1B1 inhibitors. - Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with elagolix. Compared to placebo, subjects treated with elagolix in the Phase 3 trials had a higher incidence of depression-related adverse reactions (2.7% with 150 mg once daily, 6.1% with 200 mg twice daily, and 2.3% with placebo) and mood changes (5.7% with 150 mg once daily, 5.2%	- All risks can be mitigated with labeling alone (including a medication guide). None require Risk Evaluation and Mitigation Strategies to ensure the benefits of Orilissa outweigh the risks. - Orilissa will be contraindicated in women who are pregnant. If pregnancy is confirmed, treatment with elagolix should be discontinued. If pregnancy is suspected, pregnancy testing should be performed. - The Applicant will conduct a pregnancy registry and an epidemiologic surveillance study as postmarketing requirements to assess pregnancy-related outcomes. - There will be a Warning for bone loss. Orilissa will be contraindicated in women with known osteoporosis. For those with normal liver function or mild impairment, treatment duration will be limited to 6 months for Orilissa 200 mg twice daily and to 24 months for Orilissa 150 mg once daily (24 months of treatment with 150 mg once daily is expected to lead to about the same amount of bone loss as 6 months of treatment with 200 mg twice daily). There will be different recommendations for women with more severe

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk and Risk Management (continued)</u>	with 200 mg twice daily, and 3.4% with placebo). Subjects who have a history of suicidality or depression also had a higher incidence of depression compared to subjects without such history. • In the Phase 3 trials, there was a dose-dependent elevation of serum alanine aminotransferase (ALT) to at least 3-times the upper limit of normal with Orilissa compared to placebo (0.2% with 150 mg once daily, 1.1% with 200 mg twice daily, and 0.1% with placebo). • In the Phase 3 trials, common adverse reactions (incidence $\geq$ 5% in either Orilissa dose group and greater than with placebo) included hot flushes or night sweats, headache, nausea, insomnia, amenorrhea, anxiety and arthralgia. • In the Phase 3 trials, 12% of Orilissa-treated subjects and 1% of placebo-treated subjects who had low density lipoprotein cholesterol (LDL-C) of 130 to 159 mg/dL at baseline had an increase in LDL-C to 190 mg/dL or higher. Four percent of Orilissa-treated subjects and 1% of placebo-treated subjects who had serum triglycerides of 150 to 300 mg/dL at baseline had an increase in serum triglycerides to at least 500 mg/dL, without pancreatitis.	hepatic impairment and in the setting of certain drug-drug interactions because of increased elagolix exposures ^{(b) (4)} • Because of high systemic concentrations, Orilissa will be contraindicated in patients with severe hepatic impairment and in those using strong OATP 1B1 inhibitors. • There will be a Warning for prescribers and information in the medication guide about mood effects, recommending immediate medical attention for suicidal ideation and behavior, prompt evaluation if depressive symptoms occur and for the prescriber to determine whether the risk of continuing treatment outweighs the benefit. • There was no evidence of severe drug-induced hepatotoxicity in the clinical program. Because of the transaminase elevation, there will be a Warning in labeling and information in the medication guide recommending prompt evaluation if there are signs or symptoms of liver injury. • We are requiring enhanced pharmacovigilance for postmarketing monitoring of hepatic-related adverse events. • The other common adverse reactions and the effects on lipid parameters will be labeled.

ALT = alanine aminotransferase, BMD = bone mineral density, CI = confidence interval, GnRH = gonadotropin-releasing hormone, LDL-C = low density lipoprotein cholesterol, OATP = organic anion transporting polypeptide

1.4. Patient Experience Data

	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
X	Clinical outcome assessment (COA) data, such as	
	X Patient reported outcome (PRO): • Primary efficacy endpoints (dysmenorrhea, non-pelvic menstrual pain) and a secondary efficacy endpoint (dyspareunia) • Patient global impression of change (PGIC)	The PGIC was discussed in the Integrated Summary of Efficacy (ISE, Module 5.3.5.3), referencing IND 064802
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
X	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	ISE, referencing IND 064802
	☐ 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

Endometriosis is a chronic condition characterized by the presence of endometrial-like tissue outside of the uterus that affects approximately 11% of women of reproductive age.¹ The condition is variable in its extent and symptoms. Significant pelvic anatomic disruption can be relatively asymptomatic for some women while a small focus can result in moderate to severe chronic pain for others. Endometriosis-related pain can be disabling, adversely impacting daily activities, sexual activity, partner relationship, and mental health. The symptoms of endometriosis consist of dysmenorrhea (DYS), nonmenstrual pelvic pain (NMPP), dyspareunia (DYSP), and infertility. Other symptoms may arise if endometriosis affects the gastrointestinal and urologic systems. Distant migration of endometriotic implants to the lung, giving rise to respiratory systems, has also been reported. Rare cases of ovarian and peritoneal carcinoma have developed in foci of endometriotic tissue.

Multifactorial etiologies have been proposed as causes for endometriosis. These include retrograde menstruation, transformation of peritoneal cells, vascular transport of endometrial cells, and immune disorders.

Risk factors include nulliparity, delayed menarche, high estrogen levels, family history, and uterine anomalies that prevent normal passage of menstrual flow.

2.2 Analysis of Current Treatment Options

The primary treatment objective in women with endometriosis is the management of pain, using both pharmacologic and surgical approaches. In addition to FDA-approved therapies for endometriosis (listed below), off-label therapies, used in decreasing frequency, include combined oral contraceptives, high-dose progestins, and aromatase inhibitors. Combined oral contraceptives are often prescribed with non-steroidal anti-inflammatory drugs (NSAIDs), both of which are approved for the treatment of dysmenorrhea as first-line therapy. Opioid analgesics are reserved as a second-line treatment.

Surgical management includes laparoscopic excision, fulgeration, and laser ablation of endometriosis lesions, drainage or resection of endometriomas, resection of rectovaginal nodules, lysis of adhesions, interruption of nerve pathways (e.g., laparoscopic uterosacral nerve ablation or presacral neurectomy), and hysterectomy with bilateral oophorectomy. Conservative surgical therapy may be used as a first-line option or following failed medical

¹ Buck Louis, GM, ML Hediger, CM Peterson, M Croughan, R Sundaram, J Stanford, Z Chen, VY Fujimoto, MW Varner, A Trumble, LC Giudice, and ENDO Study Working Group, 2011, Incidence of endometriosis by study population and diagnostic method: the ENDO study, 96(2):360-365.

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therapy. However, recurrence of symptoms within 6 to 12 months is common following conservative surgery.²

Presented in Table 2 are drug products approved for the management of endometriosis, by chronological order of approval.

Table 2. Summary of Approved Treatment Armamentarium for Endometriosis

Product Name	Relevant Indication	Year Approved	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Danazol (NDA 017557) ^a Oral capsule	Treatment of endometriosis amenable to hormonal management	1976	400 mg BID in patients with moderate to severe disease 100 to 400 mg BID in patients with mild disease	Not described in labeling; Literature ^b noted improvement in symptoms and in reduction in endometriotic implants (based on second-look laparoscopy and histology)	Contraindications: Undiagnosed vaginal bleeding Markedly impaired hepatic, renal, or cardiac function Pregnancy/breastfeeding Porphyria Active or history of thrombosis or thromboembolic disease Androgen dependent tumor Warnings: Thrombotic events including strokes Peliosis hepatis and benign hepatic adenoma Intracranial hypertension Lipoprotein changes Androgen effects Precautions: Fluid retention Use with caution in patients with diabetes mellitus Increases in liver transaminases Drug interactions with warfarin, carbamazepine, cyclosporine, statins Interference with some laboratory assays

Continued

^a The Applicant requested the withdrawal of this NDA in 2011; the FDA announced the withdrawal on July 19, 2013 (78 FR 43210). In a review dated December 21, 2017, DBRUP determined that the drug was not withdrawn from sale for reasons of safety or effectiveness.

^b Dmowski WP and MR Cohen, 1975, Treatment of endometriosis with an antigonadotropin, Danazol. A laparoscopic and histologic evaluation, *Obstet Gynecol*, 46(2):147-154.

² Giudice LC, 2010, Clinical practice. Endometriosis, *N Engl J Med*, 362(25):2389-2398.

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Table 2. (continued) Summary of Approved Treatment Armamentarium for Endometriosis

Product Name	Relevant Indication	Year Approved	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Goserelin acetate (NDA 19726)	Management of endometriosis	1989	3.6 mg SC implant placed q 28 days Duration of treatment limited to 6 months Optimal drugs, dose and duration has not been established	Active controlled trial, goserelin vs. danazol 800 mg QD for 6 months Active controlled trial, goserelin vs. danazol 600 mg QD for 6 months Reduction in pain (b) (4) and decreasing the size of endometrial lesions as determined by laparoscopy	Contraindications: Pregnancy Warnings and Precautions: Use nonhormonal contraception Hyperglycemia and increased risk of developing diabetes Adverse Reactions: Loss of bone mineral density Hypoestrogenism Changes in serum lipids
Leuprolide Acetate (NDA 20011)	Management of endometriosis including pain relief and reduction of endometriotic lesions	1990	3.75 mg IM q month Initial treatment is limited to 6 months Duration of retreatment is limited to 6 months	Two active-controlled trials vs. danazol 800 mg/d for 6 months Reduction in pain using modified B&B scale ^c and in reducing endometrial implant size as evidenced by laparoscopy	Contraindications: Undiagnosed abnormal vaginal bleeding Pregnancy/breastfeeding Warnings: Loss of bone mineral density Worsening depression and memory disorders Hypersensitivity Breakthrough bleeding/risk of pregnancy Convulsions

Continued

^c The Biberoglu and Behrman scale includes three symptoms – dysmenorrhea (DYS), dyspareunia (DYSP), and chronic pelvic pain not related to menses (non-menstrual pelvic pain, NMPP), and two signs – pelvic tenderness and induration, each of which are graded on a scale from 0 to 3 or 4, with higher numbers indicating more severe symptoms.

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Table 2. (continued) Summary of Approved Treatment Armamentarium for Endometriosis

Product Name	Relevant Indication	Year Approved	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Leuprolide Acetate (NDA 20708)	Management of endometriosis including pain relief and reduction of endometriotic lesions	1997	11.25 mg IM q 3 months Initial treatment (± add-back therapy) is limited to 6 months Retreatment may be given for 6 months only with add-back therapy if symptoms recur Do not use alone for retreatment Total duration of therapy not to exceed 12 months with add-back	PK/PD study; 3-month injection vs. leuprolide monthly injection relieved clinical signs and symptoms of endometriosis.	See leuprolide monthly injection above
Nafarelin Acetate (NDA 19886)	Management of endometriosis including pain relief and reduction of endometriotic lesions	(b) (4)	1 spray (200 µg) in nostril in AM; 1 spray in alternate nostril in PM May be increased to 800 µg/day (1 spray per nostril q 12 hours) if amenorrhea not achieved Treatment duration beyond 6 months not recommended	Active-controlled trial, 400-800 µg/day vs. danazol 800 mg/day for 6 months Active-controlled trial, 400 µg/day vs. leuprolide 3.75 mg IM Reduction in pain (b) (4) and reduction of endometrial implant size as determined by laparoscopy	Contraindications: Undiagnosed abnormal vaginal bleeding Pregnancy/breastfeeding Warning: Use nonhormonal contraception Precautions: Loss of bone mineral density Hypoestrogenism Changes in serum lipids Worsening of depression symptoms

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Table 2. (continued) Summary of Approved Treatment Armamentarium for Endometriosis

Product Name	Relevant Indication	Year Approved	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Medroxy-progester-one Acetate (NDA 021583) Suspension for injection	Management of endometriosis-associated pain	2005	104 mg SC q3 months x 2 No data on persistence of benefit with longer treatment	2 active-controlled trials vs. leuprolide for 6 months Reduction in pain using modified B&B scale	Contraindications: Undiagnosed vaginal bleeding Known or suspected pregnancy Known or suspected malignancy of the breast Active thrombophlebitis, current or history of thromboembolic disorders, or cerebral vascular disease Significant liver disease Warnings: Loss of bone mineral density Thromboembolic disorders Breast cancer risk Ocular disorders Ectopic pregnancy Bleeding irregularities Precautions: Fluid retention Weight gain Depression Injection Site Reactions Decreased glucose tolerance Liver dysfunction Interference with some laboratory test results

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Table 2. (continued) Summary of Approved Treatment Armamentarium for Endometriosis

Product Name	Relevant Indication	Year Approved	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Leuprolide acetate; norethindrone acetate (NEA) - copackaged (NDA 203696 Lupaneta Pack)	Initial management of the painful symptoms of endometriosis Management of recurrence of symptoms	2012	Leuprolide 3.75 mg IM q month + NEA 5 mg QD Leuprolide 11.25 mg IM q 3 months + NEA 5 mg QD Use longer than 12 months is not recommended	Active-controlled trial Lupaneta vs. Leuprolide 3.75 mg IM monthly x 12 months Open-label, single-arm study Lupaneta x 12 months Assessed reduction in pain (b) (4)	Contraindications: Undiagnosed abnormal uterine bleeding Pregnancy/breastfeeding Known, suspected or history of breast or other hormone-sensitive cancer Thrombotic or thromboembolic disorders Liver tumors or liver disease Warnings and Precautions: Loss of bone mineral density Use nonhormonal contraception Discontinue in case of proptosis, diplopia or migraine Recurrence of depression Assess and manage risk factors for cardiovascular disease before starting Fluid retention Initial flare of endometriosis symptoms Convulsions

SC = subcutaneous, BID = twice daily, IM = intramuscular, B&B = Biberoglu and Behrman scale, PK/PD = pharmacokinetic/pharmacodynamic, NEA = norethindrone acetate, q = every

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Elagolix is a new molecular entity that is being developed for the treatment of pain with endometriosis (IND 064802) and heavy menstrual bleeding due to uterine fibroids (b) (4).

In this submission, elagolix, as monotherapy, is evaluated for its effect on dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP) in women with endometriosis-associated pain (EAP). Because the use of elagolix alone is limited by the adverse effect of estradiol suppression on bone mineral density, add-back therapy for EAP, consisting of elagolix with estradiol and norethindrone acetate, is currently being developed under (b) (4).

3.2. Summary of Presubmission/Submission Regulatory Activity

The clinical development of elagolix has been conducted under IND 064802, which was opened on July 21, 2013. AbbVie, Inc. (formerly Abbott Laboratories) in-licensed the compound from Neurocrine Biosciences, Inc. (NBI) in June 2010.

In an October 6, 2006, guidance meeting, the Division recommended that diagnosis of endometriosis be based on laparoscopic confirmation, preferably by pathology from tissue biopsy, within 60 months of treatment in Phase 3 studies. The Division also recommended daily pain assessment using a modified Biberoglu and Behrman (B&B) scale instead of a Visual Analog Scale, in accordance with the leuprolide and depot medroxyprogesterone acetate clinical programs.

In the March 28, 2011, End-of-Phase 2 meeting, the Division conveyed the following:

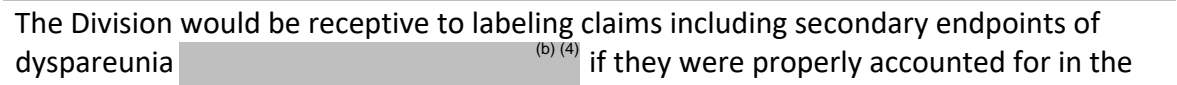
- General agreement with the proposal to demonstrate efficacy support with two randomized, placebo-controlled, 6-month efficacy trials in adult premenopausal women (aged 18 to 49 years) who have laparoscopy-confirmed endometriosis and moderate to severe endometriosis-associated pain.
- Agreement with the proposed co-primary endpoints: the proportion of responders at (b) (4) in pain scores assessed by the daily modified pain scale for dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP). Elagolix will need to demonstrate a statistically significantly (2-sided alpha of 0.05) greater proportion of responders for both dysmenorrhea and NMPP for a study to be considered successful.
- Agreement with the use of a responder analysis, such as the Patient Global Impression of Change (PGIC) scale. However, the definition of a responder should be based on the magnitude of reduction in pain that is clinically meaningful to women being treated. The Division prefers a cut point in the PGIC between those who report “moderately or very improved” compared to those who report “minimally improved or worse.”
- The responder definition for benefit should also be determined during the study, through an appropriate anchor question derived from treatment and receiver operator characteristics (ROC) methodology. Therefore, criteria should be proposed for

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determining that the responder rate difference is both clinically and statistically significant for the study to be declared successful.

- Agreement with the plans to conduct the ROC analysis on data pooled from both efficacy studies, then to calculate the response criterion individually for dysmenorrhea and for NMPP.
- With respect to evaluating bone mineral density (BMD), the Division noted that:
 - DXA results at the spine and hip are of equal interest. Hip BMD is of concern due to the potential risk of hip fracture.
 - Interpretation of changes at one year of treatment may be difficult in the absence of a placebo control arm, particularly since younger subjects, who have not attained peak bone mass, would be expected to have a positive change in BMD over time.
 - Persistent decrements in BMD at the month 12 post-treatment follow-up evaluation and BMD loss that did not show resolution after a year off treatment would be of concern.

In a September 23, 2011, guidance meeting, the Division noted the following:

- Agreement with evaluation of efficacy at 3 months to minimize the impact for possible unblinding and disproportionate early discontinuation in the placebo arm. However, persistence of efficacy at 6 months would also be required for approval.
-  (b) (4)
- 
- The Division would be receptive to labeling claims including secondary endpoints of dyspareunia  (b) (4) if they were properly accounted for in the statistical analysis plan and the overall type 1 error is preserved.
- The Division requested that at least 50% of Phase 3 subjects be enrolled at study sites in the U.S. or Canada.

A Phase 3 protocol (Study M12-665) was submitted on February 2, 2012, for Special Protocol Assessment. In a non-agreement letter dated March 19, 2012, the Division disagreed with numerous aspects of the protocol  (b) (4)

In an April 24, 2012 Type A meeting to discuss the Special Protocol Assessment review, the Division agreed with the proposed plan to limit rescue analgesics to two medications—naproxen 500 mg and hydrocodone 5 mg/acetaminophen 325 mg (or global equivalents in countries where these two medications are not available). In collaboration with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), the Division noted that, subjects

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identified as responders based on the ROC analysis of pain scores should be reclassified as non-responders if they had a 15% or greater increase in average daily dose of rescue analgesic. The Division further requested an additional secondary analysis to evaluate the proportion of subjects in each treatment arm who experience improvement in pain ranging from 0 to 100%, as a cumulative distribution. The Applicant opted to reach agreement with the Division through “informal discussions” rather than submitting a revised protocol for a second Special Protocol Assessment review.

In a May 23, 2013 advice letter, the Division agreed with extending the laparoscopic diagnosis interval to 10 years (from (b) (4) years) for the trial eligibility criteria. The Division continued to disagree (b) (4)

In preliminary responses dated March 6, 2014, in response to a guidance meeting request (which the Applicant canceled prior to the meeting), the Division explicitly disagreed with the proposal (b) (4)

The Division also disagreed (b) (4)
PGIC is not considered a well-defined and reliable measure of endometriosis-associated pain. The Division encouraged evaluating dyspareunia as a key secondary endpoint that could support a labeling claim, by moving dyspareunia higher in the list of ranked secondary endpoints.

In preliminary responses dated December 5, 2016, in response to a pre-NDA meeting request (which the Applicant canceled prior to the meeting), Division generally agreed with the proposed format and content of the planned NDA submission.

In a January 4, 2017 advice letter, the Division recommend that, for both Phase 3 trials (Studies 665 and 671), the Applicant provide additional analyses. Specifically, the Applicant was recommended to use all modified intent-to-treat (mITT) subjects, pooled across all study arms and irrespective of treatment assignment. With these data, the Applicant should produce the empirical cumulative distribution functions (CDF) for the changes from baseline to month 3 in the dysmenorrhea (DYS) score and the non-menstrual pelvic pain (NMPP) score, using the PGIC as an anchor for both.

The NDA was submitted on August 23, 2017, with a request for Priority Review because elagolix will treat a serious condition (endometriosis with associated pain) and provide a significant improvement in safety compared to available therapies, such as opioids.

On October 13, 2017, the Division notified the Applicant that the review of this application was classified as Priority, with a user fee goal date of April 23, 2018.

In January 2018, the Division sought information regarding a liver case that was close to meeting the criteria for Hy’s law case and requested detailed, hepatic safety analyses on data from all Phase 2 and 3 trials (including the ongoing trials for the uterine fibroid indication). The Applicant’s extensive response, submitted on March 19, 2018, was deemed a major

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amendment to the application. On March 26, 2018, the Division informed the Applicant that the goal date would be extended by 3 months to July 23, 2018.

3.3. Foreign Regulatory Actions and Marketing History

Elagolix is not marketed in other countries.

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

4.1. Office of Scientific Investigations

The Office of Scientific Investigations (OSI) was consulted for this NDA. Five clinical sites participating in the two 6-month efficacy trials and the two extension trials were inspected.

Site 45069, Alvadore Osborn, DO, West Des Moines, Iowa, was selected due to involvement in all four studies, a moderate treatment effect, and low rate of protocol violations. The inspection did not identify any objectionable conditions or practices that would justify enforcement action. On May 15, 2018, this site was classified as no deviation from regulation (NAI).

Site 51673, Krzysztof Wilk, MD, PhD, Katowice, Poland, was selected due to the highest risk rank score identified by the Site Selection Tool, treatment effect, and low rates of discontinuations and protocol violations. The inspector noted no evidence of underreporting of adverse events, but issued a Form 483, FDA Establishment Inspection Report, noting that an ineligible subject (having only mild endometriosis pain) was enrolled and treated with the study drug. After reviewing Dr. Wilk's response to the inspectional finding, OSI made a preliminary determination on March 1, 2018 that the subject likely did not have an impact on the study's safety or efficacy results.

Site 53501, Shivkamini Somasundaram, MD, Columbus, Ohio, was selected due to high enrollment in Study M12-671 and an overall second highest risk rank per the Site Selection Tool. The inspection did not identify any objectionable conditions or practices that would justify enforcement action. On April 26, 2018, this site was classified as NAI.

Site 17011, James Simon, MD, Washington, DC, was selected due to high enrollment in Study M12-671 and an overall third highest risk rank score per the Site Selection Tool. A Form 483, FDA Establishment Inspection Report, was issued because of failure to conduct the investigation in accordance with the investigator's signed statement and investigational plan concerning one subject. After reviewing all pertinent records and Dr. Simon's response to the Inspectional Observation, OSI determined that the study had been conducted adequately and

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the data generated by this site could be used in support of the indication. Per a memorandum dated April 20, 2018, this site was classified as Deviation(s) from regulations (VAI).

Site 52473, David Young, MD, Pleasant Grove, Utah, was selected due to a large treatment effect in Study M12-665. A Form 483, FDA Establishment Inspection Report, was issued, citing several protocol violations, including enrolling a subject who was ineligible per protocol and recording the intake of prohibited medication by the wrong subject. After reviewing all pertinent records and Dr. Young's response to the inspection findings, OSI determined that the study had been conducted adequately and the data generated by this site could be used in support of the indication. Per a memorandum dated May 18, 2018, this site was classified as VAI.

Despite the regulatory violations noted at Drs. Simon's, Wilk's, and Young's sites, OSI concluded in a March 1, 2018 summary memorandum that the findings at these three sites were unlikely to significantly impact data reliability.

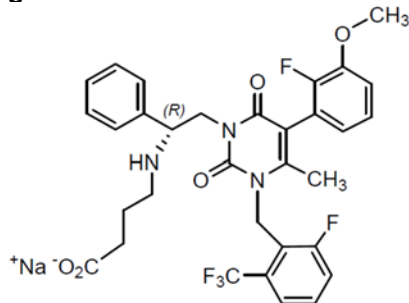
4.2. Product Quality

The review team from the Office of New Drug Products (ONDP)/Division of New Drug Products II recommends approval. ONDP concludes that the Applicant has provided sufficient information to assure the identity, strength, purity, potency, and bioavailability of the drug product, at release and throughout the proposed expiration dating period of 24 months.

Drug Substance

Elagolix sodium is a small synthetic molecule. The chemical name of elagolix is sodium 4-((1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-[[2-fluoro-6-(trifluoromethyl)phenyl]methyl]-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl)amino) butanoate. Its chemical structure is shown in Figure 1.

Figure 1. Chemical structure of elagolix



Drug Product

The drug product is a film-coated, immediate-release tablet containing 150 mg or 200 mg of elagolix, equivalent to 155.2 mg or 207.0 mg of elagolix sodium, respectively. There are no

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novel excipients, nor are there any impurities of concern.

Facilities

Drug substance for commercial tablets is manufactured by AbbVie Singapore Pte. Ltd. While this facility initially appeared to be high risk, it was subsequently found acceptable to carry out the proposed functions described in the NDA. (b) (4)

The drug product is manufactured by AbbVie Ireland and packaged at AbbVie, N. Waukegan Rd., Chicago. Release and stability testing are performed at the AbbVie Sheridan Rd. facility. All three facilities have been found “acceptable for the functions and responsibilities listed in the application.”

An Overall Inspection Recommendation of APPROVE was issued on January 9, 2018.

Environmental Assessment

Due to the hormonal activity triggered by the active moiety, the Applicant has not requested categorial exclusion from the environmental assessment, citing FDA’s Estrogenic, Androgenic, or Thyroid Activity Guidance.³ The final environmental assessment was submitted by the Applicant in a June 29, 2018 amendment. Based on an evaluation of the information provided by the Applicant, the ONDP team concluded that “no significant adverse environmental impacts are expected” if the product is approved. The ONDP team filed a Finding of No Significant Impact report on July 11, 2018, and recommends using labeling to provide guidance regarding environmentally protective disposal practices.

(b) (4)

The Applicant has made the following post-approval stability commitments:

- To continue the long-term stability testing of the primary stability batches manufactured by AbbVie, North Chicago (b) (4) through the expiration dating period granted at approval of application (b) (4)
- To continue the accelerated stability testing of the primary stability batches manufactured (b) (4)
- To place the first three commercial batches of the drug product at each tablet strength and each packaging configuration on long-term stability.
- To annually place one production batch of each tablet strength and of each packaging configuration, if manufactured, on long-term stability.
- To report to the FDA as per 21 CFR 314.81(b)(1)(ii) any batches of drug product that fall outside of the approved specification.

³ FDA 2016 Guidance for Industry, Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. <https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf>

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ONDP found these commitments to be satisfactory.

4.3. Clinical Microbiology

This section is not applicable because the proposed product is an oral tablet.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable; there are no issues related to devices or companion diagnostics.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Proposed clinical use:

The maximum recommended human dose (MRHD) for elagolix (code name NBI 56418) is 200 mg BID. The proposed maximum duration of use for the high dose is 6 months. For purposes of calculating multiples of exposure (MOEs) compared to the MRHD, the human C_{max} value used is for a single 200 mg dose: 774 ng/mL (1.2 μ M). The area under the concentration-time curve (AUC) for a single 200 mg dose in humans is 1725 ng*hr/mL. This value is doubled to reflect the BID dosing and to give the approximate exposure over 24 hrs: 3450 ng*hr/mL (5.5 μ M*hr), which is the value used for comparison to daily animal dosing.

Characterization of the drug substance impurities:

The elagolix drug substance has many impurities that have structural alerts for genotoxicity, which led to an extensive program of impurity testing (reviewed under IND 64802; see reviews dated November 22, 2017 and December 19, 2017). Some compounds were tested using a non-standard, 6-well Ames format that was deemed acceptable. During review, attention was paid to verifying that testing was sufficient to rule out false negatives. Consultation with the CMC reviewer verified that (b) (4) impurities are controlled to appropriate levels. Qualification of specified impurities was achieved in repeat-dose toxicity studies, and in a 6-week dietary study in the rat using spiked feed.

Adequacy of the nonclinical development program:

The pharmacology and toxicology of elagolix was adequately characterized in a standard full nonclinical development program. The pivotal safety pharmacology and repeat-dose toxicity studies were conducted in rats and dogs. Reproductive toxicity studies were conducted in rats and rabbits, and standard two-year carcinogenicity studies were conducted in mice and rats.

Pharmacology:

The mechanism of action of elagolix is antagonism at the GnRH receptor. Elagolix binds reversibly with high affinity to the human GnRH receptor ($K_d = 54$ pM) and inhibits GnRH action

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in vitro in functional assays with K_i values in the low nM range (1.5, 2.8nM). The rank order of binding across species is: human > monkey ~ rabbit >>> rat. There were no binding studies conducted against the dog GnRH receptor. Functional assays demonstrated activity at the rabbit, monkey, and human GnRH receptors.

Efficacy of elagolix was not assessed in nonclinical species for several reasons:

- (1) there are no animal models of endometriosis
- (2) binding of elagolix to the GnRH receptor in nonclinical species was weak (rat, rabbit) or not characterized (dog, mouse)
- (3) sufficient exposure could not be achieved with repeat dosing (monkey)

Receptor-mediated pharmacological effects were largely absent in nonclinical species. These included (when they were measured) reductions in LH, FSH, estrogen or testosterone, or changes in reproductive organs that would be expected from prolonged reductions in sex steroids. BMD was not measured in any nonclinical species. Toxicity that might result from prolonged reduction of sex steroids could not be reliably assessed in nonclinical studies due to low affinity of elagolix at the GnRH receptor in the nonclinical species. However, the pivotal nonclinical studies are deemed sufficient to evaluate non-receptor-mediated or off-target effects of elagolix.

There were no findings in a screen of 100 receptors for off-target binding of elagolix.

Safety pharmacology studies were conducted in rats and monkeys at adequate multiples of exposure (> 20) and were negative. In agreement with nonclinical findings, a clinical thorough QT study was negative for arrhythmia risk.

Absorption, Distribution, Metabolism, Excretion (ADME):

The pharmacokinetics of elagolix were determined in CD-1 mice, Sprague Dawley rats, Beagle dogs and cynomolgus monkeys. In vivo absorption, distribution, metabolism and excretion (ADME) studies were conducted in rats and dogs with radiolabeled compound and compared to absorption, metabolism, and excretion studies conducted with [^{14} C]elagolix in humans.

The pharmacokinetic profile of elagolix was generally characterized by rapid absorption, high plasma clearance, moderate volumes of distribution and a short elimination half-life in mouse, dog, and monkey. Bioavailability ranged from ~10% (mouse and monkey) to 100% (dog). Humans and rats had similar bioavailability (~50%). Protein binding ranged from 78 to 90% across species.

Distribution after oral dosing was primarily to the gastrointestinal tract. Elagolix did not cross the blood brain barrier, did not accumulate in pigmented tissue, and did not partition into red blood cells. It did, however; freely cross the placenta (assessed in the rat).

Elagolix is not extensively metabolized, circulating primarily as unchanged drug in plasma and remaining largely intact through clearance. Metabolic pathways were similar across species

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including humans. There were no major metabolites in any species (although M14 and M15 were borderline major in the rat), and no unique human metabolites. There were six active metabolites. The two most significant were the O-demethyl metabolite (M3, code name NBI 61962), and N-dealkyl metabolite (M6x, code name NBI 54048). M3 has a binding affinity comparable to elagolix, and M6x has a 6-fold *higher* affinity. These metabolites were monitored throughout the nonclinical development program and were verified to remain below 10% of parent across species.

Clearance of elagolix was primarily via the fecal route. Excretion into milk was not determined.

In vitro and in vivo studies demonstrated the following potentially clinically relevant interactions of elagolix with metabolizing enzymes and drug transporters: elagolix is a substrate for cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp), and organic-anion-transporting polypeptide (OATP) 1B1. Elagolix is also a weak to moderate inducer of CYP3A and CYP2B6, and an inhibitor of P-gp and OATP1B1 and OATP1B3.

In vitro metabolism studies were conducted with the two active metabolites, M3 (O-demethyl metabolite) and M6x (N-dealkyl metabolite). The most significant potential effect was inhibition of CYP3A4/5, CYP2C9, and CYP2C19 by M6x. However, concentrations of this metabolite would have to reach micromolar levels for inhibition to become significant, which is not clinically relevant.

Toxicokinetics of elagolix were similar in mice, rats, dogs, and humans. Exposure was proportional or somewhat greater than proportional to dose, there were no strong gender differences, and there was no evidence of accumulation. Toxicokinetics were strikingly different in rabbit and monkey. In the rabbit, repeat dosing in the dose range of < 300 mg/kg led to dramatic increases in exposure that were not associated with accumulation. In the monkey, repeat dosing led to a dramatic reduction in exposure that was unexplained.

Toxicology:

Single and repeat-dose toxicology studies were conducted in mice, rats, rabbits, dogs, and monkeys. The Sprague Dawley rat and Beagle dog were chosen for the pivotal repeat-dose toxicology studies based on the ability to achieve higher systemic exposures when compared to mice and monkeys. However, as was previously discussed, affinity of elagolix for the rat GnRH receptor was poor (~1000-fold less compared to humans), and receptor affinity in the dog was not measured.

In the rat, elagolix would have to reach free concentrations in the range of 12 μ M (C_{max} = 7740 ng/mL) to fully inhibit the GnRH receptor. The highest plasma concentration (C_{max}) seen in the rat was at a single dose of 2000 mg/kg (~60 μ M or ~6 μ M free). For that reason, the toxicities seen in the rat pivotal studies should generally be interpreted as being non-receptor-mediated. The toxicities seen in the dog pivotal studies should also be interpreted as possibly being non-receptor mediated, since few or no pharmacodynamic effects were observed even at high doses.

Single dose studies:

Single dose toxicity studies were conducted in rats and monkeys at the same doses: 300, 600, 1200, or 2000 mg/kg with ~4-fold higher exposures achieved in the monkey than the rat per unit dose. The dose at which no adverse effects were observed (no observed adverse effect level or NOAEL) was 300 mg/kg for both species, but maximum tolerated doses (MTDs) diverged, being set at the low dose for the monkey and the high dose for the rat.

Repeat-dose studies:

A significant feature of the repeat-dose studies that complicated interpretation of the results was mortality that was apparently related to the drug formulation and not the toxicity of elagolix itself. In the rat 2-week study, there was ~50% mortality at the high dose (1200 mg/kg/d) that was attributed to gavage error or aspiration of the dose that resulted in ulcerative tracheitis/bronchitis. The subsequent repeat-dose studies (6-, 13-, and 26-week) reduced the high dose to 600 mg/kg/d but still had significant dose-related mortality (sometimes > 50% at the high dose). The main clinical sign was respiratory distress with confirmatory histological findings in the trachea and bronchi.

In the dog, mortality associated with dosing error/aspiration of test article was observed in both the 6-week (high dose 300 mg/kg/d) and 26-week (high dose 150 mg/kg/d) studies, and led the sponsor to reformulate the drug as a capsule for the 9-month study. In that study, a high dose of 150 mg/kg/d was administered without mortality.

Putting aside the mortality in the repeat-dose studies that was likely due to aspiration leading to respiratory toxicity, the overall toxicity profile of elagolix is fairly benign and is summarized below by species.

RAT:

In the rat, the highest oral dose administered in the 6-, 13-, and 26-week studies was 600 mg/kg/d. The NOAEL decreased with increasing duration in each study, from 600 to 300 to 100 mg/kg/d; exposures corresponded to 19, 11, and 2-fold the MRHD, respectively.

There were no new toxicities in the 26-week studies that had not appeared in the shorter duration studies, but not all toxicities were consistently present. Liver toxicity, which manifested in the 13-week study as increased liver weight (up to 45%), mild hepatocellular hypertrophy, and elevated enzymes (< 3-fold) at the high dose, were not reported in the 26-week study. Inconsistent changes in adrenal weights in the shorter duration studies were not seen in the 26-week studies. Elevations in platelets and reticulocytes observed in shorter duration studies were also not observed in the 26-week study.

Estradiol and testosterone levels were assessed in the 6-week study and, unsurprisingly, were found to be highly variable. For that reason, the sponsor did not attempt to draw any conclusions about the effect of elagolix on sex hormone levels in the rat.

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Studies by the dietary route were conducted at 6, 15, and 28-week durations. These studies were conducted to qualify impurities, determine dose-ranging for carcinogenicity studies, and bridge from the liquid formulation. The highest dose administered in these studies was 800 mg/kg/d. As expected, exposures by the dietary route were less than by oral gavage for a given dose. However, maximum exposures still reached ~9-fold the human MRHD.

A unique adverse finding in the 28-week dietary study was reported: focal degeneration/necrosis localized to the limiting ridge of the glandular stomach at both test doses (600 and 800 mg/kg/d). Erosion, inflammation, ulceration, and hyperplasia were noted, and the applicant suggested that this finding might explain the minimally lower hemoglobin (Hb) and hematocrit (Hct), and mildly elevated white blood cell counts. In the 2-year carcinogenicity study (top dose 800 mg/kg/d), dose-dependent erosion and hyperkeratosis were noted in the stomach. The limiting ridge is a structure unique to the rat, and microscopic findings in the stomach were not noted in other species. Relevance to humans is therefore low.

DOG:

In the dog, the highest dose administered in the 6- and 26-week studies by gavage was 300 mg/kg/d, and the NOAELs were similar: 50 and 75 mg/kg/d, respectively. Exposures were higher than in the rat per unit dose, and reached an MOE of 23 based on AUC at the higher NOAEL. However, continuing problems with aspiration of the liquid formulation led the applicant to reformulate elagolix as a capsule for the pivotal 9-month study. The NOAEL in the longer duration study was 30 mg/kg/d (MOE = 8).

The pattern of toxicity in the dog was similar to that in the rat. Body weights were reduced ~20% for both males and females at the high dose. There were reactive changes in the liver that were reflected in elevated alkaline phosphatase (7.5-fold max) and increased organ weight. There were mild reductions in Hb and Hct and slight elevations in white blood cells. Relative spleen weight was reduced, but there were no corresponding histological findings. There was gallbladder irritation at the high dose that recovered.

The only pharmacodynamic signal in the dog was reduced prostate weight in the 9-month study (up to 56% at the high dose that did not recover). Estradiol and testosterone levels were assessed in the 6- and 26-week studies, and no treatment-related effects were noted. Testosterone values were highly variable.

MONKEY:

Use of the monkey as a nonclinical model for the action of elagolix was limited due to unusual toxicokinetics in this species. Repeat-dosing in the monkey led to a very rapid reduction in exposure, the cause of which was not explained by the applicant. Two-, 6-, and 13-week studies were conducted in the monkey using the liquid formulation by oral gavage. The NOAEL for all three studies was the same: 300 mg/kg/d. MOEs were calculated based on exposure at day 1, since exposure fell off by ~50% within 2 weeks of dosing and continued to fall. At the NOAEL, the highest MOE based on AUC was 49.

Findings included modestly increased liver and kidney weights that did not have corresponding histology, were reversible, and were considered reactive and not adverse. At the highest dose tested (600 mg/kg/d), the thymus showed involution and atrophy. An electrocardiographic (ECG) study was included in the 13-week study that was negative, but this finding is not useful since it was conducted at the end of the study when exposures were low.

There was a pharmacodynamic signal of atrophy in the uterus, cervix, and vagina in the 6-week study. No effects were noted in sex organs of the males, but the applicant considered the male animals to be sexually immature. Estradiol and testosterone levels were assessed and found to be highly variable. For that reason, the applicant did not attempt to draw any conclusions about the effect of elagolix on sex hormone levels in the monkey.

Genotoxicity/Carcinogenicity:

Elagolix was not genotoxic by the standard battery of in vitro and in vivo genotoxicity tests. Carcinogenicity was evaluated in 2-year studies in the mouse and rat by the dietary route that achieved exposures of greater than 10-fold the MRHD. Elagolix was not carcinogenic in the mouse. In the rat, liver and thyroid neoplasms were observed that were deemed species specific. The potential for carcinogenic risk in humans is negligible.

Reproductive toxicity:

Fertility and early embryonic development was evaluated in the rat at doses of 30, 150, and 300 mg/kg/d. Mortality in this study followed the pattern of the repeat-dose toxicity studies, that is, with signs of aspiration and respiratory distress. Treatment with elagolix had no effect on reproductive parameters (estrous cycle, reproductive performance, sperm count, sperm motility, pregnancy rate, mating behavior) or observations at Cesarean section related to implantation or embryo-fetal viability. However, as discussed above, these negative findings are likely due to the low affinity of elagolix for the rat GnRH receptor.

The NOAEL for maternal and paternal effects was 50 mg/kg/day. For reproductive performance, fertility, and embryo/fetal viability, no effects (adverse or nonadverse) were observed at any dose, so a NOEL (no observed effect level) was set at ≥ 300 mg/kg/d. With respect to the AUC at the MRHD, the exposure multiple for women based on the AUC at the NOEL of 300 mg/kg/day for the fertility effects in the female rat is ~ 4.6 -fold. However, the applicant calculated that, when adjusted for the difference in affinity of elagolix for the rat and human GnRH receptor, this exposure multiple translates to 0.007-fold, or essentially zero as compared to humans. Thus, this fertility study is not informative for human risk, because the rat reproductive system is insensitive to elagolix.

Teratogenicity of elagolix was evaluated in the rat and the rabbit. There was a striking difference between the rat and the rabbit in the ability to tolerate dosing, possibly due to the large difference in affinity of elagolix for the rat versus the rabbit GnRH receptor (low versus moderate), and/or possibly due to a striking increase in exposure that occurred in the rabbit

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with repeat dosing. In both the rat and rabbit, dose range finding studies were conducted using the liquid formulation by oral gavage to establish the doses for the definitive study. Rats were dosed from gestation day (GD) 6 to GD17 up to 1200 mg/kg/d and rabbits were dosed from GD7 to GD20 up to 600 mg/kg/d. Pregnant rat dams tolerated dosing well but pregnant rabbit dams did not; there was a high rate of mortality and abortion which led to a low and very limited dose range being set for the definitive study.

In the rat, an embryofetal development (EFD) study was successfully completed using doses of 300, 600, and 1200 mg/kg/d. The NOEL for both maternal toxicity and fetal viability and growth was set at less than or equal to the low dose, based on unscheduled deaths in the dams (likely due to aspiration of the test article) and decreased fetal weight and increased post-implantation loss (likely due to reduced feed consumption and body weight loss in the dams). There were no treatment-related external, visceral, or skeletal findings, so the NOAEL for fetal teratogenicity was set at the high dose. Elagolix was shown in distribution studies to freely cross the placental barrier, so it can be assumed that fetuses were fully exposed to the drug. This study was useful for evaluating teratogenicity of elagolix to the developing fetus that was independent of changes in estrogen or progesterone. Using rat AUC values obtained on GD17 compared to the human AUC at the MRHD of 3.5 ug·hr/mL, at 300 mg/kg/day, the MOE is 6.5 and at 1200 mg/kg/day, the MOE is 39.4.

In the rabbit, the definitive EFD study was conducted at lower doses than in the rat, and was conducted over a very limited dose range (100, 150, and 200 mg/kg/d). Exposures at the high dose in this study were roughly comparable to exposures at the low dose in the rat EFD study. There was significant maternal and fetal toxicity at the high dose, as reflected in mortality, abortion, and reduced fetal weight. The NOAEL for maternal toxicity was thus set at the mid dose (MOE = 6.6). One mid-dose and one high-dose dam had litters with no viable fetuses, which resulted in an increase in post-implantation loss at those two doses. Based on these findings plus reduced fetal weight, the NOEL for embryofetal toxicity was the low dose (MOE = 2.7). Fetal external, visceral, and skeletal examinations were negative, indicating no teratogenic effects of elagolix. The NOEL for teratogenicity was set at the high dose (MOE = 11.6).

Taken together, the results from the rat and rabbit EFD studies are informative for human teratogenic risk. Exposures were achieved that were greater than the exposures expected at the MRHD and because elagolix crosses the placental barrier, fetuses can assume to have been exposed. Elagolix was found negative for teratogenicity in both species.

However, the EFD studies are less informative for risk of early pregnancy loss in humans. In the rat, hormones necessary for maintenance of pregnancy were likely not affected, so the lack of effect of elagolix on litter viability does not translate to the human. In the rabbit, the species that is more sensitive to the pharmacological action of elagolix, it was concerning that there were single instances of total litter loss at both the mid and high doses. The applicant has recognized that an effect of elagolix on pregnancy maintenance in the human cannot be ruled out, and appropriately contraindicates its use during pregnancy.

Lastly, a pre- and post-natal development study was conducted in the rat, using the dietary route of administration. Only two, relatively low doses were assessed: 100 and 300 mg/kg/d. Dams were dosed from GD2 through lactation day 20 (LD20). Steady state plasma concentrations measured in dams on LD21 were roughly 10-fold lower than C_{max} concentrations via oral gavage at the same doses. There were minimal findings. The NOAEL for F1 neonatal/early postnatal toxicity/developmental toxicity was 100 mg/kg/d and the NOAEL for toxicity for F1 post-weaning/reproductive toxicity and F2 neonatal/early postnatal toxicity was 300 mg/kg/d. Because AUC data were not generated, calculation of the safety margins could not be made.

Conclusion:

Elagolix has been thoroughly evaluated in a full set of nonclinical toxicity studies. Based on in vitro and in vivo animal data, the safety profile of elagolix does not raise concerns for administration to women at the proposed doses and durations. Appropriate information to inform pregnancy risk will be included in labeling. From the nonclinical pharmacology/toxicology perspective, elagolix can be approved. Refer also to the nonclinical review finalized in DARRTS on May 10, 2018.

5.2. Referenced NDAs, BLAs, DMFs

None; elagolix is a new molecular entity.

5.3. Pharmacology

5.3.1. Primary pharmacology

GnRH is a decapeptide that controls the synthesis and release of FSH and LH from the anterior lobe of the pituitary gland. The pharmacodynamic effects of GnRH receptor antagonists result from reduced levels of the sex hormones estrogen, progesterone, and testosterone, and are well understood for this class of drug. The applicant did not conduct pharmacology studies to specifically characterize the effect of elagolix on levels of sex hormones in animal studies, but did characterize some of these parameters in the repeat-dose toxicology studies.

Mechanism of action

Parent compound – binding to the GnRH receptor and functional activity:

Elagolix binds reversibly with high affinity to the human GnRH receptor. It is a potent antagonist of the mammalian GnRH receptor with a rank order of affinity as follows: human > monkey ~ rabbit >>> rat. There were no binding studies conducted against the dog GnRH receptor. In vitro functional assays (inositol trisphosphate (IP_3) production and calcium flux) demonstrated activity at the rabbit, monkey, and human GnRH receptors.

Table 3. Elagolix binding and in vitro functional assays

Species	K _d (nM) Equilibrium Binding	K _i (nM) Pituitary Membrane Binding	K _i (nM) Cloned Receptor Membrane Binding	IC ₅₀ (nM) Cloned Receptor Function IP ₃ Production	IC ₅₀ (nM) Cloned Receptor Function Ca ⁺⁺ Flux
Rat		566	1046/4400		
Rabbit		3.3	44.5	342	
Monkey	0.39		3.0/3.5	50	
Human	0.054		0.87/0.9	1.5	2.8

Reviewer's table

Metabolites – binding to the GnRH receptor and functional activity:

The pharmacological activity of the primary metabolite of elagolix (M3) as well as M6x, and four additional degradants or metabolites was characterized in in vitro binding assays (cloned receptor membrane binding) and in cell-based functional assays (IP₃ production). Of these, only M6x showed significant affinity for the GnRH receptor. M6x, which is present in humans, monkeys, dogs and rats, was found to have a K_d at the human GnRH receptor of 0.009 nM, which is 6-fold higher than elagolix. All the others tested, which included the enantiomer of elagolix, had significantly lower activity than elagolix. None of these metabolites are expected to affect the pharmacodynamics of elagolix since they are either not formed (elagolix enantiomer) or produced at low levels in humans. Levels of M3 and M6x were monitored throughout nonclinical and clinical testing, and were always found to be low. Mean human C_{max} and AUC values for the M3 and M6x metabolites were approximately 1.7% and 2.4%, and 0.6% and 3.3%, respectively (see Module 2.7.2 Clinical Pharmacology Section 2.7.2.2.1 Table 3 p 15).

Drug mechanism related to indication

Because there are no animal models of endometriosis, there were no mechanistic studies conducted that could be extrapolated to humans. Pharmacodynamic effects of elagolix on plasma hormone levels were assessed in some of the repeat-dose toxicology studies. Bone parameters were not monitored in any of the long duration repeat-dose studies.

5.3.2. Secondary Pharmacology

Of the 100 receptor sites examined, no activity was found with greater than 50% inhibition of binding of the cognate ligand or enzymatic activity at concentrations of 10µM.

5.3.3. Safety Pharmacology

CNS

The neurobehavioral responses to orally administered elagolix were evaluated in a rat modified Irwin assay (functional observational battery) that was conducted using doses of 30, 300 or 1200 mg/kg (n = 10/sex/dose). Satellite groups of 6/sex/dose were used for toxicokinetics (TK). There were no treatment-related effects. NOAEL = 1200 mg/kg. Systemic exposure at this dose level in the rat as measured by C_{max} and AUC₍₀₋₂₄₎ was 10.5 µg/mL and 133 µg*h/mL, respectively in the male, and 31.9 µg/mL and 202 µg*h/mL in the female. The applicant's Pharmacology written summary reports C_{max} at the NOAEL as 21.2 µg/mL, which is the average of the male and female exposures. MOE based on human AUC of 3.5 µg*hr/mL = 48.

Cardiovascular

In vitro hERG and sodium (Na) channel assays: Elagolix and its primary metabolite, M3 (NBI-61692), were tested for their effects on potassium (hERG channel) and sodium currents. hERG channels were expressed in HEK cells, and native Na channels were assessed in rat primary neuronal cell cultures. There were no effects in the therapeutically relevant concentration range. Human C_{max} for a 200-mg dose is 774 ng/mL or 1.2 μ M.

The effect of elagolix on Na current was assessed as part of the non-GLP assay and found negative at up to 10 μ M.

Cardiac action potential assay: Effect of Elagolix on Canine Purkinje Fiber Repolarization In Vitro.

Isolated canine (N = 4) Purkinje fibers were exposed to elagolix sodium: 1, 5, 10 and 50 μ M. Action potential parameters were assessed at stimulation frequencies of 0.5, 1, and 3 Hz. There were no effects in the therapeutically relevant concentration range.

In vivo cardiovascular assays: rat and monkey

Rat: Elagolix was orally administered by gavage to conscious male rats (n = 5/dose and 3/dose for TK) at 600 mg/kg or 1200 mg/kg. Elagolix had no effects on mean arterial pressure, heart rate or the QRS and PR intervals. At 600 and 1200 mg/kg, elagolix caused a slight non-dose-dependent increase in QTc. MOE based on human AUC of 3.5 μ g*hr/mL = 26 and 68 for the low and high doses, respectively.

Monkey: The cardiovascular effects of orally administered elagolix were evaluated in telemetry instrumented male (n = 4) and female (n = 4) monkeys. Doses were 30, 150, or 300 mg/kg (n = 8 per group) and the cardiovascular parameters were monitored continuously for 48 hours. Elagolix had no effect on mean arterial pressure, heart rate, core body temperature, QTc, QRS and PR intervals at all tested doses. Drug administration was associated with emesis, which led to plasma concentrations being highly variable. Blood samples were taken ~4 and 24 hrs post dose. To calculate an MOE, TK data were used from the monkey respiratory safety study described below, which had more extensive sampling. MOE for the high dose based on human AUC of 3.5 μ g/hr/mL = 43. MOE for the high dose based on human C_{max} of 774 ng/mL = 24.

Respiratory:

The respiratory effects of elagolix were evaluated in the conscious monkey using whole body plethysmography. Male (n = 4) and female (n = 4) cynomolgus monkeys were orally administered elagolix at doses of 30, 150 and 300 mg/kg (n = 8 per group). The vehicle and test drug were administered on 4 separate occasions, with 7 days between each treatment. Tidal volume, minute volume, and respiratory rate were collected and recorded one-hour pre-dose and for up to 3.5 hours post-dose and for approximately 1 hour at 24 hours post-dose. Femoral artery blood samples were collected from each animal for TK at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hrs post dose. Parent and active metabolite were measured.

Results: Elagolix had no effect on respiratory rate, tidal volume, or minute volume at all tested doses. Emesis was reported immediately following dosing in all groups. For this reason, exposure may have been underestimated.

TK: Mean of male and female for the parent compound at 300 mg/kg: $C_{max} = 18.5 \mu\text{g/mL}$; $AUC_{0-48} = 151.5 \mu\text{g*hr/mL}$. T_{max} at the highest dose occurred after the 3.5 hr sampling time. Exposure to the primary metabolite was ~7.4% of parent. MOE for the high dose based on human AUC of $3.5 \mu\text{g/hr/mL} = 43$. MOE for the high dose based on human C_{max} of $774 \text{ ng/mL} = 24$.

5.4. ADME/PK

The pharmacokinetics of elagolix were determined in CD-1 mice, Sprague Dawley rats, Beagle dogs, and cynomolgus monkeys. In vivo ADME studies were conducted in rats and dogs with radiolabeled compound and compared to absorption, metabolism and excretion studies conducted with [¹⁴C]elagolix in humans. The pharmacokinetic profile of elagolix was generally characterized by rapid absorption, high plasma clearance, moderate volumes of distribution and a short elimination half-life in mouse, dog and monkey.

Table 4. ADME Studies and Findings

Type of Study	Major Findings
Absorption	Bioavailability ranged from ~10% (mouse and monkey) to 100% (dog). Human and rat had similar bioavailability (~50%). Protein binding ranged from 78 to 90% across species.
Distribution	Protein binding ranged from 78 to 90% across species. Distribution after oral dosing (assessed using ¹⁴ C-labeled elagolix) was primarily to the gastrointestinal tract. Elagolix did not cross the blood brain barrier, did not accumulate in pigmented tissue, and did not partition into red blood cells. It did, however; freely cross the placenta (assessed in the rat).
Metabolism	Elagolix is not extensively metabolized, circulating primarily as unchanged drug in plasma and remaining largely intact through clearance. Metabolic pathways were similar across species including humans. Elagolix is primarily metabolized by O-demethylation, with minor metabolites formed via N-dealkylation, dehydration (lactam formation), glucuronidation, and oxidation. There were no major metabolites in any species, and no unique human metabolites. There was no chiral inversion of elagolix to its enantiomer in vitro, which is consistent with in vivo findings. In vitro and in vivo studies demonstrated the following potentially clinically relevant interactions of elagolix with metabolizing enzymes and drug transporters: elagolix is a substrate for CYP3A, P-gp and OATP1B1, a weak to moderate inducer of CYP3A and 2B6, and an inhibitor of P-gp and OATP1B1 and 1B3.
Metabolism	In vitro metabolism studies were conducted with two active metabolites, M3 (NBI-61692) and M6x (NBI-54048). The most significant potential effect was inhibition of CYP3A4/5, 2C9, and 2C19 by M6x. However, concentrations of this metabolite would have to reach micromolar levels for inhibition to become significant, which is not clinically relevant.

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Type of Study	Major Findings																																			
Excretion	Excretion of elagolix was determined in rats (intact and bile-duct cannulated; M/F), dogs (M/F), and humans (M), using radiolabeled compound. Orally administered elagolix (parent and metabolites) was mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance, in both nonclinical species and humans. No notable sex differences were noted. Excretion into milk was not determined.																																			
TK data from general toxicology studies	Toxicokinetics of elagolix were similar in mice, rats, dogs, and humans. Exposure was proportional or somewhat greater than proportional to dose, there were no strong gender differences, and there was no evidence of accumulation. Toxicokinetics were strikingly different in rabbit and monkey. In the rabbit, repeat dosing in the dose range of < 300 mg/kg led to dramatic increases in exposure that were not associated with accumulation. In the monkey, repeat dosing led to a dramatic reduction in exposure that was unexplained. Elagolix was poorly tolerated by all species in the liquid formulation. The formulation was altered to the capsule form for the 9-month dog study, and to the dietary form for the 6-month rat study, and the 2-year mouse and rat carcinogenicity studies. A 9-Month Toxicity and Toxicokinetic Study of Elagolix Administered by Oral Capsule to Beagle Dogs with a 1-Month Recovery Period. Study RD101101 <table border="1" data-bbox="451 884 1369 1045"> <thead> <tr> <th data-bbox="451 884 594 947">AUC µg*hr/mL</th> <th colspan="2" data-bbox="597 884 724 915">10 mg/kg/d</th> <th colspan="2" data-bbox="727 884 854 915">30 mg/kg/d</th> <th colspan="2" data-bbox="857 884 984 915">150 mg/kg/d</th> </tr> <tr> <th data-bbox="451 951 594 982"></th> <th data-bbox="597 951 724 982">M</th> <th data-bbox="727 951 854 982">F</th> <th data-bbox="857 951 984 982">M</th> <th data-bbox="987 951 1114 982">F</th> <th data-bbox="1117 951 1243 982">M</th> <th data-bbox="1247 951 1373 982">F</th> </tr> </thead> <tbody> <tr> <td data-bbox="451 984 594 1016">Day 1</td> <td data-bbox="597 984 724 1016">2.97</td> <td data-bbox="727 984 854 1016">3.79</td> <td data-bbox="857 984 984 1016">26.6</td> <td data-bbox="987 984 1114 1016">17.0</td> <td data-bbox="1117 984 1243 1016">277</td> <td data-bbox="1247 984 1373 1016">189</td> </tr> <tr> <td data-bbox="451 1018 594 1050">Day 91</td> <td data-bbox="597 1018 724 1050">4.96</td> <td data-bbox="727 1018 854 1050">4.8</td> <td data-bbox="857 1018 984 1050">24.4</td> <td data-bbox="987 1018 1114 1050">16.3</td> <td data-bbox="1117 1018 1243 1050">193</td> <td data-bbox="1247 1018 1373 1050">234</td> </tr> <tr> <td data-bbox="451 1052 594 1083">Day 273</td> <td data-bbox="597 1052 724 1083">6.63</td> <td data-bbox="727 1052 854 1083">5.18</td> <td data-bbox="857 1052 984 1083">26.0</td> <td data-bbox="987 1052 1114 1083">31.4</td> <td data-bbox="1117 1052 1243 1083">280</td> <td data-bbox="1247 1052 1373 1083">299</td> </tr> </tbody> </table>	AUC µg*hr/mL	10 mg/kg/d		30 mg/kg/d		150 mg/kg/d			M	F	M	F	M	F	Day 1	2.97	3.79	26.6	17.0	277	189	Day 91	4.96	4.8	24.4	16.3	193	234	Day 273	6.63	5.18	26.0	31.4	280	299
AUC µg*hr/mL	10 mg/kg/d		30 mg/kg/d		150 mg/kg/d																															
	M	F	M	F	M	F																														
Day 1	2.97	3.79	26.6	17.0	277	189																														
Day 91	4.96	4.8	24.4	16.3	193	234																														
Day 273	6.63	5.18	26.0	31.4	280	299																														
TK data from reproductive toxicology studies	<u>Rat</u> Oral gavage study for effects on embryo-fetal development and toxicokinetics with elagolix in rats. Study RD101078 AUC (µg*hr/mL) at 17 weeks: 300 mg/kg/d 55.5 MOE for the MRHD based on AUC is 6.5 600 mg/kg/d 68.6 MOE for the MRHD based on AUC is 19.9 1200 mg/kg/d 138.0 MOE for the MRHD based on AUC is 39.4 <u>Rabbit</u> Oral gavage study for effects on embryo-fetal development and toxicokinetics with elagolix in rabbits. Study RD101080 AUC (µg*hr/mL) at 20 weeks: 100 mg/kg/d 9.3 MOE based on AUC relative to MRHD is 2.7 150 mg/kg/d 23.2 MOE based on AUC relative to MRHD is 6.6 200 mg/kg/d 40.5 MOE based on AUC relative to MRHD is 11.6																																			

Type of Study	Major Findings
TK data from Carcinogenicity studies	2-Year Dietary Carcinogenicity and Toxicokinetic Study with Elagolix in Mice. Study RD101102. The week 26 AUC_{0-t} for elagolix at the highest dose tested (500 mg/kg/day) was 40.5 µg*hr/mL for males and 66.5 µg*hr/mL for females. This corresponds to an MOE of 12 and 19, respectively, as compared to the human AUC of 3.5 µg*hr/mL at the highest proposed therapeutic dose of 200 mg BID. There was relatively minor exposure to metabolites M3 and M6x. 2-Year Dietary Carcinogenicity and Toxicokinetic Study with Elagolix in Rats. Study RD101103. The week 26 AUC_{0-t} for elagolix at the highest dose tested (800 mg/kg/day) was 43.3 µg*hr/mL for males and 45.4 µg*hr/mL for females. This corresponds to an MOE of 12 and 13, respectively, as compared to the human AUC of 3.5 µg*hr/mL at the highest proposed therapeutic dose of 200 mg BID. Exposure to metabolites M3 and M6x was minor.

AUC = area under the curve, MOE = multiple of exposure, MRHD = maximum recommended human dose, TK = toxicokinetic, ADME = absorption, distribution, metabolism, excretion, OATP = organic-anion-transporting polypeptide, CYP = cytochrome P450

5.5. Toxicology

5.5.1. General Toxicology

A 9-Month Toxicity and Toxicokinetic Study of Elagolix Administered by Oral Capsule to Beagle Dogs with a 1-Month Recovery Period. Study #RD101101.

Key Study Findings

Clinical observations included soft/mucoid stools, diarrhea, decreased mean body weights and decreased food consumption. There were test article-related effects on hematology, coagulation, and clinical chemistry parameters for males and females at the high dose. Decreased spleen weights were noted in males and females, which were persistent in recovery for males, but did not have histological correlates. There were decreased prostate weights in males, without histological correlates, that did not recover. Histopathological effects were noted in the gallbladders of males in the high dose group that were absent in recovery.

The NOAEL was 30 mg/kg/day. Exposure at this dose was 8.4 µg/mL and 10.5 µg/mL for C_{max} and 26.0 µg*hr/mL and 31.4 µg*hr/mL for AUC on day 273 for males and females, respectively. The MOE relative to the AUC at the MRHD was 8.3 (males/females averaged).

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

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Table 5. Methods of 9-Month Toxicity and Toxicokinetic Study with Beagle Dogs

Doses:	0, 10, 30, 150 mg/kg/d
Frequency of dosing:	Daily
Route of administration:	Oral capsule
Dose volume:	N/A
Formulation/Vehicle:	(b) (4)
Species/Strain:	Beagle dog
Number/Sex/Group:	6/sex/group; 2/sex/group for recovery (except the low dose had no recovery group)
Age:	6 months
Weight:	Males: 6.4-8.8 kg; Females: 5.4-7.8 kg
Satellite groups:	None
Deviation from study protocol:	None significant

USP = United States Pharmacopeia

Table 6. Observations and Results: Changes from Control

Parameters	Major findings
Mortality	There was no mortality
Clinical signs	Soft/mucoid stools, vomitus, diarrhea that increased in a dose-dependent manner throughout the dosing period. Because control groups had a significant incidence of vomiting, the applicant attributed this to palatability.
Body weights and feed consumption	Mean body weight was decreased throughout the dosing period for both males (19.4%) and females (18.7%) in the high dose group. Decreased mean body weight for the high dose males and females reached toxicological significance (i.e., more than 10% less than controls) by day 8 and remained decreased throughout the remainder of the dosing phase (ending at day 274). No other toxicologically meaningful differences in mean body weight were noted in the remaining dose groups. Body weight gains rebounded in the recovery animals. Statistically significant decreases in mean food consumption (21.4% to 68.0%) were noted for weeks 1 to 4 and week 10 for high dose males and (26.7% to 30.7%) for weeks 1 and 2 for the females administered 150 mg/kg/day. No other significant test article-related differences in mean food consumption were noted during the dosing or recovery periods.
Ophthalmoscopy	No test-article related findings
ECG	No test-article related findings
Hematology	Test article-related effects on hematology and coagulation parameters relative to control included: For males in the high dose group: ↓ decreased erythrocytes (15.1% to 19.7%) ↓ hemoglobin (12.7% to 16.6%) ↓ hematocrit (11.6% to 15.7%) ↑ lymphocytes (19.9%) and monocytes (29.7%) For females in the high dose group ↑ platelets (29.1% to 54.8%) All changes returned to normal following the recovery period
Clinical chemistry	Test article-related changes in clinical chemistry parameters relative to control during the treatment period in the high dose group included: ↑ ALP (82.1% to 356.7% for males and 211.5% to 754.7% for females), ↑ phosphorus (14.5% to 18.5% for males and 18.8% to 27.9% for females) ↑ chloride (3.7% to 4.9% for males and 2.8% to 4.2% for females) ↓ albumin (21.4% to 25.4% for males and 13.0% to 20.5% for females) ↓ total protein (8.9% to 14.8% for males and 8.3% to 13.4% for females) ↓ albumin/globulin ratio (20.3% to 30.5% for males and 10.6% to 27.8% for females) All changes returned to normal following the recovery period.

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Urinalysis	No treatment-related findings
Gross pathology	No treatment-related findings
Organ weights	Spleen weight relative to body weight was decreased in males at the mid and high doses (max 43%) and in females at the high dose (max 50%). At recovery, relative spleen weight was still reduced in males but not females. Relative prostate weight was decreased at the high dose, up to 56% and did not recover. There were no histological correlates of decreased organ weight in the spleen or prostate. Decreased prostate weight was likely due to the exaggerated pharmacology of elagolix. Relative liver, adrenal, lung and salivary gland weights were increased at the high dose in males and females. Relative pituitary weight was increased in high dose males.
Histopathology adequate battery: Yes	In two high dose males, there were findings in the gall bladder: granulomatous inflammation occurred in the lamina propria of the mucosa, and was characterized by mononuclear cell infiltrates as well as the formation of multinucleated giant cells which contained variably sized clear intracytoplasmic spicules. There were no findings at the end of the recovery period.
Other evaluations	Estradiol and testosterone measurements were not done in this study.

ALP = a alkaline phosphatase, ECG = electrocardiogram

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

***Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with Elagolix. Study #RD101068.**

Key Study Findings:

- The study was negative for mutagenicity.
- Cytotoxicity was observed with tester strain TA100 at 5000 µg/plate in the absence of S9 mix, as evidenced by a decrease in the background lawn and decrease in the number of revertants. No cytotoxicity was observed with the other strains and conditions tested.

GLP compliance: Yes

Test system: *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537), and *Escherichia coli* strain WP2uvrA up to 5000 µg/plate; ± S9

Study is valid: Yes

In Vitro Assays in Mammalian Cells

L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay with Elagolix. Study #RD10165.

Key Study Findings: Elagolix was negative for chromosome aberration

GLP compliance: Yes

Test system: mouse lymphoma L5178Y cell line, heterozygous at the TK locus.

Doses in the definitive study: 10.0 to 250 µg/mL without S9; 10.0 to 400 µg/mL with S9.

Range finding studies indicated that elagolix was cytotoxic, demonstrating weak cytotoxicity at 15.7 (~25µM) and 31.3 µg/mL, moderate cytotoxicity at 62.5 µg/mL, and high cytotoxicity at 125 µg/mL (~200µM). Higher concentrations were 100% lethal.

Study is valid: Yes

NDA Multi-Disciplinary Review and Evaluation {NDA 210450}
{Orilissa and elagolix sodium}

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Mammalian Erythrocyte Micronucleus Test. Study #RD101091

Key Study Findings: Elagolix up to a dose of 2000 mg/kg was negative in the mouse micronucleus assay.

GLP compliance: Yes

Test system: ICR mouse micronuclei; Single dose; Doses tested: 500, 1000, 2000 mg/kg
Study is valid: Yes.

5.5.3. Carcinogenicity

2-Year Dietary Carcinogenicity and Toxicokinetic Study with Elagolix in Mice. Study #RD101102.

Elagolix was administered via diet to Crl:CD1(ICR) mice for at least 102 weeks at doses of 0, 50, 150, 500 mg/kg/d. N = 60/sex/group.

Range finding studies identified 500 mg/kg/d as the MTD for the carcinogenicity study, based on decline in body weight gain. 500 mg/kg/d was also the NOAEL for the range-finding study.

Key Study Findings:

- No statistically or biologically significant neoplastic findings related to elagolix were found.
- Elagolix did not alter the trend in mortality rates. The study achieved an MTD as the percent difference in body weight change (g) for the 500 mg/kg/day group (males and females) from controls was greater than 10% at week 13 and at terminal necropsy.

TK: N = 57/sex/group. Three animals/sex/group were bled for each collection time point and removed from the study. Blood samples (~0.3 mL) were collected during weeks 4, 13 and 26 from unfasted animals at 6:00, 10:00, 14:00, 18:00, 22:00, and 06:00 (on the following day).

The week 26 AUC_{0-t} at the 500 mg/kg/day dose was 40.5 µg*hr/mL for males and 66.5 µg.hr/mL for females. This corresponds to an MOE of 12 and 19, respectively, as compared to the human AUC of 3.5 µg*hr/mL at the highest proposed therapeutic dose of 200 mg BID. Exposure to the O-demethyl metabolite (M3) and the N-dealkyl metabolite (M6x) was minor.

Appropriateness of the test model: Binding of elagolix to the GnRH receptor in the mouse was not characterized. Elagolix binding to the GnRH receptor in two other rodent species (rats and rabbits) is significantly less potent (orders of magnitude) than in monkeys or humans. In addition, there were no obvious pharmacodynamic signs of drug activity. Therefore, any elagolix toxicity is assumed to be non-receptor mediated. The test model was deemed appropriate.

2-Year Dietary Carcinogenicity and Toxicokinetic Study with Elagolix in Rats. Study #RD101103

NDA Multi-Disciplinary Review and Evaluation {NDA 210450}
{Orilissa and elagolix sodium}

Elagolix was administered via diet to Sprague Dawley rats for at least 102 weeks at doses of 0, 150, 300, or 800 mg/kg/d. N = 60/sex/group.

Range-finding studies: 600 mg/kg/d was the NOAEL in the range-finding studies. The 800 mg/kg dose was likely the MTD based on reduced body weight gain. Higher doses (> 1200 mg/kg) resulted in decreased exposure at weeks 8 and 15 presumably due to liver enzyme induction.

Key study findings:

- Elagolix administered via diet at dose levels of 150, 300, and 800 mg/kg/day resulted in reduction in survival of males at 300 and 800 mg/kg/day. However, an adequate number of animals survived in all dose groups to provide a valid study for statistical analysis. Survival was unaffected in females.
- The highest target dose of 800 mg/kg/day was associated with increased incidences of hepatic (males) and thyroid tumors (males and females) that were likely a rat-specific effect and were predominantly benign. No correlation was observed between survival and tumors.
- The study achieved an MTD as the percent difference in body weight change (g) for the high dose group (males and females) was greater than 10% at terminal necropsy. Mean body weights were 17% and 13% lower than control for females and males, respectively.

TK: 5/sex/dose. Blood samples were collected via the jugular vein from each nonfasted animal during weeks 3, 13, and 26 at approximately 06:00, 10:00, 14:00, 18:00, 22:00, and 06:00 (on the following day). The week 26 AUC_{0-t} for the 800 mg/kg/day dose was 43.3 µg*hr/mL for males and 45.4 µg*hr/mL for females. This corresponds to an MOE of 12.4 and 13, respectively, as compared to the human AUC of 3.5 µg*hr/mL at the highest proposed therapeutic dose of 200 mg BID. Exposure to the O-demethyl metabolite (M3) and the N-dealkyl metabolite (M6x) was minor.

Appropriateness of the test model: binding of elagolix to the GnRH receptor in the rat is ~1000 fold weaker than in humans. In addition, there were no obvious pharmacodynamic signs of drug activity (atrophy of reproductive organs in males or females). Therefore, any elagolix-related findings are assumed to be non-receptor mediated. The test model was deemed appropriate.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Fertility and Early Development to Implantation in Rats After Oral Administration of Elagolix. Study #RD101081.

NDA Multi-Disciplinary Review and Evaluation {NDA 210450}
 {Orilissa and elagolix sodium}

Key Study Findings

- There was slight to no effect on estrous cycle, reproductive performance, fertility parameters in males and females, and cesarean section (implantation or embryo/fetal viability) parameters.

The Applicant's NOAEL for maternal and paternal toxicity was 150 mg/kg/day due to respiratory distress leading to excessive mortality at the 300 mg/kg/day dose. However, given the dose dependence of the mortality, we set the NOAEL at 50 mg/kg/day. Other repeat dose studies had similar mortality findings due to aspiration but had higher NOAELs. TK values at the 50 mg/kg/day dose were:

Males: $C_{max} = 0.7 \mu\text{g/mL}$ and $\text{AUC} = 1.8 \mu\text{g}\cdot\text{h/mL}$ on day 28.
 Females: $C_{max} = 0.8 \mu\text{g/mL}$ and $\text{AUC} = 2.3 \mu\text{g}\cdot\text{h/mL}$ on day 14.

The NOEL for reproductive performance, fertility, and embryo/fetal viability was 300 mg/kg/day, the highest dose tested. TK values at this dose were:

Males: $C_{max} = 2.8 \mu\text{g/mL}$ and $\text{AUC} = 41.6 \mu\text{g}\cdot\text{h/mL}$ on day 28
 Females: $C_{max} = 2.2 \mu\text{g/mL}$ and $\text{AUC} = 16.1 \mu\text{g}\cdot\text{h/mL}$ on day 14.

The exposure multiple for women based on the AUC at the NOEL of 300 mg/kg/day for the fertility effects in the female rat is approximately 4.6-fold the MRHD. However, because elagolix binds so poorly to the rat GnRH receptor (~1000-fold less than to the human receptor), this study does not effectively assess the effect of elagolix on fertility in humans.

Conducting laboratory and location: (b) (4)
 GLP compliance: Yes

Table 7. Methods of Fertility and Early Development Study in Rats

Doses*:	0, 50, 150, 300 mg/kg/d
Frequency of dosing:	Once daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water
Species/Strain:	Crl:CD (Sprague Dawley) rats
Number/Sex/Group:	25/sex/group
Satellite groups:	9/sex/group
Study design:	Dosing schedule: Males were dosed for at least 28 days prior to mating and throughout the mating period through the day prior to termination (at least 10 weeks prior to sacrifice). Females were dosed for at least 14 days prior to mating, throughout the mating period and through GD7. Females were necropsied on GD13.
Deviation from study protocol:	Group 2 dosing in week 6 was 65.8% of the target concentration.

GD = gestation day

* Dose selection was based on an EFD rat study where maternal and in-utero toxicity was assessed in pregnant rats at dose levels of 300, 600 and 1200 mg/kg/day. There were six unscheduled deaths (one in the 300, four in the 600 and one in the 1200 mg/kg/day groups). Treatment-related clinical observations included excessive salivation immediately following dosing and labored/audible respiration at 1200 mg/kg/day. There was significant decreased maternal body weight gain and food consumption during dosing in all treated groups. Caesarean section data indicated increased post-implantation loss and decreased fetal weight at 600 mg/kg/day. Also in the 6-month toxicology study (RD101044) there was over 50% mortality in the 600 mg/kg/day dosing group and over 25% mortality in the 300 mg/kg/day dosing group. Based on these observations, 300 mg/kg/day was selected as the highest dose.

Table 8. Observations and Results of Fertility and Early Development Study in Rats

Parameters	Major findings
Mortality	Unscheduled deaths (9 males/13 females) were dose-related and occurred between 2 and 30 days post-dosing. One high dose male had convulsions prior to dying. There were dose-related clinical signs of nasal discharge, salivation, labored breathing and hypoactivity, and necropsy findings of mottled lungs and material in the thoracic cavity. The Applicant proposed that the deaths were related to aspiration of test article and that aspiration became more likely with higher doses because the animals had a taste aversion to the formulation.
Clinical Signs	For the surviving animals, remarkable clinical signs included primarily clear oral/nasal discharge in the low dose group and audible/labored respiration and hypoactivity in the mid and high dose groups, the incidence and severity of which increased with dose. Other clinical observations were sporadic and considered unrelated to treatment.
Body Weights	There was a slightly reduced body weight in high dose males attributable to reduced body weight gain over the first few days of dosing
Necropsy findings [Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]	There was slight to no effect on estrous cycle, reproductive performance, fertility parameters in males and females, and Cesarean section (implantation or embryo/fetal viability) parameters.

Embryo-Fetal Development (rat and rabbit)

Oral Gavage Study for Effects on Embryo-Fetal Development and Toxicokinetics with Elagolix in Rats. Study #RD101078

Key Study Findings

- Elagolix was not teratogenic in the rat.
- Distribution studies indicated complete penetration of elagolix across the placental barrier in the rat. Fetal exposures can therefore be assumed to be equal to maternal exposures. Exposures were achieved that were greater than the exposures expected at the MRHD.
- Because binding of elagolix to the rat GnRH receptor is ~1000-fold lower than to the human receptor, this study was useful for evaluating effects on fetal development that were independent of changes in estrogen or progesterone.

The NOEL for maternal toxicity was ≤ 300 mg/kg/day, based on the likelihood that unscheduled deaths were related to aspiration of the test article.

The NOEL for fetal viability and growth was 300 mg/kg/day based on increased post-implantation loss and decreased fetal weight at 600 mg/kg/day (MOE = 20). These effects were attributed to decreased food consumption and excessive body weight loss at 600 mg/kg/day and not to a direct effect of the test article.

The NOAEL for fetal teratogenicity was 1200 mg/kg/day, the highest dose tested in this study.

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Using rat AUC values obtained on GD17 compared to the AUC at the MRHD of 3.5 µg*hr/mL:
At 300 mg/kg/day, the MOE for the MRHD based on AUC is 6.5.
At 1200 mg/kg/day, the MOE for the MRHD based on AUC is 39.4.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Table 9. Methods of Embryo-Fetal Development and Toxicokinetics Study in Rats

Doses:	300, 600, 1200 mg/kg/d
Frequency of dosing:	Daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water
Species/Strain:	Sprague-Dawley Rat
Number/Sex/Group:	25 females/group
Satellite groups:	6 females/group for TK
Study design:	Animals were dosed on GD6-GD17
Deviation from study protocol:	None significant

TK = toxicokinetic, GD = gestation day

Table 10. Observations and Results of Embryo-Fetal Development and Toxicokinetics Study in Rats

Parameters	Major findings
Mortality	Mortality: There were six unscheduled deaths occurring between GD13 and 18: one each in the low and high dose groups and four in the mid dose group. The cause of death was not determined and there were minimal clinical signs.
Clinical signs	Clinical observations included labored and audible respiration in all treated groups (with the highest incidence at the mid dose) and a dose related increase in urine stains, thin appearance and few or no feces. Increased alopecia was observed at 1200 mg/kg/day. Significant post-dose observations included excessive salivation and an increased incidence of labored and audible respiration at the mid and high doses.
Body weights	Elagolix produced significantly decreased mean maternal body weight gain (up to ~33% below control) in all treated groups. The decreased body weights (up to ~13% below control) correlated with significantly decreased food consumption (up to 19% below control for the treatment period). Effects on food consumption appeared to be reversible during the postdose phase (GD18 to 20).
Necropsy findings cesarean section data <i>[implantation sites, pre- and post-implantation loss, etc.]</i>	All animals were pregnant. There were no abortions or early deliveries. All surviving dams had litters with viable fetuses. There was a slight increase in postimplantation loss at the mid dose (8.9% versus 3.5% for control), which resulted in a slight decrease in the mean number of live fetuses in this group (12.8% versus 13.6% for control). This was attributed primarily to an increase in the late resorption in a single litter and decreased food consumption and excessive body weight loss in this group. Covariant adjusted mean fetal weight was significantly decreased (~10%) at the mid dose.
Necropsy findings offspring <i>[malformations, variations, etc.]</i>	Fetal observations: There were no fetal external anomalies or soft tissue or skeletal malformations in treated groups. Fetal skeletal variations consisted of unossified bones. Although the type of fetal skeletal variations observed were those commonly seen in this strain of rat, an increased fetal incidence occurred in all treated groups (up to 90% of fetuses versus 62% of fetuses in the control group). These increases correlated with decreased fetal weight and were considered to represent a delay in fetal development and not a direct effect of elagolix.

GD = gestation day

Oral Gavage Study for Effects on Embryo-Fetal Development and Toxicokinetics with Elagolix in Rabbits. Study #101080.

Key Study Findings

- The pregnancy rate was unaffected by treatment. The pregnancy rate was 90% for the control group, 100% for the low and mid-dose groups, and 95% for the high dose group. Fetal growth was retarded in the high dose group as reflected by decreased gravid uterine weight gain. This was attributed to maternal toxicity due to reduced feed consumption and reduced body weight gain.
- One mid-dose and one high dose dam had litters with no viable fetuses, which resulted in an increase in postimplantation loss and a decrease in number of live fetuses in these groups.

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- There was no treatment-related teratogenicity.

The NOAEL for maternal toxicity was 150 mg/kg/day based on reduced maternal weight gain and decreased feed consumption.

The Applicant's NOEL for embryo/fetal toxicity was 150 mg/kg/day based on significantly decreased fetal weights at 200 mg/kg/day. However, we disagree, based on the finding of increased postimplantation loss at both the mid and high doses. Postimplantation loss was a factor in setting the NOEL in the rat EFD study, but for some reason was discounted by the applicant in this rabbit study. Our NOEL for embryofetal toxicity in the rabbit is thus set at 100 mg/kg/d.

The NOEL for teratogenicity was 200 mg/kg/day, the highest dose used in this study.

At 100 mg/kg/day on GD20:

C_{max} = 3.5 µg/mL and AUC = 9.3 µg*hr/mL. MOE based on AUC relative to MRHD is 2.7.

At 150 mg/kg/day on GD20:

C_{max} = 8.4 µg/mL and AUC = 23.3 µg*hr/mL. MOE based on AUC relative to MRHD is 6.6

At 200 mg/kg/day on GD20:

C_{max} = 9.1 µg/mL and AUC = 40.5 µg*hr/mL. MOE based on AUC relative to MRHD is 11.6.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Table 11. Methods of Oral Gavage Study of Embryo-Fetal Development and Toxicokinetics in Rabbits

Doses:	0, 100, 150, 200 mg/kg/d
Frequency of dosing:	Daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/vehicle:	Sterile water
Species/strain:	Rabbit/Hra(NZW)SPF
Number/sex/group:	20 females/group
Satellite groups:	5 females/group for TK
Study design:	Dosing on days 7 to 20 of gestation
Deviation from study protocol:	None significant

TK = toxicokinetics

Table 12. Major Findings of Oral Gavage Study of Embryo-Fetal Development and Toxicokinetics in Rabbits

Parameters	Major findings
Mortality	There were six unscheduled deaths: two at the mid-dose (one of these was a gavage error) and four at the high dose. Other than a gavage error in one animal at the mid-dose, cause of death was not established. Of the four deaths at the high dose, three were euthanizations following abortion.
Clinical signs	Increased incidence of few or no feces at the mid and high dose.
Body weights	Elagolix produced significantly decreased (-28%) mean body weight gain at the high dose, which was largely attributable to reduced gravid uterine weight. Effects on food consumption correlated with body weight changes. Effects on food consumption and body weight change were reversible.
Necropsy findings cesarean section data <i>[implantation sites, pre- and post-implantation loss, etc.]</i>	Necropsy findings: no treatment-related necropsy findings were reported. Mean gravid uterine weight was significantly decreased (-21%) at the high dose and was attributed to the decreased maternal weight and food consumption during the dosing period. When corrected for body weight the uterine weights were similar in all groups. Cesarean section data were generally unremarkable and indicated that fetal viability was unaffected by elagolix. However, mean fetal weight was significantly decreased (-9%) in the high dose group (more pronounced in female fetuses). This finding was attributed to the decreased maternal food consumption and subsequent decreased body weight in this group.
Necropsy findings, offspring <i>[malformations, variations, etc.]</i>	There were no treatment-related fetal external, visceral, or skeletal findings.

Prenatal and Postnatal Development

A Dietary Study of the Effects of Elagolix on Pre- and Postnatal Development, Including Maternal Function in Rats. Study #RD13581.

Key Study Findings

- Due to lower F1 postnatal survival and lower F1 birth weights and pre-weaning body weights and body weight gains at 300 mg/kg/day, the NOAEL for F1 neonatal/early postnatal toxicity was 100 mg/kg/day.
- Lower mean maximum startle response and average response values were noted on postnatal day (PND) 20 for F1 males and females in the high dose group. These effects were considered to be, in part, secondary to the effects on F1 body weights noted during the pre- and post-weaning periods, and were attributable to F0 maternal test article exposure. Therefore, the NOAEL for F1 developmental toxicity, including neurobehavioral development was 100 mg/kg/day.
- No toxicity was observed in the F0 maternal animals, in F1 animals during the post-weaning period, or in the F2 pups. Therefore, the NOAEL for F0 systemic toxicity, F1 post-weaning systemic toxicity, F1 reproductive toxicity, and F2 neonatal/early postnatal toxicity was 300 mg/kg/day.

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- The maternal plasma concentration (measured 2 hours after the initiation of light cycle) for elagolix on LD21 was 47.2 and 125 ng/mL for the 100 and 300 mg/kg/day dose groups, respectively. These values are roughly 10-fold lower than oral gavage at the same doses. Because AUC data were not generated, calculation of MOEs could not be done.

Conducting laboratory and location: (b) (4)
 GLP compliance: Yes

Table 13. Methods of Dietary Study on Pre- and Postnatal Development in Rats

Doses:*	0, 100, 300 mg/kg/d The 100 mg/kg/day group was offered the test diet beginning on GD2. The 300 mg/kg/day group was offered the test diet on an escalating schedule as follows: 100 mg/kg/day on GD2 and 3, 200 mg/kg/day on GD4 and 5, and 300 mg/kg/day from GD6 onward.
Frequency of dosing:	Daily in the diet
Dose volume:	N/A
Route of administration:	Oral
Formulation/vehicle:	(b) (4) Formulation analysis verified concentration and homogeneity
Species/strain:	Sprague Dawley rat
Number/sex/group:	25 females/group
Satellite groups:	On LD/PND21, blood samples (for plasma analysis of the parent drug) were collected from 4 F ₀ females/group and 1 F ₁ pup/sex/litter from the same 4 F ₀ females
Study design:	Exposure from GD2 through LD20; F ₀ animals were ~14 wks of age at the beginning of exposure
Deviations:	None significant

*
 Doses were chosen based on findings from a dose-range finding study conducted at 400 and 1500 mg/kg/d. Mortality at the high dose and incidences of total litter loss at both doses led to a reduction in dosing for the definitive study.

Table 14. Observations and Results of Dietary Study on Pre- and Postnatal Development in Rats

Generation	Major Findings
F0 Dams	One animal was found dead, but clinical findings were otherwise minimal. At the high dose, two dams had total litter loss, and one failed to deliver. There were no effects on the mean number of F1 pups born, live litter size, percentage of males at birth, or pup necropsy findings at any exposure level.
F1 Generation	Postnatal survival was decreased from birth to PND4 (pre-selection) at the highest dose of 300 mg/kg/day, with a corresponding increased number of pups found dead or missing prior to weaning (total of 39 pups) compared with controls (total of 2 pups). There were no effects on postnatal survival at 100 mg/kg/day. There were lower mean birth weights and lower mean body weight gains for F1 males and females at the high dose, resulting in mean body weights that were generally lower than the control group throughout the pre-weaning period. Furthermore, a higher incidence of small stature (which is defined as small body size in relation to littermates) was noted for the F1 pups in the high dose group (four pups from four litters affected compared to one pup from one litter in the control group), which corresponded to the lower pup weights in this group. Mean pup body weights and body weight gains for the low dose group were similar to the control group during the postnatal period. Developmental landmarks (balanopreputial separation and vaginal patency) in the F1 offspring were unaffected all doses. In addition, there were no effects on behavior, including startle response on PND20 and 60, locomotor activity on PND21 and 61, and learning and memory assessments on PND22 and 62. Lower mean overall maximum startle response and average response values were noted on PND20 for F1 males and females in the 300 mg/kg/day group. Although these effects on startle response were in part attributed to the lower body weights noted in the males and females at this exposure level, they were considered elagolix-related effects. No effects on survival, clinical condition, or mean body weights or body weight gains were noted for F1 males and females at any exposure level. F1 reproductive endpoints (pre-coital intervals, estrous cycle lengths, and mating, fertility, and copulation/conception indices) were unaffected. Furthermore, there were no effects on the F1 gestation lengths or parturition. There were no macroscopic findings in the F1 males and females in any group or effects on the mean numbers of implantation sites, unaccounted-for sites, and corpora lutea at any exposure level.
F2 Generation	There were no effects of F0 maternal exposure on the mean number of F2 pups born, viability on PND0, postnatal survival, physical condition, mean body weights, body weight gains, or necropsy findings of F2 pups that were found dead or euthanized due to the death of the dam.

PND = post-natal day

5.5.5. Other Toxicology Studies

Impurities: Elagolix has 15 specified and 11 unspecified impurities. Four specified and three unspecified impurities were identified as (b) (4) impurities and were controlled to appropriate levels. Specified impurities were qualified either through general toxicity studies, or through an additional rat 6-week dietary impurity qualification study, which used feed spiked with three of the impurities.

Local tolerance was assessed in a mouse local lymph node assay and there were no notable findings.

6. Clinical Pharmacology

6.1. Executive Summary

6.1.1. Clinical Pharmacology Recommendations

The Office of Clinical Pharmacology's Divisions of Clinical Pharmacology-3 and Pharmacometrics, and the Genomics and Targeted Therapy Group have reviewed the submitted information and recommend approval of this NDA. The key review issues with specific recommendations and comments are summarized in Table 15 below:

Table 15. Summary of Clinical Pharmacology Key Review Issues

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Substantial evidence of effectiveness was demonstrated in the two Phase 3 trials (see Section 8 Statistical and Clinical Evaluation). Dose-dependent suppression of pituitary hormones, ovarian hormones, and ovulation provided supportive evidence of efficacy.
General dosing instructions	Orally 150 mg once daily or 200 mg twice daily, with or without food. The Clinical Pharmacology review team recommends that the duration of treatment with 200 mg BID be limited to 6 months.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The Applicant proposed no dose adjustment in women with mild hepatic impairment, only 150 mg QD for women with moderate hepatic impairment, and a contraindication in women with severe hepatic impairment. The Clinical Pharmacology review team recommends that the duration of treatment with elagolix 150 mg QD in women with moderate hepatic impairment be limited to 6 months.
Labeling	Refer to Section 11 for the review team's recommendations.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed 200 mg elagolix tablet is bioequivalent to two 100-mg tablets. An in vivo bioequivalence study for the 150 mg strength is waived.
Other (specify)	None.

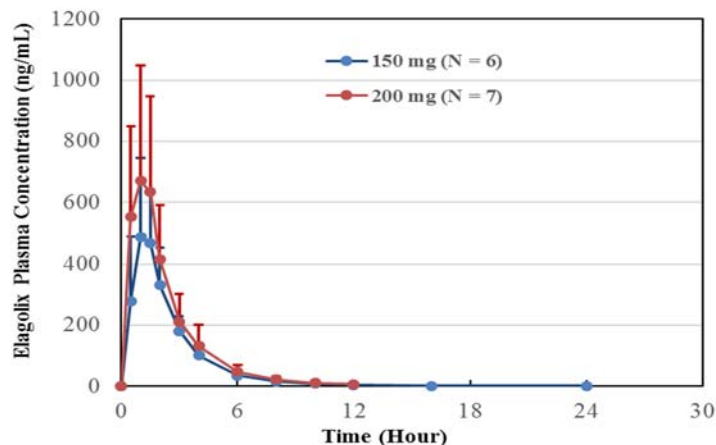
BID = twice daily, QD = once daily

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Elagolix is available as either 150 mg tablets (once daily, QD) or 200 mg tablets (twice daily, BID), to be taken orally with or without food.

Figure 2. Plasma Concentration-Time Profiles of Elagolix in Healthy Premenopausal Female Subjects After Oral Administration of a Single Dose of Elagolix 150 mg (N = 6) or 200 mg (N = 7)



Absorption: Elagolix is rapidly absorbed upon oral administration with C_{max} occurring at approximately 1 hour post-dose. It is absorbed throughout the gastrointestinal tract, except the colon where it is minimally absorbed. When elagolix is administered under fed conditions with a high-fat meal, C_{max} and AUC are on average 38% and 26% lower, respectively, and the median T_{max} is delayed by approximately 1 hour in comparison with that under fasting conditions.

Distribution: The apparent volume of distribution of elagolix was 1674 L and 881 L after multiple doses of 150 mg QD and 200 mg BID, 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. The contribution of CYP2D6 is 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 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-life ($T_{1/2}$) of elagolix is approximately 4 to 6 hours.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The proposed elagolix dose is either 150 mg tablets QD or 200 mg tablets BID, to be taken orally with or without food, initiated within ^{(b) (4)} days of a menstrual cycle. The Applicant proposes the use of the lowest effective dose based on the severity of symptoms and treatment objectives.

Patients in two pivotal Phase 3 studies and one extension study were given elagolix under fasting conditions while the second Phase 3 extension study (M12-821) was conducted without regard to meals. The proposed drug administration with or without food is acceptable. The proposed 150 mg QD dosing regimen is acceptable for the general population of premenopausal women with endometriosis.

Due to the loss in BMD observed with 200 mg BID, we recommend that the duration of treatment with elagolix 200 mg BID be limited to 6 months.

6.2.2.2. Therapeutic Individualization

Hepatic Impairment: In a dedicated hepatic impairment study, the PK of a single 150 mg oral dose of elagolix was investigated in adult females with normal hepatic function (N = 6), mild stable chronic hepatic impairment (N = 6, Child-Pugh A), moderate stable chronic hepatic impairment (N = 6, Child-Pugh B), or severe stable chronic hepatic impairment (N = 4, Child-Pugh C). 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 AUC values from subjects with normal hepatic function. For the O-demethyl metabolite (M3), AUC values were similar between subjects with mild hepatic impairment and subjects with normal hepatic function. The AUC values of M3 in subjects with moderate hepatic impairment and subjects with severe hepatic impairment were approximately 5.5-fold and 17-fold, respectively, of AUC values from subjects with normal hepatic function. The elagolix AUC was about 59 times the M3 AUC in subjects with normal hepatic function. In addition, the GnRH inhibition activity of M3 ($IC_{50} = 14\text{nM}$) is lower compared to elagolix ($IC_{50} = 1.5\text{nM}$). Thus, the 5.5-fold increase in M3 exposure in subjects with moderate hepatic impairment is not likely to contribute significantly to the overall GnRH inhibition. Based on the PK data, the Applicant proposed no dose adjustment in women with mild hepatic impairment, only 150 mg QD in women with moderate hepatic impairment, and a contraindication in women with severe hepatic impairment.

Due to the risk of bone loss, the clinical pharmacology review team recommends that the duration of treatment with elagolix 150 mg QD in women with moderate hepatic impairment be limited to 6 months, like the 200 mg BID dose in women with normal hepatic function. This recommendation is based on the 3-fold increase in elagolix AUC with the 150 mg QD dose in women with moderate hepatic impairment.

OATP1B1 Transporter Genotype Status: Pharmacogenetic samples from 1777 subjects in Phase 1 and 3 studies (N = 463 Phase 1, N = 1314 Phase 3) were assessed for the *SLCO1B1* 521T>C polymorphism. This analysis identified 74.1% subjects with extensive transporter (ET) function (*SLCO1B1* 521T/T genotype), 24.6% subjects with intermediate transporter (IT) function (*SLCO1B1* 521T/C), 2.1% subjects with poor transporter (PT) function (*SLCO1B1* 521C/C), and < 1% subjects with non-analyzable samples. A population PK analysis using data from 1624 subjects from five Phase 1 studies (Studies M12-790, M12-653, M13-995, M14-731, and M12-673) and four Phase 3 studies (Studies M12-665, M12-667, M12-671, and M12-821) was

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conducted by the Applicant to investigate the effect of covariates such as genotype on elagolix PK. Subjects included in the population PK analysis included genotyped subjects and OATP1B1 status was identified as a significant covariate in the elagolix PK model. Our population PK analysis using the Applicant's model showed that the AUC of elagolix is expected to increase by 24% and 78% in subjects predicted to be IT and PT respectively, compared to subjects predicted to be ETs. The expected mean steady state AUC values ranged from 14.8-148.2 ng*hr/mL in ETs, 21.1- 209.1 ng*hr/mL in ITs, 50.5-195.1 ng*hr/mL in PTs, and 16.8 – 407.2 ng*hr/mL in subjects who had no genotype information, presenting an overlap of exposure across OATP1B1 subgroups and the non-genotyped subgroup (Refer to the clinical pharmacology review in DARRTS for pharmacometrics assessment). For IT subjects, a 24% increase in the exposure of elagolix is not expected to have a clinically meaningful impact on efficacy and safety. A 78% increase in AUC seen in PTs in comparison with ETs is approximately two standard deviations away from the mean of the ET AUC but falls within the range of values observed for extensive, intermediate and non-genotyped subgroups.

Considering 1) the variability in exposure across OATP1B1 subgroups, 2) the frequency of the *SLCO1B1* 521C/C genotype (PT), which is generally lower than 5% in most racial/ethnic groups, and 3) the burden that an OATP1B1 genotyping requirement would place on all patients taking elagolix, the clinical pharmacology review team does not recommend screening for the PT genotype or dose adjustment for women with the PT genotype.

Drug Interactions: The Applicant conducted 10 clinical drug interaction studies. The major clinical drug interaction findings and management strategies are summarized in Table 16.

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Table 16. The Major Clinical Drug Interaction Study Findings and Management Strategies

Evaluation	Results	The Applicant's Management Strategies	Review Team's Management Strategies
CYP3A4 inhibition by ketoconazole, 400 mg QD	↑C _{max} by 77% ↑AUC by 120%	(b) (4)	Concomitant use of elagolix 200 mg BID and strong CYP3A inhibitors for more than 1 month is not recommended. Concomitant use of elagolix 150 mg QD and strong CYP3A inhibitors should be limited to 6 months.
OATP1B1 inhibition by a single dose of rifampin, 600 mg	↑C _{max} by 337% ↑AUC by 458%	(b) (4)	Concomitant use of elagolix and potent OATP1B1 inhibitors (except rifampin – see results with daily rifampin dosing below) is contraindicated.
CYP3A4/P-gp induction by rifampin, 600 mg QD	↑C _{max} by 100% ↑AUC by 65%	(b) (4)	Concomitant use of elagolix 200 mg BID and rifampin is not recommended. Concomitant use of elagolix 150 mg QD and rifampin should be limited to 6 months.
P-gp inhibition by elagolix 200 mg BID	↑C _{max} by 71% ↑AUC by 26% (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.	Concur with the Applicant.
BCRP/OATP1B1 inhibition by elagolix 300 mg BID	↓AUC by 40% ↔ C _{max} (rosuvastatin)	Consider increasing the dose of rosuvastatin. No dose adjustment for elagolix.	Concur with the Applicant
CYP3A4 induction by elagolix 150 mg QD and 300 mg BID	↓AUC by 35 - 55% ↓C _{max} by 19 - 44% (midazolam)	Consider increasing the dose of midazolam and individualize therapy based on patient's response.	Concur with the Applicant

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Evaluation	Results	The Applicant's Management Strategies	Review Team's Management Strategies
CYP3A4 induction by elagolix 150 mg QD	AUC and C _{max} ↔ (norethindrone) AUC of EE ↑ 30% (EE + norgestimate)	No dose adjustment is required for concomitant use of elagolix with progestin-only oral contraceptives.	No dose adjustment for concomitant use of elagolix 150 mg QD with oral norethindrone. The potential drug-drug interactions (DDIs) between elagolix 200 mg BID and norethindrone and other progestins are unknown.
DDI with sertraline (elagolix 300 mg BID) (Study M15-973)	↑AUC by 42% ↑C _{max} by 34% (sertraline)	No dose adjustment for sertraline or elagolix.	Concur with the Applicant
DDI with fluconazole (elagolix 300 mg BID) (Study M15-974)	No change in fluconazole exposure. AUC of elagolix ↑ by 31%	No dose adjustment.	Concur with the Applicant

DDI = drug-drug interactions, AUC = area under the curve, EE = ethinyl estradiol, BID = twice daily, QD = once daily, P-gp = P-glycoprotein, BCRP = breast cancer resistance protein

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 17. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	Elagolix is a GnRH receptor antagonist that blocks endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of elagolix results in dose dependent suppression of LH and FSH levels, leading to decreased blood levels of the ovarian sex hormones, estradiol and progesterone.
Active moieties	Elagolix
QT prolongation	No QT interval prolongation of clinical concern was observed with a single dose of 1200 mg.
General Information	
Bioanalysis	LC-MS/MS methods were used to measure elagolix and its metabolites in plasma and urine. LC-MS/MS methods were used to determine serum estradiol and progesterone.
Healthy vs. patients	No dedicated comparative PK study between healthy subjects and patients was conducted. Population PK prediction showed that the exposures of elagolix were similar between healthy women and women with endometriosis [150 mg QD, AUC ₀₋₂₄ (Mean ± SD): 1140 ± 501 ng*h/mL vs. 1120 ± 526 ng*h/mL].
Drug exposure at steady state (Mean ± SD)	150 mg QD, AUC ₀₋₂₄ : 1292 ± 403 ng*h/mL 200 mg BID, AUC ₀₋₁₂ : 1725 ± 990 ng*h/mL
Range of effective dose or exposure	150 mg QD to 300 mg BID
Maximally tolerated dose or exposure	The maximally tolerated dose 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, 200 mg BID was tested in women with endometriosis for

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	48 weeks, 300 mg BID and 600 mg QD were tested in women with uterine fibroids for 24 weeks.		
Pharmacodynamics	Elagolix causes dose-dependent suppression of LH, FSH, estradiol, and progesterone. Reduction of estradiol to approximately 12 pg/mL was observed following treatment with 200 mg BID. Elagolix 150 mg QD and 200 mg BID resulted in an ovulation rate of approximately 50% and 32%, respectively.		
Dose proportionality	For multiple-dose PK, on day 1, elagolix shows a 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.		
Accumulation	Repeated daily administration of elagolix (QD or BID) at a dose $\geq$ 200 mg resulted in a decrease in drug exposure from day 1 to day 21. The accumulation ratio was 0.98 for 150 mg QD and 0.89 for 200 mg BID.		
Variability	Between-subject variability (Phase 1 studies): 150 mg QD, C_{max} 43%, AUC 40%; 200 mg BID, C_{max} 49%, AUC 44% Within-subject variability: C_{max} 6.4%, AUC 3.3%		
Absorption			
Bioavailability	The absolute bioavailability in humans has not been established.		
T_{max} (Mean $\pm$ SD)	150 mg QD: 0.9 $\pm$ 0.2 hours; 200 mg BID: 1.1 $\pm$ 0.4 hours		
Food effect following a high fat meal (fed/fasted) [90% CI]	AUC_{0-∞}	C_{max}	T_{max}
	76 % [70% - 82%]	64% [53% - 76%]	185% [161% - 212%]
Distribution			
Volume of distribution	150 mg QD: 1674 L; 200 mg BID: 881 L		
Plasma protein binding	Independent of concentration, fraction unbound of elagolix in rat, dog, monkey and human plasma is 0.15, 0.17, 0.21 and 0.20, respectively. The blood to plasma ratio of elagolix in human is 0.6.		
Substrate transporter systems	Elagolix is a substrate of P-gp and OATP1B1. Population PK analysis shows OATP1B1 genotype status is the only significant covariate on elagolix oral clearance (CL/F).		
Elimination			
Terminal elimination half-life (Mean $\pm$ SD)	150 mg QD: 6.42 $\pm$ 3.20 h; 200 mg BID: 4.29 $\pm$ 0.47 h		
CL/F (Mean $\pm$ SD)	150 mg QD: 123 $\pm$ 26 L/h; 200 mg BID, 144 $\pm$ 62 L/h		
Metabolism			
Fraction metabolized (% dose)	69% of dose recovered in feces and urine is metabolized.		
Primary metabolic pathway(s)	Elagolix is extensively metabolized in liver, primarily by CYP3A4, to a lesser extent by CYP2D6, and minor metabolism by CYP2C8. In human plasma, two oxidative metabolites, O-demethyl metabolite (M3, NBI-61962 or A-1323217) and N-dealkyl metabolite (M6x, NBI-54048 or A-1298847) constitute 2.4% and 3.3% of exposure relative to elagolix. Both metabolites can bind to the GnRH receptor. Elagolix, the O-demethylated metabolite and the N-dealkylated metabolite inhibit the function of the human GnRH receptor expressed in RBL-1 cells with an IC ₅₀ of 1.5nM, 14nM and 0.8nM, respectively.		

Excretion	
Primary excretion pathways (% dose) ± SD	--Feces: 90.1% (approximately 26.3% unchanged elagolix) --Urine: 2.9% (approximately 2.6% unchanged elagolix)
In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	Elagolix is a time-dependent inhibitor of CYP3A4/5 (K _i 74µM), CYP2C8 (K _i 82µM) and CYP2C19 (K _i 34µM) and an inducer of CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19.
Inhibition/Induction of transporter systems	Elagolix is an inhibitor of OATP1B1, OATP1B3, P-gp and BCRP.

AUC = area under the curve, QD = once daily, BID = twice daily, PK = pharmacokinetic, SD = standard deviation, GnRH = gonadotropin-releasing hormone, FSH = follicle-stimulating hormone, LH = leutinizing hormone, CL/F = oral clearance, P-gp = P-glycoprotein, BCRP = breast cancer resistance protein

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The clinical pharmacology information that provides supportive evidence of effectiveness includes (1) exposure-response information for DYS and NMPP responder rates; (2) dose-dependent suppression of pituitary and ovarian hormones; and (3) dose-dependent suppression of ovulation.

Exposure-response information for DYS and NMPP:

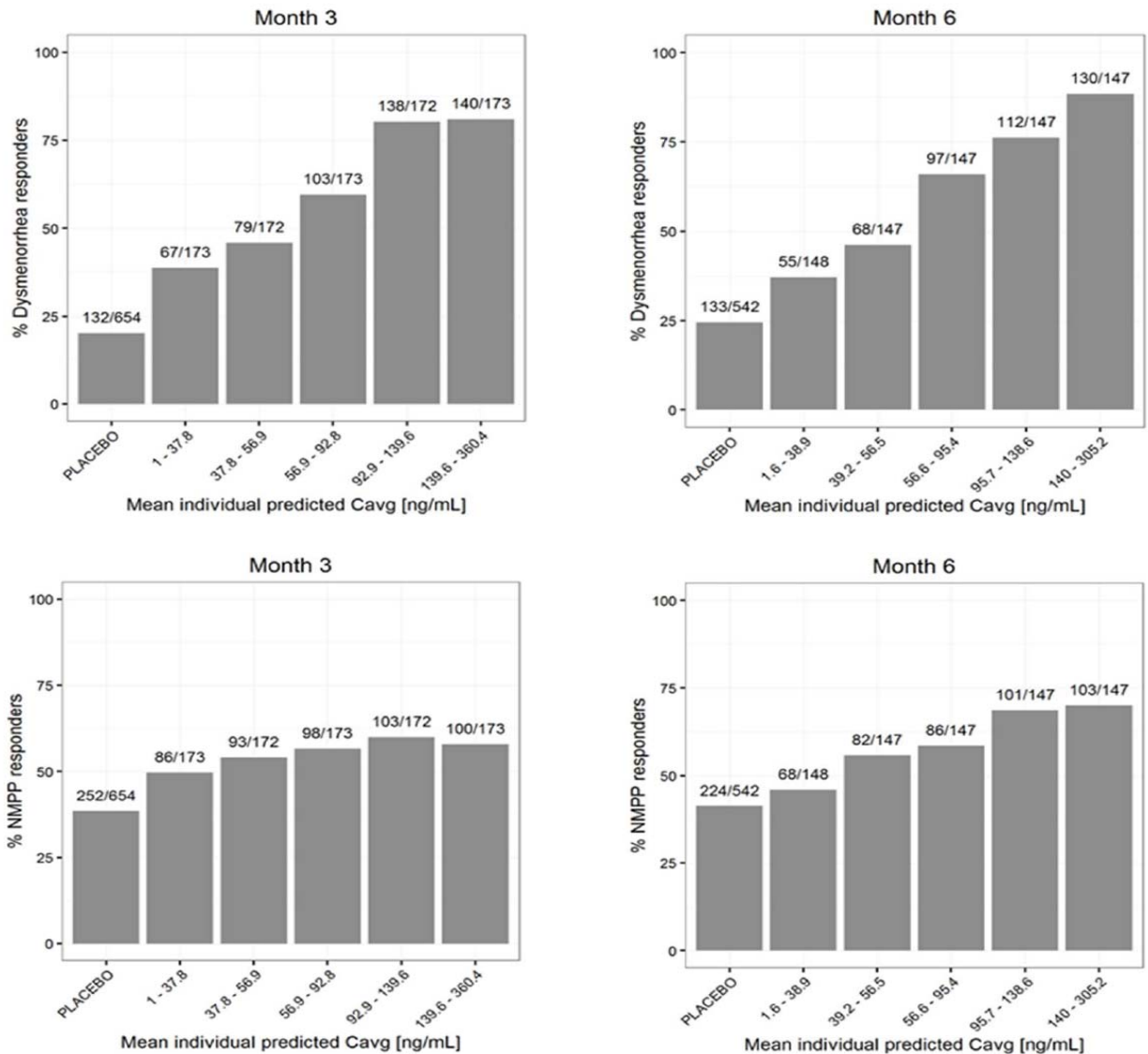
To support the effectiveness of elagolix, the Applicant conducted exposure-response analyses for the co-primary efficacy endpoints (DYS and NMPP) using data from four Phase 3 trials: Studies M12-665, M12-667, M12-671, and M12-821. The relationship between elagolix monthly average concentrations (C_{avg}) and percentage of subjects achieving DYS and NMPP responder status at month 3 and month 6, respectively, is shown in quintile plots presented in Figure 3. C_{avg} values were determined as monthly average AUC₀₋₂₄ divided by 24. However, the apparent relationship between average concentrations and response may be confounded by the effect of dosing frequency as shown in two studies (NBI-56418-0503 and NBI-56418-0603) conducted by NBI (the Sponsor of the IND prior to Abbvie) (b) (4)

In Study NBI-56418-0503, a 12-47% higher daily exposure of elagolix was observed with 150 mg QD compared to 75 mg BID. The main reason for the lower AUC₀₋₂₄ for the 75 mg BID dose was due to a significantly lower AUC with the evening dose compared to the morning dose. Subjects were fasted for 4 hours before and after the morning dose and for 2 hours before and after the evening dose. The different elagolix exposure between morning and evening doses might be partially caused by the different fasting conditions. In the other study (NBI-56418-0603), higher responder rates for NMPP (86.0% versus 76.9%) and DYS (86.0% versus 73.8%) were observed with 150 mg QD compared to 75 mg BID.

Although AbbVie used immediate-release (IR) formulations in its Phase 1 and Phase 3 studies and there were no apparent differences in plasma elagolix concentrations at 4 hours post dosing between the morning and evening doses in AbbVie's PK study (Study M12-790), the effects of dosing frequency on the PK and efficacy of the immediate release formulations were not assessed. Therefore, it is unknown whether dosing frequency affects the PK and efficacy endpoints of

AbbVie’s immediate release formulations, and a dose-response relationship for DYS and NMPP cannot be conclusively demonstrated.

Figure 3. Quintile Plots for Dysmenorrhea (DYS) and Nonmenstrual Pelvic Pain (NMPP) Responses at Month 3 and Month 6 vs. Elagolix Average Concentrations (C_{avg})



NMPP = non-menstrual pelvic pain

Note: Median of average concentrations (month 1 to 3) (ng/mL): quintile 1, 30.1; quintile 2, 46.9; quintile 3, 70.6; quintile 4, 114; quintile 5, 181. Median of average concentrations (month 1 to 6) (ng/ml): quintile 1, 30.6; quintile 2, 47.1; quintile 3, 72.7; quintile 4, 115; quintile 5, 180.

Population PK model predicted mean C_{avg} for 150 mg QD = 46.5 ng/mL and for 200 mg BID = 130 ng/mL.

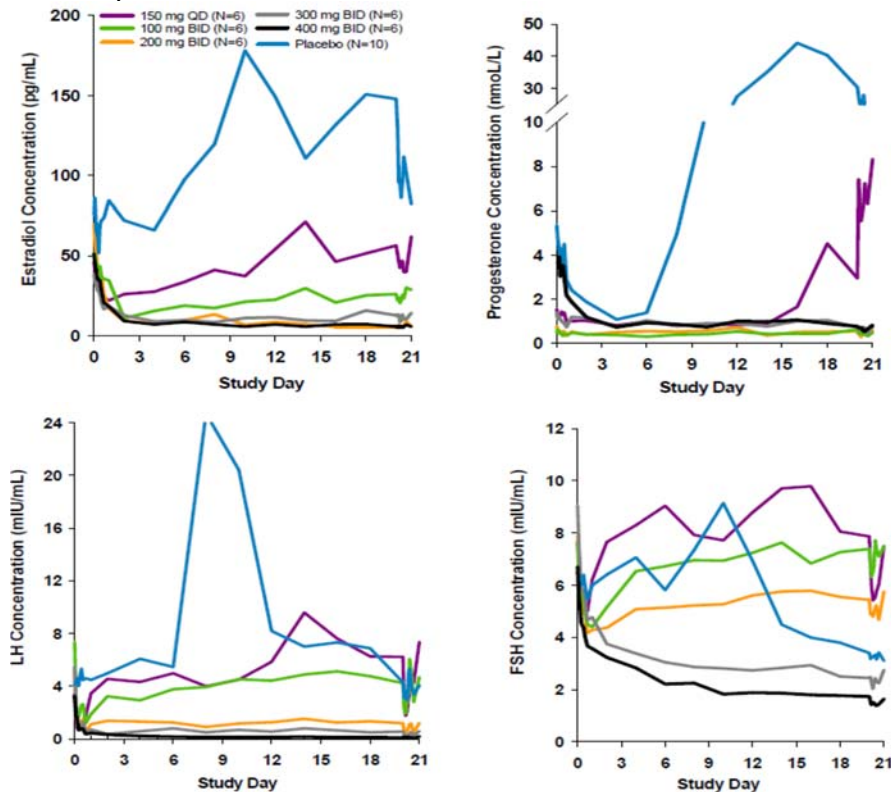
Dose-dependent suppression of pituitary and ovarian hormones:

Similar to other approved hormonal therapies for endometriosis, elagolix primarily acts by suppressing ovulation and inducing a hypoestrogenic state. Pharmacodynamic (PD) data (LH, FSH, estradiol, and progesterone) were collected in multiple-dose Phase 1 studies (Studies M12-790, M12-654, and M12-673) in healthy premenopausal women, as well as in the pivotal Phase 3 trials

(Studies M12-665 and M12-671) and extension studies (M12-667 and M12-821). Elagolix caused a dose-dependent suppression of LH and FSH levels, leading to decreased blood levels of the ovarian sex hormones, estradiol and progesterone. Partial suppression of estradiol at low doses (e.g., 150 mg QD) and nearly full suppression of estradiol at high doses (e.g., 400 mg BID) was maintained throughout the treatment periods.

The multiple ascending dose study (Study M12-790) in 45 healthy premenopausal female volunteers assessed dose-dependent suppression of LH, FSH, estradiol and progesterone. Within 2 days after the start of their menstrual cycle, the enrolled subjects received one of 5 dose regimens of elagolix (100 mg BID, 150 mg QD, 200 mg BID, 300 mg BID, and 400 mg BID) or matching placebo for 21 consecutive days under fasting conditions. Figure 4 shows the mean hormone concentration-time profiles for each dose group. Dose-dependent suppression of LH, estradiol and progesterone was observed at all five dose levels and dose-dependent suppression of FSH at doses ≥ 200 mg BID compared to placebo. Partial suppression of estradiol appeared to be achieved at doses of 150 mg QD and 100 mg BID. Maximal suppression of estradiol appeared to be achieved at doses ≥ 200 mg BID.

Figure 4. Mean Hormone Concentrations Following Multiple Doses of Placebo and Elagolix (Study M12-790)

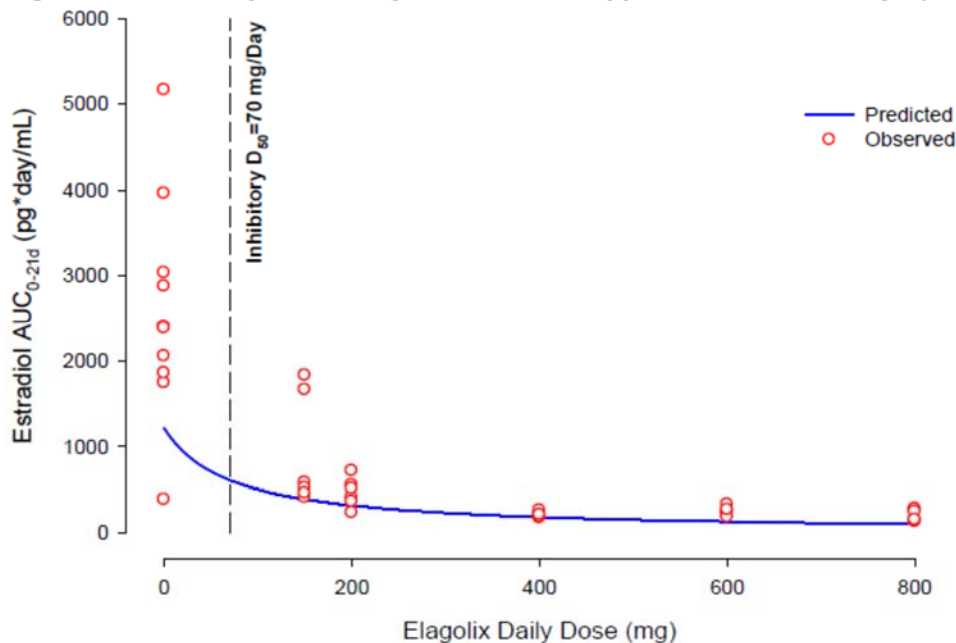


BID = twice daily, QD = once daily, LH = luteinizing hormone

Dose-response for estradiol suppression (**APPEARS THIS WAY ON ORIGINAL** Figure 5) was assessed at steady state using elagolix dose and estradiol $AUC_{0-21\text{day}}$. An elagolix daily dose of approximately 70 mg/day is estimated to suppress estradiol by 50% relative to placebo. Maximal suppression of estradiol appears to be achieved at approximately 200 mg BID.

A 7-day, multiple-dose study (Study M12-654) conducted in Asian subjects showed similar dose-dependent hormonal suppression at doses of 150 mg QD and 200 mg BID. In another 84-day study (Study M12-673) conducted in 205 adult premenopausal women at doses of 100 mg BID, 100 mg QD, 150 mg QD, 200 mg QD, 200 mg BID, and 300 mg BID; similar dose-dependent suppression of LH, LSH, estradiol, and progesterone was observed over the treatment period.

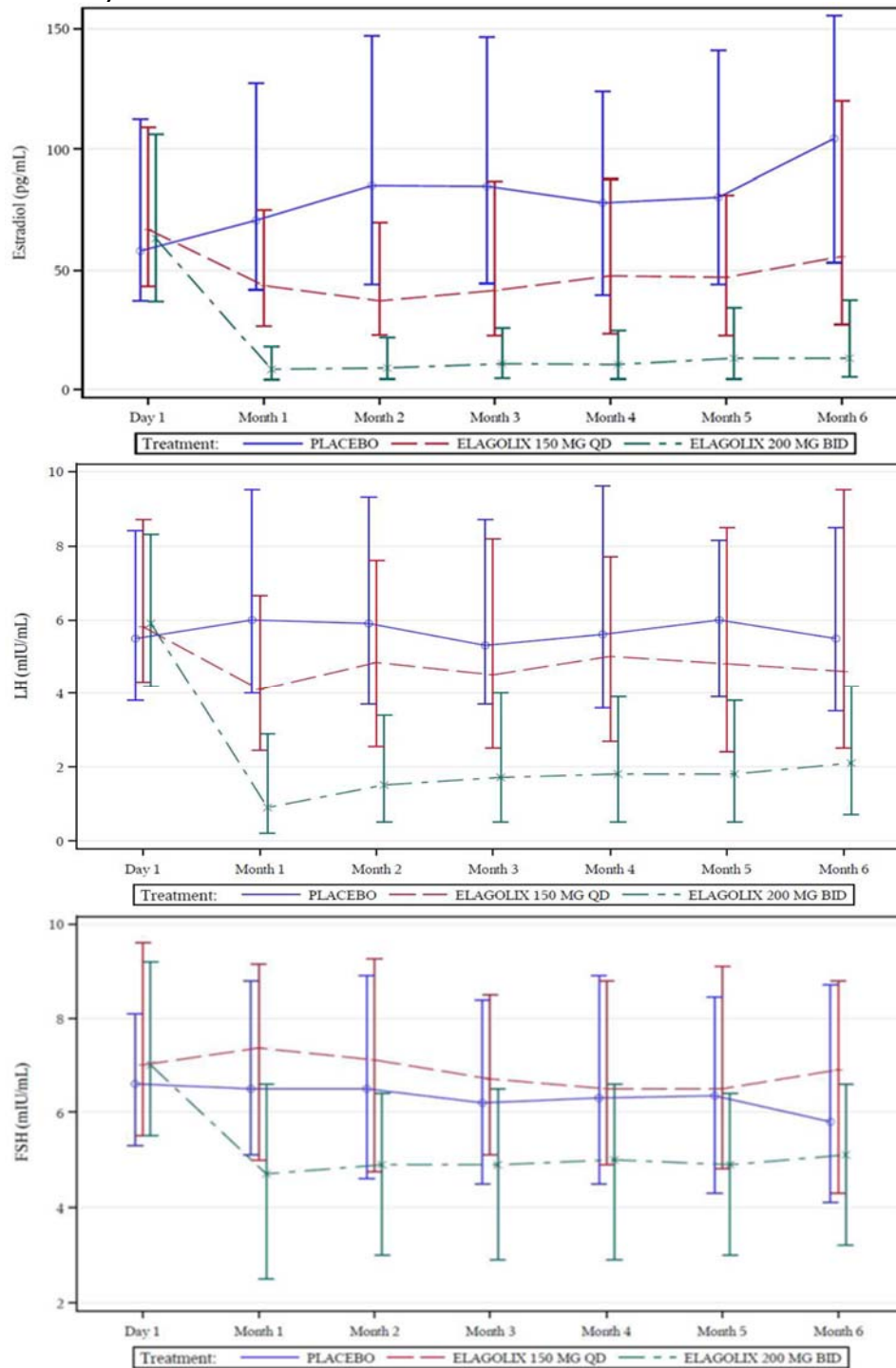
Figure 5. Dose-Response Analysis Estradiol Suppression Over 21 Days (Study M12-790)



AUC = area under the curve, D_{50} = dose to suppress by 50%

The long-term effects of elagolix on LH, LSH, and estradiol were assessed in Phase 3 studies. As shown below in Figure 6, in the pivotal efficacy Study M12-671, both 150 mg QD and 200 mg BID dosing regimens suppressed estradiol and LH compared to placebo during the 6-month treatment period. However, the effects on FSH differed between these two regimens—elagolix 200 mg BID appeared to lower FSH concentrations compared to placebo, while elagolix 150 mg QD appeared to slightly raise FSH concentrations compared to placebo. Similar results were observed in the second pivotal Study M12-665 (not shown). Similar findings of hormonal suppression were also seen in the extension Phase 3 Studies M12-667 and M12-821 up to 12 months of treatment (not shown).

Figure 6. Median Estradiol, LH and FSH Concentration–Time Profiles by Treatment Group (Study M12-671)



QD = once daily, BID = twice daily, FSH = follicle-stimulating hormone, LH = leutinizing hormone

Dose-dependent suppression of ovulation:

In women with endometriosis, ovulation can make the symptoms of endometriosis worse. In Study M12-673, the Applicant assessed the effect of different dosing regimens of elagolix (alone or with the hormonal add-back therapy Activella, estradiol 1.0 mg/norethindrone acetate 0.5

mg) on ovulation for up to 84 days of treatment. Ovulation was defined by an adjudication committee and manual adjudication was conducted for each cycle for each subject (Refer to the clinical pharmacology review in DARRTS for details). As shown in Table 18, the ovulation rate was the highest for the 100 mg QD treatment. The ovulation rates with elagolix 150 mg QD, 200 mg QD and 100 mg BID were similar, at approximately 50% by subject count. The ovulation rate with 200 mg BID was 31.7% and further decreased with 300 mg BID alone and with 300 mg BID hormonal add-back. Overall, the results showed a dose-dependent suppression of ovulation, which provided supportive evidence of the effectiveness of elagolix.

Table 18. Adjudication Definition of Ovulation Rates (Study M12-673)

	100 mg QD N = 9	150 mg QD N = 40	200 mg QD N = 35	100 mg BID N = 38	200 mg BID N = 41	300 mg BID N = 22	300 mg BID + Activella N = 20
Number (%) of subjects who ovulated	7 (78%)	20 (50%)	20 (57%)	18 (47%)	13 (32%)	6 (27%)	2 (10%)

QD = once daily, BID = twice daily

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

Yes, the proposed elagolix dose regimens (150 mg tablets QD or 200 mg tablets BID, to be taken orally with or without food) are appropriate for adult premenopausal women with moderate to severe pain associated with endometriosis. The proposed regimens are supported by clinical efficacy, safety, PK and PD data. However, due to BMD loss, the duration of treatment with elagolix 200 mg BID and 150 mg QD will be limited to 6 months and 24 months, respectively. See Section 8 for a detailed discussion of the efficacy and safety findings.

QT prolongation

The effect of elagolix on QT prolongation was evaluated in healthy premenopausal women. There was no significant QTc prolongation with a single dose of 300 mg or 1200 mg. With 1200 mg, the mean C_{max} value (13229 ± 4218 ng/mL) was ~17-fold the mean steady-state C_{max} (774 ± 530 ng/mL) at the maximum recommended dose of 200 mg BID.

Bone Mineral Density:

Long-term estradiol suppression by elagolix causes a decrease in BMD. As discussed in detail in Section 8, there were dose-dependent and treatment duration-dependent decreases in BMD at the lumbar spine, femoral neck and total hip, with partial recovery of BMD during the 12-month post-treatment period.

PK/PD:

The steady-state PK/PD profiles of elagolix 150 mg QD and from 100 mg BID to 400 mg BID were characterized in multiple clinical studies. Dose-dependent suppression of LH, FSH, estradiol and progesterone was demonstrated (Refer to section 6.3.2.1).

Applicability of Efficacy Data to the U.S. Population:

Among the 1,686 treated subjects in the two pivotal Phase 3 trials, most were white (88.1%); the remainder were: 8.8% black or African American, 0.9% Asian, and 14.7% Hispanic or Latino ethnicity. Three quarters (74.8%) of the subjects were enrolled at study sites in the U.S. and Canada. Population PK analyses did not indicate that race, ethnicity, or study region (U.S. sites or non-U.S. sites) were significantly associated with elagolix PK parameters.

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

Renal Impairment:

In a dedicated renal impairment study (Study M12-655), the PK of a single 200 mg oral dose of elagolix was characterized in adult women with normal renal function or mild renal impairment (eGFR $\geq$ 60 mL/min/1.73m², N = 6), moderate to severe renal impairment (eGFR between 15 and < 60 mL/min/1.73m², N = 3), and end stage renal disease (ESRD, eGFR < 15 mL/min/1.73m², N = 6) with 5 subjects requiring dialysis. The mean PK parameters of elagolix in female subjects with normal renal function or mild impairment, moderate to severe renal impairment, or ESRD are summarized in Table 19. Comparable exposure of elagolix was observed in subjects with varying renal function status. Renal impairment did not result in a significantly higher exposure of elagolix.

Table 19. Mean $\pm$ SD Pharmacokinetic (PK) Parameters of Elagolix in Female Subjects with Normal Renal Function or Mild Impairment, Moderate to Severe Renal Impairment, or End-Stage Renal Disease (ESRD)

PK Parameters	Treatment Group		
	Normal Function or Mild Impairment N = 5*	Moderate to Severe N = 3	ESRD N = 6
C _{max} (ng/mL)	987 $\pm$ 402	857 $\pm$ 370	1063 $\pm$ 330
AUC _{0-t} (ng*h/mL)	2593 $\pm$ 734	2387 $\pm$ 860	2800 $\pm$ 817
AUC _{0-inf} (ng*h/mL)	2596 $\pm$ 735	2390 $\pm$ 861	2806 $\pm$ 819
CL/F (L/h)	83.7 $\pm$ 30.4	93.9 $\pm$ 42.5	76.3 $\pm$ 21.1

* Subject (b) (6) was excluded from analysis. Refer to the clinical pharmacology review in DARRT for more information. AUC = area under the curve, PK = pharmacokinetic, CL/F = oral clearance, ESRD = end-stage renal disease, SD = standard deviation

A plasma binding study showed that renal impairment status did not impact protein binding of elagolix. We agree with the Applicant's proposal that no dose adjustment is recommended in women with any degree of renal impairment or ESRD (including women on dialysis).

The effect of hemodialysis on the PK of elagolix in subjects with ESRD was not studied. Based on the large volume of distribution of elagolix (1674 L for 150 mg QD and 881 L for 200 mg BID) and high nonrenal clearance of elagolix (approximately 2 L/min), only a small fraction of elagolix in the body is expected to be removed by dialysis. Therefore, no dose adjustment of elagolix is required in patients with ESRD maintained on intermittent hemodialysis.

Hepatic Impairment:

In a dedicated hepatic impairment study, the PK of a single 150 mg oral dose of elagolix was investigated in adult women with normal hepatic function (N = 6), mild stable chronic hepatic impairment (N = 6, Child-Pugh A), moderate stable chronic hepatic impairment (N = 6, Child-Pugh B), or severe stable chronic hepatic impairment (N = 4, Child-Pugh C).

As shown in Table 20, the mean AUC value of elagolix is 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 AUC values in subjects with normal hepatic function.

Table 20. Mean ± SD Pharmacokinetic (PK) Parameters of Elagolix in Female Subjects with Normal Hepatic Function, Mild, Moderate or Severe Hepatic Impairment

PK Parameters	Treatment Group			
	Normal Function N = 6	Mild N = 6	Moderate N = 6	Severe N = 4
C _{max} (ng/mL)	617 ± 166	566 ± 362	1896 ± 1275	3713 ± 367
T _{max} (h)	1.1 ± 0.3	1.3 ± 0.5	1.0 ± 0.4	0.7 ± 0.2
AUC _{0-t} (ng*h/mL)	1517 ± 384	1491 ± 1401	4615 ± 2533	10363 ± 3979
AUC _{0-inf} (ng*h/mL)	1520 ± 384	1494 ± 1401	4624 ± 2533	10374 ± 3988
CL/F (L/h)	104.6 ± 29.0	145.6 ± 61.9	43.3 ± 24.7	15.7 ± 4.4

AUC = area under the curve, CL/F = oral clearance, PK = pharmacokinetic

The human mass balance study (Study NBI-56418-0601) showed that two oxidative metabolites (O-demethy and N-dealkyl metabolites) constitute 2.4% and 3.3% of exposure relative to elagolix. For the O-demethy metabolite (M3), AUC values were similar between subjects with mild hepatic impairment and subjects with normal hepatic function. The AUC values of M3 in subjects with moderate hepatic impairment and subjects with severe hepatic impairment were approximately 5.4-fold and 17-fold, respectively, of AUC values in subjects with normal hepatic function. The M3 to elagolix AUC ratio observed in subjects with normal hepatic function was small (1.7%). Furthermore, the human GnRH receptor inhibition activity of M3 (IC₅₀ = 14 nM) is lower compared to elagolix (IC₅₀ = 1.5 nM). Thus, the increased exposure of M3 in subjects with moderate hepatic impairment is not likely to contribute significantly to the overall GnRH receptor inhibition. For the N-dealkyl metabolite (M6x), AUC_{0-inf} appeared to be 32% and 22% lower in subjects with mild and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. M6x AUC_{0-inf} was 27% higher in subjects with moderate impairment. The 20 to 30% changes in M6x exposure is unlikely to have a clinically relevant impact on efficacy or safety in subjects with hepatic impairment.

Based on the PK data of elagolix and its metabolites, the Applicant proposed no dose adjustment in women with mild hepatic impairment, only the elagolix 150 mg QD regimen to be used by women with moderate hepatic impairment, and a contraindication of both 150 mg QD and 200 mg BID regimens in women with severe hepatic impairment. Due to the risk of bone loss with the 3-fold increase in elagolix systemic exposures, we recommend that the

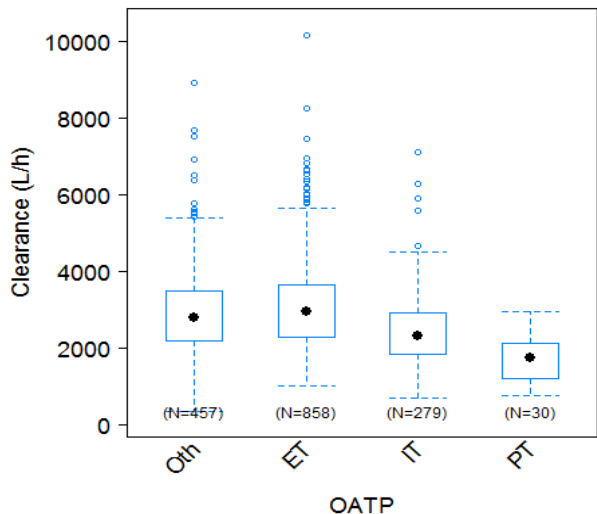
duration of treatment with elagolix 150 mg QD in women with moderate hepatic impairment be limited to 6 months.

OATP1B1 Transporter Genotype Status:

Population PK analysis identified that the OATP1B1 genotype status was a significant covariate for elagolix CL/F. In this analysis, subjects were divided into three groups: unknown status group, extensive transporter function (ET) group and combined intermediate/poor transporter function (IT/PT) group. The population PK analysis showed that subjects in the IT/PT combined group had 14% lower elagolix CL/F compared to subjects in the ET group. The Applicant claimed that the minor decrease in elagolix CL/F would not result in clinically meaningful changes in elagolix exposure and no dose adjustment in subjects with OATP1B1 IT or PT status was proposed.

The clinical pharmacology review team does not agree with pooling OATP1B1 IT and PT subjects in the population PK analysis because a pooling analysis does not show the difference in elagolix CL/F between IT and PT subjects and the sample size of PT subjects (N = 30) is reasonably adequate for a categorical analysis. Our population PK analysis showed that the mean CL/F values of elagolix in IT subjects and PT subjects were lower than that in subjects with the ET genotype and undetermined genotype (see Figure 7 and refer to the clinical pharmacology review in DARRTS for more information). As shown in Table 21, the AUC of elagolix in subjects with the IT genotype or PT genotype is expected to increase by 24% and 78%, respectively, compared to subjects with the ET genotype (normal OATP1B1 transporter function).

Figure 7. OATP1B1 Genotype and Elagolix Clearance Covariate Relationships



OATP = organic anion transporting polypeptide, ET = extensive transporter function, IT = intermediate transporter function, PT = poor transporter function

Table 21. Mean Steady-State AUC Values for the 150 mg QD Dose in Subjects with Various OATP1B1 Genotypes Predicted by FDA’s Population Pharmacokinetic Analysis

OATP Type	Predicted Steady-State AUC ₀₋₂₄ for the 150 mg QD Treatment					Predicted Change in AUC Compared to Extensive Genotype
	N	Mean	Std Dev	Minimum	Maximum	
Extensive	858	55.3	20.7	14.8	148.2	--
Intermediate	279	68.3	24.4	21.1	209.1	↑ 23.5%
Poor	30	98.5	37.1	50.5	195.1	↑ 78.1%
Others	457	59.1	29.1	16.8	407.2	↑ 6.9%

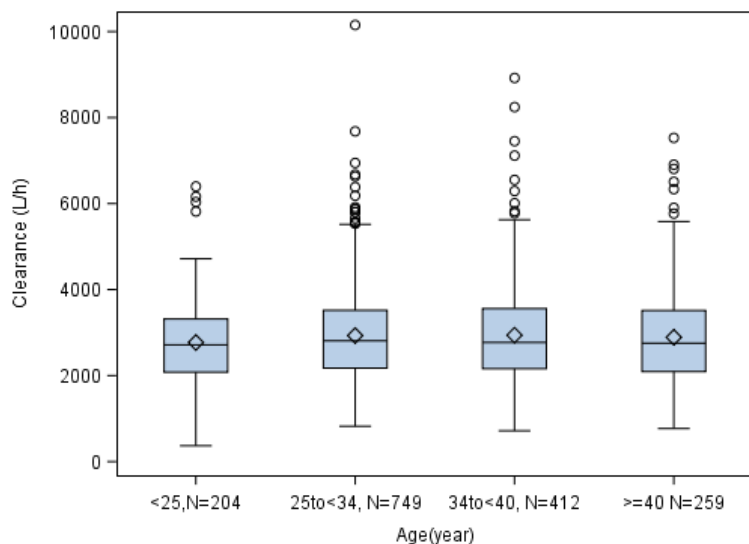
OATP = organic-anion-transporting polypeptide, AUC = area under the curve, QD = once daily

The 24% increase in the exposure of elagolix in ITs is not expected to have a clinically meaningful impact on efficacy and safety and no dose adjustment is recommended in this subgroup. Because of the variability of elagolix exposures across OATP1B1 subgroups, the 78% increase in elagolix AUC among the PTs overlaps with exposures in the other subgroups and the clinical pharmacology review team does not recommend dose adjustment for these women.

Age:

The mean age of the subjects included in the population PK analysis was 32.3 ± 6.5 years and the age range was 18 to 49 years. Our population PK analysis confirmed the Applicant’s finding that age did not affect the clearance of elagolix (see Figure 8 and refer to the clinical pharmacology review in DARRTS for more information). These data do not suggest a need for age-based dose adjustment.

Figure 8. Box-plot Comparison of Elagolix CL/F Grouped by Age



CL/F = oral clearance

The Applicant’s subgroup analysis for BMD showed that there was no apparent trend in mean percent changes in femoral neck, hip and lumbar spine BMD from baseline corresponding with increasing age compared to placebo at month 6 of 150 mg QD or 200 mg BID treatments (Table 22).

Overall, consistent elagolix PK and changes in BMD were observed in subjects aged 18 to 49 years. The clinical pharmacology review team agrees with the Applicant that no age-based dose adjustment is recommended for premenopausal women with endometriosis.

Table 22. Mean Percent Changes in BMD by Age Compared to Placebo at Month 6 of Treatment
Mean (95% CI)

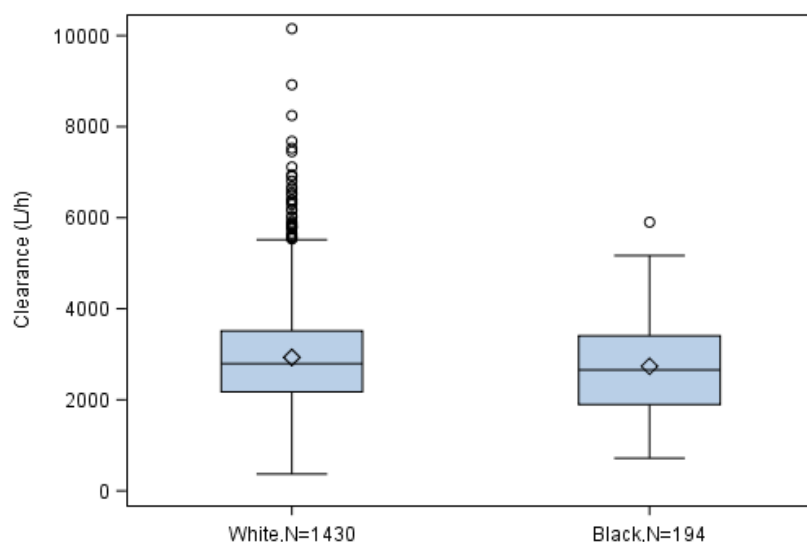
Treatments	Anatomic Region	< 25 Years	25 to 34 Years	35 to 39 Years	≥ 40 Years
150 mg QD	Femoral neck	-0.33 (-1.75 to 1.10)	-0.36 (-0.94 to 0.23)	-0.58 (-1.50 to 0.35)	-1.28 (-2.18 to -0.39)
	Total hip	-0.45 (-1.41 to 0.51)	-0.84 (-1.24 to -0.44)	-0.72 (-1.37 to -0.08)	-0.96 (-1.53 to -0.40)
	Spine	-0.18 (-1.16 to 0.80)	-1.31 (-1.76 to -0.85)	-0.93 (-1.75 to -0.12)	-1.19 (-2.10 to -0.29)
200 mg BID	Femoral neck	-2.28 (-3.66 to -0.89)	-1.38 (-1.97 to -0.79)	-2.18 (-3.10 to -1.27)	-2.34 (-3.19 to -1.48)
	Total hip	-2.06 (-2.99 to -1.13)	-1.71 (-2.11 to -1.30)	-2.27 (-2.91 to -1.63)	-2.19 (-2.73 to -1.64)
	Spine	-3.46 (-4.40 to -2.51)	-3.02 (-3.48 to -2.56)	-3.59 (-4.39 to -2.79)	-2.38 (-3.25 to -1.51)

BID = twice daily, BMD = bone mineral density, CI = confidence interval, QD = once daily

Race and Ethnicity:

Our population PK analysis evaluating the effect of race on elagolix clearance between black subjects (N = 194, 11.9%) and white/other subjects (N = 1430, 88.1%) did not detect a significant difference in elagolix CL/F between these two racial groups (Figure 9). Our population PK analysis evaluating the effect of ethnicity on elagolix clearance between Hispanics (N = 272, 16.7%) and others (N = 1352, 83.3%) did not detect a significant difference in elagolix CL/F between these two ethnic groups (Refer to the clinical pharmacology review in DARRTS for more information).

Figure 9. Box-plot Comparison of Elagolix CL/F Grouped by Race



CL/F = oral clearance

The Applicant conducted a multiple-dose PK study (Study M12-654) in California to compare the PK and PD of elagolix in Japanese and Han Chinese. The PK results are shown in the table below. The mean C_{max} and AUC values between Japanese and Han Chinese were comparable. The Applicant compared the Asian PK parameters with the PK parameters of white and black subjects collected from Study M12-790. Based on this cross-study comparison, the Applicant concluded that elagolix PK parameters are similar between Japanese, Han Chinese, white and black subjects and no dose adjustment is required based on race.

Table 23. A Cross-study Comparison of PK Parameters of Japanese, Han Chinese, and Western Subjects

Dose Regimens	PK Parameters	Japanese (M12-654) N = 7	Han Chinese (M12-654) N = 8	Western (M12-790) N = 6
150 mg QD		Day 7		Day 21
	T_{max} (h)	1.07 ± 0.53	0.75 ± 0.38	0.9 ± 0.2
	C_{max} (ng/mL)	749 ± 128	711 ± 170	574 ± 164
	AUC_{0-24} (ng*h/mL)	1490 ± 540	1378 ± 421	1292 ± 403
	$T_{1/2}$ (h)	6.58 ± 4.18	9.80 ± 9.47	6.42 ± 3.20
200 mg BID		Japanese N = 8	Han Chinese N = 6	Western (M12-790) N = 7
		Day 7		Day 21
	T_{max} (h)	1.25 ± 0.27	0.84 ± 0.40	1.1 ± 0.4
	C_{max} (ng/mL)	929 ± 305	833 ± 376	774 ± 530
	AUC_{0-12} (ng*h/mL)	2059 ± 619	1851 ± 845	1725 ± 990
	$T_{1/2}$ (h)	5.26 ± 1.04	7.04 ± 2.27	4.29 ± 0.47

AUC = area under the curve, QD = once daily, BID = twice daily

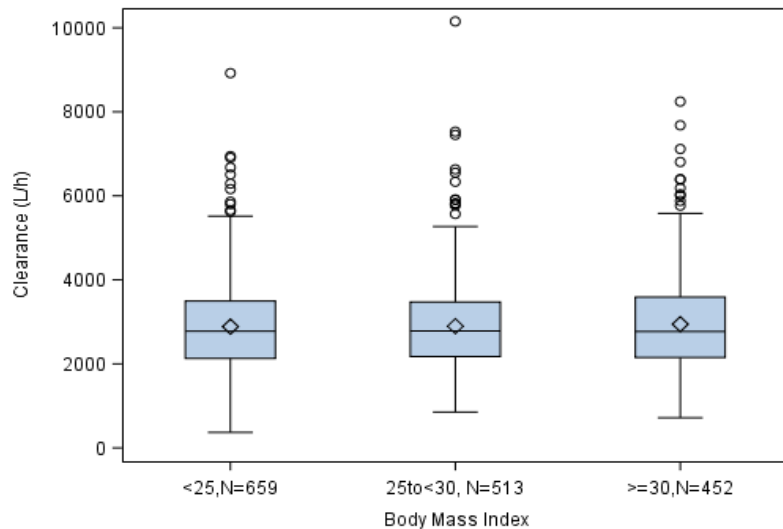
Based on these population PK results, we concur that there is no clinically meaningful difference in the PK of elagolix between white and black subjects or between Hispanics and non-Hispanics. We also concur that there is no clinically meaningful difference in the PK of

elagolix between Japanese and Han Chinese. However, it is not possible to draw definitive conclusions based on the cross-study PK comparison between Asian and Western subjects. In addition, only 16 Asian subjects were enrolled in the two pivotal Phase 3 trials and only 7 of them received elagolix treatment. Neither a population PK analysis nor efficacy/safety subgroup analysis for the Asian group was conducted due to the very limited data from Asian subjects.

Body Weight and Body Mass Index (BMI):

The mean body weight of the 1624 subjects included in the population PK analysis was 73.7 ± 17.3 kg and the body weight range was 40 to 148 kg. The mean BMI was 27.3 ± 6.2 kg/m² and the BMI range was 16.2 to 55.6 kg/m². Our population PK analysis showed that the CL/F of elagolix was not affected by body weight or BMI (Figure 10, Refer to the clinical pharmacology review in DARRTS for more information). These data do not suggest a need for body weight-based or BMI-based dose adjustment.

Figure 10. Box-plot Comparison of Elagolix CL/F Grouped by Body Mass Index (BMI)



CL/F = oral clearance

The Applicant's subgroup analysis showed no apparent trend in mean percent changes from baseline in femoral neck, hip, and lumbar spine BMD across BMI subgroups for elagolix 150 mg QD compared to placebo at month 6. For elagolix 200 mg BID compared to placebo at month 6, there was an apparent trend in mean percent changes from baseline in femoral neck, hip and lumbar spine BMD corresponding with increasing BMI (lower BMI, larger decrease in BMD).

Table 24. Percent Changes in BMD by BMI Compared to Placebo at Month 6 of Treatment

Treatments	Anatomic Region	Mean (95% CI)		
		BMI < 25 kg/m ²	BMI ≥ 25 and < 30 kg/m ²	BMI ≥ 30 kg/m ²
150 mg QD	Femoral neck	-0.60 (-1.26, 0.07)	-0.43 (-1.13, 0.27)	-0.59 (-1.37, 0.20)
	Total hip	-0.92 (-1.36, -0.49)	-0.76 (-1.24, -0.27)	-0.69 (-1.23, -0.14)
	Spine	-0.92 (-1.45, -0.39)	-0.71 (-1.30, -0.12)	-1.52 (-2.17, -0.87)
200 mg BID	Femoral neck	-2.23 (-2.86, -1.60)	-1.55 (-2.29, -0.80)	-1.40 (-2.19, -0.61)
	Total hip	-2.41 (-2.82, -2.00)	-1.78 (-2.29, -1.26)	-1.36 (-1.90, -0.81)
	Spine	-3.74 (-4.24, -3.24)	-2.77 (-3.39, -2.15)	-2.36 (-3.02, -1.70)

QD = once daily, BID = twice daily, BMD = bone mineral density, BMI = body mass index

Overall, population PK analysis showed that subject body weight or BMI is not a significant covariate associated with elagolix CL/F. For 200 mg BID treatment, the large BMD decrease from baseline to month 6 (-3.74%) observed in BMI < 25 kg/m² subgroup is a safety concern, which we believe can be mitigated with the 6-month limitation in treatment duration. We do not recommend dose adjustment based on body weight or BMI.

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

Food Effects:

Elagolix was administered at least 1 hour before or 2 hours after a meal in three Phase 3 trials (Studies M12-665, M12-667, and M12-671), and was administered without regard to meals in extension trial Study M12-821. A dedicated food effect study, using a single 200 mg dose (Study M15-817), was conducted with the commercial formulation in healthy premenopausal women. The Applicant's calculation showed that under high-fat meal conditions, there was a decrease of 24% and 36% in elagolix AUC and C_{max}, respectively, relative to fasted conditions (see Table 25). The Applicant's exposure-response analyses and simulations showed that the decrease of elagolix exposure under fed conditions did not have a clinically meaningful impact on efficacy. We concur with the Applicant that elagolix can be taken without regard to meals and no dose adjustment is recommended under fed conditions.

Table 25. The Effect of Food on the PK parameters of the Elagolix Commercial Formulation 200 mg Tablet (Study M15-817): Applicant's Calculation

Parameter	Least Squares Geometric Means		% Fed/Fasted Ratio (90% CI)
	Fed Conditions	Fasting Conditions	
C _{max} (ng/mL)	437	689	63.5 (53.2–75.9)
AUC _{0-t} (ng*h/mL)	1401	1859	75.4 (69.4–81.8)
AUC _{0-inf} (ng*h/mL)	1412	1865	75.7 (69.8–82.1)

AUC = area under the curve, CI = confidence interval, PK = pharmacokinetic

The magnitude of the food effect is formulation-dependent. In addition to Study M15-817, the effect of food on the PK of different elagolix formulations was assessed in Study NBI-56418-0701, Study M12653, Study M13995, and Study M14731. As shown in Table 26, a high-fat meal consistently decreased the exposure of elagolix across all the formulations. However, the

(b) (4) formulation 150 mg tablet had the greatest decrease in elagolix AUC (42%) and C_{max} (66%) under fed conditions. The (b) (4) formulation was administered under fasted conditions in Phase 3 studies (M12-665, M12-667, and M12-671) and thus the observed food effect on this formulation did not affect the efficacy and safety findings in the Phase 3 studies. Under fed conditions, a decrease in elagolix exposure was also observed with the NBI (b) (4) formulation 50 mg tablet, the (b) (4) formulation 150 mg tablet, the (b) (4) formulation 200 mg tablet, and (b) (4) formulation 200 mg tablet. These four formulations were not used in any other clinical studies.

Table 26. The Effect of Food on the PK parameters of Different Elagolix Formulations

Study No.	Formulations and Strengths	Study Dose	Geometric Mean Ratio (%) (Fed/Fasted)		
			AUC _{0-inf}	AUC _{0-t}	C _{max}
NBI-56418-0701	NBI (b) (4) formulation, 50 mg	150 mg	67.2	66.9	47.0
M12-653	(b) (4) 150 mg	150 mg	59.1	58.0	35.1
	(b) (4) 150 mg, Phase 3 formulation	150 mg	57.7	56.5	33.9
M13-995	(b) (4) 200 mg	200 mg	64.3	63.7	49.5
M14-731	(b) (4) 200 mg	200 mg	68.3	68.0	53.9

AUC = area under the curve, PK = pharmacokinetic, IR = immediate release

Drug-Drug Interactions:

Elagolix is extensively metabolized in the liver, primarily by CYP3A4, and to a lesser extent by CYP2D6, followed by CYP2C8. In vitro tests showed that elagolix is a time-dependent inhibitor of CYP3A4/5 (K_i 74µM), CYP2C8 (K_i 82µM) and CYP2C19 (K_i 34µM), an inducer of CYP3A4, CYP2B6, CYP2C8, and a potential inducer of CYP2C9 and CYP2C19. In vitro drug interaction studies revealed that elagolix is a substrate of P-gp and OATP1B1 transporters and an inhibitor of OATP1B1 (IC₅₀ 1.7µM), OATP1B3 (IC₅₀ 4.7µM), P-gp (IC₅₀ 54µM), and breast cancer resistance protein (BCRP; IC₅₀ 150µM) transporters. With an observed mean elagolix C_{max} of 774 ng/ml (1.23µM) following dosing of elagolix 200 mg twice daily, the in vitro studies suggest that therapeutic doses of elagolix are not expected to inhibit CYP enzymes but may cause inhibition of OATP1B1.

The Applicant conducted ten clinical studies and one physiologically-based pharmacokinetics modeling study to assess the drug-drug interactions (DDIs) of elagolix. The clinical DDI study findings and management strategies are summarized in Table 16.

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%. A mean decrease of 3.22% in BMD was observed in 13 subjects who were treated with elagolix 200 mg BID for less than 6 months in Phase 3 trials. Due to the concern over bone loss which is heightened when elagolix exposures are increased, we recommend that concomitant use of elagolix 200 mg BID dose and strong CYP3A inhibitors be limited to 1 month and that concomitant use of elagolix 150 mg QD dose and strong CYP3A inhibitors be limited to 6 months.

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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 a potent OATP1B1 inhibitor, the 150 mg QD regimen of elagolix would result in a drug exposure around 800 mg QD elagolix administered alone. The maximum single-dose exposure of elagolix in human was 1200 mg and the maximum multi-dose exposures in humans were 400 mg BID for 21 days and 600 mg QD for 24 weeks. Based on the 5.6-fold increase in elagolix AUC with potent OATP1B1 inhibitors, we recommend that concomitant use of elagolix and potent OATP1B1 inhibitors be contraindicated. Rifampin is a special case with complex drug interactions with elagolix. Study M12-659 also evaluated the effect of administering rifampin 600 mg QD for 10 days, which 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. When co-administered with rifampin 600 mg QD, the 150 mg QD regimen of elagolix would result in a drug exposure equivalent to 800 mg elagolix daily dose on day 1 and 250 mg elagolix daily dose on day 10. Concomitant use of rifampin 600 mg QD and elagolix 200 mg BID would result in an exposure of elagolix equivalent to 1100 mg BID on day 1 and 330 mg BID on day 10. Considering both the OATP1B1 inhibition and CYP3A/P-gp/OATP1B1 induction by rifampin, we recommend that concomitant use of elagolix 200 mg BID and rifampin be avoided and concomitant use of elagolix 150 mg QD dose and rifampin be limited to 6 months.

Co-administration of rosuvastatin 20 mg QD at steady-state with the first 300 mg dose of elagolix resulted in an increase of rosuvastatin C_{max} by 67% and a comparable AUC to rosuvastatin administered alone (Study M13-756). Co-administration of rosuvastatin 20 mg QD at steady-state with multiple dose of elagolix 300 mg BID resulted in a comparable rosuvastatin C_{max} to rosuvastatin administered alone and a decrease of rosuvastatin AUC by approximately 40%. The mechanisms for the decrease in rosuvastatin AUC when co-administered with multiple doses of elagolix is unknown. OATP1B1 induction by elagolix may be one of the possible mechanisms.

The Applicant assessed the DDIs between elagolix 150 mg QD and norethindrone 0.35 mg QD in Study M12-765. No clinically meaningful changes in the PK of norethindrone were observed. The Applicant proposed that no dose adjustment is required for concomitant use of elagolix with progestin-only oral contraceptives. However, because norethindrone is not the most sensitive substrate of CYP3A enzymes among orally administered progestins, results from Study M12-765 cannot be generalized to other progestins. In addition, the dose of elagolix (150 mg QD) assessed in Study M12-765 did not cover the proposed 200 mg BID dosing regimen. While we recommend no dose adjustment for concomitant use of elagolix 150 mg QD with oral norethindrone, the potential DDIs between elagolix 200 mg BID and progestins remain unknown. The Applicant also assessed the DDIs between elagolix 150 mg QD and ethinyl estradiol/norgestimate in Study M12-651. However, that study also did not cover the proposed 200 mg BID dosing regimen. Study M12-651 showed no clinically meaningful changes in the PK of norgestimate metabolites (norelgestromin and norgestrel) but reported an unexpected 30% increase in exposure of ethinyl estradiol. We recommend a postmarketing commitment to

assess the effect of elagolix 200 mg BID on the pharmacokinetics of an oral combination hormonal contraceptive.

6.3.2.5. 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 to-be-marketed formulation (commercial (b) (4) formulation) is different from the formulations (b) (4) used in the two placebo-controlled Phase 3 trials. The Applicant conducted a pivotal bioequivalence (BE) study (Study M15-817) to bridge the to-be-marketed formulation to the (b) (4) formulation and conducted another BE study (Study M13-995) to bridge the Phase 3 (b) (4) formulation to the (b) (4) formulation. Both BE study results met the Agency's bioequivalence criteria.

As shown in Table 27, the commercial (b) (4) 150 mg and (b) (4) 200 mg tablets are the proposed to-be-marketed formulation. The (b) (4) formulation was used in two pivotal Phase 3 studies (M12-665 and M12-671) and one Phase 3 extension study (Study M12-667). The (b) (4) formulation was used in the second Phase 3 extension study (M12-821). The commercial (b) (4) 200 mg tablet was bridged to the (b) (4) formulation 100 mg tablet using clinical BE Study M15-817. Comparative in vitro dissolution data were submitted to support the biowaiver request for the commercial (b) (4) 150 mg tablet. Clinical BE Study M13-995 was conducted to bridge two Phase 3 formulations, (b) (4) 200 mg tablet and (b) (4) 100 mg tablet. In vitro dissolution data were submitted to bridge the Phase 3 (b) (4) 150 mg tablet and the (b) (4) 100 mg tablet. The commercial (b) (4) has the same (b) (4) tablet composition as the Phase 3 (b) (4). Minor changes between the Phase 3 (b) (4) and commercial (b) (4) were made: (b) (4)

(b) (4)
The Applicant provided in vitro dissolution data to bridge the changes between the Phase 3 (b) (4) and commercial (b) (4)

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Table 27. Phase 3 Clinical Formulations, the To-Be-Marketed Formulation and Bridging Studies

Products	Strength	Phase 3 Studies	Bridging BE Studies
(b) (4) (pivotal Phase 3 formulation)	100 mg IR tablet	M12-665	M13-995, M15-817
		M12-667	
		M12-671	
	150 mg IR tablet	M12-665	
		M12-667	
		M12-671	
(b) (4) (Phase 3 extension study formulation)	150 mg IR tablet	M12-821	M13-995
	200 mg IR tablet	M12-821	
	300 mg IR tablet	---	
Commercial (b) (4) (TBM formulation)	(b) (4) 150 mg light pink	---	Biowaiver request
		200 mg light orange	M15-817

TBM = to-be-marketed, IR = immediate release, BE = bioequivalence

Table 28. Study M15-817: Bioequivalence Assessment for Elagolix (FDA's analysis)

Parameter	Least Squares Geometric Means		% A/B Ratio (90% CI)
	Regimen A [Test]	Regimen B [Ref]	
C _{max} (ng/mL)	640.7	672.1	95.34 (87.31–104.10)
AUC _{0-t} (ng*h/mL)	1695.2	1713.8	98.92 (94.50–103.54)
AUC _{0-inf} (ng*h/mL)	1700.3	1718.0	98.97 (94.56–103.58)

Regimen A: One elagolix 200 mg immediate release tablet (commercial (b) (4) light orange) administered under fasting conditions (test); Regimen B: Two elagolix 100 mg immediate release tablets (Phase 3 (b) (4) administered under fasting conditions (reference))
 AUC = area under the curve, CI = confidence interval

Table 29. Study M13-995: Bioequivalence Assessment for Elagolix (FDA's analysis)

Parameter	Least Squares Geometric Means		% A/B Ratio (90% CI)
	Regimen A [Test]	Regimen B [Ref]	
C _{max} (ng/mL)	788.8	808.9	97.5 (89.24–106.56)
AUC _{0-t} (ng*h/mL)	2062.6	2223.4	92.8 (87.33–98.54)
AUC _{0-inf} (ng*h/mL)	2068.7	2230.3	92.8 (87.34–98.51)

Regimen A: One elagolix 200 mg immediate release tablet (Phase 3 (b) (4) administered under fasting conditions (test))
 Regimen B: Two elagolix 100 mg immediate release tablets (Phase 3 (b) (4) administered under fasting conditions (reference))
 AUC = area under the curve, CI = confidence interval

As shown in the tables above, both Study M15-817 and Study M13-995 met the bioequivalence criteria. Although our calculations are slightly different from the Applicant's calculations (Refer to the clinical pharmacology review in DARRTS for more information), we concur with the Applicant that the commercial (b) (4) 200-mg light orange tablet and Phase 3 (b) (4) 200-mg tablet are bioequivalent to two Phase 3 (b) (4) 100-mg tablets. In addition, we found the submitted in vitro dissolution data to be adequate to support the biowaiver for the (b) (4) 150-mg light pink tablet and to bridge the 150 mg strengths of the Phase 3 (b) (4) and commercial (b) (4) formulations.

A (b) (4) formulation (50 mg/tablet and 150 mg/tablet) was used in 16 Phase 1 studies. Study M12-653 was conducted to bridge the Phase 3 (b) (4) 150 mg tablet to the Phase 1 (b) (4) 150-mg tablet. As shown in the table below, those two formulations are bioequivalent.

Table 30. Study M12-653: Bioequivalence Assessment for Elagolix

Parameter	Least Squares Geometric Means		% A/B Ratio (90% CI)
	Regimen B [Test]	Regimen C [Ref]	
C _{max} (ng/mL)	465.9	468.5	99.4 (88.1 – 1.122)
AUC _{0-t} (ng•h/mL)	1196.2	1158.7	103.2 (97.5 – 109.3)
AUC _{0-∞} (ng•h/mL)	1205.0	1168.1	103.2 (97.5 – 109.2)

Regimen B: One elagolix 150 mg IR tablet (Phase 3 ^{(b) (4)} administered under fasting conditions (test)
Regimen C: One elagolix 150 mg IR tablet (Phase 1 ^{(b) (4)} administered under fasting conditions (reference)
AUC = area under the curve, CI = confidence interval

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The application includes the following clinical studies:

- 7 bioavailability studies
- 1 ADME study
- 22 pharmacokinetic and/or pharmacodynamic studies
- 6 Phase 2 placebo-controlled trials of 12- or 24-weeks duration in subjects with endometriosis-associated pain
- 2 Phase 3 efficacy and safety trials in subjects with moderate to severe endometriosis-associated pain of 6-month duration
- 2 Phase 3 safety extension trials of 6-month duration
- 2 Phase 2/3 efficacy and safety trials in subjects with heavy uterine bleeding associated with fibroids of 12-week and 24-week duration

The clinical review will focus primarily on the two pivotal Phase 3 efficacy and safety trials in subjects with moderate to severe endometriosis-associated pain (EAP) and the two safety extension trials.

Phase 2 Trials:

Data from six Phase 2 trials are included in this application. All were randomized, double-blind trials and all utilized elements of EAP as endpoints with treatment duration of 12 or 24 weeks (see Table 31). Among these six Phase 2 trials, ^{(b) (4)} three evaluated the immediate-release (IR) elagolix formulation. The placebo-controlled portion of the trials assessing the IR elagolix formulation up to 200 mg per day (Studies 702, 703, and 901 only) were of 8- to 12-week duration; these three trials formed the basis for dose-ranging investigation prior to Phase 3. Notably, of the two dosing regimens

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proposed for marketing (elagolix 150 mg QD and elagolix 200 mg BID) only the former was assessed in Phase 2.

Table 31. Phase 2 Clinical Trials Evaluating Elagolix for the Treatment of Endometriosis-Associated Pain

Trial ID	Study Design	Treatment (Number of Subjects Treated)	Treatment Duration
NBI-56418-501	R, DB, PC	Placebo (28) Ela (b) (4) 75 mg QD (25) Ela (b) (4) 150 mg QD (23)	12 weeks
NBI-56418-504	R, DB, PC	Placebo (20) Ela (b) (4) 50 mg BID (23) Ela (b) (4) 100 mg BID (25)	12 weeks
NBI-56418-603	R, DB, active-controlled	Ela (b) (4) 75 mg BID (84) Ela (b) (4) 150 mg QD (84) Depo Provera* (84)	24 weeks
NBI-56418-702	R, DB, PC	Placebo (52, 38 re-randomized to Ela after 12 weeks) Ela IR 150 mg QD (51) Ela IR 250 mg QD (52)	24 weeks
NBI-56418-703	R, DB, PC and active-controlled	Placebo (43, 41 re-randomized to Ela after 12 weeks) Ela IR 150 mg QD (43) Ela IR 250 mg QD (44) Leuprorelin acetate (44, all re-randomized to Ela after 12 weeks)**	24 weeks
NBI-56418-901	R, DB, PC for 8 weeks, then open-label for 16 weeks	Placebo x 8 weeks (6) Ela IR 150 mg QD x 24 weeks (68) Placebo x 8 weeks/Ela 150 mg QD x 16 weeks (63)	24 weeks

R= randomized, DB= double-blind, PC= placebo-controlled, Ela = elagolix, QD = once daily, BID = twice daily, ID = identification number, (b) (4) IR = immediate release

*Depo Provera injection was given subcutaneously at week 1 and week 12 of the trial as active control.

**Subjects who received leuprorelin acetate intramuscular injection 3.75 mg monthly for 12 weeks were re-randomized to either elagolix 150 mg QD or elagolix 250 mg QD

Source: Tabular Listing of Clinical Studies 2.7.6 Synopses of Individual Studies

Phase 3 Trials:

As shown in Table 32 below, two Phase 3, randomized, double-blind, placebo-controlled trials, each followed by an open-label extension provide the efficacy and safety data for the proposed use. The first controlled trial was conducted exclusively in the U.S. and Canada while the other had global sites.

Table 32. Pivotal and Extension Clinical Trials to Support Efficacy and Safety

Trial ID and NCT #	Study Design	Treatment (Number of Subjects Treated)	Treatment Duration	Comments
Pivotal Trials				
M12-665 NCT 01620528	R, DB, PC	• Placebo (374) • Ela 150 mg QD (249) • Ela 200 mg BID (248) • Total – 871	6 months	U.S. sites
M 12-671 NCT 01931670	R, DB, PC	• Placebo (360) • Ela 150 mg QD (226) • Ela 200 mg BID (229) • Total – 815	6 months	U.S. and global sites
Extension Trials				
M 12-667 NCT 01760954	R, DB	• Ela 150 mg/Ela 150 mg QD (149)* • Ela 200 mg/Ela 200 mg BID (138)* • Placebo/Ela 150 mg QD (108)* • Placebo/Ela 200 mg BID (109)* • Total – 504	6 months	U.S. sites
M12-821 NCT 02143713	R, DB	• Ela 150 mg/Ela 150 mg QD (142)* • Ela 200 mg/200 mg BID (140)* • Placebo/Ela 150 mg QD (102)* • Placebo/Ela 200 mg BID (111)* • Total – 495	6 months	U.S. and global sites

R= randomized, DB= double-blind, PC= placebo-controlled, Ela = elagolix, BID = twice daily, QD = once daily
 * Ela/Ela refers to patients who received elagolix during the placebo-controlled trial and extension trial. Placebo/Ela refers to patients who received placebo during the placebo-controlled trial and were randomized to elagolix for the extension trial.
 Source: Tabular Listing of Clinical Studies 2.7.6 Synopses of Individual Studies

7.2. Review Strategy

Evaluation of efficacy data was undertaken jointly by the clinical reviewer for efficacy, Abby Anderson, MD, and the statistical review team. Assessment of overall safety was conducted by the clinical reviewer for safety, Gerald Willett, MD, who focused on all clinical safety except for bone loss; the Division’s bone team Linda Jaffe, MD, and Theresa Kehoe, MD, provided a dedicated review of the bone safety findings.

7.2.1. Data Sources

The sources of data used for the evaluation of the efficacy and safety of elagolix 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\NDA210450\0000\m5\datasets>

7.2.2. Data and Analysis Quality

After the applicant's clarifying responses to FDA's information requests, the statistical reviewer could reproduce the analysis results using the submitted analysis datasets. No other data or analysis quality issues were identified.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design and Endpoints

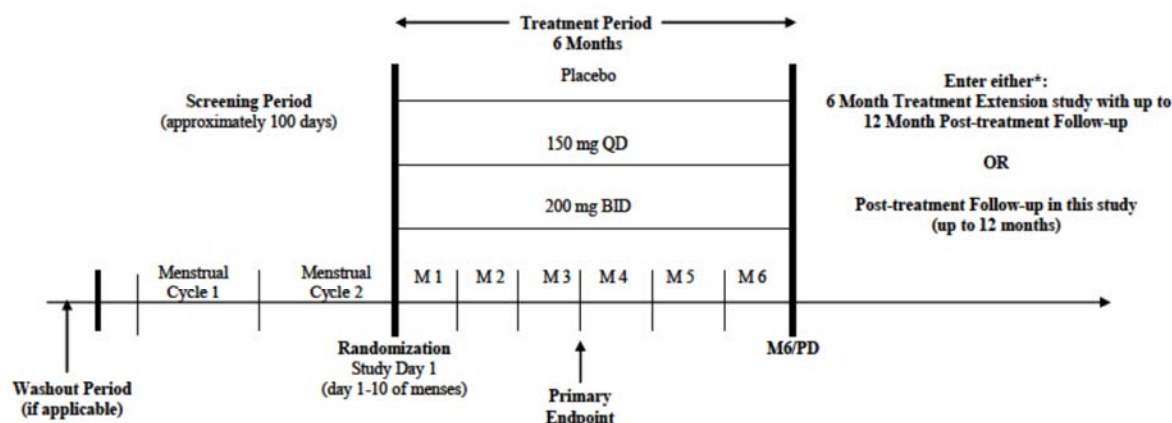
Trial Design

The purpose of both studies M12-665 (hereafter, Study 665) and M12-671 (hereafter, Study 671) was to evaluate the safety, tolerability, and efficacy of two doses of elagolix for 3 months in the management of moderate to severe endometriosis-associated pain.

In both Studies 665 and 671, subjects were randomized into one of three parallel dose arms – elagolix 150 mg QD, elagolix 200 mg BID, and placebo – in a 3:2:2 ratio.

The study consisted of a wash out period (if applicable), a screening period (up to 100 days), a 6-month treatment period, and if the subject declined the extension trial, a post treatment follow up period (PTFU) for up to 12 months, until the subject had return of menses and had demonstrated pre-specified bone recovery. Subjects who prematurely withdrew from the treatment period would enter the PTFU period upon discontinuation of drug. An extension trial for an additional 6 months of treatment was available for subjects who were eligible and desired continued treatment (see Studies M12-667 and M12-821). A diagram of the four study periods is shown in Figure 11 below.

Figure 11. Schema of Study Periods



* After completing the Treatment Period, subjects will enter either the Post-treatment Follow-up Period (up to 12 months) **OR**, if eligible, a separate continuous use extension study. Subjects will only enter the Post-treatment Follow-up Period in this study, if they prematurely discontinue from treatment, do not qualify for or decline to participate in the separate continuous use extension study.

Source: Protocol M12-665 Final Protocol p 40. One month was defined as 28 days.
BID = twice daily, QD = once daily

The study plan called for premenopausal women aged 18 to 49 years from approximately 200 sites in the U.S./Canada (Study 665) and approximately 240 international sites and the U.S. (Study 671) with a diagnosis of EAP.

A Washout period was required for subjects who were taking any hormonal contraceptives, estrogen or progestin preparations (including a progestin intrauterine system [IUS]), GnRH agonists or antagonists, aromatase inhibitors, and Danazol. Dual non-hormonal contraception was required for participation and monthly pregnancy tests were performed.

A subject's eligibility was determined by self-assessment of EAP, medical history and examination, and baseline laboratory and imaging studies. Once eligible, subjects enrolled into the treatment period starting the first dose of study drug between days 1 to 10 of menses. Subjects maintained an electronic daily diary (e-Diary) recording of EAP intensity, numeric rating score (NRS), analgesic medication and time study medication was taken.

Key inclusion criteria:

1. Premenopausal woman between 18 to 49 years of age
2. Clinical diagnosis of endometriosis established by documentation of surgical visualization within 10 years of entry
3. Must agree to use only analgesic rescue medication (i.e. not prophylaxis) for EAP and use only the two medications provided for in the study
4. Must agree to use two forms of non-hormonal contraception unless sterilization of subject or sexual partner
5. Must have a menstrual cycle of 24 to 38 days prior to Screening and at least two menstrual cycles each with 24 to 38 days duration prior to starting study drug

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6. Normal Pap test
7. Normal mammogram in subjects ≥ 40 years of age

To ensure the subjects had moderate to severe EAP for inclusion into the treatment period, the subject:

1. Must have a Composite Pelvic Signs and Symptoms Score (CPSSS, see below) total score of ≥ 6 at screening with a score of at least 2 for DYS and at least 2 for NMPP
2. Have at least 2 days of moderate or severe pain for both DYS and NMPP during the last 35 calendar days of the screening period, prior to starting study drug
3. Have an average daily e-Diary score of at least 0.5 for NMPP during the last 35 calendar days of the Screening period
4. Subject must have at least one of the following: (a) average of NMPP during screening of at least 1 during the last 35 calendar days of the screening period or (b) at least 4 days of moderate or severe NMPP during the last 35 calendar days of the Screening period
5. Must have moderate or severe pain for DYS and NMPP using the Monthly Assessment of Endometriosis Pain instrument on day 1

Key exclusion criteria:

1. History of hysterectomy, bilateral oophorectomy, surgery that might interfere with gastrointestinal motility or absorption (gastric, bowel, vagotomy); recent surgery for endometriosis (major within 6 months, any within 3 months)
2. Pregnant, breast feeding, or planning pregnancy within 24 months, less than 6 months post-partum or post-pregnancy
3. History of previous non-response to medical treatment for endometriosis, chronic pelvic pain not caused by endometriosis or other chronic pain syndrome, history of drug or alcohol abuse within 1 year
4. History of significant sensitivity to elagolix, use of prohibited drugs within 1 month, bone disease or major depression within 2 years
5. IUS in place
6. Positive hepatitis testing or positive HIV
7. Abnormality in chemistry, hematology, urinalysis; abnormal electrocardiogram (ECG); or abnormal BMD
8. Undiagnosed abnormal genital bleeding or a gynecologic abnormality found on screening, including: complex ovarian cyst > 3 cm or simple ovarian cyst > 5 cm that persists, endometrial pathology, single fibroid > 4 cm, or more than four fibroids that measure ≥ 2 cm, or a symptomatic submucosal fibroid of any size.

Instruments used in the Phase 3 trials:

Because the predominant clinical manifestation of endometriosis is pain, the primary outcome measures in the elagolix trials evaluated elagolix's effect on pain. Development of the efficacy endpoints originated from the 1981 Biberoglu and Behrman (B&B) scale, which assesses function and quality of life in general but not pain in women with endometriosis.

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The B&B includes three symptoms – dysmenorrhea, chronic pelvic pain, and dyspareunia, and two signs – pelvic tenderness and induration, each of which are graded on a scale from 0 to 3 (or 4 for dyspareunia), with higher numbers indicating more severe symptoms. After convening an international meeting in 2010, the National Institutes of Health and the American Society of Reproductive Medicine concluded that the B&B appeared “not to have been used or administered in a consistent manner, and it has never been validated or shown to be reproducible.”⁴

In their Phase 2 studies, the Applicant began using a rating instrument – the Composite Pelvic Signs and Symptoms Score (CPSSS) – to assess pain. The CPSSS consisted of two sections. Section 1 asked the subjects to respond to the original B&B questions regarding dysmenorrhea, non-menstrual pelvic pain, and dyspareunia and was to be completed by the study coordinator based on the subject’s verbal responses from a 28-day recall period. Section 2 was to be completed by the investigator based on pelvic examination findings (i.e., pelvic tenderness and induration). Each individual component of the CPSSS was recorded on a scale of 0 to 3 (0 = absent; 1 = mild; 2 = moderate; 3 = severe). A modified version of CPSSS (which posed questions to subjects using wording modified from the original B&B) was used in the elagolix Phase 3 program.

Using the CPSSS as the prototype, the Applicant developed the Endometriosis Daily Pain Impact Scale, which utilized an electronic diary for the subjects to record a daily assessment of dyspareunia and non-menstrual pelvic pain using a 4-point scale that assessed both pain and daily function, to address the recommendations from the 2010 National Institutes of Health and the American Society of Reproductive Medicine meeting. At the End-of-Phase 2 meeting held on March 28, 2011, the FDA agreed that this scale would be appropriate for Phase 3 studies and that dysmenorrhea, non-menstrual pelvic pain, and dyspareunia would be assessed using this scale in the clinical program. Samples of the response options are listed below in Table 33 to Table 35.

Table 33. Response Options for Dysmenorrhea (DYS)

None	No discomfort.
Mild	Mild discomfort but I was easily able to do the things I usually do.
Moderate	Moderate discomfort or pain. I had some difficulty doing the things I usually do.
Severe	Severe pain. I had great difficulty doing the things I usually do.

Source: Protocol, Study 665, p 87-88

⁴ Vincent, K, S Kennedy, and P Stratton, 2010, Pain scoring in endometriosis: entry criteria and outcome measures for clinical trials, Report from the Art and Science of Endometriosis meeting, Fertil Steril, 93(1):62-67.

Table 34. Response Options for Non-Menstrual Pelvic Pain (NMPP)

None	No discomfort.
Mild	Mild discomfort but I was easily able to do the things I usually do.
Moderate	Moderate discomfort or pain. I had some difficulty doing the things I usually do.
Severe	Severe pain. I had great difficulty doing the things I usually do.

Source: Protocol, Study 665, p 87-88

Table 35. Response Options for Dyspareunia

Not applicable	I was not sexually active for reasons other than my endometriosis or did not have sexual intercourse.
None	No discomfort during sexual intercourse.
Mild	I was able to tolerate the discomfort during sexual intercourse.
Moderate	Intercourse was interrupted due to pain.
Severe	I avoided sexual intercourse because of pain.

Source: Protocol, Study 665, p89

The screening period involved assessment of the subject's baseline pain scores to confirm moderate to severe EAP. Evaluation of the CPSSS, the Monthly Assessment of Endometriosis Pain instrument, and e-Diary for endometriosis pain assessment and NRS were also used to determine severity of EAP.

Each element of the CPSSS is scored from 0 (absent) to 3 (severe) for a maximal value of 15. A total score for CPSSS of ≥ 6 , with a score of at least 2 for DYS and at least 2 for NMPP was required to qualify for randomization.

During the 6-month treatment period, monthly clinic visits occurred with laboratory testing, assessments of pain and function, and dispensation of the study drug. The Monthly Assessment of Endometriosis Pain instrument asked the subject to evaluate her EAP, both DYS and NMPP, over the last 28 days at the end of the screening period and before randomization occurred.

The e-Diary was an electronic patient-reported outcomes (ePRO) device developed to evaluate each subject's pain (DYS, NMPP, DYSP), presence of uterine bleeding, use of rescue analgesics for EAP, NRS, and the time medication was taken. The subject was to complete the diary every 24 hours, preferably at approximately the same time each day.

The e-Diary response options for DYS and NMPP were identical to those included in the Monthly Assessment of Pain instrument. Use of rescue analgesia for EAP captured medication name, dose and total number of pills taken within each 24-hour period. The NRS was an 11-point scale used to measure EAP with and without menstruation and asked the subject to "Choose the number that best describes your endometriosis pain over the last 24 hours at its worst," between 0 and 10.

The Patient Global Impression of Change (PGIC) was collected monthly and queried the subject to evaluate the change in her EAP since the initiation of the study drug by choosing one of seven responses. The PGIC asks the subject, “Since I started taking the study medication, my endometriosis related pain has: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7).”

The Assessment of Menstruation and Endometriosis Pain instrument was completed by a study coordinator based on verbal subject responses regarding menstrual bleeding pattern and EAP after study drug was discontinued. This outcome scale was used to assess when menstruation returned in the PTFU period. In months 7 to 12 in the PTFU period, when the e-Diary was no longer used, the Assessment of Menstruation and Endometriosis Pain instrument was utilized for durability of effect and return of endometriosis symptoms.

Analgesic rescue therapy was provided by the study site and was to be used for rescue EAP only. There were slight variations of the pain medication due to availability and standard of care in the different countries, as shown in Table 36.

Table 36. Permitted Rescue Therapy for Endometriosis-Associated Pain

Medication Class	Medication Name	Permitted Doses*	Countries
NSAID	naproxen	500 mg**	All
Narcotic Analgesics	hydrocodone + acetaminophen	5 mg hydrocodone + 300 mg or 325 mg acetaminophen	United States
	codeine + acetaminophen	30 mg codeine + 500 mg acetaminophen	Argentina, Australia, Brazil, Italy, United Kingdom
	codeine	30 mg codeine	New Zealand
	tramadol + acetaminophen	37.5 mg tramadol + 325 mg acetaminophen	Austria, Czech Republic, Hungary, Poland, South Africa, Spain

* Use of these analgesic medications should be according to the product prescribing information.

** 550 mg tablets of naproxen are allowed if 500 mg tablets are not locally available.

Source: Protocol, Study 671, p70

Removal of subjects occurred if the subject withdrew consent, safety issues developed, the subject used exclusionary medications or had surgical intervention for treatment of endometriosis or uterine bleeding, and for noncompliance. Subjects who prematurely withdrew during the treatment period were expected to continue in the PTFU period for up to 12 months. However, subjects having surgical intervention for treatment of endometriosis did not enter the PTFU period. Follow up dual-energy X-ray absorptiometry (DXA) scans, if required in these subjects, was to be performed according to study schedule. Subjects with ongoing adverse events (AEs) or abnormal laboratory results were followed by the investigator until resolution of the result or AE.

If a subject became pregnant during the Treatment or PTFU periods, the subject was to discontinue the study drug. An ultrasound examination in the first trimester of pregnancy to assess the conception date was performed. Information regarding pregnancy occurrence and the outcome of the pregnancy was collected. For pregnancies resulting in delivery of a live infant, the health of the infant was obtained at routine post-partum visit, 6 months, and 12 months after delivery.

Subject compliance with the study drug was based on documentation by study site personnel of returned drug containers. The study drugs were taken orally, twice a day. The doses were to be taken under fasting conditions (at least 1 hour before or 2 hours after a meal) with water, approximately 12 hours apart.

Protocol Amendments

There were three amendments to Study 665 protocol, the last one dated August 4, 2014.

The amendments allowed expanded time for diagnosis of endometriosis, the screening period, and days from menses to initial treatment. The final protocol included the final ranking of secondary endpoints and updated statistical information to reflect the statistical analysis plan.

There were four amendments to Study 671 protocol, the last one dated July 13, 2015.

The amendments reflected the amendments noted in Study 665; additionally, post-traumatic stress disorder and attempted suicide were added to exclusion criteria and buprenorphine was added to prohibited narcotic analgesics. Management of BMD loss was updated.

Endpoints

The studies have two co-primary efficacy endpoints:

- (1) The proportion of DYS responders at month 3
- (2) The proportion of NMPP responders at month 3

The data for these endpoints came from the mutually exclusive scales for daily assessment of DYS and NMPP measured by the modified B&B scales using the daily electronic Diary. This assessment is termed the Endometriosis Daily Pain Impact Scale by the Applicant. A responder was to be determined by a receiver operator characteristic (ROC) curve using the PGIC responses at month 3 from the blinded data to identify the point on the curve where a clinically meaningful result occurred. The use of analgesic medication for EAP was included in the responder definition, as explained in further detail below. These endpoints were also assessed at 6 months for persistence of efficacy.

Secondary efficacy endpoints were assessed using the e-Diary and questionnaires. The secondary efficacy variables were ranked as follows:

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1. Change from baseline to month 3 in the NRS for pain
2. Change from baseline to month 6 in DYS
3. Change from baseline to month 6 in NMPP
4. Change from baseline to month 3 in analgesic use across both classes of rescue analgesics based on pill counts
5. Change from baseline to month 6 in analgesic use across both classes of rescue analgesics based on pill counts
6. Change from baseline to month 3 in dyspareunia
7. Change from baseline to month 3 in use of narcotics based on pill counts

The ranking of secondary endpoints changed with each protocol amendment. In 2014, the Division encouraged prioritizing dyspareunia in the secondary endpoint hierarchy by moving it to the first position in this list. The Division also encouraged assessment of dyspareunia at month 6 to demonstrate persistence of treatment benefit for dyspareunia.

There were numerous non-ranked secondary efficacy, exploratory, pharmacokinetic, and additional endpoints.

8.1.2. Statistical Methodologies

Sample Size Consideration

Both studies assumed responder rates of 55% for the elagolix dose groups and 29% for placebo. Study 665 planned to enroll approximately 875 subjects, with 250 subjects in the elagolix 150 mg QD group, 250 subjects in the elagolix 200 mg BID group, and 375 subjects in the placebo group, representing a randomization ratio of 2:2:3. Study 671 planned to enroll approximately 788 subjects, with 225 subjects in the elagolix 150 mg QD group, 225 subjects in the elagolix 200 mg BID group, and 338 subjects in the placebo group, also representing a randomization ratio of 2:2:3. In each study, these sample sizes provided greater than 90% power to detect a difference between either elagolix dose group and placebo in response rate based on a two-sided test at the significance level of $\alpha = 0.025$.

Analysis Populations

The Applicant's statistical analysis plan predefined the modified intent-to-treat (MITT) analysis population for all efficacy analyses and the Safety analysis population for safety analyses. For both studies, the MITT and Safety analysis populations were identical, including all randomized subjects who had received at least one dose of study drug.

Handling of Missing Data

Missing data were handled using the following methods when applicable:

- Last Observation Carried Forward (LOCF), and
- Observed Cases (OC): no imputation was done

If a subject reported only one type of pain (DYS or NMPP, mutually exclusive Biberoglu and Behrman scale) and the other type of pain was reported as missing in the corresponding time

frame of interest (e.g., month 3 DYS score is missing because the subject only reported NMPP in the 35-calendar-day period prior to and including the month 3 PGIC assessment), then the monthly average pain score for the relevant parameter (DYS or NMPP) was set to zero.

The responder analyses for the two co-primary efficacy endpoints were based on observed data except for subjects who prematurely discontinued at or before month 3. Subjects who prematurely discontinued at or before month 3 and had missing data had their last nonmissing values carried forward (LOCF) from the previous time point when both monthly average pain score and analgesic use were observed.

Handling of Multiplicity

The Bonferroni adjustment was used to control the overall type I error rate of 0.05 for the co-primary endpoints. For each of the two elagolix dose groups, the comparison to placebo was considered statistically significant for each co-primary endpoint if the two-sided P-value was less than or equal to 0.025. Both co-primary endpoints must achieve statistical significance for an elagolix dose group for that dose to be considered more efficacious than placebo.

For each elagolix dose group that was statistically significantly more efficacious than placebo for the co-primary endpoints, a fixed-sequence approach was applied to maintain the family-wise type I error rate for the ranked secondary endpoints. For an elagolix dose group to be considered statistically significantly better than placebo on a ranked secondary endpoint, the two-sided P-value must be less than or equal to 0.025 for that secondary endpoint and for all higher-ranking secondary endpoints (and for the co-primary endpoints). The ranked secondary endpoints were tested in the order stated above.

Analysis of Co-Primary Efficacy Endpoints

For each of the co-primary endpoints, a subject was considered to be a responder at month 3 if:

- (1) she had an absolute reduction of X or greater from baseline in pain scores (DYS or NMPP); and
- (2) she was not a non-responder based on her analgesic use (see Appendix, section Analgesic Use).

We agreed with determining the threshold X in each study based on a ROC analysis using the PGIC assessment at month 3 as an anchor using the blinded data before database lock.

The threshold determination was carried out in the following steps for each co-primary endpoint:

- Step 1: Before data unblinding, all subjects in the MITT population regardless of treatment assignment were categorized into two groups (i.e., PGIC responder and PGIC non-responder) based on the PGIC response at month 3. Subjects were defined as PGIC responders if their response was "much improved" or "very much improved;" subjects with all other responses were classified as PGIC non-responders.
- Step 2: Using PGIC responder/nonresponder as a dependent variable, a logistic

regression model was fit with change from baseline in the pain endpoint as the covariate to perform a ROC analysis.

- Step 3: Chose the threshold for the change from baseline in the pain endpoint to minimize $\sqrt{(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2}$ for all possible thresholds (i.e. all values of change from baseline in the pain endpoint).

In the ROC analysis, subjects who prematurely discontinued at or before month 3 had their pain scores and PGIC response carried forward (LOCF) – from the previous time point when both PGIC and pain score data were observed. PGIC scores of 4 ("No change") were assigned to some individuals with missing data. These were subjects who: a) prematurely discontinued at or before month 3 and had no PGIC data to carry forward; or b) prematurely discontinued after month 3 and had no month 3 PGIC score; or c) completed the treatment period of the study, but were missing the month 3 PGIC score. Individuals missing month 3 change from baseline pain values were assigned change from baseline pain values of 0 in a similar fashion.

The primary analysis of each of the co-primary endpoints was based on a logistic regression model with the responder/non-responder categorization as the dependent variable, treatment as the main effect, and baseline pain score (DYS or NMPP) as the covariate.

One sensitivity analysis classified all subjects who prematurely discontinued the study drug at or before month 3 as non-responders. Another sensitivity analysis used only observed data. Other sensitivity analyses were also prespecified in the Applicant's analysis plan.

Analysis of Ranked Secondary Efficacy Endpoints

All ranked secondary efficacy endpoints data were evaluated with mixed-effects model repeated measures analysis. The mixed-effects model repeated measures analysis included the treatment group, visit, and treatment group-by-visit interaction, and the continuous baseline score of the endpoint being analyzed as a covariate. A random subject effect term was included to account for the correlation among the repeated measurements in the changes from baseline.

FDA's Additional Analysis

To evaluate the appropriateness of the Applicant's responder thresholds, we explored the data further by examining the cumulative distribution function and probability density function by each level of categorical change on the anchor to find responder thresholds and reanalyzed the co-primary efficacy endpoints using these thresholds to define responders.

8.1.3. Study Results

Patient Disposition

Subject disposition was similar in Study 665 and Study 671 (Table 37). Study 665 screened a total of 2248 subjects with 872 (38.7%) of the subjects randomized. One subject failed screening but was randomized in error and was never dispensed the study drug. Study 671 screened a total of 2163 subjects with 817 (37.8%) of the subjects randomized. Two subjects were randomized in error and never received the study drug and one subject was enrolled 3 times. A total of 815 subjects were treated with the study drug.

Duration of treatment was 6 months and about 75% of subjects in both studies completed the treatment period. About 60% of subjects randomized into the double-blind trials enrolled in the respective extension studies.

Table 37. Subject Disposition by Study and Treatment

	Placebo N (%)	150 mg QD N (%)	200 mg BID N (%)	Total N (%)
Study 665				
Randomized and treated	374	249	248	871
Completed	274 (73.3)	196 (78.7)	183 (73.8)	653 (75.0)
Discontinued	100 (26.7)	53 (21.3)	65 (26.2)	218 (25.0)
Entered Extension	218 (58.3)	150 (60.2)	138 (55.6)	506 (58.1)
Study 671				
Randomized and treated	360	226	229	815
Completed	270 (75.0)	178 (78.8)	184 (80.3)	632 (77.5)
Discontinued	90 (25.0)	48 (21.2)	45 (19.7)	183 (22.5)
Entered Extension	213 (59.2)	142 (62.8)	141 (61.6)	496 (60.9)

Source: Study 665, Report Table 12 P 263, Figure 9 P 264; Study 671, Report Table 12 P 259, Figure 7 P 261

In both studies, reasons for premature withdrawal were categorized identically except for “lack of efficacy,” which was a reason in study 671 but not in study 665. The subjects’ reasons for withdrawal in the treatment period as presented by the Applicant are shown in Table 38.

Table 38. Reasons for Premature Discontinuations by Treatment, Study 665

	Placebo N = 374 n (%)	150 mg QD N = 249 n (%)	200 mg BID N = 248 n (%)	Total N = 871 n (%)
Adverse event (AE)	17 (4.5)	13 (5.2)	21 (8.5)	51 (5.9)
Withdrew consent	35 (9.4)	21 (8.4)	16 (6.5)	72 (8.3)
Lost to follow-up	16 (4.3)	8 (3.2)	14 (5.6)	38 (4.4)
Other*	9 (2.4)	5 (2.0)	7 (2.8)	21 (2.4)
Subject noncompliant	11 (2.9)	2 (0.8)	2 (0.8)	15 (1.7)
Pregnancy	7 (1.9)	2 (0.8)	2 (0.8)	11 (1.3)
Surgery or invasive intervention for treatment of endometriosis	5 (1.3)	1 (0.4)	3 (1.2)	9 (1.0)
Exclusionary medication received	0	1 (0.4)	0	1 (0.1)
Transvaginal ultrasound finding	0	0	0	0

*Other category included moving out of area, wishes to become pregnant, lack of efficacy, did not meet entry criteria, no longer wanted to participate.

Source: Study Report, Table 12 p263

Premature discontinuation due to adverse events (AE) was highest in the 200 mg BID treatment arm while discontinuation due to withdrawn consent and subject noncompliance was highest in the placebo arm (see Table 39). Pregnancy occurred in all three arms with a larger proportion in the placebo arm. A low incidence of invasive intervention for endometriosis was reported in all three arms.

We do not agree with the primary reason for withdrawal of consent for several subjects. Review of comments on withdrawal shows 18 subjects with lack of efficacy, 10 additional subjects with AEs, and 6 subjects with exclusionary criteria including 3 with low BMD. Recalculation of the percentages for withdrawal of consent leads to more similar incidences across treatment arms – 6.9%, 7.2%, and 6.0% for placebo, 150 mg QD, and 200 mg BID respectively. Lack of efficacy was reported for 3.2%, 1.6%, and 0.8% of subjects in the placebo, 150 mg QD and 200 mg BID treatment arms, respectively.

Table 39. Reasons for Premature Discontinuations by Treatment, Study 671

	Placebo N = 360 n (%)	150 mg QD N = 226 n (%)	200 mg BID N = 229 n (%)	Total N = 815 n (%)
Adverse event	19 (5.3)	8 (3.5)	21 (9.2)	48 (5.9)
Withdrew consent	17 (4.7)	12 (5.3)	7 (3.1)	36 (4.4)
Lost to follow-up	19 (5.3)	5 (2.2)	7 (3.1)	31 (3.8)
Lack of efficacy	11 (3.1)	2 (0.9)	2 (0.9)	15 (1.8)
Pregnancy	7 (1.9)	2 (0.9)	0	9 (1.1)
Other	8 (2.2)	7 (3.1)	2 (0.9)	17 (2.1)
Subject noncompliant	4 (1.1)	9 (4.0)	5 (2.2)	18 (2.2)
Surgery or invasive intervention for treatment of endometriosis	4 (1.1)	2 (0.9)	0	6 (0.7)
Exclusionary medication received	1 (0.3)	1 (0.4)	1 (0.4)	3 (0.4)
Transvaginal ultrasound finding	0	0	0	0
Endometrial biopsy	0	0	0	0

Source Study Report Table 12 P 259
 BID = twice daily, QD = once daily

Early withdrawal due to an AE was highest in the 200 mg BID arm while lack of efficacy was highest in the placebo arm. The placebo arm had the highest incidence of intervention for endometriosis treatment and pregnancies although event rates were low.

We do not agree with the primary reason for withdrawal for several subjects. Eight subjects with the reasons “other” and “noncompliant” had comments consistent with withdrawn consent. Five (5) subjects whose withdrawal was attributed to withdrawn consent or noncompliance also had an AE; their premature termination should have been categorized as withdrawal due to AEs. These differences increased the proportions of subjects withdrawn due to AEs to 6.3%, 4.0%, 9.6% for placebo, 150 mg QD, and 200 mg BID, respectively. Conversely, the proportion of subjects in each arm with noncompliance and “other” decreased. Withdrawn consent showed minimal change in all three arms.

At the end of the treatment period, subjects could enroll in a 6-month extension study unless they did not complete the treatment period, declined participation or had an exclusionary criterion emerge during treatment. In Study 665, approximately 10% of subjects in the placebo and 200 mg BID arms and 14% of subjects in the 150 mg QD arm declined participation in the extension study. In Study 671, 11% of all arms declined participation in the extension study. Reasons for ineligibility to enroll in the two extension studies due to DXA and transvaginal ultrasound (TVU) findings are shown below. Subjects with BMD decrease $\geq 8\%$ at the lumbar spine, femoral neck, or total hip were not eligible to enter the extension studies. Subjects with TVU findings of persistent simple ovarian cyst (> 5 cm) or complex ovarian cyst (> 3 cm) on repeat TVU at 2-6 weeks were also not eligible to enter extension studies.

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Table 40. DXA and Transvaginal Ultrasound Ineligible Subjects at the End of the Treatment Period

Reason for ineligibility	Placebo	150 mg QD	200 mg BID	Total
Study 665	N = 374 (%)	N = 249 (%)	N = 248 (%)	N = 871 (%)
DXA finding	3 (0.8)	3 (1.2)	16 (6.5)	22 (2.5)
TVU finding	10 (2.7)	1 (0.4)	1 (0.4)	12 (1.4)
Endometrial biopsy finding	0	1 (0.4)	0	1 (0.1)
Study 671	N = 360 (%)	N = 226 (%)	N = 229 (%)	N = 815 (%)
DXA finding	2 (0.6)	1 (0.4)	10 (4.4)	13 (1.6)
TVU finding	11 (3.1)	6 (2.7)	3 (1.3)	20 (2.5)
Endometrial biopsy finding	0	0	0	0

Source: Study reports Table 13, p 266, 263

DXA = dual-energy X-ray absorptiometry, TVU = transvaginal ultrasound, BID = twice daily, QD = once daily

The 200 mg BID arms had higher proportions of subjects with exclusionary DXA findings than the 150 mg QD arms or the placebo arms. Conversely, the placebo arms had more exclusionary TVU findings than either of the treatment arms.

The mechanism of action of decreasing estrogen and progesterone would explain the higher incidence of decreased BMD in the 200 mg BID arm. Abnormal TVU findings included complex or hemorrhagic ovarian cysts and endometriomas, fibroids, and endometrial abnormalities of polyps and thickened lining of > 12mm. In Study 665, the placebo arm had six ovarian cysts while the 150 mg QD arm had one ovarian cyst. In Study 671, complex ovarian cysts were found in nine, three, and zero subjects in the placebo, 150 mg QD, and 200 mg BID arms respectively.

Subjects who did not enter the extension studies and subjects who withdrew early (with the exception of pregnancy) were to enter the PTFU period. The PTFU period lasted for 6 months and up to one year. To complete the PTFU period, each subject was to resume menses and have an acceptable BMD increase off therapy.

In Study 665, 167 subjects of the 871 (19.2%) randomized subjects entered the PTFU period and 116 of the 167 subjects (69.5%) completed the PTFU (see Table 41). In Study 671, 155 subjects of the 815 (17.8%) randomized subjects entered the PTFU period and 103 of the 155 subjects (66.5%) completed the PTFU.

Table 41. Disposition during the Post-Treatment Follow-up Period

Disposition	Placebo	150 mg QD	200 mg BID	Total
Study 665				
Entered PTFU period	N = 68	N = 48	N = 51	N = 167
	n (%)	n (%)	n (%)	n (%)
Completed PTFU 6 months	46 (67.6)	26 (54.2)	18 (35.3)	90 (53.9)
Completed PTFU 12 months	2 (2.9)	5 (10.4)	19 (37.3)	26 (15.6)
Withdrew for AE	0	0	0	0
Withdrew for invasive intervention for endometriosis	8 (11.8)	3 (6.3)	4 (7.8)	15 (9.0)
Study 671				
Entered PTFU period	N = 61	N = 40	N = 54	N = 155
	n (%)	n (%)	n (%)	n (%)
Completed PTFU 6 months	42 (68.8)	24 (60.0)	18 (33.3)	84 (54.2)
Completed PTFU 12 months	0	4 (10.0)	15 (28.8)	19 (12.3)
Withdrew for AE	0	2 (5.0)	1 (1.9)	3 (1.9)
Withdrew for invasive intervention for endometriosis	4 (6.6)	4 (10.0)	2 (3.7)	10 (6.5)

Source: Study Reports, Table 14, p 268, 264

AE = adverse event, BID = twice daily, BMD = bone mineral density, PTFU = post-treatment follow-up

A higher proportion of subjects in the 200 mg BID arms took longer than 6 months to meet the criteria for resumed menses and acceptable BMD decrease. The number of subjects without menses at 6 months for both studies combined were 1, 4, and 3 respectively for placebo, 150 mg QD and 200 mg BID. Unacceptable BMD change was the reason why most subjects in the 200 mg BID arm were not eligible to complete the PTFU in 6 months. All treatment arms had subjects that left the PTFU period for invasive intervention for endometriosis.

One month after treatment ended, 75% of subjects in the placebo arms and about 60% of subjects in the elagolix arms had reported menses. By 6 months post treatment, 99.2%, 95.3%, and 96.1% of subjects had reported resumption of menses in the placebo, 150 mg QD, and 200 mg BID arms, respectively. The need for invasive intervention for endometriosis in all arms after completion of active treatment suggests that some subjects did not have persistence of effect once treatment was discontinued.

Demographic Characteristics

Subjects in Study 665 were from the U.S. and Canada; subjects in Study 671 were from N. America, S. America, Australia, New Zealand, Europe, and S. Africa.

Table 42. Demographic Characteristics in the Phase 3 Double-Blinded Trials

		Placebo	150 mg QD	200 mg BID	Total
Study 665		N = 374	N = 249	N = 248	N = 871
Race, n (%)	White	323 (86.4)	221 (88.8)	215 (86.7)	759 (87.1)
	Black or African American	33 (8.8)	19 (7.6)	24 (9.7)	76 (8.7)
	Asian	5 (1.3)	2 (0.8)	2 (0.8)	9 (1.0)
	American Indian/Alaska Native	2 (0.5)	4 (1.6)	0	6 (0.7)
	Multi race	9 (2.4)	3 (1.2)	6 (2.4)	18 (2.1)
	Native Hawaiian or other Pacific Islander	2 (0.5)	0	1 (0.4)	3 (0.3)
	Ethnicity n (%)	Hispanic or Latino	63 (16.8)	36 (14.5)	40 (16.1)
Age, yrs.	Mean (SD)	31.7 (6.4)	31.5 (6.0)	31.2 (6.3)	31.5 (6.2)
BMI, kg/m ²	Mean (SD)	28.0 (6.2)	28.4 (6.3)	28.1 (6.5)	28.1 (6.3)
Study 671		N = 360	N = 226	N = 229	N = 815
Race, n (%)	White	322 (89.4)	198 (87.6)	207 (90.4)	727 (89.2)
	Black or African American	29 (8.1)	25 (11.1)	18 (7.9)	72 (8.8)
	Asian	4 (1.1)	2 (0.9)	1 (0.4)	7 (0.9)
	American Indian/Alaska Native	2 (0.6)	0	0	2 (0.2)
	Multi race	2 (0.6)	0	2 (0.9)	4 (0.5)
	Native Hawaiian or other Pacific Islander	1 (0.3)	1 (0.4)	1 (0.4)	3 (0.4)
	Ethnicity, n (%)	Hispanic or Latino	44 (12.2)	32 (14.2)	33 (14.4)
Age, yrs.	Mean (SD)	33.1 (6.7)	33.1 (6.8)	33.4 (6.7)	33.2 (6.7)
BMI, kg/m ²	Mean (SD)	27.3 (6.5)	26.7 (6.8)	26.7 (6.7)	27.0 (6.6)

Source: Study reports Table 16 p 277, 273

BMI = body mass index, SD = standard deviation, BID = twice daily, QD = once daily

Both studies had similar demographics: about 85% white, mean age 31-33 years, and mean BMI in the overweight category, as shown in Table 42. There were no large differences between arms in each of the studies for any of the parameters.

ther Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)).

Baseline characteristics collected included EAP scores and rescue analgesic use during the screening period, medical/surgical/gynecologic histories, and prior endometriosis treatment. The screening CPSSS and baseline EAP (DYS, NMPP, NRS) scoring were to represent moderate-severe pain as defined by the inclusion criteria. The CPSSS components were similar for all arms in both studies (data not shown). The baseline pain scores shown in Table 43 are averages over the 35 days prior to beginning the study drug. The arms were similar in baseline pain scores including DYS in both studies. The DYS, NMPP, and DYS were on a 4-point scale (with 0= no pain and 3=severe pain). The NRS scale was 11 points, with 10=worst pain ever.

Table 43. Mean (SD) Endometriosis-Associated Pain (EAP) Scores at Baseline

	Placebo	150 mg QD	200 mg BID
Study 665	N = 374	N = 249	N = 248
mean score (SD)			
DYS	2.17 (0.4)	2.18 (0.5)	2.19 (0.5)
NMPP	1.60 (0.5)	1.64 (0.5)	1.57 (0.5)
DYSP	1.51 (0.8)	1.52 (0.8)	1.55 (0.9)
NRS	5.58 (1.6)	5.72 (1.7)	5.48 (1.6)
Study 671	N = 360	N = 226	N = 229
mean score (SD)			
DYS	2.16 (0.5)	2.15 (0.5)	2.07 (0.5)
NMPP	1.58 (0.5)	1.65 (0.5)	1.55 (0.5)
DYSP	1.45 (0.8)	1.48 (0.9)	1.43 (0.9)
NRS	5.56 (1.8)	5.69 (1.8)	5.33 (1.8)

Source Study Reports Table 18, p 280, 276

DYS = dysmenorrhea, NMPP = non-menstrual pelvic pain, DYSP = dyspareunia, NRS = numeric rating scale, SD = standard deviation, QD = once daily, BID = twice daily

Pain scores for DYS were consistent with moderate-severe pain. Mean NMPP and DYSP pain scores were consistent with mild-moderate pain.

Table 44. Subjects Rescue Analgesic Use at Baseline by Study and Treatment

	Placebo	Elagolix	Elagolix	Total
	n (%)	150 mg QD	200 mg BID	n (%)
		n (%)	n (%)	
Study 665, n (%)	N = 374	N = 249	N = 248	N = 871
None	27 (7.2)	34 (13.7)	15 (6.0)	76 (8.7)
NSAID only	136 (36.4)	65 (26.1)	80 (32.3)	281 (32.3)
Opioid only	71 (19.0)	45 (18.1)	53 (21.4)	169 (19.4)
NSAID + opioid	140 (37.4)	105 (42.2)	100 (40.3)	345 (39.6)
Study 671, n (%)	N = 360	N = 226	N = 229	N = 815
None	34 (9.4)	21 (9.3)	23 (10.0)	78 (9.6)
NSAID only	101 (28.1)	77 (34.1)	69 (30.1)	247 (30.3)
Opioids only	56 (15.6)	33 (14.6)	28 (12.2)	117 (14.4)
NSAID + opioids	169 (46.9)	95 (42.0)	109 (47.6)	373 (45.8)

Source Table 20 p 283 in study 665 report; Table 20 p 279 in study 671 report.

BID = twice daily, NSAID = non-steroidal anti-inflammatory drug, QD = once daily

The majority of subjects used both NSAID and opioid rescue analgesia at baseline with 6% to 14% of subjects not using any analgesia.

The medical/surgical/gynecologic histories among treatment groups in each study were similar but there were differences between the two studies. In Study 665, the subjects' most common medical conditions were migraine (23%), depression (21%), drug allergies/reactions (20%), asthma (14%), and gastroesophageal reflux disease (11%). Over 50% of the subjects had a history of at least one pregnancy prior to entering the studies. An inclusion criterion was for all subjects to have surgical diagnosis of endometriosis. One hundred and nine subjects (12.5%) had missing or unknown location of endometriotic lesions. Slightly more than two-thirds of subjects (70%) had endometriotic lesions noted on the peritoneum at time of surgery. The length of time since surgical diagnosis of endometriosis ranged from 3 months to 15 years, the placebo arm having the longest length of time (15 years).

In Study 671, the subjects' most common medical conditions were seasonal allergy (20%), depression (17%), skin/dermatological disorder (16%), migraine (15%), anxiety (14%), drug allergies/reactions (14%), asthma (12%), and gastroesophageal reflux disease (10%). Again, over 50% of the subjects had a history of at least one pregnancy prior to enrollment. All subjects were required to have had a surgical diagnosis of endometriosis. Seventy-four subjects (9.1%) had missing or unknown location of endometriotic lesions, and 70% had endometriotic lesions noted on the peritoneum at time of surgery. The length of time since surgical diagnosis of endometriosis ranged from 2.3 months to 25 years, the placebo arm having the longest length of time (25 years).

Note that the inclusion criterion specified subjects to have a clinical diagnosis of endometriosis established by documented surgical visualization performed within 10 years of study entry. Some subjects may have had more than one surgery over several years.

Prior medical treatment of endometriosis within each study's arms were similar and, other than the use of leuprolide, the two studies have similar patterns of medication use. Almost 90% of the subjects had a previous medical treatment, with 50% using combined hormonal contraceptives, 35% using propionic acid derivatives, and 25-30% using analgesics (including opioids). In Study 665, 29% of subjects had used leuprolide while only 17% of the subjects in Study 671 used leuprolide. The difference in leuprolide treatment between the studies suggests geographic differences in the treatment of endometriosis.

Protocol Violations

In Study 665, there were 243 deviations, involving approximately 28% of subjects. Deviations involved subjects entering the study but not satisfying entry criteria, developing withdrawal criteria but not being withdrawn, receiving wrong treatment or incorrect dose, and receiving excluded concomitant treatment. Deviations due to inclusion/exclusion criteria included surgical diagnosis within 10 years (prior to a protocol amendment changing this criterion from within 5 years of surgical diagnosis), length of menstrual cycles, pain criteria based on CPSSS, e-Dairy pain scores, presence of psychiatric disorders, and low BMD or metabolic bone disease. There were 12 subjects who were enrolled despite having low BMD or metabolic bone disease. Seven of the 12 did not satisfy the Z-score criteria (2 in the 150 mg QD arm, 5 in the 200 mg BID arm), two of whom had exclusionary Z-scores from the central imaging core laboratory but were approved for enrollment by AbbVie based on their local imaging results. Five subjects with exclusionary Z-score criteria received the study drug for only a few days before the results were known. One subject completed the study before it was noted that the screening DXA result was not available. One hundred and eighty-three subjects (21.0%) received a prohibited concomitant treatment during the study (screening, treatment, and PTFU). A subject's continued participation in the study upon use of a prohibited medication for an AE or a preexistent condition other than endometriosis was evaluated by the investigator and the AbbVie medical monitor. Seventy-seven subjects (8.8%) used a prohibited analgesic for non-endometriosis pain. Although, the withdrawal criteria include removal of subjects who

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required use of an exclusionary medication for endometriosis, 52 subjects (6.0%) used prohibited analgesics for EAP, and 62 (7.1%) subjects used prohibited corticosteroid. Overall 25 subjects (2.9%) used pain medication for ≥ 30 days. There were also 322 “other” study deviations from protocol compliance. Most of the deviations involved extended time for screening and randomization. There were 14 subjects who received the wrong dose of rescue medication and 8 reported use of the rescue medication for ≥ 30 days.

In Study 671, there were 207 deviations involving approximately 25% of subjects. Deviations due to inclusion/exclusion criteria included surgical diagnosis within 10 years (prior to a protocol amendment permitting a remote history of surgical diagnosis), length of menstrual cycles, pain criteria based on CPSSS, e-Dairy pain scores, baseline assessment of EAP, timing and type of surgery prior to randomization, and participation in another investigational study. There were 35 subjects (4.3%) who had no analysis of baseline EAP when inclusion criteria specified subjects to have moderate or severe pain for DYS and NMPP. Two subjects with exclusionary Z-score criteria were enrolled and received study drug for only a few days with both discontinued from the study within three days. One hundred and four subjects (12.8%) received a prohibited concomitant treatment during the study (screening, treatment, and PTFU). A subject’s continued participation in the study upon use of a prohibited medication for an AE or a preexistent condition other than endometriosis was evaluated by the investigator and the AbbVie medical monitor. Forty-one (5.0%) subjects used a prohibited analgesic for non-endometriosis pain. Although, the withdrawal criteria include removal of subjects who required use of an exclusionary medication for endometriosis, 34 subjects (4.2%) used prohibited analgesics for EAP and 21 subjects (2.6%) used prohibited corticosteroid. Overall 35 subjects (4.3%) used pain medication for ≥ 30 days. There were also 369 “other” study deviations from protocol compliance. Most of the deviations involved extended time for screening or randomization.

Treatment Compliance

Study drug compliance was defined as the total number of tablets taken divided by the total number of tablets a subject was supposed to take each day times the length of time that the subject was in the treatment period of the study. The number of tablets taken was defined as the difference between the total number of tablets dispensed and the total number of tablets returned. If a subject did not return a kit, the site recorded that zero pills were returned and assumed that the subject took the entire amount of study drug for that time period.

In study 665, the treatment compliance was $> 95\%$ in all three arms. In study 671, the treatment compliance was $> 91\%$ in all three arms.

A $> 90\%$ compliance rate in a BID regimen for 6 months seems unusually high. Compliance was confirmed at the study sites. It is unknown how many kits were not returned.

Concomitant Medications

In Study 665, most subjects (73.4 to 92.0%) took one or more concomitant medications. Medications of interest are noted in the table below segregated by the study period. Concomitant analgesic medications included all analgesic medications except protocol-specific analgesic medications taken for EAP and included treatment for AEs or other conditions. For each study period, there were no significant differences between the 3 treatment groups. However, there were differences between the three study periods. Concomitant analgesic use increased during the treatment period and did not completely decrease in the posttreatment period to pretreatment levels. Use of calcium and Vitamin D increased from baseline in the treatment and posttreatment period. Selective serotonin reuptake inhibitor use increased slightly from pretreatment to posttreatment periods.

Table 45. Selected Concomitant Medications Taken During Study 665

665 Concomitant Medication	Placebo	150 mg QD	200 mg BID	Total
Pretreatment	% (N = 374)	% (N = 249)	% (N = 248)	% (N = 871)
MS anti-inflammatory	18.2	14.1	15.7	16.3
NS analgesics	18.4	14.9	15.3	16.5
NS opioids	5.1	3.6	3.6	4.2
NS other analgesics	13.1	10.4	10.1	11.5
SSRI	9.6	13.3	11.7	11.3
Calcium	17.6	15.7	16.1	16.6
Vitamin D	13.4	15.7	11.7	13.5
Drugs for peptic ulcer/GERD	11.0	8	7.7	9.2
Hormonal contraception for systemic use	3.7	1.2	0.8	2.2
During Treatment	% (N = 374)	% (N = 249)	% (N = 248)	% (N = 871)
MS anti-inflammatory	23.3	27.3	21.4	26.5
NS analgesics	30.7	27.7	23	27.7
NS opioids	13.1	8	7.3	10
NS other analgesics	20.3	19.3	15.3	18.6
SSRI	12	14.1	14.1	13.2
Calcium	47.1	49.4	45.2	47.2
Vitamin D	36.9	44.6	36.7	39
Drugs for peptic ulcer/GERD	14.4	10.4	10.5	12.2
Hormonal contraception for systemic use	0.8	0.4	0.4	0.6
Posttreatment	% (N = 156)	% (N = 99)	% (N = 110)	% (N = 365)
MS anti-inflammatory	18.6	16.2	13.6	16.4
NS analgesics	19.2	16.2	20.9	18.9
NS opioids	7.1	5.1	7.3	6.6
NS other analgesics	13.5	13.1	12.7	13.2
SSRI	15.4	15.2	18.2	16.2
Calcium	49.4	50.5	44.5	48.2
Vitamin D	31.4	41.4	31.8	34.2
Drugs for peptic ulcer/GERD	14.7	9.1	10	11.8
Hormonal contraception for systemic use	1.9	4	6.4	3.8

MS=musculoskeletal system, NS= nervous system, GERD = gastroesophageal reflux disease, SSRI = selective serotonin reuptake inhibitor

Source Study Report Tables 14.1_2.2.1-2.2.3 p 708

The increase in analgesic use in the treatment period, especially in the 150 mg QD group, is unexpected. Analgesics were taken for painful conditions not attributed to endometriosis – e.g., migraine, musculoskeletal pain. Calcium and Vitamin D supplementation was encouraged at all visits which explains the sustained increase in these medications. There was a small increase in combined hormonal contraceptive use in the posttreatment period because subjects could start these contraceptives 3 months into the posttreatment follow up period.

In Study 671, most subjects across treatment groups (50.7% to 99.1%) took one or more concomitant medications and the patterns of usage were similar to Study 665 and not shown in table form. Again, analgesic use was highest in the treatment period in all arms, slightly decreasing in the posttreatment period but not to pretreatment levels. Selective serotonin reuptake inhibitor use increased over the three periods from 10.4% to 12.3% to 15.0%. Calcium and Vitamin D supplementation increased to > 50% during the treatment period with a slight drop to > 40% in the Post treatment period. Hormonal contraception increased to 8.5% in the posttreatment period.

Concomitant Analgesic Medication for EAP

Concomitant analgesic medication use for EAP was collected separately from concomitant analgesic medication use for non-EAP (above) and from rescue analgesic medication use for EAP (efficacy data).

In study 665, during both the pretreatment and treatment periods, less than 5% of subjects used any analgesic. In the posttreatment period, there was a small increase to 7% in the 150 mg QD and 200 mg BID arms compared to 5.1% in the placebo arm. The numbers of subjects were small (each arm seven to eight subjects). The Applicant notes that only two of the subjects used opioids repeatedly and most used the analgesics for “short-term.”

In Study 671, the overall use of concomitant analgesic medication for EAP during the pretreatment, treatment, and posttreatment periods were 4.7% to 6.9% to 8.2%, respectively. The placebo group had more analgesic use than either of the active treatment groups during the pretreatment and treatment periods. However, the active treatment groups had more analgesic use than the placebo group in the posttreatment period. Again, the number of subjects in the posttreatment period is small (10 or few subjects per arm). The Applicant notes that only six subjects had repeated opioid use and most were for “short-term” use.

There does not appear to be a clear relationship between treatment with elagolix and use of concomitant analgesic medication for EAP.

Efficacy Results – Co-Primary Endpoints

The coprimary endpoints for both studies were the proportion of responders at month 3 for daily assessment of DYS and the proportion of responders at month 3 for daily assessment of

NMPP, taking into account the use of rescue analgesic medication for EAP. Table 46 presents the thresholds for DYS and NMPP using the pre-specified ROC analysis.

Table 46. Receiver Operating Characteristics (ROC) Thresholds

Study	Change from Baseline to Month 3	
	Dysmenorrhea	Non-Menstrual Pelvic Pain
665	-0.81	-0.36
671	-0.85	-0.43

Source: Appendix in Study SAP

Based on the above thresholds, the results show statistically significant higher responder rates for both DYS and NMPP pain reduction for both the 150 mg QD and 200 mg BID arms compared with the placebo arm. The results for Studies 665 and 671 are comparable. The 200 mg BID arms had numerically greater proportions of responders for both DYS and NMPP than the 150 mg QD arms (See Table 47 and Table 48).

Table 47. Study 665 - Proportion of Responders at Month 3 for Daily Assessment of DYS and NMPP – LOCF (MITT)

	Placebo (N = 374)	Elagolix 150 mg QD (N = 249)	Elagolix 200 mg BID (N = 248)
DYS responder		115/248 (46.4%)	185/244 (75.8%)
Difference vs. placebo	73/373 (19.6%)	26.8%	56.2%
P-value		< 0.001	< 0.001
NMPP responder		125/248 (50.4%)	133/244 (54.5%)
Difference vs. placebo	136/373 (36.5%)	13.9%	18.0%
P-value		< 0.001	< 0.001

Responder thresholds were determined based on a receiver operating characteristic analysis.

DYS responder threshold: a reduction of -0.81 or greater from baseline in DYS pain score

NMPP responder threshold: a reduction of -0.36 or greater from baseline in NMPP score

P-value for test of difference between each elagolix treatment group and placebo is from a logistic regression model with treatment as the main effect and baseline value as a covariate.

Source: Study 665 CSR Table 14.2_1.1.1, Table 14.2_1.2.1

LOCF = last observation carried forward, BID = twice daily, QD = once daily, NMPP = nonmenstrual pelvic pain, DYS = dysmenorrhea, MITT = modified intention-to-treat

Table 48. Study 671 - Proportion of Responders at Month 3 for Daily Assessment of DYS and NMPP – LOCF (MITT)

	Placebo (N = 360)	Elagolix 150 mg QD (N = 226)	Elagolix 200 mg BID (N = 229)
DYS responder		96/221 (43.4%)	163/225 (72.4%)
Difference vs. placebo	80/353 (22.7%)	20.7%	49.7%
P-value		< 0.001	< 0.001
NMPP responder		110/221 (49.8%)	130/225 (57.8%)
Difference vs. placebo	129/353 (36.5%)	13.3%	21.3%
P-value		0.003	< 0.001

Responder thresholds were determined based on a receiver operating characteristic analysis.

LOCF = last observation carried forward, BID = twice daily, QD = once daily, NMPP = nonmenstrual pelvic pain, DYS = dysmenorrhea, MITT = modified intention-to-treat

DYS responder threshold: a reduction of -0.85 or greater from baseline in DYS pain score

NMPP responder threshold: a reduction of -0.43 or greater from baseline in NMPP score

P-value for test of difference between each elagolix treatment group and placebo is from a logistic regression model with treatment as the main effect and baseline value as a covariate.

Source: Study 671 CSR Table 14.2_1.1.1, Table 14.2_1.2.1

About 25% of subjects prematurely withdrew from the placebo-controlled trials. Sensitivity analyses of the co-primary efficacy endpoints using only observed data (i.e. without data imputation for missing values), and sensitivity analyses that treated all premature discontinuations as non-responders showed that the responder rate difference between each elagolix dose 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 co-primary endpoints.

FDA also conducted a sensitivity analysis of the DYS responder rates at month 3 excluding subjects with amenorrhea, which showed that the responder rates were very close to the rates obtained in the primary analysis. This suggests that absence of menses is not the reason for response to treatment.

Efficacy Results – Secondary and Other Relevant Endpoints

The results of the secondary endpoints for both studies are shown in the two tables below. The 150 mg QD arms showed statistically significant reduction from baseline in the NRS pain score at month 3 and in the DYS and NMPP pain scores at month 6 compared to placebo. The 200 mg BID arms showed statistically significant reduction in the above three endpoints as well as reduction of analgesic use at months 3 and 6, reduction in DYSP at month 3, and reduction of opioid use at month 3 compared to placebo. Analgesic use was based on pill counts of each type of analgesic (NSAID and opioids). As explained below, while the reductions in opioid use were statistically significant, the clinical relevance of those findings have not been demonstrated.

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Table 49. Study 665 – Summary of Ranked Secondary Efficacy Endpoints – (MITT)

Secondary Endpoint		Statistics	Placebo (N = 374)	Elagolix 150 mg QD (N = 249)	Elagolix 200 mg BID (N = 248)
NRS	Baseline change to month 3	Mean (SD)	5.58 (1.57)	5.72 (1.73)	5.48 (1.59)
		LS mean (SE)	-1.09 (0.10)	-1.74 (0.12)	-2.39 (0.12)
		Difference vs. placebo		-0.65 (0.16)	-1.30 (0.16)
		97.5% CI		(-1.00, -0.30)	(-1.65, -0.95)
		P-value		< 0.001	< 0.001
DYS	Baseline change to month 6	Mean (SD)	2.17 (0.45)	2.18 (0.45)	2.19 (0.47)
		LS mean (SE)	-0.35 (0.04)	-1.03 (0.05)	-1.73 (0.05)
		Difference vs. placebo		-0.68 (0.07)	-1.39 (0.07)
		97.5% CI		(-0.83, -0.53)	(-1.54, -1.23)
		P-value		< 0.001	< 0.001
NMPP	Baseline change to month 6	Mean (SD)	1.60 (0.48)	1.64 (0.54)	1.57 (0.48)
		LS mean (SE)	-0.32 (0.03)	-0.44 (0.04)	-0.61 (0.04)
		Difference vs. placebo		-0.12 (0.05)	-0.29 (0.05)
		97.5% CI		(-0.23, -0.01)	(-0.41, -0.18)
		P-value		0.017	< 0.001
Analgesic use (pill counts)	Baseline change to month 3	Mean (SD)	0.87 (0.87)	0.87 (0.94)	0.85 (0.89)
		LS mean (SE)	-0.29 (0.03)	-0.29 (0.04)	-0.55 (0.04)
		Difference vs. placebo		-0.01 (0.05)	-0.26 (0.05)
		97.5% CI		(-0.12, 0.11)	(-0.37, -0.14)
	change to month 6	LS mean (SE)	-0.27 (0.04)	-0.35 (0.04)	-0.56 (0.04)
		Difference vs. placebo		-0.07 (0.06)	-0.28 (0.06)
		97.5% CI		(-0.20, 0.05)	(-0.41, -0.15)
		P-value		-	< 0.001
Dyspareunia	Baseline change to month 3	Mean (SD)	1.51 (0.83)	1.52 (0.82)	1.55 (0.86)
		LS mean (SE)	-0.29 (0.04)	-0.39 (0.05)	-0.49 (0.05)
		Difference vs. placebo		-0.09 (0.07)	-0.20 (0.07)
		97.5% CI		-0.24, 0.05	(-0.35, -0.05)
		P-value		-	0.003
Narcotics use (pill counts)	Baseline change to month 3	Mean (SD)	0.37 (0.59)	0.42 (0.67)	0.42 (0.72)
		LS mean (SE)	-0.10 (0.02)	-0.07 (0.03)	-0.22 (0.03)
		Difference vs. placebo		0.03 (0.04)	-0.12 (0.04)
		97.5% CI		(-0.05, 0.11)	(-0.20, -0.03)
		P-value		-	0.002

LS means, differences and p-values are from the repeated measurements mixed effect model.

BID = twice daily, CI = confidence interval, DYS = dysmenorrhea, LS = least squares, MITT = modified intent-to-treat, NMPP = nonmenstrual pelvic pain, NRS = numeric rating score, QD = once daily, SD = standard deviation, SE = standard error

*The hierarchical testing stops and no further testing was conducted for this treatment group.

Source: CSR Table 14.2_11.4.1, Table 14.2_11.1.1, Table 14.2_11.2.1, Table 14.2_12.1.1, Table 14.2_11.3.1, Table 14.2_12.1.3

Table 50. Study 671 – Summary of Ranked Secondary Efficacy Endpoints – (MITT)

Secondary Endpoint	Time point	Statistics	Placebo (N = 360)	Elagolix 150 mg QD (N = 226)	Elagolix 200 mg BID (N = 229)
NRS	Baseline change to month 3	Mean (SD) LS mean (SE) Difference vs. placebo 97.5% CI P-value	5.56 (1.76) -1.33 (0.10)	5.69 (1.78) -1.90 (0.12) -0.57 (0.16) (-0.92, -0.22) < 0.001	5.33 (1.78) -2.55 (0.12) -1.22 (0.16) (-1.57, -0.87) < 0.001
	Baseline change to month 6	Mean (SD) LS mean (SE) Difference vs. placebo 97.5% CI P-value	2.16 (0.48) -0.45 (0.04)	2.15 (0.50) -0.97 (0.05) -0.53 (0.07) (-0.68, -0.37) < 0.001	2.07 (0.50) -1.70 (0.05) -1.25 (0.07) (-1.40, -1.09) < 0.001
NMPP	Baseline change to month 6	Mean (SD) LS mean (SE) Difference vs. placebo 97.5% CI P-value	1.58 (0.52) -0.48 (0.04)	1.65 (0.54) -0.63 (0.04) -0.15 (0.06) (-0.27, -0.02) 0.009	1.55 (0.55) -0.80 (0.04) -0.32 (0.06) (-0.45, -0.19) < 0.001
Analgesic use (pill counts)	Baseline change to month 3	Mean (SD) LS mean (SE) Difference vs. placebo 97.5% CI P-value	0.80 (1.01) -0.31 (0.03)	0.85 (1.15) -0.36 (0.04) -0.05 (0.04) (-0.15, 0.05) 0.260*	0.73 (0.96) -0.49 (0.03) -0.18 (0.04) (-0.28, -0.08) < 0.001
	change to month 6	LS mean (SE) Difference vs. placebo 97.5% CI P-value	-0.32 (0.03)	-0.40 (0.04) -0.08 (0.05) (-0.19, 0.03) -	-0.52 (0.04) -0.21 (0.05) (-0.31, -0.10) < 0.001
Dyspareunia	Baseline change to month 3	Mean (SD) LS mean (SE) Difference vs. placebo 97.5% CI P-value	1.45 (0.83) -0.30 (0.04)	1.48 (0.88) -0.39 (0.05) -0.09 (0.07) (-0.24, 0.06) -	1.43 (0.85) -0.60 (0.05) -0.30 (0.07) (-0.45, -0.15) < 0.001
Narcotics use (pill counts)	Baseline change to month 3	Mean (SD) LS mean (SE) Difference vs. placebo 97.5% CI P-value	0.34 (0.60) -0.12 (0.02)	0.36 (0.83) -0.12 (0.02) 0.00 (0.03) (-0.07, 0.07) -	0.33 (0.74) -0.21 (0.02) -0.08 (0.03) (-0.15, -0.01) 0.007

Source: CSR Table 14.2_11.4.1, Table 14.2_11.1.1, Table 14.2_11.2.1, Table 14.2_12.1.1, Table 14.2_11.3.1, Table 14.2_12.1.3

BID = twice daily, CI = confidence interval, DYS = dysmenorrhea, LS = least squares, MITT = modified intent-to-treat, NMPP = nonmenstrual pelvic pain, NRS = numeric rating score, QD = once daily, SD = standard deviation, SE = standard error
 LS mean, Difference and p-value are from the repeated measurement mixed effect model.

* The hierarchical testing stops and no further testing was conducted for this treatment group.

The NRS, which rates EAP every 24 hours, should reflect the DYS and NMPP pain scores so it is not surprising that the superiority of elagolix to placebo is shown in NRS. The NRS finding supports the primary efficacy findings. The change from mean baseline to month 6 for DYS and NMPP used the same pain scores as the coprimary endpoints so again, the level of statistical significance seen is not surprising. The findings at month 6 for DYS and NMPP for both doses support continued efficacy of elagolix beyond month 3.

The change in analgesic use was based on average daily pill counts. There was one NSAID and one narcotic permitted rescue medication for each study which was based on availability in

each country. The fourth, fifth, and seventh-ranked secondary endpoints involved the change in analgesic use from baseline compared to the placebo group. In both studies, the 200 mg BID arms showed a statistically significant decrease in rescue analgesic use compared to the placebo group but the 150 mg QD arms did not show statistically significantly decrease.

Consultation with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) further elucidated the change in analgesic use. The absolute difference in the average pill count for both classes of analgesics was approximately 0.5 pills/day and for opioids 0.21 pills per day.⁵ Further, when the average daily opioid use was converted to morphine equivalents, the resultant decrease was only one morphine equivalent per day. The Applicant has not shown this amount of decrease to be clinically meaningful.

Therefore, although the 200 mg BID dose of elagolix showed a statistically significant decrease in analgesic pill use, this decrease has not been shown to be clinically meaningful.

The Division encouraged the Applicant on numerous occasions to rank DYSP higher in the list of prespecified secondary endpoints and recommended showing improvement of dyspareunia to month 6. The Applicant chose to rank DYSP at month 3 towards the bottom of the list of prespecified secondary endpoints and did not include DYSP at month 6 in the ranking. The 150 mg QD dose was not tested for dyspareunia because hierarchical testing for that dose had stopped when an earlier secondary endpoint failed. The 200 mg BID dose showed statistically significantly less dyspareunia at month 3 compared to placebo in both trials.

Labeling should state that both doses of elagolix are effective for moderate-severe DYS and NMPP and be clear that only the 200 mg BID dose showed efficacy for DYSP and only at month 3.

Narcotic Use

A statistically significant change from baseline to month 3 in the use of narcotics based on pill count (7th ranked secondary endpoint) was observed in both trials for elagolix 200 mg BID relative to placebo. No significant reduction in the use of narcotic class of medication based on pill count was seen for elagolix 150 mg QD.

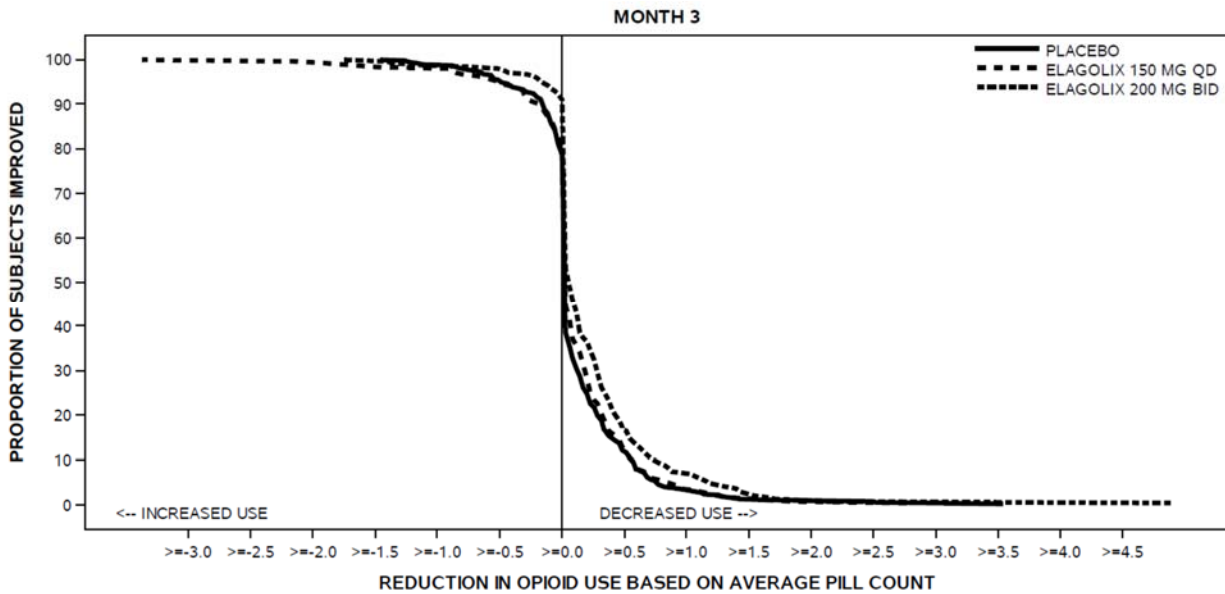
(b) (4)
(b) (4)

The Division requested additional analysis of reduction in opioid use using CDFs and sought input from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to assess the clinical meaningfulness of these results. The CDFs for month 3 are shown in

Figure 12 and Figure 13 below; the curves for month 6 are similar and are not shown.

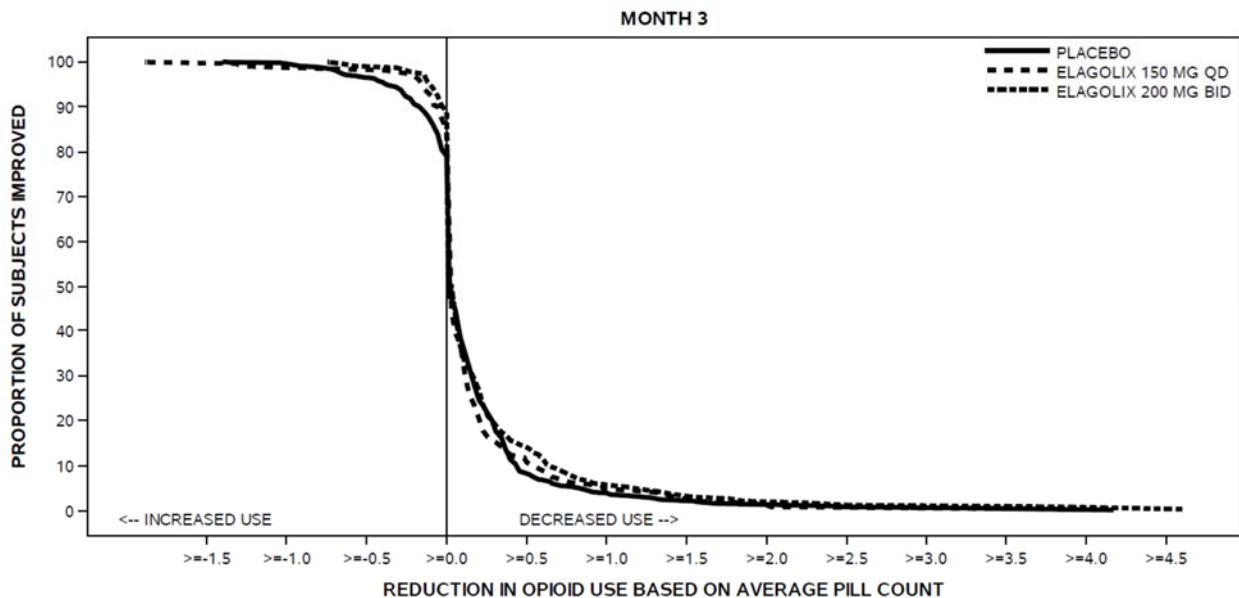
⁵ DAAAP consults in DARRTS, dated March 21, 2018

Figure 12. Cumulative Distribution Function of Reduction from Baseline in Opioid Use Based on Average Pill Count by Treatment Group at Month 3 (Modified Intent-To-Treat Set, Study 665)



Source: Figure 665_3a, 1.2.1, page 75, Response to Information Request submitted on May 18, 2018
BID = twice daily, QD = once daily

Figure 13. Cumulative Distribution Function of Reduction from Baseline in Opioid Use Based on Average Pill Count by Treatment Group at Month 3 (Modified Intent-To-Treat Set, Study 671)



Source: FIGURE 671_3a 1.2.1, page 88, Response to Information Request submitted on May 18, 2018
BID = twice daily, QD = once daily

The absolute decrease at month 6 was approximately one morphine milligram equivalence (MME) per day for subjects treated with elagolix 200 mg BID. We conclude, with DAAAP's

concurrence,⁶ that the data in this application are not sufficient to support a clinically meaningful decrease in opioid use. In response to our request, the Applicant submitted the following table (Table 51) and summary data to describe rescue opioid use in Studies 665 and 671. Agreement was reached among the review team, DAAAP, and the Applicant that this table may be included in product labeling, provided that a declarative statement “The clinical relevance of these data has not been demonstrated” is also included.

Table 51. Opioid Rescue Analgesic Use in Studies 665 and 671

	Study M12-665			Study M12-671		
	ORILISSA 150 mg QD	ORILISSA 200 mg BID	Placebo	ORILISSA 150 mg QD	ORILISSA 200 mg BID	Placebo
Tablets per month at baseline (mean ± SD)	15 ± 24	15 ± 25	13 ± 21	13 ± 29	12 ± 26	12 ± 21
Tablets per month at baseline [Median (Min, Max)]	4 (0, 184)	4 (0, 195)	4 (0, 146)	4 (0, 236)	3 (0, 214)	4 (0, 152)
Tablets per month at Month 3 (mean ± SD)	12 ± 29	7 ± 18	10 ± 17	8 ± 22	5 ± 14	8 ± 15
Tablets per month at Month 3 [Median (Min, Max)]	0 (0, 251)	0 (0, 162)	2 (0, 144)	0 (0, 168)	0 (0, 136)	2 (0, 142)
Tablets per month at Month 6 (mean ± SD)	11 ± 26	7 ± 17	11 ± 19	7 ± 19	5 ± 14	8 ± 15
Tablets per month at Month 6 [Median (Min, Max)]	0 (0, 224)	0 (0, 157)	3 (0, 185)	0 (0, 185)	0 (0, 157)	2 (0, 142)
Number and % of patients on any dose of opioid rescue at baseline who were off opioid at Month 3 ^a	46/150 (31%)	59/151 (39%)	36/211 (17%)	44/124 (36%)	68/134 (51%)	54/220 (25%)
Number and % of patients on any dose of opioid rescue at baseline who were off opioid at Month 6 ^a	43/149 (29%)	66/150 (44%)	36/211 (17%)	50/124 (40%)	78/134 (58%)	70/222 (32%)
Number and % of patients not on opioid rescue at baseline who were on any opioid at Month 3 ^b	9/98 (9%)	6/93 (7%)	17/162 (11%)	10/97 (10%)	10/91 (11%)	29/133 (22%)
Number and % of patients not on opioid rescue at baseline who were on any opioid at Month 6 ^b	16/98 (16%)	6/93 (7%)	32/161 (20%)	13/97 (13%)	6/91 (7%)	32/133 (24%)

BID = twice daily, QD = once daily, Min = minimum, Max = maximum, SD = standard deviation

Monthly calculations are based on a 35-day interval.

^a Denominator is the number of subjects on opioid rescue at baseline.

^b Denominator is the number of subjects not on opioid rescue at baseline.

Additional Analyses Conducted for Each Trial

Subgroup Analyses for the Co-Primary Efficacy Endpoints

The sponsor pre-defined subgroup analyses for the co-primary efficacy endpoints. As shown in Table 52 to Table 55, the responder rates of DYS and of NMPP were generally consistently

⁶ DAAAP consults dated March 22, June 20, and July 20, 2018, in DARRTS.

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higher for elagolix 150 mg QD and 200 mg BID compared to placebo across the categories of age, race, ethnicity, baseline pain score for DYS, NMPP, and DYSP, baseline analgesic use, time to endometriosis diagnosis and history of pregnancy at baseline.

Table 52. Study 665 - Proportion of Responders at Month 3 for Daily Assessment of DYS by treatment and subgroups – LOCF (MITT)

Subgroup Category	Placebo		Elagolix 150 mg QD		Elagolix 200 mg BID	
	N	%	N	%	N	%
Age (Years)						
< 25	51	19.6%	32	40.6%	39	79.5%
25 to 35	218	15.6%	156	46.2%	145	73.8%
> 35	104	27.9%	60	50.0%	60	78.3%
Race						
white	322	19.6%	220	46.9%	213	77.5%
Non-white	51	19.6%	28	42.9%	31	64.5%
Ethnicity						
Hispanic	63	17.5%	35	62.9%	40	72.5%
Other	310	20.0%	213	43.7%	204	76.5%
Baseline pain score for DYS						
< Median (2.17)	184	16.3%	116	44.0%	117	71.8%
≥ Median (2.17)	189	22.8%	132	48.5%	127	79.5%
Baseline pain score for NMPP						
< Median (1.57)	184	20.1%	122	48.4%	126	77.8%
≥ Median (1.57)	189	19.0%	126	44.4%	118	73.7%
Baseline pain for DYSP						
< Median (1.50)	158	19.0%	102	47.1%	97	74.2%
≥ Median (1.50)	160	19.4%	101	46.5%	99	71.7%
Baseline analgesic use						
None	27	29.6%	34	55.9%	14	78.6%
Narcotic only	71	19.7%	45	46.7%	52	82.7%
NSAID only	135	22.2%	64	60.9%	79	75.9%
Both	140	15.0%	105	34.3%	99	71.7%
Time since diagnosis						
< 2	117	23.1%	95	44.2%	82	74.4%
2 to 5	147	12.9%	88	53.4%	99	74.7%
≥ 5	109	24.8%	65	40.0%	62	79.0%
History of pregnancy						
No	138	21.7%	101	47.5%	111	73.9%
Yes	235	18.3%	147	45.6%	133	77.4%

Source: Study 665 CSR Table 14.2_6.1.1

BID = twice daily, DYS = dysmenorrhea, DYSP = dyspareunia, LOCF = last observation carried forward, MITT = modified intent-to-treat, NMPP = nonmenstrual pelvic pain, NRS = numeric rating score, NSAID = non-steroidal anti-inflammatory drug, QD = once daily

Table 53. Study 665 - Proportion of Responders at Month 3 for Daily Assessment of NMPP by treatment and subgroups – LOCF (MITT)

Subgroup Category	Placebo		Elagolix 150 mg QD		Elagolix 200 mg BID	
	N	%	N	%	N	%
Age (Years)						
< 25	51	31.4%	32	43.8%	39	43.6%
25 to 35	218	34.4%	156	54.5%	145	54.5%
> 35	104	43.3%	60	43.3%	60	61.7%
Race						
white	322	36.6%	220	51.8%	213	54.9%
Non-white	51	35.3%	28	39.3%	31	51.6%
Ethnicity						
Hispanic	63	47.6%	35	71.4%	40	55.0%
Other	310	34.2%	213	46.9%	204	54.4%
Baseline pain score for DYS						
< Median (2.17)	184	33.7%	116	50.9%	117	47.0%
≥ Median (2.17)	189	39.2%	132	50.0%	127	61.4%
Baseline pain score for NMPP						
< Median (1.57)	184	28.8%	122	47.5%	126	47.6%
≥ Median (1.57)	189	43.9%	126	53.2%	118	61.9%
Baseline pain for DYSP						
< Median (1.50)	158	30.4%	102	52.0%	97	52.6%
≥ Median (1.50)	160	40.0%	101	46.5%	99	57.6%
Baseline analgesic use						
None	27	44.4%	34	50.0%	14	64.3%
Narcotic only	71	25.4%	45	53.3%	52	46.2%
NSAID only	135	43.7%	64	59.4%	79	57.0%
Both	140	33.6%	105	43.8%	99	55.6%
Time since diagnosis						
< 2	117	33.3%	95	45.3%	82	58.5%
2 to 5	147	35.4%	88	54.5%	99	46.5%
≥ 5	109	41.3%	65	52.3%	62	61.3%
History of pregnancy						
No	138	37.0%	101	51.5%	111	44.1%
Yes	235	36.2%	147	49.7%	133	63.2%

Source: Study 665 CSR Table 14.2_6.2.1

BID = twice daily, DYS = dysmenorrhea, DYSP = dyspareunia, LOCF = last observation carried forward, MITT = modified intent-to-treat, NSAID = non-steroidal anti-inflammatory drug, QD = once daily

Table 54. Study 671 - Proportion of Responders at Month 3 for Daily Assessment of DYS by treatment and subgroups – LOCF (MITT)

Subgroup Category	Placebo		Elagolix 150 mg QD		Elagolix 200 mg BID	
	N	%	N	%	N	%
Age (Years)						
< 25	40	20.0%	25	56.0%	26	65.4%
25 to 35	195	21.5%	118	44.9%	109	70.6%
> 35	118	25.4%	78	37.2%	90	76.7%
Race						
white	317	22.7%	196	42.3%	203	74.9%
Non-white	36	22.2%	25	52.0%	22	50.0%
Ethnicity						
Hispanic	42	31.0%	32	37.5%	33	60.6%
Other	311	21.5%	189	44.4%	191	74.5%
Region						
U.S.	174	23.0%	106	34.9%	110	60.9%
Non-U.S.	179	22.3%	115	51.3%	115	83.5%
Baseline pain score for DYS						
< Median (2.14)	173	16.2%	105	41.0%	120	76.7%
≥ Median (2.14)	180	28.9%	116	45.7%	105	67.6%
Baseline pain score for NMPP						
< Median (1.52)	170	27.1%	101	49.5%	127	78.0%
≥ Median (1.52)	183	18.6%	120	38.3%	98	65.3%
Baseline pain for DYSP						
< Median (1.33)	137	26.3%	91	45.1%	91	80.2%
≥ Median (1.33)	147	22.4%	93	40.9%	94	73.4%
Baseline analgesic use						
None	33	18.2%	21	42.9%	22	68.2%
Narcotic only	55	16.4%	33	51.5%	28	75.0%
NSAID only	100	20.0%	76	56.6%	69	71.0%
Both	165	27.3%	91	29.7%	106	73.6%
Time since diagnosis						
< 2	125	22.4%	94	38.3%	72	66.7%
2 to 5	117	22.2%	67	50.7%	77	75.3%
≥ 5	111	23.4%	60	43.3%	76	75.0
History of pregnancy						
No	166	22.9%	92	51.1%	99	64.6%
Yes	187	22.5%	129	38.0%	126	78.6%

Source: Study 671 CSR Table 14.2_6.1.1

BID = twice daily, DYS = dysmenorrhea, DYSP = dyspareunia, LOCF = last observation carried forward, MITT = modified intent-to-treat, NMPP = nonmenstrual pelvic pain, NSAID = non-steroidal anti-inflammatory drug, QD = once daily

Table 55. Study 671 - Proportion of Responders at Month 3 for Daily Assessment of NMPP by treatment and subgroups – LOCF (MITT)

Subgroup Category	Placebo		Elagolix 150 mg QD		Elagolix 200 mg BID	
	N	%	N	%	N	%
Age (Years)						
< 25	40	37.5%	25	60.0%	26	50.0%
25 to 35	195	33.8%	118	44.9%	109	52.3%
> 35	118	40.7%	78	53.8%	90	66.7%
Race						
white	317	36.3%	196	50.0%	203	57.6%
Non-white	36	38.9%	25	48.0%	22	59.1%
Ethnicity						
Hispanic	42	40.5%	32	46.9%	33	63.6%
Other	311	36.0%	189	50.3%	191	56.8%
Region						
U.S.	174	36.2%	106	38.7%	110	52.7%
Non-U.S.	179	36.9%	115	60.0%	115	62.6%
Baseline pain score for DYS						
< Median (2.14)	173	31.8%	105	52.4%	120	60.8%
≥ Median (2.14)	180	41.1%	116	47.4%	105	54.3%
Baseline pain score for NMPP						
< Median (1.52)	170	31.2%	101	53.5%	127	54.3%
≥ Median (1.52)	183	41.5%	120	46.7%	98	62.2%
Baseline pain for DYSP						
< Median (1.33)	137	35.0%	91	50.5%	91	59.3%
≥ Median (1.33)	147	38.8%	93	44.1%	94	57.4%
Baseline analgesic use						
None	33	30.3%	21	38.1%	22	63.6%
Narcotic only	55	29.1%	33	66.7%	28	53.6%
NSAID only	100	37.0%	76	55.3%	69	62.3%
Both	165	40.0%	91	41.8%	106	54.7%
Time since diagnosis						
< 2	125	39.2%	94	47.9%	72	50.0%
2 to 5	117	36.8%	67	52.2%	77	58.4%
≥ 5	111	33.3%	60	50.0%	76	64.5%
History of pregnancy						
No	166	34.3%	92	53.3%	99	52.5%
Yes	187	38.5%	129	47.3%	126	61.9%

Source: Study 671 CSR Table 14.2_6.2.1

BID = twice daily, DYS = dysmenorrhea, DYSP = dyspareunia, LOCF = last observation carried forward, MITT = modified intent-to-treat, NMPP = nonmenstrual pelvic pain, NSAID = non-steroidal anti-inflammatory drug, QD = once daily

FDA's Additional Analyses

To evaluate the appropriateness of the Applicant's determined thresholds for defining responders for DYS and NMPP, we explored the data further by examining the data distribution.

Table 56 shows the rate of each response to PGIC for each treatment group at month 3. The response rates of "very much improved" and "much improved" were higher in both elagolix groups than placebo. And the response rates for all the other categories were lower in the elagolix groups than placebo.

Table 56. Summary of PGIC at Month 3 by Study and Treatment - LOCF

PGIC Outcome (%)	Study 665			Study 671		
	Placebo (N = 373)	Elagolix 150 mg QD (N = 248)	Elagolix 200 mg BID (N = 244)	Placebo (N = 355)	Elagolix 150 mg QD (N = 221)	Elagolix 200 mg BID (N = 225)
Very much Improved	9.2%	23.1%	37.9%	7.8%	18.5%	34.9%
Much Improved	19.7%	29.1%	34.8%	24.7%	37.4%	39.7%
Minimally Improved	35.5%	28.4%	19.4%	31.6%	26.1%	17.7%
No Change	25.1%	13.5%	4.4%	23.8%	11.8%	4.8%
Minimally Worse	5.2%	3.1%	3.1%	5.1%	3.3%	1.9%
Much Worse	4.6%	1.7%	0.4%	5.4%	2.4%	1.0%
Very worse	0.6%	0.9%	0	1.5%	0.5%	0

Source: Table 14.2_21.1.1 in Study CSRs

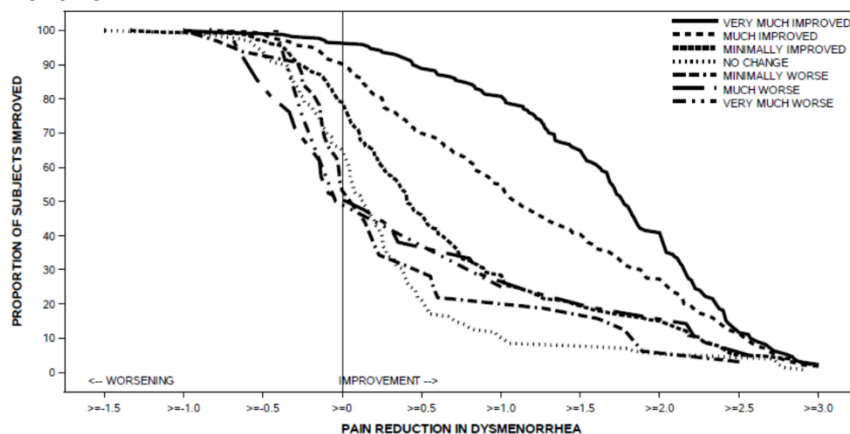
BID = twice daily, LOCF = last observation carried forward, PGIC = Patient Global Impression of Change, QD = once daily

The CDFs for changes from baseline in DYS and NMPP by PGIC categories were also explored by pooling all subjects across treatment groups in the MITT population. Each CDF shows a continuous plot of the proportion of subjects at each point along the scale score continuum who experience reduction in pain at that level or greater. In the context of the responder assessment, the y-axis represents the proportion of subjects who are considered responders at that threshold value on the x-axis.

By visual examination of the CDF plots (**APPEARS THIS WAY ON ORIGINAL** Figure 14 to **APPEARS THIS WAY ON ORIGINAL**

Figure 17), there is consistent separation between the patients who were “very much improved” or “much improved” on the PGIC compared to the other PGIC categories for both DYS and NMPP at month 3, except for some overlap between “much improved” and “very much worse” for NMPP at month 3 in Study 665. Therefore, grouping the “very much improved” and “much improved” categories in the ROC analysis was appropriate.

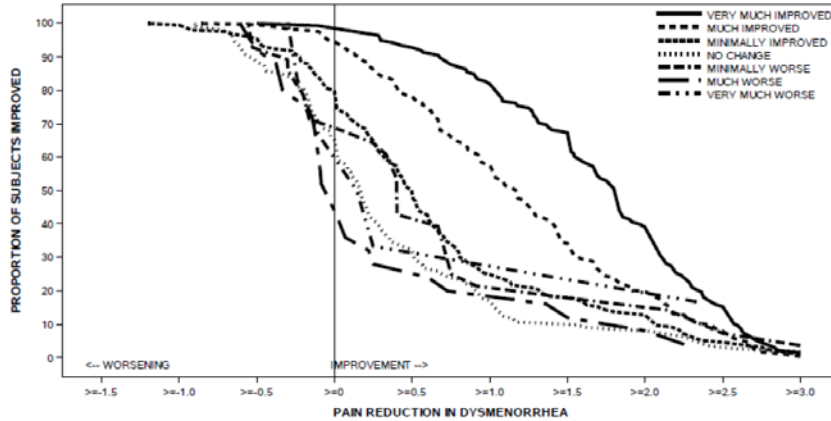
Figure 14. Study 665 Cumulative Distribution Function of Change from Baseline in DYS by PGIC at Month 3



Source: Study 665 CSR Figure 14.2_8.1.2.

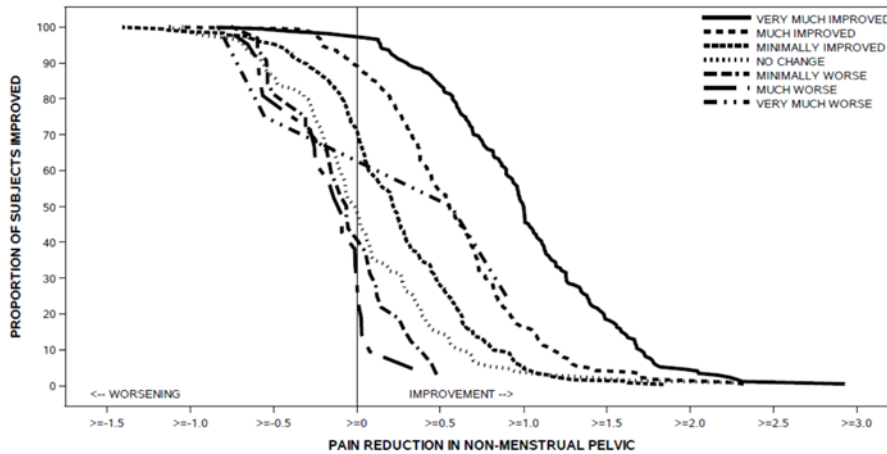
DYS = dysmenorrhea, PGIC = Patient Global Impression of Change

Figure 15. Study 671 Cumulative Distribution Function of Change from Baseline in DYS by PGIC at Month 3



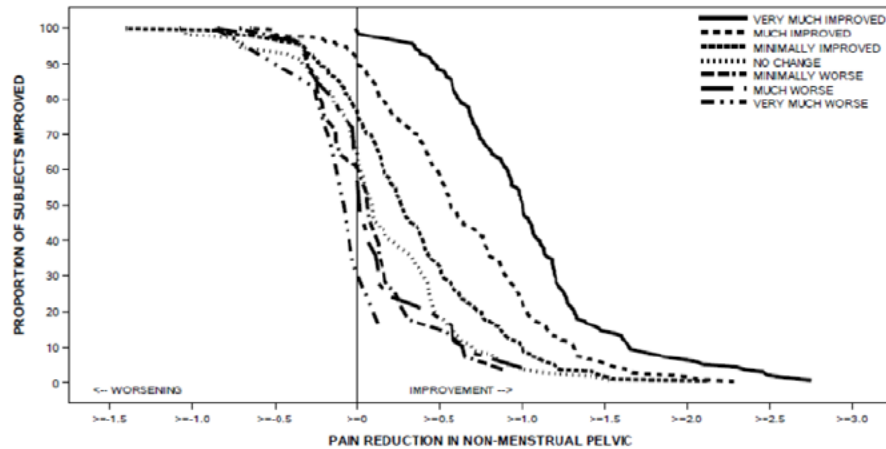
Source: Study 671 CSR Figure 14.2_8.1.2.
DYS = dysmenorrhea, PGIC = Patient Global Impression of Change

Figure 16. Study 665 Cumulative Distribution Function of Change from Baseline in NMPP by PGIC at Month 3



Source: Study 665 Figure 14.2_8.2.2
NMPP = nonmenstrual pelvic pain, PGIC = Patient Global Impression of Change

Figure 17. Study 671 Cumulative Distribution Function of Change from Baseline in NMPP by PGIC at Month 3



Source: Study 671 Figure 14.2_8.2.2
 NMPP = nonmenstrual pelvic pain, PGIC = Patient Global Impression of Change

Table 57 presents the median change from baseline to month 3 for DYS and NMPP for the “much improved” PGIC category. We reanalyzed the co-primary efficacy endpoints using these median values as the thresholds in each study and found that the results were consistent with the primary efficacy results. This sensitivity analysis supports the robustness of the efficacy findings.

Table 57. FDA Additional Analysis - DYS and NMPP Thresholds

Study	Change from Baseline to Month 3	
	Dysmenorrhea	Non-Menstrual Pelvic Pain
665	-1.08	-0.55
671	-1.17	-0.56

Source: FDA’s analysis and Figure 14.2_8.2.3 in Study CSRs
 DYS = dysmenorrhea, NMPP = nonmenstrual pelvic pain

Table 58. FDA Additional Analysis for Proportion of Responders at Month 3 for Daily Assessment of DYS and NMPP – LOCF

Study	Endpoint	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID
		n/N (%)	n/N (%)	n/N (%)
665	DYS responder Difference vs. placebo	47/373 (12.6%)	98/248 (39.5%) 26.9%	147/244 (65.3%) 42.7%
	NMPP responder Difference vs. placebo	98/373 (26.3%)	96/248 (38.7%) 12.4%	115/244 (47.1%) 20.8%
671	DYS responder Difference vs. placebo	45/353 (12.7%)	78/221 (35.3%) 22.6%	147/225 (65.3%) 42.6%
	NMPP responder Difference vs. placebo	102/353 (28.9%)	89/221 (40.3%) 11.4%	118/225 (52.4%) 23.5%

Source: FDA's analysis.

BID = twice daily, DYS = dysmenorrhea, LOCF = last observation carried forward, NMPP = nonmenstrual pelvic pain, QD = once daily

Responder thresholds were determined based on CDF plots.

Study 665 - DYS responder threshold: a reduction of -1.08 or greater from baseline in DYS pain score

NMPP responder threshold: a reduction of -0.55 or greater from baseline in NMPP score

Study 671 - DYS responder threshold: a reduction of -1.17 or greater from baseline in DYS pain score

NMPP responder threshold: a reduction of -0.56 or greater from baseline in NMPP score

Durability of Response

Numerous non-ranked efficacy endpoints were explored in this submission relating to onset and persistence of response. In the placebo controlled studies, each co-primary (proportion of responders) and ranked secondary (mean changes from baseline) endpoints were evaluated at monthly time points. The two placebo-controlled studies had similar findings for each of the endpoints. Onset of efficacy for DYS appeared to occur at month 1 for both 150 mg QD and 200 mg BID arms. Reduction in NMPP appeared to occur by month 2 for the 200 BID arms and by month 3 for the 150 mg QD arms. Reduction in NRS appeared to occur at month 1 for both 150 mg QD and 200 mg BID arms. Only the 200 BID arms showed reduction in DYSP and this occurred by month 3. Once efficacy was obtained, the response continued through the 6-month treatment period.

Dose Response

The mechanism of action of elagolix is suppression of GnRH with resultant suppression of FSH, LH, and estradiol. These effects were assessed in the Phase 3 studies and are discussed in section 6.3.2.1.

The 200 mg BID treatment arms had low estradiol, FSH, and LH concentrations consistent with suppression of the pituitary gonadotropin hormones expected with GnRH antagonists. The 150 mg QD treatment arms showed less suppression of estradiol and LH concentrations. The FSH concentrations with the 150 mg QD dose were similar to the placebo groups. Overall, these data support a dose response to elagolix. With incomplete suppression of FSH, pregnancy during treatment is a concern.

Dose Finding

There were three Phase 2 dose-finding studies that utilized the IR formulation of elagolix. The 200 mg BID dose was not studied in these Phase 2 studies.

Study NBI-56418-0702 was a randomized, double-blind trial that compared elagolix 150 mg QD or 250 mg QD to placebo for 12 weeks, followed by randomization of the placebo group to one of the active treatment arms for an additional 12 weeks. The endpoint was the change from baseline in the monthly mean NRS (assessed daily) for endometriosis pain at week 12. The decreases from baseline in the 150 mg QD and 250 mg QD arms were greater compared to the decrease from baseline in the placebo group but the differences were not statistically significant. BMD as measured by DXA showed small decreases from baseline at week 24 with a larger decrease observed in the 250 mg QD group compared to the 150 mg QD group.

Study NBI-56418-0703 replicated Study 0702 and added a fourth arm of intramuscular leuprolide 3.75 mg monthly for 12 weeks followed by randomization of the placebo and leuprolide arms to either elagolix 150 mg QD or 250 mg QD for an additional 12 weeks. There was a follow up visit 6 weeks after elagolix was discontinued for a total study duration of 30 weeks. There was no primary efficacy endpoint. Key endpoints included the change from baseline in the monthly mean NRS for endometriosis pain at week 12, the change from baseline in monthly mean DYS and NMPP (using daily assessment with a 4-point pain impact scale) at week 12, and percentage of days with prescription analgesic use. At the end of week 12, the differences in the monthly mean NRS between the active treatment groups and placebo were not statistically significant. Decreases in monthly mean DYS in the three active treatment arms appeared to be larger than those observed in the placebo arm. There were no statistically significant decreases in the monthly mean NMPP score of either elagolix arms at week 12 compared with the placebo arm. However, the monthly mean NMPP score for the leuprolide arm appeared to decrease compared with placebo at week 12. Analgesic use showed little change overall in all study groups. BMD showed the largest decrease at week 12 in the leuprolide group. Mean decreases in BMD were slightly greater at week 24 than week 12 in the elagolix groups with the 250 mg QD group having a slightly greater decrease in BMD than the 150 mg QD group at both time points.

Study NBI-5648-0901 was a randomized, double-blind trial comparing elagolix 150 mg QD and placebo for 8 weeks, followed by an open-label phase where all subjects received elagolix 150 mg QD for an additional 16 weeks. There was a follow up visit at week 30, six weeks after the last dose of study drug was administered. There were numerous efficacy endpoints including changes in monthly mean scores from baseline in DYS, NMPP, DYSP, and analgesic use for endometriosis pain compared with placebo. PGIC scores and percentages of responders compared to baseline for DYS, NMPP, and DYSP were also evaluated. At the end of the 8-week placebo-controlled study, there was a numerically larger decrease in DYS, NMPP, and DYSP from baseline in the elagolix group compared to placebo. Use of any analgesics and prescription analgesics appeared to show a larger decrease from baseline in the elagolix group

compared to placebo with the use of narcotic analgesics compared to placebo showing a similar trend. PGIC scores appeared to be lower for the elagolix group compared to placebo at week 8 (lower value = more improvement). A higher percentage of elagolix-treated subjects (60.3%) reported being much improved and very much improved than placebo subjects (30.2%). The percentage of responders for DYS, NMPP, and DYSP appeared to be higher for the elagolix group compared to the placebo group at most responder thresholds. BMD was not evaluated in this study.

Dose finding in these phase 2 trials are limited. Only two doses, 150 mg QD and 250 mg QD were evaluated. Studies 702 and 703 did not show significant changes in efficacy for both DYS and NMPP over placebo for either 150 mg QD or 250 mg QD of elagolix, but did show greater BMD loss with the higher dose of elagolix. In Study 901, elagolix 150 mg QD appear to have efficacy over placebo (elagolix 250 mg QD was not studied). The reason for the different results might be related to the baseline pain scores. In Studies 702 and 703, the mean baseline pain scores corresponded to mild pain intensity while in Study 901 the mean baseline pain scores corresponded to moderate-severe pain intensity. Efficacy in the Phase 3 trials was established only in patients with moderate to severe EAP, which will be reflected in the indication. The label will mention the Phase 3 trial inclusion criteria used to enroll patients with moderate to severe EAP to help guide clinical use.

There were no efficacy trials utilizing BID dosing of the IR formulation of elagolix for EAP. The Applicant notes that Phase 1 PK studies suggested increased hormonal suppression with higher doses and BID regimens and this was the rationale for studying the 200 mg BID regimen in Phase 3.

There were no efficacy trials that titrated the elagolix dose in subjects who had not responded to lower elagolix doses. Therefore, it is unclear if increasing the dose of elagolix in nonresponders will result in responder status.

The Applicant has proposed that the starting dose be based on the severity of symptoms and treatment objectives with the lowest effective dose being utilized. When the predominant symptom is dyspareunia, the Applicant proposes consideration to start with the 200 mg BID dose. This latter recommendation acknowledges that the 150 mg QD dose of elagolix did not show efficacy for DYSP. This proposed dosing appears reasonable. There is no recommended approach to dose titration from 150 mg QD to 200 mg BID.

8.1.4. Assessment of Efficacy Across Trials

The two placebo-controlled Phase 3 trials – Studies 665 and 671, had virtually identical designs. Study 665 was conducted entirely in the U.S. and Canada while Study 671 enrolled patients across different continents (U.S., Europe, South America, Australia, New Zealand, and South Africa). Results were consistent across these two adequate and well-controlled trials, providing replicative evidence of efficacy.

In early clinical development, statistically significant treatment effects were not consistently observed in Phase 2 trials (enrollment in two of those trials was open to patients with mild EAP). The two Phase 3 trials were enriched to include only women with moderate to severe EAP. Therefore, treatment benefit should not be extrapolated to women with only mild EAP. The Applicant has agreed to limit the target population to women with moderate to severe EAP.

8.1.5. Integrated Review of Effectiveness

As noted previously, other than enrolling subjects from different regions of the world, the two six-month Phase 3 trials had virtually identical designs. Results from these trials were highly consistent and clearly demonstrated that both the 150 mg QD and 200 mg BID regimens resulted in improvement in DYS and NMPP in women with moderate to severe EAP. In both trials, the 200 mg BID dose resulted in less dyspareunia than placebo at month 3, the only timepoint included for this endpoint in the hierarchical statistical testing strategy. In both trials, the 200 mg BID dose resulted in statistically significantly less opioid use by pill count than placebo but the absolute decrease (1 morphine milligram equivalent) is not adequate to demonstrate clinically meaningfulness. The highly consistent results across the two adequate and well-controlled Phase 3 trials clearly establish substantial evidence of effectiveness for elagolix as a treatment of moderate to severe EAP.

8.2. Review of Safety

8.2.1. Safety Review Approach

The review of safety for this submission focused on the Phase 3, placebo-controlled, six-month endometriosis Studies M12-665 and M12-671. Long-term supportive safety data were submitted from Phase 3 extension studies M12-667 and M12-821, which provided an additional 6 months of data. Additional supportive data were derived from 6 Phase 2 studies, 13 multiple-dose Phase 1 studies, the 120-day safety update to the NDA, and other ongoing trials for this product that are being studied in women with fibroids. This product has not been previously approved in any other country.

The major safety findings that were anticipated based on elagolix's mechanism of action are those related to its activity in lowering estrogen and progesterone, including bone loss and vasomotor symptoms. There was also a focus on depression and other mood disorders for this centrally acting drug product. We also considered the adverse reactions associated with the study drug that occurred in the fibroid clinical program.

8.2.2. Review of the Safety Database

Overall Exposure

The overall elagolix exposure data is shown in Table 59.

Table 59. Overall Elagolix Exposure Data (as of June 19, 2017)

Elagolix Exposure	≥ 1 Dose	6 Months^a	12 Months^a
≥ 1 treatment with elagolix (and dosage)	3611	1557	425
Endometriosis Phase 3 studies	1382	1015	425
Endometriosis Phase 2 studies	708	268	0
Phase 1 studies	876	0	0
Uterine fibroid studies	645	274	0
Total daily dose ≥ 400 mg	1574	784	204
Endometriosis Phase 3 studies	697	510	204
Endometriosis Phase 2 studies	0	0	0
Phase 1 studies	265	0	0
Uterine fibroid studies	612	274	0
Total daily dose ≥ 150 mg	3492	1557	425
Endometriosis Phase 3 studies	1382	1015	425
Endometriosis Phase 2 studies	660	268	0
Phase 1 studies	805	0	0
Uterine Fibroid studies	645	274	0

^a Six- and 12-month exposures are defined as ≥ 168 days and ≥ 336 days, respectively (the Applicant defined 1 month as 28 days)
Source: Table 3, Summary of Clinical Safety, page 17 of 105

The exposure data are acceptable to support safety of this new molecular entity.

Relevant characteristics of the safety population:

The demographics of the Phase 3 trials was covered in the Efficacy section. The U.S. population was well represented in the Phase 3 trials such that the safety findings are generalizable to the target population expected to use this product after approval.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

In general, the safety database appears well organized and easy to navigate. The Applicant's text and summary statements appear to be backed up by the tabulations in the Integrated Summary of Safety (ISS), subject narratives, analyses with JMP software, and case report forms.

Of note, one case of severe hepatic injury (Subject (b) (6) in Study 821, further described below in section 8.2.4.6) was not described in the ISS. Starting on day 125 of treatment with elagolix 150 mg QD, she had increasingly abnormal elevations of liver function tests, reaching peak AST (730 U/L), ALT (1340 U/L), alkaline phosphatase (202 U/L), lactate dehydrogenase (LDH; 354 U/L), and bilirubin (2.2µMol/L) on day 183 of treatment. When first queried, the Applicant was not able to provide any explanation for not highlighting this case other than that

her liver tests partially normalized. A number of Information Requests relating to this case were sent. Given an imbalance in liver tests between the elagolix-treated group and placebo group already identified, the Division consulted the Division of Gastroenterology and Inborn Errors Products (DGIEP) and a hepatologist with expertise in drug-induced liver injury in the Office of Surveillance and Epidemiology. In response to the Agency's request, the Applicant sought medical records from the investigator in (b) (6), ultimately providing documents (original and translated into English) to substantiate a diagnosis of hepatitis A. At the late-cycle meeting with FDA, the Applicant acknowledged insufficient oversight and inadequate real-time safety monitoring for this hepatitis A case; the Applicant further volunteered that this case resulted from alterations in their internal processes. As a result of these activities and delay in receiving information, the review clock was extended by 3 months to allow FDA sufficient time to fully review a major amendment related to liver safety across the development program.

Categorization of Adverse Events

Other than the hepatitis A case, the Applicant's categorization of adverse events is generally acceptable. The definitions of adverse events, serious adverse events and treatment-emergent adverse events (TEAE) were acceptable. The TEAE events were defined to extend for 30 days post treatment. The Phase 3 controlled and extension studies were uniformly coded using MedDRA version 19.1. There was adequate hierarchy in the JMP database to assess adverse events. The preferred terms were used most often but the verbatim terms helped to analyze the drug-induced rash cases to a better extent.

Routine Clinical Tests

Clinical safety laboratory testing was performed centrally at screening, day 1 and then monthly throughout the 6-month pivotal studies. Monthly pregnancy testing and endocrine laboratory assessments were also performed. Exploratory bone biomarkers were evaluated at day 1, month 3 and month 6.

8.2.4. Safety Results

8.2.4.1. Deaths

In the NDA submission, the Applicant reported two deaths in the elagolix endometriosis clinical program to date. We also identified a neonatal death (described in the subsequent section of Phase 1 serious adverse events) and a completed suicide in a subject prior to treatment (fibroid Study 815).

Subject (b) (6); Study M12-662

This was a 49-year-old white female with a pertinent history of alcoholism, liver cirrhosis and ascites who participated in the elagolix single-dose liver impairment study. This subject had severe impairment (Group IV in the study). Her Child-Pugh score was 10 (encephalopathy score = 2; ascites score = 3; bilirubin score = 2; albumin score = 2 and INR score = 1). She received a single dose of 150 mg of elagolix on study day 1 (b) (6).

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The subject was found deceased on [REDACTED] (b) (6) by a relative. The relative noted excessive blood in the mouth and nose area. The body was taken to the medical examiner but no autopsy was performed.

The single 150 mg elagolix dose was taken approximately 20 days before death. Although the location and quantity of the bleeding noted by the relative suggests the possibility of ruptured esophageal varices, the lack of a post mortem examination hinders that assessment.

Table 60 and Table 61 provide the liver function testing (LFT) results and coagulation parameters for this subject:

Table 60. Liver Function Test Results for Subject (b) (6)

Study Day	ALT ULN = 48 U/L	AST ULN = 42 U/L	Total Bilirubin ULN = 1.3 mg/dL	ALP ULN = 125 U/L	GGTP ULN = 45 U/L
-20	17	42	3.0	156	60
-1	18	50	2.9	231	48
2	17	49	3.0	160	43
4	18	50	3.3	139	44

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGTP = gamma-glutamyltranspeptidase, ULN = upper limit of normal

Table 61. Coagulation Parameters for Subject (b) (6)

Study Day	Platelet count $\times 10^3/\mu\text{L}$	INR ULN = 1.1
-20	184	1.3
-1	198	1.3
2	186	1.3
4	185	1.3

INR = International Normalised Ratio of blood clotting time, ULN = upper limit of normal

The liver function test values pre- and post- dosing appear to be stable, except for the isolated increase in alkaline phosphatase shortly before dosing. No further liver function testing is noted in the narrative after study day 4 so it is undetermined whether there was any deterioration prior to the subject's demise or a change in coagulation parameters. See the further discussion of liver enzyme increases seen with elagolix in the laboratory safety section of this review and in the Division of Gastroenterology and Inborn Errors Products (DGIEP) consultative review submitted to DARRTS.

Note that there is a 7-fold increase in elagolix exposure in subjects with severe hepatic impairment and that elagolix will be contraindicated in such patients.

Subject (b) (6); Study M12-671

This was a 44-year-old female who died of a completed suicide; she took a mixture of drugs that included methadone, alprazolam and diazepam. The subject was enrolled in this randomized, placebo-controlled Phase 3 endometriosis study. Her past medical history included migraine headaches treated with atenolol 50 mg daily. She had a history of endometriosis for 10 years prior to study entry. She took 150 mg elagolix daily from [REDACTED] (b) (6)

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(b) (6) through (b) (6). The subject committed suicide on (b) (6), two days after her last dose of elagolix. Pertinent social history included the death of her spouse eight months prior to study enrollment and significant behavioral problems in her two children, with one child being evaluated for long-term placement.

Although the significant life stressors for this subject (loss of spouse and persistent family problems) probably were the main contributors to her suicide, an association with elagolix cannot be completely excluded. (See section 7.4.5 of this review regarding depression and associated symptoms).

8.2.4.2. Serious Adverse Events

Summary Statement Regarding Serious Adverse Events

Most of the serious adverse events reported in the clinical study were deemed to be unrelated to elagolix. One area of concern was related to psychiatric disorders. Reports of suicidal ideation, depression and anxiety were among the serious adverse events (SAEs) reported. Additionally, findings from common adverse events show an increased incidence in elagolix-treated subjects compared to placebo for these and similar events. Labeling will address these concerns.

Many of the SAEs of endometriosis, abdominal pain and pelvic pain relate to the subject's underlying endometriotic condition and the fact that elagolix is not always efficacious.

Phase 1 Studies - SAEs

There were seven serious adverse events reported in Phase 1 studies in subjects taking elagolix. These included:

- Pelvic abscess (1) = Subject (b) (6) in Study NBI-56418-0301
- Induced abortion (3) = Subjects (b) (6) and (b) (6) in Study M12-673, Subject (b) (6) in Study M12-659
- Cholecystitis/abdominal abscess (1) = Subject (b) (6) in Study M12-673
- Ectopic pregnancy (1) = Subject (b) (6) in Study M12-673
- Premature delivery/neonatal death (1) = Subject (b) (6) in Study M12-661

Notable narrative information regarding the above SAEs includes the following:

- The pelvic abscess symptoms manifested themselves in a 26-year-old subject (Subject (b) (6)) 3 days after a single dose of elagolix 25 mg. Abscess material obtained at laparoscopy grew *Fusobacterium* and *Prevotella*. Relevant medical history included an in situ intrauterine device. A relationship between the single dose elagolix administration and the pelvic abscess is unlikely.

- Subject (b) (6) who developed cholecystitis and an abdominal abscess was 40 years old and took elagolix 200 mg BID for 82 days. Sixteen days after her last treatment she developed epigastric/right upper quadrant pain, nausea and vomiting. She underwent a laparoscopic cholecystectomy and cholangiogram, showing common bile duct obstruction from gallstones. Postoperative complications included pancreatitis secondary to cystic duct obstruction, abdominal abscess and pleural effusion. Some literature suggests increased levels of estrogen and progestins in association with gall bladder and bile duct disease but elagolix typically lowers ovarian hormones; therefore, gallstones are the most likely cause of this subject's symptoms and complications.
- The 27-year-old subject (Subject (b) (6)) with the ectopic pregnancy completed her elagolix (300 mg BID) on study day 82. Her pregnancy test results were not positive until study day 143. The ectopic pregnancy was treated surgically and unlikely to be related to treatment with elagolix.
- The premature delivery and neonatal death occurred in a 21-year-old subject (Subject (b) (6)) who took two doses of elagolix in the QT study (300 mg on day 1, 1200 mg on day 8). The subject's estimated conception date by sonography was 38 days after her last dose of elagolix on day 8. The subject had premature rupture of membranes and premature labor at 23 weeks. The infant expired 1 hour following vaginal delivery. We find no association with the pregnancy complications and elagolix administration.

Phase 2 Studies - SAEs

All 29 SAEs were treatment-emergent events in the Phase 2 studies. There were 18 subjects with 19 SAEs in subjects taking elagolix. There were 6 SAEs reported for other active comparators and 4 SAEs reported for subjects taking placebo.

The 19 SAEs for subjects taking elagolix included:

- Appendicitis (1) = Subject (b) (6) in Study NBI-56418-0703
- Anaphylactoid reaction (1) = Subject (b) (6) in Study NBI-56418-0501 (see the narrative for this subject in the discussion of anaphylactoid and drug-induced rashes in section 8.2.5.3 of this review)
- Abortion spontaneous (2) = Subject (b) (6) in Study NBI-56418-0702, Subject (b) (6) in Study NBI-56418-0901
- Abdominal pain (1) = Subject (b) (6) in Study NBI-56418-0901
- Bipolar disorder (1) = Subject (b) (6) in Study NBI-56418-0901
- Cholelithiasis (1) = Subject (b) (6) in Study NBI-56418-0501
- Depression suicidal (1) = Subject (b) (6) in Study NBI-56418-0603
- Dehydration (2) = Subject (b) (6) in Study NBI-56418-0501 and subject (b) (6) in Study NBI-56418-0603
- Endometriosis (2) = Subjects (b) (6) and (b) (6) in Study NBI-56418-0504
- Migraine (1) = Subject 1 (b) (6) in Study NBI-56418-0603

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- Ovarian dysgerminoma (1) = Subject (b) (6) in Study NBI-56418-0603
- Benign paranasal sinus retention cyst = (1) Subject (b) (6) in NBI-56418-0703
- Pelvic pain (2) = Subject (b) (6) in Study NBI-56418-0603; Subject (b) (6) in Study NBI-56418-0702
- Pneumonia (1) = Subject (b) (6) in Study NBI-56418-0603
- Type 2 Diabetes (1) = Subject (b) (6) in Study NBI-56418-0703

Notable narrative information regarding the above SAEs includes the following:

- Pregnancy results (including spontaneous abortions) will be discussed in section 8.2.5.
- Subject (b) (6) was a 33-year-old-female who presented with right lower quadrant pain. She underwent surgery for an incarcerated incisional hernia. Evidence of peri-appendicitis and a ruptured ovarian cyst were also found. She resumed her elagolix study drug after the hospitalization. This event does not appear to be drug-related.
- Subject (b) (6) (bipolar disorder) and subject (b) (6) (depression suicidal) are discussed in section 8.2.5.
- Subject (b) (6) was a 33-year-old female who presented to an emergency room with gallbladder symptoms approximately 21 days (b) (6) after starting study drug (elagolix 150 mg QD). She had previously seen her physician for xiphoid and substernal pain prior to starting study drug and at which time the gallstones were diagnosed by ultrasound. The subject underwent laparoscopic cholecystectomy. Study drug was restarted after the hospitalization. The SAE narrative reported that the subject also developed dehydration 7 weeks (b) (6) after starting study drug. The case report form noted the adverse events of nausea, vomiting, and refractory diarrhea at the same time point as the hospitalization for dehydration. A stool sample was negative for WBCs, erythrocytes, and ova and parasites. No salmonella, shigella, campylobacter, or E. coli were found. The only gastrointestinal finding was a tubulovillous polyp that was removed at colonoscopy. The case report form also noted some intermittent diarrhea 2 months later in (b) (6) but no additional information. Study drug was not interrupted during the dehydration episode. It is unlikely that either SAE was associated with elagolix.
- Subject (b) (6) was a 21-year-old female who was treated for dehydration that was felt to be secondary to food poisoning.
- Subject (b) (6) was a 36-year-old who completed her 12-week treatment phase (elagolix 100 mg BID) but experienced a worsening of her endometriosis 27 days after her last dose of study drug. She elected to have a total abdominal hysterectomy and bilateral salpingo-oophorectomy.

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- Subject (b) (6) was a 26-year-old who was randomized to receive elagolix 100 mg BID. She discontinued after approximately 38 days because of uterine bleeding and increasing pain. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy.
- Subject (b) (6) was a 39-year-old female with a 9-year history of migraines who was hospitalized for a migraine on study day 95. Six days before her hospitalization, she received a botulinum injection for prophylactic migraine treatment. Later that day she had a migraine. Her migraine subsided during the hospitalization and she completed the study without interruption of study drug. Although the investigator judged the event to be unlikely related to study drug, it is not possible to definitively rule out hormonal shift factors and an associative role for elagolix.
- Subject (b) (6) was a 22-year-old female who was diagnosed with an ovarian dysgerminoma on day 218 after starting study drug (elagolix 150 mg QD) and 43 days after taking the last dose. The subject was treated with surgery and chemotherapy. Ovarian dysgerminomas have not been associated with hormonal treatment and we find no association with elagolix.
- Subject (b) (6) was a 29-year-old female who was randomized to receive elagolix 150 mg QD for 24 weeks. She was hospitalized approximately 3 months after her final dose of study drug for pelvic pain. A diagnostic laparoscopy was performed and numerous filmy adhesions were lysed. The pelvic pain resolved after surgery. We find no association with elagolix.
- Subject (b) (6) was a 40-year-old female who was randomized to receive elagolix 150 mg QD for 24 weeks. This subject was relatively pain free during treatment but had pelvic pain 3 days after her last dose of study drug. She was hospitalized and underwent a laparoscopic assisted vaginal hysterectomy and right salpingo-oophorectomy. We find no association with elagolix.
- Subject (b) (6) was a 39-year-old female who was randomized to receive elagolix 75 mg BID for 24 weeks. On study day 174 the subject experienced pneumonia approximately 7 days after her last oral dose of study drug. She was hospitalized for 7 days with resolution of her pneumonia. We find no association with elagolix.
- Subject (b) (6) was a 34-year-old female diagnosed with type 2 diabetes and admitted to the hospital with hyperglycemic symptoms.

Phase 3 Placebo-Controlled Studies (elagolix-arm subjects)

There were a total of 44 elagolix-treated subjects with 68 SAEs in the Phase 3, placebo-controlled studies. Of these, there were 26 elagolix-treated subjects with 39 treatment-emergent SAEs in the Phase 3, placebo-controlled studies. Treatment-emergent adverse events

were defined as those during treatment and within 30 days after the last dose of study drug.

These 68 total SAEs include the following (Note: subjects with treatment-emergent SAEs are highlighted in bold font)

- Abdominal hernia (1) = Subject (b) (6) in Study M12-671
- Abdominal pain (4) = Subjects (b) (6) and (b) (6) in Study M12-671
- Abortion induced (2) = Subject (b) (6) in Study M12-665, Subject (b) (6) in Study M12-671
- Abortion spontaneous (5) = Subjects (b) (6) and (b) (6) in Study M12-671
- Abscess oral (1) = Subject (b) (6) in Study M12-671
- Adnexal mass (1) = Subject (b) (6) in Study M12-665
- Anxiety (1) = Subject (b) (6) in Study M12-665
- Appendicitis (3) = Subject (b) (6) in Study M12-665; Subjects (b) (6) and (b) (6) in Study M12-671
- Back pain (3) = twice for Subject (b) (6) (who had a kidney stone) and once for Subject (b) (6) (who had lumbar disk herniation) in Study M12-671
- Blood pressure increased (1) = Subject (b) (6) in Study M12-665 (occurred after study participation while she was pregnant)
- Chest pain (1) = Subject (b) (6) in Study M12-665
- Completed suicide (1) = Subject (b) (6) in Study M12-671
- Dyspnea (1) = Subject (b) (6) in Study M12-665
- Endometriosis (8) Subjects (b) (6) and (b) (6) in Study M12-665; Subjects (b) (6) and (b) (6) in Study M12-671
- Frequent bowel movements (1) = Subject (b) (6) in Study M12-671
- Gallbladder polyp (1) = Subject (b) (6)
- Hydronephrosis (1) = Subject (b) (6) (from nephrolithiasis) in Study M12-665
- Hypokalemia (1) = Subject (b) (6) (occurring post study at the same time as recurrent nephrolithiasis symptoms) in Study M12-665
- Immune thrombocytopenic purpura (1) = Subject (b) (6) in Study M12-665 (see reviewer comment about this and pulmonary embolism)
- Intervertebral disc protrusion (1) = Subject (b) (6) in Study M12-671
- Intestinal obstruction (1) = Subject (b) (6) (due to adhesions from prior surgeries) in Study M12-665
- Jaw cyst (1) = Subject (b) (6) in Study M12-671
- Ligament sprain (1) = Subject (b) (6) in Study M12-671
- Lumbar radiculopathy (1) = Subject (b) (6) in Study M12-671
- Menorrhagia (1) = Subject (b) (6) (possibly related to hypothyroidism according to report) in Study M12-671
- Nausea (1) = Subject (b) (6) in Study M12-671
- Nephrolithiasis (1) = Subject (b) (6) in Study M12-665
- Ovarian adhesion (1) = Subject (b) (6) in Study M12-671

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- Ovarian cyst (1) = Subject (b) (6) (post study event, not attributed to endometriosis) in Study M12-671
- Ovarian cyst ruptured (2) = Subjects (b) (6) and (b) (6) in Study M12-665
- Pharyngeal abscess (1) = Subject (b) (6) in Study M12-671
- Postoperative abscess (1) = Subject (b) (6) (perineal abscess post rectocele repair) in Study M12-671
- Procedural pain (2) = Subjects (b) (6) (post renal procedure) and (b) (6) (post dermoid surgery and appendectomy) in Study M12-671
- Pulmonary embolism (1) = Subject (b) (6) (see reviewer note below) in Study M12-665
- Pyelonephritis (1) = Subject (b) (6) in Study M12-665
- Renal colic (1) = Subject (b) (6) in Study M12-671
- Respiratory rate decreased (1) = Subject (b) (6) in Study M12-671
- Seroma (1) = Subject (b) (6) in Study M12-671
- Sleep apnea (1) = Subject (b) (6) in Study M12-671
- Synovitis (1) = Subject (b) (6) in Study M12-665
- Ureteric stenosis (1) = Subject (b) (6) in Study M12-665
- Ureterolithiasis (2) = both in Subject (b) (6) in Study M12-665
- Uterine polyp (2) = Subjects (b) (6) and (b) (6) in Study M12-671
- Vaginal hemorrhage (1) = Subject (b) (6) in Study M12-671
- Wound abscess (1) = Subject (b) (6) (post ventral hernia repair) in Study M12-671

Of the previously listed SAEs from the Phase 3 placebo-controlled studies, the following are noteworthy:

- The completed suicide (Subject (b) (6)) was previously described in this review (in the beginning of section 8.2.4.1.)
- Of the four SAEs of abdominal pain in study 671, one case was related to kidney stones and renal colic (b) (6); a second case was related to frequent bowel movement (b) (6); a third case involved endometriotic pain resulting in hysterectomy after the end of study participation (b) (6) and the fourth was epigastric pain in a subject who also had gallbladder findings (b) (6)
- The adnexal mass for Subject (b) (6) in Study M12-665 was evaluated after the end of the study and was related to worsening endometriosis.
- Psychiatric and pregnancy cases will be discussed in section 8.2.5.
- Subject (b) (6) was a 33-year-old who began having dyspnea and chest pain on day 12 of study treatment. She was admitted to the hospital on day 15. Testing ruled out heart conditions and pulmonary embolism. Her health care providers suggested an alternative etiology of pleuritic chest pain. Computed tomography identified some pulmonary nodules and the subject was recommended for follow-up with a

pulmonologist. No further information was provided regarding the nodules. Her study drug (elagolix 150 mg QD) was not discontinued.

- Of the eight subjects with serious events labeled as endometriosis, all had worsening of their disease. Hospitalization and medical treatment were provided for five of these subjects and three subjects required surgical treatment.
- Subject (b) (6) (elagolix 200 mg BID) underwent gallbladder and splenic surgery due to no improvement in her pre-existing immune thrombocytopenic purpura approximately 5 months following her study involvement. A pulmonary embolism was reported during this hospitalization. We find no association between elagolix and these reported events.
- Subject (b) (6) was a 30-year-old female who experienced an event of ureteric stenosis that was caused by endometriosis. The stenosis resulted in hydronephrosis. A left ureterostomy with stent placement was performed. Discontinuation of study drug occurred with this event.

Phase 3 Placebo-Controlled Studies (placebo-arm subjects)

There were 24 subjects with 32 treatment-emergent SAEs in the placebo arms of the Phase 3 controlled studies (M12-665 and M12-671).

These 32 treatment-emergent SAEs include:

Abdominal pain (3), abortion induced (1), abortion spontaneous (2), appendicitis (1), blood potassium decreased (2), blood pressure fluctuation (1), chest pain (1), clostridium difficile colitis (1), constipation (1), deep vein thrombosis (1), dizziness (1), dyspnea (1), ectopic pregnancy (1), endometriosis (2), hemorrhagic ovarian cyst (1), headache (1), large intestinal obstruction (1), viral meningitis (1), nausea (1), pelvic pain (2), perineal pain (1), rheumatoid arthritis (1), syncope (1), upper limb fracture (1), urinary tract infection (1), victim of sexual abuse (1)

Some of these adverse events could be related to worsening of endometriosis. The 48-year-old placebo-arm subject with the deep vein thrombosis also had concurrent chest pain and dyspnea (noted above) and was hospitalized and treated. There was no study documentation of a pulmonary embolism.

The subject with low potassium levels was noted to have a long history of this laboratory abnormality. No explanatory diagnosis for the hypokalemia was noted in the study report. There were no hypokalemia-related symptoms noted in the study report.

Phase 3 Extensions Studies

There were 46 subjects with 59 treatment-emergent SAEs in the Phase 3 extensions studies (treatment-emergent SAEs are highlighted in bold font by subject number in the following bulleted list).

- Abdominal Hernia (1) = Subject (b) (6) in Study M12-821
- Abdominal pain (6) = Subjects (b) (6) and (b) (6) in Study M12-821; Subject (b) (6) in Study M12667 (see reviewer' comment below)
- Abortion induced (7) = Subjects (b) (6) in Study M12-821; Subjects (b) (6) in Study M12667
- Abortion spontaneous (6) = Subjects (b) (6) in Study M12-821; Subjects (b) (6) in Study M12667
- Adverse drug reaction (1) = Subject (b) (6) in Study M12667
- Affective disorder (1) = Subject (b) (6) in Study M12667
- Ankle fracture (1) = Subject (b) (6) in Study M12667
- Anxiety (1) = Subject (b) (6) in Study M12-821
- Arthralgia (1) = Subject (b) (6) in Study M12-821
- Asthma (1) = Subject (b) (6) in Study M12667
- Blighted ovum (1) = Subject (b) (6) in Study M12-821
- Carbon monoxide poisoning (1) = Subject (b) (6) (accidental due to faulty stove) in Study M12-821
- Cerebrovascular accident (1) = Subject (b) (6) (see reviewer's note below) in Study M12667
- Cholelithiasis (2) = Subject (b) (6) in Study M12667; Subject (b) (6) (report suggested obesity as risk factor) in Study M12-821
- COPD (1) = Subject (b) (6) (long smoking history and history of asthma) in Study M12-821
- Colitis (1) = Subject (b) (6) in Study M12667
- Dengue Fever (1) = Subject (b) (6) in Study M12-821
- Depression (1) = Subject (b) (6) in Study M12-821
- Diverticulitis (2) = Subject (b) (6) in Study M12-667; Subject (b) (6) in Study M12-821
- Dyspnea (1) = Subject (b) (6) (Concurrent SAEs of abdominal hernia, abdominal pain and pyrexia – hernia repair performed) in Study M12-821
- Ectopic pregnancy (1) = Subject (b) (6) in Study M12-667
- Endometriosis (10 subjects, 11 events) = Subjects (b) (6) in Study M12-667; Subjects (b) (6) (twice), (b) (6) in Study M12-821 (see reviewer's note below)
- Foot deformity (1) = Subject (b) (6) in Study M12-821
- Gastric ulcer (1) = Subject (b) (6) in Study M12-821
- Gastrointestinal hemorrhage (1) = Subject (b) (6) in Study M12-667
- Gastrointestinal motility disorder (1) = Subject (b) (6) in Study M12-821
- Incarcerated umbilical hernia (1) = Subject (b) (6) in Study M12-667
- Incisional hernia (1) = Subject (b) (6) in Study M12-821
- Intervertebral disc protrusion (2) = Subject (b) (6) in Study M12-667; Subject (b) (6) in Study M12-821
- Irritable bowel syndrome (1) = Subject (b) (6) in Study M12-821

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- Joint injury (1) = Subject (b) (6) in Study M12-667
- Ligament rupture (1) = Subject (b) (6) in Study M12-821
- Lower limb fracture (1) = Subject (b) (6) in Study M12-821
- Lung adenocarcinoma (1) = Subject (b) (6) (see reviewer's note below) in Study M12-667
- Migraine (1) = Subject (b) (6) in Study M12-667
- Nasal polyps (1) = Subject (b) (6) in Study M12-821
- Nausea (3) = Subjects (b) (6) (twice) and (b) (6) in Study M12-667
- Neck pain (1) = Subject (b) (6) in Study M12-667
- Osteochondrosis (1) = Subject (b) (6) in Study M12-821
- Ovarian cyst (3) = Subject (b) (6) (right salpingo-oophorectomy revealed hemorrhagic corpus luteum) in Study M12-667; Subjects (b) (6) in Study M12-821
- Ovarian cyst ruptured (1) = Subject (b) (6) in Study M12-667
- Pancreatitis acute (1) = Subject (b) (6) (post study event, history of chronic narcotic use and alcohol) in Study M12-821
- Pelvic neoplasm (1) = Subject (b) (6) in Study M12-821
- Pelvic pain (9 subjects, 10 events) = Subjects (b) (6) (twice) in Study M12-667; Subjects (b) (6) in Study M12-821
- Pericarditis (1) = Subject (b) (6) in Study M12-821
- Perineal pain (1) = Subject (b) (6) in Study M12-821
- Postoperative wound infection (1) = Subject (b) (6) (post cholecystectomy) in Study M12-821
- Premenstrual dysphoric disorder (1) = Subject (b) (6) in Study M12-667
- Procedural hypertension (1) = Subject (b) (6)
- Pyrexia (1) = Subject (b) (6) in Study M12-821
- Rash (1) = Subject (b) (6) (see section 7.4.5 for discussion on anaphylactoid reactions and rash) in Study M12-821
- Suicidal ideation (1) = Subject (b) (6) in Study M12-667
- Supraventricular tachycardia (1) = Subject (b) (6) (see reviewer's comment below) in Study M12-667
- Teratoma (1) = Subject (b) (6) (left ovarian cystic teratoma) in Study M12-821
- Tibia fracture (1) = Subject (b) (6) in Study M12-821
- Tuberculosis (1) = Subject (b) (6) in Study M12-821
- Umbilical hernia (1) = Subject (b) (6) in Study M12-821
- Uterine polyp (2) = Subjects (b) (6) in Study M12-821
- Meckel's diverticulum (1) = Subject (b) (6) in Study M12-821
- Vomiting (2) = Subject (b) (6) (twice) in Study M12-667

Of the previously listed SAEs from the Phase 3 extension studies the following are noteworthy:

- Pregnancy and psychiatric events are discussed in section 8.2.5.

- Of the six subjects with SAEs of abdominal pain, there were three in which the investigators suggested the possibility of worsening endometriosis. The other three included abdominal hernia (1), acute pancreatitis (1) and peptic ulcer disease (1).
- Subject (b) (6) in Study M12-667 was a 39-year-old female with a history of heavy smoking for 20 years, emphysema and numerous psychiatric problems (depression, anxiety, bipolar disorder). She was on placebo in Study M12-665 and then switched to elagolix 150 mg/day in extension Study M12-667. On day 116 in the extension study the subject was found to have a lung tumor. On day 179 (post-treatment day 25) she underwent a left thoracoscopy with wedge resection and left upper lobectomy. The pathology revealed grade 3 adenocarcinoma. Her study drug was not interrupted and her last scheduled dose was on day 154. Following the study (day 364), the subject also suffered a cerebrovascular accident. Even though lung adenocarcinomas have been identified with hormone receptors, an association between elagolix and cancer is unlikely. Elagolix lowers hormones which should lessen any impact that tumor hormone receptors may play in tumor progression. Her heavy smoking is the most likely cause of her lung cancer.
- Of the 10 subjects with endometriosis listed as SAEs, all had worsening of their disease. Surgical therapy was performed on 5 of the subjects. Conservative and/or medical therapy was used for the remainder.
- Of the nine subjects with SAEs of pelvic pain, seven were thought by investigators to be related to endometriosis. Subject (b) (6) was thought to have pelvic pain secondary to a urinary tract infection. Subject (b) (6) developed pelvic pain post study and this was thought to be related to an ovarian cyst. We concur with the investigators' assessments.
- Subject (b) (6) was a 24-year-old female with a prior history of supraventricular tachycardia. During her enrollment in Study M12-665, she took placebo. During this extension study, she developed anxiety while treated with elagolix 150 mg daily. On day 2 of the extension study she went to the emergency room with tachycardia, chest pain, shortness of breath and numbness in her fingers. The study drug was discontinued. Both the Investigator and the Applicant considered the event of supraventricular tachycardia as having a reasonable possibility of being related to study drug. The relevance to study drug is unclear as this subject had a history of supraventricular tachycardia before receiving study drug.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The overall number and percentage of discontinuations for treatment-emergent adverse events (TEAEs) in the pivotal placebo-controlled studies (665 & 671) and extension studies (667 & 821) are shown below:

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Studies 665 & 671

- Placebo 44/734 (6.0%)
- Ela 150 mg QD 26/475 (5.5%)
- Ela 200 mg BID 46/477 (9.6%)

Source: Table 2.1_1.11.4, ISS, page 1601 of 5658

Studies 667 & 821

- Ela 150 mg QD 14/291 (4.8%)
- Ela 200 mg BID 25/278 (9.0%)

Source: Table 2.2_1.11.2, ISS, page 2484 of 5658

There is a dose-response with the 200 mg BID dosing for TEAEs leading to study drug discontinuation.

The following tables (Table 62 and Table 63) show the most common (at least two in any study arm) TEAEs leading to study drug discontinuation.

Table 62. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Phase 3 Endometriosis Controlled Analysis Set -Studies 665 & 671)

MedDRA 19.1 Preferred Term (PT)	Placebo (N = 734) n (%)	Elagolix	
		150 mg QD (N = 475) n (%)	200 mg BID (N = 477) n (%)
Adverse Events Leading to Discontinuation			
Nausea	4 (0.5)	4 (0.8)	7 (1.5)
Vomiting	2 (0.3)	3 (0.6)	2 (0.4)
Headache	2 (0.3)	4 (0.8)	5 (1.0)
Migraine	0	1 (0.2)	2 (0.4)
Depression	2 (0.3)	2 (0.4)	3 (0.6)
Depressed mood	1 (0.1)	0	2 (0.4)
Insomnia	1 (0.1)	2 (0.4)	2 (0.4)
Irritability	1 (0.1)	2 (0.4)	2 (0.4)
Mood swings	1 (0.1)	2 (0.4)	1 (0.2)
Hot flush	0	4 (0.8)	12 (2.5)
Abdominal pain	0	1 (0.2)	2 (0.4)
Abdominal pain upper	2 (0.3)	0	0
Diarrhea	2 (0.3)	0	3 (0.6)
ALT/AST increased	0	1 (0.2)	2 (0.4)
Arthralgia	0	0	3 (0.6)
Endometriosis	2 (0.3)	2 (0.4)	0
Pelvic pain	6 (0.8)	2 (0.4)	1 (0.2)
Acne	0	1 (0.2)	2 (0.4)
Rash	2 (0.3)	0	2 (0.4)
Facial swelling	0	0	2 (0.4)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BID = twice daily, QD = once daily
 Source: Table 2.1_1.11.4, ISS, pages 1601-08 of 5658

Table 63. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Long-Term Phase 3 Endometriosis Analysis Set -Studies 667 & 821)

MedDRA 19.1 Preferred Term Adverse Events Leading to Discontinuation	Elagolix	
	150 mg QD (N = 291) n (%)	200 mg BID (N = 278) n (%)
Bone density decreased	1 (0.3)	10 (3.6)
Headache	0	1 (0.4)
Hot flush	0	2 (0.7)
Weight increased	1 (0.3)	2 (0.7)

Source: Table 2.2_1.11.2, ISS, pages 2484-87 of 5658
 BID = twice daily, QD = once daily

Comparing the two tables, it is noteworthy that most of the adverse events leading to discontinuation are less in the extension studies (667 & 821). The only exception is the bone density decrease which has a large number in the 200 mg BID dosing arm of the extension studies. It is probable that the reduction in these events is related to the fact those who are greater risk for the events have dropped out in the first 6 months. The dose effect for hot flush is evident in the placebo-controlled studies.

8.2.4.4. Significant Adverse Events

Significant adverse events considered to be submission specific are described in in section 8.2.5. Severity grading is discussed when appropriate in that section and in the following section that describes treatment-emergent adverse events. The National Cancer Institute Common Terminology Criteria for Adverse Events was modified by the Applicant to assess lipid shift changes. Lipid and liver function testing are described separately in the “Laboratory Findings” section below.

8.2.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 64 provides data on treatment-emergent adverse events occurring in $\geq 5\%$ subjects in any treatment group in the Phase 3 controlled trials (665 & 671):

Table 64. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Occurring in ≥ 5% Subjects by Primary MedDRA Preferred Term (Phase 3 Endometriosis Controlled Analysis Set – Studies 665 & 671)

MedDRA 19.1 Preferred Term	Placebo (N = 734) n (%)	Elagolix	
		150 mg QD (N = 475) n (%)	200 mg BID (N = 477) n (%)
Nausea**	92 (12.5)	51 (10.7)	76 (15.9)
Fatigue	38 (5.2)	22 (4.6)	25 (5.2)
Nasopharyngitis	28 (3.8)	28 (5.9)	27 (5.7)
Sinusitis	31 (4.2)	24 (5.1)	27 (5.7)
Upper respiratory tract infection	40 (5.4)	30 (6.3)	20 (4.2)
Urinary tract infection	63 (8.6)	29 (6.1)	35 (7.3)
Arthralgia	19 (2.6)	16 (3.4)	24 (5.0)
Headache**	88 (12.0)	80 (16.8)	95 (19.9)
Anxiety**	25 (3.4)	15 (3.2)	24 (5.0)
Insomnia**	21 (2.9)	29 (6.1)	42 (8.8)
Amenorrhea**	2 (0.3)	19 (4.0)	34 (7.1)
Hot flush**	63 (8.6)	110 (23.2)	214 (44.9)

Source: Table 2.1_1.3, ISS, pages 1008-1010 of 5658; Table 2.1_1.4, ISS, pages 1010-1101

BID = twice daily, QD = once daily

** considered adverse reactions by the Reviewer.

Most of the treatment-emergent adverse events were classified by investigators as mild to moderate in severity. Those preferred terms that had more severe grades are addressed in this comment.

The severe graded adverse events of abdominal pain, endometriosis and pelvic pain events reflect the subject population's underlying disease of moderate/severe endometriosis.

Nausea was a frequently AE.

In the Phase 3 controlled studies, the numbers of subjects with severe nausea AEs were the following:

- Placebo = 8/92 (8.7%)
- Ela 150 mg QD = 3/51 (5.9%)
- Ela 200 mg BID = 3/76 (3.9%)
- Overall Ela = 6/127 (4.7%)

Headache was a frequently AE. In the Phase 3 controlled studies, the numbers of subjects with severe headache AEs were the following:

- Placebo = 7/88 (8.0%)
- Ela 150 mg QD = 7/80 (8.8%)
- Ela 200 mg BID = 6/95 (6.3%)
- Overall Ela = 13/175 (7.4%)

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Hot flush was a frequently AE. In the Phase 3 controlled studies the numbers of subjects with severe hot flush AEs were the following:

- Placebo = 1/63 (1.6%)
- Ela 150 mg QD = 4/110 (3.6%)
- Ela 200 mg BID = 17/214 (7.9%)
- Overall Ela = 21/324 (6.5%)

Table 65 provides data on treatment-emergent adverse events occurring in $\geq 5\%$ subjects in any treatment group in the extension trials (667 & 821).

Table 65. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ Subjects by Primary MedDRA Preferred Term (Long-Term Endometriosis Analysis Set- Studies 667 & 821)

System Organ Class/ MedDRA 19.1 Preferred Term	Elagolix		
	150 mg QD (N = 291) n (%)	200 mg BID (N = 278) n (%)	Overall (N = 569) n (%)
Any adverse event	266 (91)	253 (91)	519 (91)
Mild	63 (24)	60 (24)	123 (24)
Moderate	160 (60)	139 (55)	299 (58)
Severe	43 (16)	54 (21)	97 (19)
Abdominal pain	20 (7)	21 (8)	41 (7)
Constipation	15 (5)	13 (5)	28 (5)
Diarrhea	19 (6)	22 (8)	41 (7)
Nausea	43 (15)	55 (20)	98 (17)
Vomiting	20 (7)	19 (7)	39 (7)
Fatigue	25 (9)	21 (8)	46 (8)
Bronchitis	18 (6)	17 (6)	35 (6)
Influenza	16 (6)	17 (6)	33 (6)
Nasopharyngitis	31 (11)	38 (14)	69 (12)
Sinusitis	29 (10)	34 (12)	63 (11)
Upper respiratory tract infection	36 (12)	24 (9)	60 (10)
Urinary tract infection	41 (14)	35 (13)	76 (13)
Bone density decreased	2 (1)	19 (7)	21 (4)
Weight increased	17 (6)	14 (5)	31 (5)
Arthralgia	20 (7)	29 (10)	49 (9)
Back pain	22 (8)	38 (14)	60 (10)
Dizziness	18 (6)	11 (4)	29 (5)
Headache	60 (21)	76 (27)	136 (24)
Anxiety	19 (6)	18 (6)	37 (6)
Depression	15 (5)	12 (4)	27 (5)
Insomnia	26 (9)	33 (12)	59 (10)
Libido decrease	9 (3)	16 (6)	25 (4)
Mood swings	16 (6)	20 (7)	36 (6)
Amenorrhea	12 (4)	28 (10)	40 (7)
Pelvic pain	13 (4)	14 (5)	27 (5)
Acne	15 (5)	17 (6)	32 (6)
Night sweats	7 (2)	14 (5)	21 (4)
Hot flush ^a	80 (28)	149 (54)	229 (40)

Source: Table 2.2_1.3, ISS, pages 1882 -84 of 5658 & Table 2.2_1.4, ISS, pages 1885-1958
 BID = twice daily, QD = once daily

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^a The percentages for hot flush show the largest differences between elagolix and placebo.

The pattern of severity in the uncontrolled extension studies was similar to that seen in the pivotal controlled studies. The TEAEs that had the most severe grade subjects included abdominal pain, headache, endometriosis and pelvic pain.

8.2.4.6. Laboratory Findings

Hematology

Minimal mean hematologic changes consistent with reduced bleeding in subjects receiving elagolix were seen.

Chemistry

Aside from the changes noted in lipids and liver function tests, the other chemistry parameters showed no significant safety signals.

Urinalysis

No safety signals were evident in the urinalysis results.

Lipids

Mean serum lipid values increased from Baseline to month 6 for total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), apolipoprotein B, and triglycerides (see Table 66). Lipid values did not increase further in the extension studies. In the post-treatment follow-up period, lipid values returned to baseline levels.

Table 66. Mean Changes from Baseline to Month 6 in Serum Lipid Parameters During the Treatment Period (Phase 3 Endometriosis Controlled Analysis Set- Studies 665 & 671)

Analyte N	Elagolix 150 mg QD			Elagolix 200 mg BID			
	Baseline Mean	Visit Mean	Mean Change (SD)	N	Baseline Mean	Visit Mean	Mean Change (SD)
LDL Cholesterol mg/dL							
345	99	104	5 (19)	337	98	111	13 (21)
HDL Cholesterol mg/dL							
348	58	60	2 (9)	339	57	61	4 (9)
Total Cholesterol mg/dL							
348	177	185	8 (22)	339	176	196	20 (25)
Non-HDL Cholesterol mg/dL							
348	119	125	6 (20)	339	119	135	16 (23)
Apolipoprotein B mg/dL							
284	82	85	3 (13)	289	82	91	9 (16)
Triglycerides mg/dL							
348	106	106	0 (56)	339	104	116	11 (53)

Source: Derived from Table 66, ISS, page 265 of 5658

BID = twice daily, HDL = high density lipoprotein, LDL = low density lipoprotein, QD = once daily, SD = standard deviation

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The Applicant modified the National Cancer Institute Common Toxicity Criteria for AEs (NCI-CTCAE) to evaluate individual shift changes in lipids. The triglyceride criteria were kept and 4 grading criteria were added to cover LDL-C.

Grading for triglycerides was the following:

- 0: ≤ 150 mg/dL
- 1: 151 to 300 mg/dL
- 2: 301 to 500 mg/dL
- 3: 501 to 1,000 mg/dL
- 4: > 1,000 mg/dL

Grading for LDL-C was the following:

- 0: ≤ 130 mg/dL
- 1: 131 to 159 mg/dL
- 2: 160 to 189 mg/dL
- 3: ≥ 190 mg/dL

Table 67 and Table 68 show the number and percentage of subjects who either showed a shift in LDL-C or triglycerides from grade 0 to 3 or from grade 1 to 3 in the pivotal controlled studies.

Table 67. Subjects with Shifts in LDL-C to the Maximum Grade During the Treatment Period (Phase 3 Endometriosis Controlled Analysis Set and Long-Term Phase 3 Endo Analysis Set)

Treatment arm	n / N (%)	
	Shift from Grade 0 to Grade 3	Shift from Grade 1 to Grade 3
Phase 3 Endo Controlled Analysis Set		
Placebo	1/587 (0.2)	1/84 (1.2)
Elagolix 150 mg QD	1/395 (0.3)	4/40 (10.0)
Elagolix 200 mg BID	7/389 (1.8)	6/44 (13.6)
Long-Term Phase 3 Analysis Set		
Elagolix 150 mg QD	2/257 (0.8)	7/26 (26.9)
Elagolix 200 mg BID	4/249 (1.6)	6/25 (24.0)

Source: Tables 70 & 72, ISS, pages 279 and 283 of 5658
 BID = twice daily, QD = once daily

Table 68. Subjects with Shifts in Triglycerides to the Maximum Grade During the Treatment Period (Phase 3 Endo Controlled Analysis Set and Long-Term Phase 3 Endo Analysis Set)

Treatment arm	n / N (%)	
	Shift from Grade 0 to Grade 3	Shift from Grade 1 to Grade 3
Phase 3 Endo Controlled Analysis Set		
Placebo	1/570 (0.2)	1/109 (0.9)
Elagolix 150 mg QD	0/378	3/63 (4.8)
Elagolix 200 mg BID	0/374	2/60 (3.3)
Long-Term Phase 3 Analysis Set		
Elagolix 150 mg QD	0/245	3/41 (7.3)
Elagolix 200 mg BID	0/236	1/35 (2.9)

Source: Tables 70 & 72, ISS, pages 279 and 283 of 5658
 BID = twice daily, QD = once daily

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Although the numbers are small, there appears to be a signal that, if a subject had a grade 1 level of LDL-C at baseline, there was a fairly high percentage chance that the level would rise to grade 3 on elagolix treatment. This information should be conveyed in the label.

Liver Function Testing

There were small mean changes in the Phase 3 controlled studies at month 6 in alkaline phosphatase, ALT and AST compared to placebo as shown below:

Table 69. Liver Function Testing - Mean Change from Baseline to Month 6 (Phase 3 Endometriosis Controlled Analysis Set)

Analyte Arm	N	Baseline Mean	Mean Change (SD)
Alkaline Phosphatase IU/L			
Placebo	497	69	-2 (11)
Ela 150 mg QD	348	71	1 (10)
Ela 200 mg BID	339	69	7 (13)
ALT, U/L			
Placebo	497	17	-1 (9)
Ela 150 mg QD	348	15	0 (9)
Ela 200 mg BID	339	16	1 (9)
AST, U/L			
Placebo	497	19	-1 (9)
Ela 150 mg QD	348	19	1 (22)
Ela 200 mg BID	339	19	1 (6)
Total Bilirubin, mg/dL			
Placebo	497	0.5	0.0 (0.2)
Ela 150 mg QD	348	0.5	-0.0 (0.2)
Ela 200 mg BID	339	0.5	-0.1 (0.2)

Source: Table 76, ISS, page 297 of 5658

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BID = twice daily, QD = once daily, SD = standard deviation

Mean changes from baseline at extension month 6 in the pooled analysis of Studies 667 and 821 were slightly greater than mean changes in the preceding table for alkaline phosphatase, ALT and AST. Bilirubin changes in the extension studies continued to show slight decreases.

Table 70, provided by the Applicant in the ISS, lists the number of subjects with significant elevations of ALT/AST in the Phase 3 controlled and extension studies. It is noteworthy that there appears to be dose-dependency manifested in ALT determinations. No total bilirubin determination more than twice the ULN was identified and there were no cases of Hy's Law.

Table 70. Number and Percentage of Subjects Meeting Potential Hepatotoxicity Criteria (Controlled -665 & 671) and (Extension Studies - 667 & 821)

Criteria	n/N (%) of Subjects		
	Placebo N = 734	Elagolix 150 mg QD N = 475	Elagolix 200 mg BID N = 477
Phase 3 Endometriosis Controlled Analysis Set – Studies 665 & 671			
ALT ≥ 3 x ULN	1/696 (0.1)	1/450 (0.2)	5/443 (1.1)
ALT ≥ 5 x ULN	1/696 (0.1)	1/450 (0.2)	3/443 (0.7)
AST ≥ 3 x ULN	3/696 (0.4)	3/450 (0.7)	3/443 (0.7)
AST ≥ 5 x ULN	0	2/450 (0.4)	1/443 (0.2)
Total bilirubin ≥ 2 x ULN	0	0	0
Alk phos ≥ 1.5 x ULN	3/696 (0.4)	1/450 (0.2)	1/443 (0.2)
ALT or AST ≥ 3 x ULN and total bilirubin ≥ 1.5 x ULN	0	0	0
Criteria	n/N (%) of Subjects		
	Elg/Elg 150 mg QD N = 291	Elg/Elg 200 mg BID N = 291	
Long-Term Phase 3 Analysis Set – Studies 667 & 821			
ALT ≥ 3 x ULN	---	1/291 (0.3)	6/278 (2.2)
ALT ≥ 5 x ULN	---	1/291 (0.3)	3/278 (1.1)
AST ≥ 3 x ULN	---	3/291 (1.0)	3/278 (1.1)
AST ≥ 5 x ULN	---	2/291 (0.7)	1/278 (0.4)
Total bilirubin ≥ 2 x ULN	---	0	0
Alk phos ≥ 1.5 x ULN	---	1/291 (0.3)	4/278 (1.4)
ALT or AST ≥ 3 x ULN and total bilirubin ≥ 1.5 x ULN	---	0	0

Source: Table 77 & 79, ISS, pages 298 and 301 of 5658

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BID = twice daily, QD = once daily, ULN = upper limit of normal

Although the preceding Applicant table specified “0” subjects in the last row (“ALT or AST ≥ 3 x ULN and total bilirubin ≥ 1.5 x ULN”), there was one subject who manifested these findings in Study 821. This subject had liver function data that was very close to Hy’s Law criteria. Subject (b) (6) was a 40-year-old female taking elagolix 150 mg daily in extension Study M12-821. She had marked peak elevations of ALT (1340 U/L) and AST (730 U/L) on study day 183. Additionally, the bilirubin was 2.2 mg/dL (more than one and a half times the ULN, but less than twice the ULN). No additional lab determinations were listed in the original submission; thus, resolution of the lab abnormalities could not be determined. An information request concerning follow-up information for Subject (b) (6) was submitted to the Applicant on January 26, 2018. On January 31, 2018, the Division requested that the Applicant provide a detailed time-line analysis of all subjects in their endometriosis and fibroid development program who had ALT/AST elevations of more than three times the ULN or more than five times the ULN, and all discontinuations due to abnormal liver function test values. Consults were sent to the Division of Gastroenterology and Inborn Errors Products (DGIEP) and Dr. Mark Avigan (hepatologist in the Office of Surveillance and Epidemiology (OSE) regarding this subject and the risk of elagolix to the liver. As a result of these consultations further information requests were sent to the Applicant regarding liver safety.

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The Applicant upon further investigation in (b) (6) determined that Subject (b) (6) experienced an infection with acute viral hepatitis A. Serologic confirmation (IgM) was sent to the Division.

DGIEP in conjunction with Dr. Avigan provided a very detailed consult review (dated April 17, 2018 in DARRTS). The consultants reviewed the findings from Subject (b) (6) and the more detailed analyses requested of the Applicant through information requests. The key findings, labeling recommendations and postmarketing recommendations from the consult review are as follows:

Key Findings

- Safety data from the clinical development program for elagolix (both endometriosis and uterine fibroids) demonstrates a hepatocellular liver injury signal. This injury signal to date appears to be self-limited and asymptomatic. Because of the small numbers in long-term Phase 3 trials, it is not possible to exclude a small risk for serious liver injury.
- In the clinical trials, there appeared to be some dose-related differences in ALT elevations between the 150 mg QD and 200 mg BID regimens.
- The consultants agreed that the liver function findings in Subject (b) (6) are attributable to acute viral hepatitis A infection.
- Of the 40 study subjects identified by the Applicant with either elevations of ALT and/or AST more than three times ULN:
 - Three were in the hepatic impairment study and the elevations noted at baseline did not worsen.
 - Of the remaining 37 subjects:
 - Two had concurrent elevated bilirubin (Subject (b) (6) – Hepatitis A and Subject (b) (6) from Study M12-821 who showed a temporal association with a flu-like illness).
 - 31 had confounding factors or alternative etiologies proposed by the Applicant.
 - Six had no alternative etiology proposed.
- The consultants generally agreed with the Applicant's expert consultant (b) (6) that 15 of the cases (ALT/AST more than five times the ULN, ALT/AST more than three times the ULN, bilirubin more than one and a half times the ULN, or treatment discontinuation due to liver events) were considered likely due to study drug.

Recommendations Regarding Clinical Use and Labeling

The consult recommendations are listed verbatim:

- “The lowest effective dose should be used in patients for the treatment of endometriosis if approved.”
- “Information regarding a potential for elagolix-associated liver injury based on observed elevations in hepatic transaminases should be added to the Warnings and Precautions section, in conjunction with an instruction to interrupt treatment and seek medical attention if symptoms or signs occur that may reflect clinically significant or serious acute liver injury, such as jaundice. Additionally, a synopsis of the Phase 3 clinical study safety results should be added to the Clinical Trials Experience subsection of Adverse Reactions.”

Recommendations Regarding Postmarketing Surveillance

The consult recommendations are listed verbatim:

- “To gain important information on the hepatotoxic risk profile of elagolix, the Applicant should institute an enhanced pharmacovigilance program. Health care providers should be encouraged to report all cases of serious liver injury to the Applicant with sufficient information to assess causality. The Applicant should actively follow-up on these cases and provide FDA with 15-day expedited reports for all serious liver injury cases in all post-market patients and ongoing clinical trial study subjects in addition to follow-up clinical and diagnostic information that will facilitate a comprehensive evaluation of causality and severity. In the Periodic Benefit-Risk Evaluation Reports to FDA, the Applicant should analyze the incidence and range of severity of liver toxicity, describe all individual cases of serious liver injury, and provide estimates of the numbers of elagolix treated patients in the U.S. market and globally if indicated.”

The Division concurs with the consult findings and recommendations regarding potential liver injury signals.

In collaboration with the Division of Pharmacovigilance II in OSE, the Division will request that the Applicant implement an enhanced pharmacovigilance plan for postmarketing surveillance. Necessary elements of enhanced pharmacovigilance were conveyed to the Applicant on June 8, 2018.

8.2.4.7. Vital Signs

There were no significant changes in systolic and diastolic blood pressure or heart rate in elagolix-treated subjects compared to placebo in the pivotal trials. Both doses of elagolix showed a greater percentage of subjects with a 7% weight increase compared to placebo:

Number and Percentage of Subjects with > 7% Increase in Weight (Phase 3 pivotal trials)

- Placebo 41/579 (7.1%)
- Ela 150 mg QD 40/384 (10.4%)
- Ela 200 mg BID 56/382 (14.7%)

Source: Table 4.1_2, ISS, page 4042 of 5658

8.2.4.8. Electrocardiograms

The Summary of Clinical Safety describes six instances of abnormal clinically significant ECG values. These are described in the following table (Table 71):

Table 71. Abnormal Electrocardiograms in Elagolix-Treated Subjects (Pivotal – 665 & 671 and Extension – 667 & 821 Studies)

Study M12-	Subject ID	Ela Dose mg	Findings
665	(b) (6)	200	Sinus arrhythmia (referred to primary care and cardiology)
665		200	First degree atrioventricular block (subject enrolled in extension study)
671		150	Nonspecific T-wave abnormality with inferior and anterolateral Q waves (further testing ruled out myocardial infarction). Referred for myocardial perfusion imaging and echocardiogram (no information on these tests) Subject also had essential hypertension
667		150/150	Sinus bradycardia (echocardiogram showed normal ventricular dynamics and no significant valvular disease)
667		150/150	Abnormal Q waves (assessed as a normal variant)
667		PBO/200	Prolonged QT interval of 616 ms compared to Baseline of 415 ms (subject referred to primary care and cardiology, reported normal ECG on follow up)

ECG = electrocardiogram, PBO = placebo

Sources: M12-665 study report, page 483 of 8446; M12-671 study report page 480 of 8198; M12-667 study report, page 489 of 11711

These appear to be single events with no evidence of a pattern that would require additional evaluation.

8.2.4.9. QT

A thorough QT interval corrected (QTc) study was conducted in 48 healthy subjects (Study M12-661) to assess the potential for QTc prolongation by elagolix in healthy premenopausal adult females. In the primary analyses, at each elagolix doses, 300 mg and 1,200 mg, the 95% one-sided upper confidence interval (CI) for the difference of mean from placebo was less than 10 msec at all time points.

The Interdisciplinary Review Team reviewed Study M12-661 and issued a report on September 23, 2015. They found no significant QTc prolongation effect of elagolix (300 mg and 1200 mg). They stated that the study was adequate to support a dose of 300 mg BID (dosing being studied

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for fibroids). The doses of 150 mg QD and 200 mg BID are less and thus supported by this Interdisciplinary Review Team review. The clinical pharmacology review team also concurs with this conclusion.

8.2.4.10. Immunogenicity

See section 8.2.5.3 (Hypersensitivity Reactions)

8.2.4.11. Safety Updates (4 Month and Others)

The Applicant submitted the 4-month Safety Update on December 13, 2017. The database lock for the original NDA 210450 submission was June 19, 2017, and the database lock for this 4-month Safety Update Report was October 19, 2017. The data presented in this report were collected during the 4-month period from June 20, 2017 through October 19, 2017.

The Applicant noted that at the time of this report, no additional data from the ongoing uterine fibroids studies or other ongoing studies had been unblinded, no new safety signals had been identified, and no safety issues had arisen that led to alterations in trial conduct.

The listing of unblinded SAEs from fibroid studies M12-815, M12-817 and M12-816 was reviewed. There are no new serious safety signals that would impact approval or labeling of elagolix for endometriosis. (b) (4)

No deaths were reported in any ongoing elagolix studies during the 4-month period from June 20, 2017 through October 19, 2017.

One event of death was reported to AbbVie on November 1, 2017. The death occurred on (b) (6). The investigator became aware of this death on November 1, 2017, and it was reported to AbbVie by the investigator on the same date. The subject's last dose of study drug was on (b) (6), and the event occurred approximately 2.5 months later. On the day of the event, the subject was noted to be intoxicated and stopped breathing at home. Emergency services were activated, and the subject was pronounced dead on arrival in the emergency department, with an unknown cause of death. Both the investigator and AbbVie considered the event of death to have no reasonable possibility of being related to study drug.

The 4-month Safety Update mentioned the case of craniosynostosis which occurred in an infant whose conception occurred after the mother's last dose of elagolix. The narrative for this case can be found in the safety section regarding pregnancies (section 8.2.5.4).

See section 8.2.7 for any 4-month safety updates to bone safety.

On December 21, 2017, the Applicant provided responses to the Division’s information requests regarding a completed suicide that occurred on [REDACTED] ^{(b) (6)} for a subject who had enrolled in the uterine fibroid study M12-815. The subject had taken an overdose of oxycodone. Concomitant medications included tramadol, naproxen and potassium supplements. There was no relation to elagolix use since the subject was still in the screening period and not randomized to study drug.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Depression and other Mood Disorders

The Applicant included mood disorders as adverse events of special interest in their NDA submission of elagolix.

According to the Applicant, the result of treatment with elagolix on the “emotional well-being” dimension in the Endometriosis Health Profile (EHP-30) in the pivotal Phase 3 controlled studies (M12-665 and M12-671) resulted in greater improvement than that demonstrated by placebo. See Table 72.

Table 72. EHP-30: Emotional Well-Being Dimension -- Mean Change from Baseline to Month 6 During the Treatment

Treatment Group	Period of Phase 3 Study M12-665				
	Baseline		Month 6		P-value
	N	Mean (SD)	N	LS Mean Change (SE)	
Placebo	373	47 (19)	250	-13 (1)	
Ela 150 mg QD	247	50 (21)	176	-20 (1)	< 0.001
Ela 200 mg BID	244	51 (19)	165	-28 (1)	< 0.001

Treatment Group	Period of Phase 3 Study M12-671				
	Baseline		Month 6		P-value
	N	Mean (SD)	N	LS Mean Change (SE)	
Placebo	357	47 (21)	223	-14 (1)	
Ela 150 mg QD	226	46 (21)	163	-21 (2)	0.001
Ela 200 mg BID	227	46 (21)	170	-25 (1)	< 0.001

Ela = elagolix; SD = Standard deviation, LS = least squares, SE = standard error
 Source: ISE; page 163 of 741; Table 48

However, the EHP-30 was not considered to be validated for this development program or intended for labeling considerations. The effect on emotional well-being is tempered both by results in another patient reported outcome (the EuroQol five-dimensional questionnaire; EQ-5D-5L) and also by the safety findings in the placebo-controlled Phase 3 studies (Studies 665 and 671). In Table 73, from EQ-5D-5L, there appears to be very little change in the final two responses (severely anxious or depressed; extremely anxious or depressed) from baseline to month 6.

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Table 73. EQ-5D-5L Anxiety/Depression Responses at Baseline and 6 Months in Study M12-671

Time Point/ Responses	Placebo n/N (%)	Ela 150 mg QD n/N (%)	Ela 200 mg BID n/N (%)
Baseline			
I am not anxious or depressed	150/360 (41.7)	88/225 (39.1)	110/229 (48.0)
I am slightly anxious or depressed	116/360 (32.2)	76/225 (33.8)	70/229 (30.6)
I am moderately anxious or depressed	75/360 (20.8)	46/225 (20.4)	38/229 (16.6)
I am severely anxious or depressed	16/360 (4.4)	12/225 (5.3)	11/229 (4.8)
I am extremely anxious or depressed	3/360 (0.8)	3/225 (1.3)	0/229 (0.0)
6 Months			
I am not anxious or depressed	127/236 (53.8)	93/162 (57.4)	100/172 (58.1)
I am slightly anxious or depressed	66/236 (28.0)	47/162 (29.0)	43/172 (25.0)
I am moderately anxious or depressed	31/236 (13.1)	15/162 (9.3)	25/172 (14.5)
I am severely anxious or depressed	11/236 (4.7)	5/162 (3.1)	3/172 (1.7)
I am extremely anxious or depressed	1/236 (0.4)	2/162 (1.2)	1/172 (0.6)

Ela = elagolix, EQ-5D-5L = EuroQol five-dimensional questionnaire, BID = twice daily, QD = once daily
 Source: Study M12-671 – Clinical Study Report; page 1604 of 8198 Table 14.2_27.1

The Applicant utilized the Depression and Suicide/Self-Injury standardized MedDRA query from MedDRA version 19.1 to compare the two doses of elagolix to placebo. The overall percentages from the query are shown in the first row of Table 74 (“Any adverse event”). The treated subjects had more adverse events than placebo and a dose-response is suggested.

Table 74. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Matching the Depression and Suicide/Self-Injury SMQ by System Organ Class and Preferred Term (Phase 3 Endometriosis Controlled Analysis Set- Studies 665 & 671)

System Organ Class/ MedDRA 19.1 Preferred Term	Placebo (N = 734) n (%)	Elagolix	
		150 mg QD (N = 475) n (%)	200 mg BID (N = 477) n (%)
Any Adverse Event	45 (6.1)	44 (9.3)	59 (12.4)
Nervous System Disorders			
Disturbance in attention	1 (0.1)	0 (0.0)	2 (0.4)
Hypersomnia	1 (0.1)	0 (0.0)	0 (0.0)
Memory impairment	1 (0.1)	1 (0.2)	4 (0.8)
Poor quality sleep	1 (0.1)	0 (0.0)	0 (0.0)
Psychiatric Disorders			
Adjustment disorder with depressed mood	0 (0.0)	2 (0.4)	1 (0.2)
Affect lability	1 (0.1)	3 (0.6)	3 (0.6)
Completed suicide	0 (0.0)	1 (0.2)	0 (0.0)
Depressed mood	1 (0.1)	2 (0.4)	10 (2.1)
Depression	16 (2.2)	11 (2.3)	17 (3.6)
Depressive symptom	0 (0.0)	0 (0.0)	1 (0.2)
Dysphoria	0 (0.0)	0 (0.0)	1 (0.2)
Initial insomnia	0 (0.0)	0 (0.0)	3 (0.6)
Mood altered	7 (1.0)	4 (0.8)	8 (1.7)
Mood swings	18 (2.5)	23 (4.8)	17 (3.6)
Suicidal ideation	0 (0.0)	1 (0.2)	1 (0.2)
Tearfulness	0 (0.0)	0 (0.0)	1 (0.2)

Source: Table 2.1_1.12.2, ISS, page 1618 of 5658
 BID = twice daily, QD = once daily, SMQ = standardized MedDRA query

More adverse events in the psychiatric disorders system organ class (SOC) are noted for elagolix than placebo especially for depressed mood, depression and mood swings. Information concerning these psychiatric disorders will be included in the Warning and Precautions section of the label.

Table 75. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Matching the Depression and Suicide/Self-Injury SMQ by System Organ Class and Preferred Term (Long-Term Phase 3 Endometriosis Analysis Set- Studies 667 & 821)

System Organ Class/ MedDRA 19.1 Preferred Term	Elagolix		Overall (N = 569) n (%)
	150 mg QD (N = 291) n (%)	200 mg BID (N = 278) n (%)	
Any Adverse Event	40 (13.7)	41 (14.7)	81 (14.2)
General Disorder			
Crying	1 (0.3)	0	1 (0.2)
Nervous System Disorder			
Disturbance in Attention	1 (0.3)	1 (0.4)	2 (0.4)
Memory Impairment	0	2 (0.7)	2 (0.4)
Psychiatric Disorders			
Adjustment disorder with depressed mood	2 (0.7)	0	2 (0.4)
Affect lability	2 (0.7)	3 (1.1)	5 (0.9)
Apathy	0	1 (0.4)	1 (0.2)
Depressed mood	2 (0.7)	5 (1.8)	7 (1.2)
Depression	15 (5.2)	12 (4.3)	27 (4.7)
Depressive symptom	1 (0.3)	0	1 (0.2)
Initial insomnia	0	1 (0.4)	1 (0.2)
Mood altered	2 (0.7)	4 (1.4)	6 (1.1)
Mood swings	16 (5.5)	20 (7.2)	36 (6.3)
Suicidal ideation	1 (0.3)	0	1 (0.2)
Tearfulness	0	1 (0.4)	1 (0.2)

Source: ISS – Table 2.2_1.12.2; page 2495 of 5658

BID = twice daily, QD = once daily, SMQ = standardized MedDRA query

The percentages for depression are higher for elagolix-treated subjects in the extension period.

As shown in Table 76, the percentages are higher for the 200 mg BID dose for discontinuation due to mood-related adverse events in the pooled Phase 3 controlled trials.

Table 76. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Matching the Depression and Suicide/Self-Injury Leading to Study Drug Discontinuation (Phase 3 Endometriosis Controlled Analysis Set)

System Organ Class/ MedDRA 19.1 Preferred Term	Placebo (N = 734) n (%)	Elagolix		Overall (N = 952) n (%)
		150 mg QD (N = 475) n (%)	200 mg BID (N = 477) n (%)	
Any Adverse Event	5 (0.7)	4 (0.8)	10 (2.1)	14 (1.5)
Nervous System Disorders				
Disturbance in attention	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Memory impairment	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Psychiatric Disorders				
Depressed mood	1 (0.1)	0 (0.0)	2 (0.4)	2 (0.2)
Depression	2 (0.3)	2 (0.4)	3 (0.6)	5 (0.5)
Dysphoria	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Mood altered	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.1)
Mood swings	1 (0.1)	2 (0.4)	1 (0.2)	3 (0.3)
Suicidal ideation	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.2)

Source: Table 2.1_1.12.8, ISS, page 1628 of 5658

BID = twice daily, QD = once daily

As shown in Table 77, there may be more concern for those with a history of depression.

Table 77. Selected Treatment-Emergent Adverse Events in the Depression and Suicide/Self-Injury SMQ – by History of Depression (Phase 3 Endo Controlled Analysis Set)

Adverse Event (Preferred term) in rows by n (%)	History of Depression					
	Yes			No		
	Placebo N = 133	Elagolix 150 mg QD N = 88	Elagolix 200 mg BID N = 103	Placebo N = 601	Elagolix 150 mg QD N = 387	Elagolix 200 mg BID N = 374
Depressed mood	0 (0.0)	0 (0.0)	5 (4.9)	1 (0.2)	2 (0.5)	5 (1.3)
Depression	8 (6.0)	6 (6.8)	10 (9.7)	8 (1.3)	5 (1.3)	7 (1.9)
Depressive symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Mood altered	3 (2.3)	1 (1.1)	1 (1.0)	4 (0.7)	3 (0.8)	7 (1.9)
Mood swings	6 (4.5)	7 (8.0)	4 (3.9)	12 (2.0)	16 (4.1)	13 (3.5)
Suicidal ideation	0 (0.0)	1 (1.1)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Completed suicide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

Source: Summary of Clinical Safety – Table 21 – page 96 of 105
 BID = twice daily, QD = once daily, SMQ = standardized MedDRA query

The following table (Table 78) is a listing of subjects with moderate and severe depression in the placebo controlled studies 665 and 671. The attempt was to analyze individual cases in terms of the subject's medical history and what steps were taken when the adverse event occurred.

Table 78. Listing of Elagolix-Treated Subjects with Moderate and Severe Depression and Depressed Mood (Phase 3 Endometriosis Controlled Analysis Set- studies M12-665 and M12-671)

Subject ID	LDD	PT	Severity	OD	RD	Pertinent History Action taken
Study M12-665 Elagolix 150 mg QD						
(b) (6) 184		Depression	Moderate	120	ONG	History of depression, anxiety Seen by MHCP, medication prescribed
(b) (6) 115		Depression	Severe	113	117	History of depression and use of citalopram x 1 year Seen by MHCP, discontinued study drug
		Anger	Severe	113	117	
		Suicidal ideation	Severe	113	117	
(b) (6) 171		Depression	Moderate	134	ONG	History of intermittent depression and anxiety Seen by MHCP, medication prescribed
		Anxiety	Moderate	134	ONG	
(b) (6) 96		Depression	Moderate	90	100	History of sadness associated with periods Discontinued study drug
Study M12-665 Elagolix 200 mg BID						
(b) (6) 168		Depressed mood	Severe	104	120	No significant history
		Mood altered	Moderate	88	120	No action taken
(b) (6) 168		Depressed mood	Moderate	114	ONG	History of depression 5 years prior No action taken
		Mood swings	Moderate	57	ONG	
(b) (6) 166		Depression	Moderate	58	ONG	History of mild depression and mood swings
		Mood swings	Moderate	58	126	

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Subject ID	LDD	PT	Severity	OD	RD	Pertinent History Action taken
						Medication prescribed
(b) (6) 41		Depression	Moderate	14	46	History of depression and anxiety No action taken
191		Depression	Moderate	21	ONG	History of depression
85		Depression	Severe	15	27	History of depression and anxiety secondary to fetal demise Study drug interrupted
174		Depression	Moderate	44	72	History of depression Medication prescribed
204		Depression	Moderate	57	163	History of insomnia Seen by MHCP Medication prescribed
190		Depression Anxiety	Severe Severe	135 135	ONG ONG	Seen by MHCP Medication prescribed
122		Depression	Moderate	92	ONG	No significant history Discontinued study drug
Study M12-671 Elagolix 150 mg QD						
(b) (6) 205		Depression	Moderate	202	ONG	History of mild depression Seen by MHCP, medication prescribed
168		Depression	Moderate	160	ONG	History of depression, Wellbutrin x 2 years Medication prescribed
Study M12-671 Elagolix 200 mg BID						
(b) (6) 162		Depressed mood Agitation	Moderate Moderate	31 31	184 184	History of situational depression and anxiety x 2 No action taken
171		Depressed mood Mood swings	Moderate Moderate	7 7	ONG ONG	No significant history No action taken
138		Depressed mood	Moderate	24	148	No significant history Discontinued study drug
158		Depressed mood	Moderate	4	ONG	History of post-partum depression Medication prescribed
171		Depression Nervousness	Moderate Moderate	44 44	ONG ONG	No significant history No action taken
197		Depression	Moderate	67	113	No significant history No action taken
156		Depression	Moderate	146	163	History of mild depression Discontinued study drug

LDD = last dose day; PT = preferred term; OD = onset day; RD = resolution day;

ONG = ongoing; MHCP = mental health care provider

Sources: 1. M12-665 Study Report; Table 76; pages 410-414 of 8446 2. M12-671 Study Report; Table 78;

Pages 410-412 of 8198

** Subjects listed as "no significant history"

Narratives for Elagolix-Treated Subjects with Suicidal Ideation or Depression Suicidal

There were four elagolix-treated subjects identified in the submission with suicidal ideation:

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Subject (b) (6) (NBI-56418-0603)

This 36-year-old female was randomized on (b) (6) to receive elagolix 75 mg BID for 24 weeks in Phase 2 study NBI-56418-0603. Pertinent medical history included depression, two suicide attempts, bipolar disorder and anxiety. Pertinent concomitant medications included zolpidem tartrate and varenicline. On (b) (6) (study day 83), the subject experienced an SAE of suicidal ideation, approximately 2.5 months after beginning study drug. On (b) (6) she was hospitalized with complaints of worsening of depression and hopelessness. She stated that she had had suicidal ideation with no specific plan and strong passive death wishes. She denied any manic or psychotic symptoms. She was previously hospitalized for suicidal attempt (overdose) in (b) (6) and for suicidal thoughts in (b) (6). She had not received outpatient psychiatric follow-up or psychotropic medications since (b) (6). The subject was treated medically and placed on close observation in the hospital. She was discharged on (b) (6). Study drug administration was interrupted for the three days she was hospitalized. The SAE resolved (b) (6). The subject had psychiatric follow-up visits with one notation that her mood was better but some depression and anxiousness persisted. The subject completed the study and took her last dose of study drug on (b) (6). Although this subject appeared to improve on rechallenge and completed the study it is unknown whether elagolix contributed to the worsening of her symptoms.

Subject (b) (6) (Study M12-667)

Prior to enrolling in Study M12-667, this subject had participated in Study M12-665 where she was randomized to the elagolix 150 mg QD treatment group and had received 183 days of treatment. She then rolled-over into Study M12-667 and continued to receive elagolix 150 mg QD. On day 29 of the extension study, the subject (age 29 at time of the events) experienced severe premenstrual dysphoric disorder and severe suicidal ideation. The subject reported suicidal ideation with a plan to cut her wrists for three days prior to menses during the previous 2 months. The subject denied relationship or situational issues or stressors. The subject denied any plan to act on the suicidal thoughts. The subject declined a psychiatric consult; therefore, she was not evaluated by a mental health provider for the events. The subject was treated with fluoxetine and study drug was not interrupted due to these events. The events were characterized as intermittent and were considered resolved on day 50. Both the Investigator and Sponsor considered the events of premenstrual dysphoric disorder and suicidal ideation as having a reasonable possibility of being related to study drug.

Subject (b) (6) (Study M12-665)

This 33-year-old white female, randomized to receive elagolix 150 mg QD, experienced events of severe anger, depression, and suicidal ideation beginning on study day 113 (b) (6). Her past medical history indicated the possibility (not formally diagnosed) of postpartum depression in (b) (6) and depression and panic attacks in (b) (6) on study day 113, the subject reported feeling angry during dinner. The following morning, the subject told her spouse that she was suicidal. The subject reported that she then left her home and spent the day at a bookstore and at the movies, with crying episodes throughout the day. After returning home, the subject slept for 14 hours. On day 115, the subject continued to have crying episodes, fatigue, and anger issues. The subject reported that she did not eat or drink much

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until the evening of day 115. No treatment was provided for the events. Study drug was permanently discontinued due to these events with the last scheduled dose administered on day 115. The events were considered resolved on day 117 (post-treatment day 2). The subject was evaluated by a mental health professional on day 138 (post-treatment day 23), who reported no overt signs of anxiety or depression, and no suicidal ideation, intent, or plan to harm or hurt herself. The Investigator considered the events of anger, depression, and suicidal ideation as having a reasonable possibility of being related to study drug.

Subject (b) (6) (M12-671)

This was a 23-year-old subject with a relevant medical history of anxiety, depression and insomnia who experienced events of worsening depression, agitation, and suicidal ideation.

On day 12 of treatment with elagolix 200 mg BID, the subject experienced an event of moderate depression, reported as worsening depression. The subject reported a lack of energy, sadness, mood swings, irritability, feeling tearful and quiet. The subject reported previously experiencing symptoms of anxiety, insomnia, intermittent and worsening depression which was treated with alprazolam and citalopram. Treatment included ongoing alprazolam and the addition of citalopram once daily for the depression. The subject was not evaluated by a mental health provider for this event. Study drug was not interrupted due to this event. On day 71, the subject experienced events of agitation, anger, mood swings and suicidal ideation. Her citalopram was increased from once daily to twice daily. The subject consulted her primary care physician and was not evaluated by a mental health provider for these events. Study drug was permanently discontinued due to these events with the last scheduled dose administered on day 84. The events of agitation and suicidal ideation were characterized as intermittent and were considered resolved on day 111 (post-treatment day 27). No further information was provided.

An additional 4 subjects had adverse events of suicidal ideation/depression suicidal who took either placebo and or another study drug. These are:

- Subject (b) (6) (Study NBI-56418-0603- Placebo & DMPA-SC) = Suicidal ideation
- Subject (b) (6) (Study NBI-56418-0901 - Placebo) = Suicidal ideation
- Subject (b) (6) (Study NBI-56418-0603 - Placebo) = Depression suicidal
- Subject (b) (6) (Study M12-663 - Placebo) = suicidal ideation

Note: DMPA-SC = depot medroxyprogesterone acetate subcutaneous

Euphoria

On (b) (6) the Applicant responded that Subject (b) (6) (23-year-old subject in Study NBI-56418-0501) experienced a severe, nonserious event of euphoric mood after 6 weeks of receiving elagolix 150 mg QD. The event began on (b) (6) and resolved on (b) (6) despite continued elagolix treatment.

There has otherwise been no signal of euphoric mood or compulsive behaviors in the submitted studies.

8.2.5.2. Hot Flashes, Night Sweats and Insomnia

As noted earlier in the review, hot flushes, night sweats and insomnia were commonly observed treatment-emergent adverse reactions that occur secondarily to estrogen reduction which is caused by the central GnRH antagonism of elagolix. The percentages of hot flushes graded in the severe category (6.5%) and the percentage of subjects prematurely discontinuing study drug (1.7%) have also been previously described in this review.

We performed an analysis of insomnia from the PA2 adverse event analysis dataset which is found in section 5.3.5.3 of the submission (this includes adverse events from all the Phase 3 trials – Studies 665, 667, 671 and 821). Of 69 subjects with a report of insomnia, 45 subjects also had reports of hot flushes. There were 24 subjects with reports of insomnia without hot flushes. Of these 24 subjects, 33% were taking placebo, 13 (54.0 %) were taking the 150 mg QD dose and 3 (12.5%) were taking the 200 mg BID dose. These percentages seem appropriate. One would expect subjects taking the higher dose to have both hot flushes and insomnia.

8.2.5.3. Hypersensitivity Reactions

Anaphylactoid Reactions

There were no anaphylactoid reactions reported in the pivotal Phase 3 controlled studies and extension studies. An anaphylactoid reaction was reported in the Phase 2 Study NBI-56418-0501. The following is a narrative of that event.

- Subject (b) (6) was a 24-year-old who experienced an anaphylactoid reaction approximately 4-6 hours after taking her seventh dose of study drug (elagolix 150 mg QD). Her medical history included depression, cerebral palsy and childhood asthma. Concomitant medications included venlafaxine, ibuprofen and multivitamins. The subject reported developing red blotches on her face, hives on her neck, swelling under the eyes, and generalized pruritus. No hospitalization or treatment was initiated. The following day, the facial redness had resolved and the pruritus had decreased while the other symptoms remained unchanged. The event resolved without sequelae 4 days after onset. Study drug was discontinued and the subject was withdrawn from the study.

This event appears probably related to study drug.

Drug-Induced Rash Company MedDRA Query (CMQ) Results

The Applicant's analysis of adverse events which are part of the drug-induced rash CMQ are shown in the following two tables (**APPEARS THIS WAY ON ORIGINAL** Table 79 and Table 80).

Table 79. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Matching the Drug-Induced Rash CMQ (Phase 3 Endometriosis Controlled Analysis Set – Studies 665 & 671)

	Placebo (N = 734) n (%)	Elagolix		
		150 mg QD (N = 475) n (%)	200 mg BID (N = 477) n (%)	Overall (N = 952) n (%)
Subjects with one or more adverse events (see note)	46 (6.3)	25 (5.3)	30 (6.3)	55 (5.8)
Leading to study drug discontinuation	4 (0.5)	1 (0.2)	3 (0.6)	4 (0.4)
Adverse events Preferred Terms MedDRA version 19.1 (superscript = SOC)				
• Oral mucosal exfoliation ¹	1 (0.1)	0	0	0
• Infusion site pruritus ²	1 (0.1)	0	0	0
• Drug hypersensitivity ³	1 (0.1)	1 (0.2)	0	1 (0.1)
• Hypersensitivity ³	2 (0.3)	1 (0.2)	0	1 (0.1)
• Conjunctivitis ⁴	4 (0.5)	1 (0.2)	1 (0.2)	2 (0.2)
• Rash pustular ⁴	0	1 (0.2)	0	1 (0.1)
• Dermatitis ⁵	3 (0.4)	1 (0.2)	0	1 (0.1)
• Dermatitis allergic ⁵	0	0	1 (0.2)	1 (0.1)
• Dermatitis atopic ⁵	0	0	1 (0.2)	1 (0.1)
• Dermatitis contact ⁵	3 (0.4)	2 (0.4)	3 (0.6)	5 (0.5)
• Eczema ⁵	2 (0.3)	2 (0.4)	2 (0.4)	4 (0.4)
• Erythema ⁵	1 (0.1)	1 (0.2)	1 (0.2)	2 (0.2)
• Hand dermatitis ⁵	1 (0.1)	0	0	0
• Photosensitivity reaction ⁵	0	0	1 (0.2)	1 (0.1)
• Pruritus ⁵	3 (0.4)	1 (0.2)	5 (1.0)	6 (0.6)
• Pruritus generalized ⁵	1 (0.1)	1 (0.2)	0	1 (0.1)
• Psoriasis ⁵	0	0	1 (0.2)	1 (0.1)
• Rash ⁵	18 (2.5)	9 (1.7)	13 (2.7)	21 (2.2)
• Rash generalized ⁵	1 (0.1)	0	0	0
• Rash macular ⁵	0	1 (0.2)	0	1 (0.1)
• Rash maculo-papular ⁵	0	0	1 (0.2)	1 (0.1)
• Rash pruritic ⁵	0	0	1 (0.2)	1 (0.1)
• Skin irritation ⁵	1 (0.1)	0	0	0
• Skin reaction ⁵	1 (0.1)	0	0	0
• Urticaria ⁵	5 (0.7)	4 (0.8)	2 (0.4)	6 (0.6)

Source: ISS – Tables 52 (page 231 of 5658) and 2.1_1.12.6 (page 1625 of 5658)

CMQ = customized MedDRA queries, BID = twice daily, QD = once daily

System Organ Classes (SOCs):

¹ gastrointestinal disorders,

² general disorders and administration site conditions,

³ immune system disorders,

⁴ infections and infestations,

⁵ skin and subcutaneous tissue disorders

Note: A subject who reports two or more different preferred terms which are in the same SOC is only counted once in the SOC.

Table 80. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Matching the Drug Induced Rash CMQ (Skin and Subcutaneous Tissue) by System Organ Class and Preferred Term (Long-Term Phase 3 Endometriosis Analysis Set)

System Organ Class/ MedDRA 19.1 Preferred Term	Elagolix		
	150 mg QD (N = 291) n (%)	200 mg BID (N = 278) n (%)	Overall (N = 569) n (%)
Subjects with one or more events	27 (9.3)	21 (7.6)	48 (8.4)
Leading to study drug discontinuation	0	1 (0.4)	1 (0.2)
• Hypersensitivity ³	2 (0.7)	1 (0.4)	3 (0.5)
• Conjunctivitis ⁴	3 (1.0)	1 (0.4)	4 (0.7)
• Rash pustular ⁴	1 (0.3)	0	1 (0.2)
• Dermatitis atopic ⁵	0	1 (0.4)	1 (0.2)
• Dermatitis contact ⁵	1 (0.3)	3 (1.1)	4 (0.7)
• Eczema ⁵	2 (0.7)	1 (0.4)	3 (0.5)
• Erythema ⁵	1 (0.3)	1 (0.4)	2 (0.4)
• Photosensitivity reaction ⁵	1 (0.3)	0	1 (0.2)
• Pruritus ⁵	1 (0.3)	4 (1.4)	5 (0.9)
• Rash ⁵	7 (2.4)	6 (2.2)	13 (2.3)
• Rash erythematous ⁵	1 (0.3)	0	1 (0.2)
• Rash generalized ⁵	0	1 (0.4)	1 (0.2)
• Rash macular ⁵	2 (0.7)	0	2 (0.4)
• Rash pruritic ⁵	1 (0.3)	1 (0.4)	2 (0.4)
• Skin irritation ⁵	0	1 (0.4)	1 (0.2)
• Urticaria ⁵	4 (1.4)	3 (1.1)	7 (1.2)

Source: ISS – Table 53, page 232 of 5658

BID = twice daily, QD = once daily

System Organ Classes (SOCs):

¹ gastrointestinal disorders

² general disorders and administration site conditions

³ immune system disorders

⁴ infections and infestations

⁵ skin and subcutaneous tissue disorders

Note: A subject who reports two or more different preferred terms which are in the same SOC

Is only counted once in the SOC.

The results from these two tables appear to show that these adverse events are not appreciably increased over that of placebo and that the number of adverse events in this query are similar for both doses of elagolix studied. Some of the components of the CMQ seem to be out of place for an evaluation of elagolix-induced skin disorders (such as infusion site pruritus). The SOC of infections and infestations would evaluate a different drug-induced mechanism than an allergic response. There does not appear to be an increase in this SOC over that of placebo.

To further explore the aspects of the adverse events the following narratives are presented.

These narratives represent adverse events that were rated as severe, involved treatment with systemic steroids and/or resulted in study drug discontinuation.

Study M12-665

Subject (b) (6) (elagolix 200 mg BID): This 38-year-old female reported a mild intermittent papular chin rash on study day 38. Oral treatment with diphenhydramine was given. The investigator provided an alternative etiology of acne. Dermatology was not consulted. Study drug was permanently discontinued due to the event.

Subject (b) (6) (elagolix 150 mg QD): This 33-year-old female developed generalized pruritus without a rash on study day 3. Her pruritus was treated with a decongestant and antiallergic medication. A dermatologist was not consulted. In addition, she experienced a dilatation of her right pupil and visual impairment. For this she was evaluated by a neurologist and ophthalmologist with negative exam findings and imaging findings. Study drug was permanently discontinued due to these events.

Subject (b) (6) (elagolix 200 mg BID): This 29-year-old female experienced a generalized rash on day 2 of treatment. The rash was described as wheal in shape, papular, raised and urticarial. The investigator reported that the rash appeared to progress with continued dosing of study drug. Dermatology was not consulted. Study drug was permanently discontinued due to the event.

Subject (b) (6) (elagolix 150 mg QD): This 25-year-old female experienced a severe contact dermatitis from poison ivy exposure.

Subject (b) (6) (elagolix 200 mg BID): This 24-year-old female experienced a pruritic macular rash on her arms and moderate intermittent diarrhea beginning on study day 2. The dermatitis was treated with diphenhydramine. Dermatology was not consulted. Study drug was permanently discontinued.

Subject (b) (6) (elagolix 200 mg BID): This 30-year-old female experienced itching and swelling of the face, neck, hands and feet. This adverse event was graded as mild and had its onset on study day 35. The event last 7 days and she was treated with diphenhydramine and prednisone. Study drug was not discontinued. There is no record that dermatology was consulted.

Study M12-671

Subject (b) (6) (elagolix 200 mg BID): This 38-year-old female experienced a moderately severe rash that involved the neck, forearms and upper chest beginning on day 38. The rash was described as papular, confluent, urticarial and pruritic. A dermatologist treated the subject with intramuscular dexamethasone and cetirizine. The duration of the rash was listed as 81 days. On day 95 the subject additionally developed lip, facial and extremity swelling. The swelling symptoms resulted in the study drug being permanently discontinued.

Study M12-667

Subject (b) (6) (elagolix 200 mg BID): This 29-year-old female with an extensive allergy history to latex, bee stings and multiple medications was 8 days past her last dose of elagolix when she developed a severe urticarial generalized rash following a flu shot.

Subject (b) (6) (elagolix 200 mg BID): This 34-year-old female with a history of allergies to domestic pets initially experienced a neck rash in Study 665. On day 2 of the extension study (also taking elagolix 200 mg BID), the subject experienced a mild macular and pruritic generalized rash. Study drug was permanently discontinued.

Subject (b) (6) (elagolix 150 mg QD): This 32-year-old female initially experienced a localized vesicular/bullous rash on her left forearm which progressed to a generalized rash. Study drug was permanently discontinued due to this event.

Subject (b) (6) (elagolix 200 mg BID): This 34-year-old female experienced dyspnea and urticaria on study day 116 of the extension study (also on elagolix 200 mg BID). Both events were graded as moderate and lasted 1 day. The subject was treated with diphenhydramine, methylprednisolone, prednisone, famotidine and ondansetron. The subject was evaluated by a dermatologist who believed the event to be related to a possible pork or beef allergy. Study drug was not discontinued.

Subject (b) (6) (elagolix 150 mg QD): This 29-year-old female experienced a contact dermatitis involving her eyes and was prescribed prednisone. The event was graded as moderate and lasted for 6 days. Study drug was not discontinued. A separate narrative was not identified for this adverse event. The event was judged as not related to elagolix use.

Study M12-821

Subject (b) (6) (elagolix 150 mg QD): This 36-year-old female was listed as having a drug hypersensitivity reaction to tramadol. This medication was stopped. Study drug was not discontinued.

Subject (b) (6) (elagolix 200 mg BID): This 34-year-old female received placebo during Study 671. On day 17 of Study 821 she experienced a rash localized to her arms and legs. Study drug was permanently discontinued due to this event.

In summary, some of these narratives strongly support other etiologies for the rash adverse events such as poison ivy, tramadol and the flu shot. Subjects (b) (6) and (b) (6) whose condition appeared to worsen while continuing their elagolix study drug provides more evidence that the use of the product was probably related.

We additionally compiled a table of selected adverse events that were derived from Phase 1 and 2 studies and from the adverse event JMP datasets for the pivotal Phase 3 controlled and extension studies (See Appendix 14.4). The selected cases from the Phase 3 studies are examples for the most part that were mild and in which the study drug was not interrupted. The highlighted case in the table (Subject ^{(b) (6)} in Study NBI-56418-0504) is an example where skipping elagolix was associated with rash improvement and restarting elagolix was associated with rash reappearance, suggestive of drug causality.

8.2

8.2.5.4. Pregnancies

As noted previously, the Applicant assessed elagolix in a folliculogenesis and ovulation study (M12-673). For elagolix 150 mg QD, the ovulation rate was approximately 50% over the 3-cycle study. For elagolix 200 mg BID, the ovulation rate was 32%. These data indicate that elagolix does not suppress ovulation to a degree consistent with hormonal contraceptives.

Additionally, based on the mechanism of action, there is a theoretical risk that elagolix may cause a decrease in luteal progesterone production in early pregnancy and may be associated with potential increased risk of pregnancy complications, such as early pregnancy loss. A post-hoc analysis was performed by the Applicant on serum progesterone concentrations measured during the luteal phase in the women who ovulated during elagolix treatment in Study M12-673. Overall the luteal serum progesterone in ovulating women during the elagolix treatment cycles is approximately 25% lower than the luteal phase progesterone concentrations measured during the untreated Screening period. The progesterone decreases based on dose are shown in Table 81 below.

Table 81. Luteal Phase Serum Progesterone Concentrations (Mean Maximal) of Women Who Ovulated During Elagolix Treatment: Comparison of Screening Period Values vs. Measurements from the Elagolix Treatment Period in Study M12-673

Elagolix Treatment Group	N	Mean ± SD Serum Peak Progesterone Concentrations (ng/mL)		
		Screening	On-Treatment	% Change (On-Treatment Versus Screening)
Overall	80	13.1 ± 4.5	9.8 ± 3.9	-25%
100 mg QD	5	9.8 ± 2.5	11.3 ± 3.9	+16%
100 mg BID	17	14.5 ± 4.3	10.1 ± 4.4	-30%
150 mg QD	20	13.9 ± 5.3	9.2 ± 3.7	-33%
200 mg QD	18	12.8 ± 4.1	9.6 ± 3.0	-24%
200 mg BID	12	12.6 ± 4.3	10.4 ± 5.2	-17%
300 mg BID	6	12.1 ± 4.3	9.1 ± 4.1	-25%
300 mg BID + SD E2/NETA	2	11.6 ± 5.6	9.6 ± 5.9	-17%

SD E2/NETA = standard-dose: estradiol 1 mg/norethindrone acetate 0.5 mg

Source: Submission section 5.3.5.3; Table 2, Technical Summary of Pregnancy, page 13 of 306
 BID = twice daily, QD = once daily, SD = standard deviation

Serum progesterone measurements vary through the cycle and certainly between subjects. It is unclear why there would be an increase in serum progesterone with the 100 mg QD dose but the 150 mg QD dose shows a greater decrease than the 200 mg BID dose. In this case, it is important to look at the pregnancy results in the clinical trials to judge whether progesterone decreases in this range will significantly affect pregnancies. Placental hormonal support (human chorionic gonadotropin, human placental lactogen, estrogen and progesterone) of pregnancy increases rapidly in the first trimester and might offset the effect of decreases in serum progesterone.

Overall Pregnancy Outcomes

As of 19 June 2017, 69 on-treatment pregnancies have been reported among women enrolled in elagolix clinical trials who received either elagolix or placebo (one additional pregnancy was reported in a subject who received oral contraceptives). On-treatment pregnancies are defined as those that had a conception date during the treatment period with study drug dosing or were deemed to have a conception date within 30 days after the last dose of study drug.

Among the 69 on-treatment pregnancies, 10 occurred in healthy female volunteers, 57 in women with endometriosis, and 2 pregnancies in women with uterine fibroids. Twenty of the 69 pregnancies occurred in women treated with placebo and 49 pregnancies occurred in women who received elagolix. The annualized on-treatment pregnancy rates among subjects with up to 12 months of treatment exposure in the elagolix Phase 3 endometriosis clinical development program were 4.81% for placebo, 4.07% for elagolix 150 mg QD, and 2.66% for elagolix 200 mg BID.

Outcomes of pregnancies during the treatment period are summarized in Table 82. Of the 49 pregnancies that occurred in subjects exposed to elagolix, 15 resulted in elective abortions, 5 resulted in spontaneous abortions, 6 were lost to follow-up, and 23 were carried to term. Among the 23 pregnancies that were carried to term, 2 subjects delivered infants with congenital anomalies (1 infant was born with cleft soft palate and 1 infant was born with a tracheo-esophageal fistula accompanied by findings of patent ductus arteriosus, tricuspid valve incompetence, pneumothorax, and atelectasis). The remainder delivered healthy infants.

Table 82. Summary of Pregnancy Outcome for On-Treatment Pregnancy (All Abbvie and NBI Studies Pregnancy Analysis Set)

Outcome	Placebo N = 1194 n (%)	150 mg QD N = 1324 n (%)	200 mg BID N = 841 n (%)	Other Doses N = 1399 n (%)	Any Ela N = 3564 n (%)	Total N = 4758 n (%)
Live birth	7 (0.6)	16 (1.2)	5 (1.0)	2 (0.1)	23 (0.6)	30 (0.6)
Congenital anomaly	0	2 (0.2)	0	0	2 (0.06)	2 (0.04)
Spontaneous abortion	5 (0.4)	2 (0.2)	2 (0.2)	1 (0.07)	5 (0.1)	10 (0.2)
Elective abortion	2 (0.2)	8 (0.6)	3 (0.4)	4 (0.3)	15 (0.4)	17 (0.4)
Lost to follow-up	3 (0.3)	2 (0.2)	2 (0.2)	2 (0.1)	6 (0.2)	9 (0.2)
Ectopic pregnancy	1 (0.08)	0	0	0	0	1 (0.02)
Stillbirth	1 (0.08)	0	0	0	0	1 (0.02)
Missing	1 (0.08)	0	0	0	0	1 (0.02)
Total	20 (1.7)	28 (2.1)	12 (1.4)	9 (0.6)	49 (1.4)	69 (0.6)

Source: Table 3, Technical Summary of Pregnancy, Page 17 of 306
 BID = twice daily, Ela = elagolix, QD = once daily

The numbers in the preceding table are small and it is difficult to establish trends. For example, it is not clear whether the slightly greater percentage of live births with the 150 mg QD over 200 mg BID is in any way indicative of a difference in ovulatory inhibition. Spontaneous abortions are discussed further in the next section.

Spontaneous Abortions

The following table (Table 83) evaluates the early pregnancy losses in the placebo versus elagolix arms by gestational age. The individual cells in the table have the study number and subject number listed. Following the table, brief narratives are provided for the elagolix cases.

Table 83. On-Treatment Spontaneous Abortions According to Gestational Age

Weeks gestation	Placebo	Elagolix		
		150 mg QD	200 mg BID	Other doses
< 6 weeks	---	671- (b) (6)	821- (b) (6)	
6 to 13 weeks	671- (b) (6) 671- 671-	---	667-	
> 13 weeks	---	---	---	---
Unknown	405- (b) (6) 901- (b) (6)	901- (b) (6)	---	702- (b) (6)

Source: Individual CSR's and ADPREG Dataset.
 BID = twice daily, QD = once daily

< 6 weeks

Subject (b) (6) in Study 821: This 24-year-old subject had no prior pregnancies. The conception date was estimated based on last menstrual period. There was no ultrasound evaluation. There was no additional information on the outcome aside from β -human chorionic gonadotropin (hCG) levels that were dropping.

Subject (b) (6) in Study 671: This 24-year-old subject had a history of one full term pregnancy and one SAB. On day 89, a borderline serum pregnancy test was reported. On day 117, an ultrasound confirmed the pregnancy. On day 120, the subject experienced a spontaneous abortion (SAB) and a dilatation and curettage was performed.

6 to 13 weeks

Subject (b) (6) in Study 667: This subject's obstetrical history was notable for one prior SAB and one prior full-term pregnancy. Sonogram showed two fetal poles without fetal heart tone. Because conception date was not determined and absence of rising hCGs, the subject was given misoprostol for termination.

Unknown gestational age

Subject (b) (6) in Study 702: This is a 28-year-old subject with a medical history of "8 miscarriages" and one caesarian section. She was initially diagnosed with having an ectopic pregnancy and treated with intramuscular methotrexate. Subsequently it was determined that there was an intrauterine pregnancy (tiny yolk sac) and the adnexal mass most likely represented a hemorrhagic corpus luteum. The subject eventually had dilatation and curettage.

Subject (b) (6) in Study 901: This is a 42-year-old subject with two prior live births and 2 prior SABs who experienced a spontaneous abortion. At the week 30 visit, the subject had positive urine and serum (beta hCG, 1881 mIU/mL) pregnancy tests. Five days later, the subject reported vaginal bleeding and cramping. Subsequent, beta hCGs decreased eventually to 22 mIU/mL and the vaginal bleeding stopped.

Although the percentage of spontaneous abortion in the elagolix-treated subjects is lower than that seen with placebo, the Applicant acknowledges that these numbers are small and proposes a prospective pharmacoepidemiology study in a mother-baby linked database. This proposed study would evaluate pregnancy outcomes and outcomes in the infant such as congenital malformations (the congenital anomalies found in subjects receiving elagolix are described next).

On (b) (6) the Applicant provided some additional information on the prospective pharmacoepidemiology study (but not a full study protocol). The Applicant stated that the surveillance study will be conducted in collaboration with (b) (6) Chief Scientific Officer). Algorithm development has been initiated already for identification of patients with endometriosis and the occurrence of pregnancy-related outcomes. The Applicant

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plans to use propensity scoring when comparing rates among those treated and not treated with elagolix. The study will use health care claims data from (b) (4)

Congenital Anomalies

Tracheo-esophageal fistula case

Subject (b) (6) (Study NBI-56418-0702)

Subject (b) (6) was a 19-year-old subject who was randomized to receive elagolix 150 mg QD for 24 weeks during a double-blind, placebo-controlled study. Concomitant medications included Vicodin, potassium, and nitrofurantoin. Approximately 7 weeks after starting the first dose of study drug, the subject went to the emergency room with complaints of abdominal pain. A urine pregnancy test was conducted and the result was positive. Her pregnancy was confirmed with a serum pregnancy test (office clinic) two days later. The subject's last dose of study drug was that day and she was discontinued from the study due to the pregnancy three days later. The infant may have been exposed, in utero to elagolix for approximately 2 weeks.

During the course of the pregnancy, the infant may have also been exposed to prenatal vitamins, amoxicillin for 10 days, Tylenol Sinus and Cold (acetaminophen, guaifenesin, and phenylephrine) for 3 days, Lortab (hydrocodone/acetaminophen), potassium and Benadryl (diphenhydramine) for an unknown duration.

At approximately gestational week 20 5/7, the subject went to the emergency room with complaints of sharp lower abdominal pains with spotting. The pain and spotting resolved and the subject was discharged home (she was not admitted to the hospital).

A female infant was born at gestation week 36 via normal vaginal delivery (however, the mother's Obstetrician/Gynecologist stated that the infant's measurements were consistent with gestational week 34). The subject had preeclampsia during delivery and was discharged three days after delivery. The subject was noted to have postpartum depression.

The infant's Apgar scores were 7 at 1 minute, 9 at 5 minutes, and 9 at 10 minutes. Her vital signs were stable and blood glucose was above 80. The infant's measurements were: weight, 5 pounds 12 ounces; length, 18.70 inches; head circumference, 13.39 inches; and chest circumference, 12.01 inches. Nuchal cord x2 was found at delivery and reduced. The infant had some signs of distress at birth (episode of being dusky) which responded to simple oxygen.

Approximately 12 hours after birth, during a feeding attempt, the infant vomited and had a choking episode associated with oxygen desaturations. The infant was diagnosed with type C trachea-oesophageal fistula.

Approximately 1 day after birth, an echocardiogram indicated that the infant had patent ductus arteriosus (measuring 0.163 cm) with a small left-to-right shunt and trace tricuspid valve insufficiency with an estimated right ventricular systolic pressure of 37 mm Hg.

Due to the small size of the patent ductus arteriosus and based on the infant's growth, the neonatal intensive care unit physician indicated that the patent ductus arteriosus would seal itself and once it seals, the trace tricuspid value would self-correct.

Approximately 2 days after birth, the infant had surgery to repair the tracheo-esophageal fistula. The infant tolerated the procedure well and remained intubated. Approximately 4 days after birth, the chest x-ray showed development of extensive left-sided atelectasis resulting in ipsilateral mediastinal shift. Approximately 5 days after birth, a chest x-ray showed development of right pneumothorax. It was thought that the pneumothorax was due to a tiny leak at the site of surgical repair. All events were assessed to have resolved by 7 days later.

External experts in reproductive toxicology reviewed this case. They felt that the potential exposure to elagolix occurred during the first 15 days of development at a time prior to the division of the cranial part of the foregut into respiratory and esophageal segments (normally seen late in the fourth week of development).

Cleft Palate Case

Subject (b) (6) was a 23-year-old subject who was randomized to receive elagolix 150 mg QD for 24 weeks during a double-blind, active-controlled Phase 2 study. Concomitant medications included ibuprofen, vicodin, and according to medical records iron, prenatal vitamin and Tylenol (paracetamol). About 11 months later, the subject gave birth to a male infant with a cleft palate. The infant may have been exposed to elagolix for approximately 1 month (based on the estimated date of conception and subject's last dose). Throughout the pregnancy, the infant may also have been exposed to iron, prenatal vitamins and Tylenol (acetaminophen).

The infant was delivered at 39 gestational weeks via cesarean section (method of delivery chosen based on prior Cesarean). The pediatrician's physical exam ruled out any additional congenital anomalies.

The infant had surgery to repair the cleft palate approximately 9 months after birth. The infant also had a bilateral myringotomy and tympanostomy tubes procedure performed immediately prior to the cleft palate repair due to chronic otitis media with effusion.

Maternal medical history includes no family history of cleft palate or cleft lip, no alcohol consumption during pregnancy, and no recreational drugs used during pregnancy. Paternal history includes no family history of cleft palate or cleft lip.

External experts in reproductive toxicology reviewed this case. They felt that the potential exposure to elagolix occurred during the first 30 days of development at a time prior to the critical period for human palatogenesis (palate development begins in the sixth week post conception and closure begins in the eighth week.)

Craniosynostosis Case

This case was included in the Safety Update to the NDA.

Subject (b) (6) was a 31-year-old subject who was randomized to receive elagolix 150 mg QD in Study M12-821, after having previously received 173 days of elagolix 150 mg QD in Study M12-671. The subject completed Study M12-821 with the last scheduled dose administered on day 175.

On day 221 (post-elagolix treatment day 46), the subject had a positive urine pregnancy test and a positive qualitative serum pregnancy test. On the same day, an ultrasound performed revealed a gestational age of 5 weeks. A subsequent second trimester ultrasound was performed on day 345 (post-elagolix treatment day 170) and revealed a gestational age of 23 weeks. No fetal abnormalities were detected on either ultrasound.

The subject's pregnancy resulted in the birth of a live male infant on day 446 (post-elagolix treatment day 271). The infant was delivered by cesarean section, due to transverse position, at a gestational age of 37 weeks and 1 day; the infant weighed 3.3 kg, and measured 55 cm in length, with no reported abnormalities. The Apgar score was reported as 10. It was reported that there were no medically significant complications during the pregnancy, labor, or delivery period.

The investigator site became aware that a birth defect of non-syndromic craniosynostosis was detected on ultrasonography at age 3 months and on computed tomography scan at age 7 months. No genetic or metabolic tests were performed. The infant was evaluated by a neurosurgeon and scheduled for neurosurgical treatment to occur at the age of 14 months.

The site estimated no fetal exposure based on the first trimester ultrasound. Lack of fetal exposure to elagolix based on the estimated conception date and the last dose date of elagolix was further confirmed by the absence of elagolix concentrations above the quantification limit in serum collected at the treatment month 6 visit prior to the estimated conception date.

8.2.5.5. Endometrial Safety

Endometrial Thickness

Endometrial thickness was measured by transvaginal ultrasound (TVU) in Studies 665 and 671 and extension Studies 667 and 821 at baseline, at month 6 and extension month 6 (or premature discontinuation). The change from baseline to pivotal month 6 are shown in the following table (Table 84).

Table 84. Change from Baseline to Pivotal Month 6 in Endometrial Thickness During the Treatment Period (Phase 3 Endometriosis Controlled Trials Analysis Set)

Treatment Group	N	Baseline mean, mm	Month 6 Mean, mm	Mean Change (SD), mm
Placebo	533	6.54	7.60	1.06 (3.331)
Elagolix 150 mg QD	362	6.48	7.03	0.55 (3.690)
Elagolix 200 mg BID	358	6.42	5.31	-1.11 (3.402)

Source: Table 94, Integrated Summary of Safety, page 352 of 5658

These findings are consistent with the endometrial biopsy results which will be discussed next in this section. The study protocol called for an ultrasound endometrial measurement during the early proliferative phase at Baseline. The Baseline means are consistent with measurements that occur in the proliferative phase of the cycle. The measurements taken at month 6 show results that are slightly greater for placebo and elagolix 150 mg QD and a decrease from Baseline for elagolix 200 mg BID. This decrease is probably due to the greater endometrial effect of the higher dose. The study protocol recommended that endometrial thickness at month 6 be performed in the proliferative phase for women with regular periods. Based on study drug effects not all women will be cycling on a regular basis at month 6 and many may be amenorrhoeic.

The endometrial thickness findings reflect the mechanism of action of a gonadotropin antagonist. These overall findings are also reassuring from a safety standpoint. Thickening of the endometrium may occur with hyperplastic and neoplastic change or with endometrial polyps. Marked increases in endometrial thickness have also been seen with another class of hormonal drugs, progesterone receptor modulators. Excessive uterine bleeding may result from marked increases in thickness.

Taking into account that the cut-off thickness for secretory endometrium in younger premenopausal subjects is 18 mm, there were some outliers in the elagolix-treated subjects related to endometrial thickness:

Subject (b) (6) (elagolix 150 mg QD) in Study M12-665 had an endometrial thickness of 20.9 mm at month 6. No subsequent TVU results were recorded. Her endometrial biopsy result revealed proliferative endometrium. The subject completed the study and enrolled into the extension study.

Subject (b) (6) (elagolix 200 mg BID) in Study M12-665 had an endometrial thickness of 18.5 mm at month 6. She completed the treatment period, but did not enroll into the extension study. By PTFU day 116, her endometrial thickness had decreased to 8.8 mm. No on-treatment endometrial biopsy results are available for this subject.

Subject (b) (6) (elagolix 200 mg BID) in Study M12-665 had an endometrial thickness of 21.7 mm on TVU at her month 6 visit (day 155), which was reported as "endometrial hyperplasia." The subject refused an endometrial biopsy. After her next menses on day 163, a repeat TVU showed an endometrial thickness of 9.3 mm. A final endometrial thickness of 6.6 mm was

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found in the post-treatment phase. Based on the history this patient most likely had a very abundant secretory endometrial growth which can occur. This biopsy should have been read as endometrial hypertrophy which is used to describe increase thickness rather than endometrial hyperplasia.

Subject (b) (6) (elagolix 150 mg QD) in Study M12-671 had an endometrial thickness of 23.2 mm at month 6. No subsequent TVU results were recorded. The subject completed the study and enrolled into the extension study.

Subject (b) (6) (elagolix 150 mg QD) in Study M12-671 had an endometrial thickness of 21.1 mm at month 6 but had a measurement of 5.8 mm 14 days later. No additional narrative was provided.

One subject in the extension trial Study M12-667 had endometrial thickness > 18 mm detected by TVU at month 6. Subject (b) (6) who received placebo during the controlled trial in Study 665 and elagolix 150 mg QD during Study 667, had an endometrial thickness of 19.0 mm on day 169. An endometrial biopsy showed secretory endometrium.

Two subjects in the placebo/elagolix 200 mg BID group had endometrial thickness > 18 mm detected by TVU at month 6 in extension study M12-821. Subject (b) (6) had an endometrial thickness of 26.0 mm on post-treatment day 178. However, the endometrial thickness following her menstrual period was only 7.4 mm. Subject (b) (6) had a similar set of events with an endometrial thickness of 20.2 mm on day 176 (last dosing day) which resolved to a measurement of 7.4 mm after her menstrual period.

The previously listed subjects who had an endometrial thickness > 18 mm either had a subsequent thickness < 18 mm or had a normal biopsy or showed no clinical symptoms precluding entering the extension phase. Since elagolix does not always inhibit ovulation there may be some women who manifest a hyper-secretory effect with increased thickening. There also may be variations in the ultrasound reading. There is no evidence of a safety signal for any of these subjects.

Endometrial Biopsy

Endometrial biopsies were routinely obtained and evaluated in only one of the pivotal studies, Study M12-665. There were no post-baseline adverse biopsy findings, such as hyperplasia or cancer, in any treatment group. The biopsy results at baseline and 6 months are shown in Table 85 below:

Table 85. Endometrial Biopsy Results in Study M12-665

Diagnostic Category/Endometrium	Number (%) of Subjects		
	Placebo N = 374	Elagolix 150 mg QD N = 249	Elagolix 200 mg BID N = 248
Baseline			
Any biopsy result	373 (99.7)	246 (98.8)	248 (100)
Normal quiescent or minimally stimulated	10 (2.7)	8 (3.2)	4 (1.6)
Proliferative	200 (53.5)	131 (52.6)	143 (57.7)
Normal secretory/mixed/breakdown/menstrual	156 (41.7)	98 (39.4)	93 (37.5)
Hyperplasia	0	1 (0.4)	0
Reactive/inflammatory	0	0	0
Polyp	0	3 ^a (1.2)	0
Tissue insufficient for diagnosis	3 (0.8)	1 (0.4)	5 (2.0)
Month 6			
Any biopsy result	282 (75.4)	186 (74.7)	176 (71.0)
Normal quiescent or minimally stimulated	6 (1.6)	26 (10.4)	107 (43.1)
Proliferative	129 (34.5)	105 (42.2)	46 (18.5)
Normal secretory/mixed/breakdown/menstrual	141 (37.7)	51 (20.5)	12 (4.8)
Reactive/inflammatory	0	1 ^b (0.4)	0
Polyp	2 ^a (0.5)	0	0
Tissue insufficient for diagnosis	5 (1.3)	4 (1.6)	15 (6.0)

Source: M12-665 Clinical Study Report; Table 123; page 536 of 8446

We concur with the Applicant’s assessment of the pathology changes in the endometrium for subjects taking elagolix. Quiescent endometrium generally shows a paucity of mitotic activity and is associated with lower levels of estrogen. There appeared to be one case of endometrial hyperplasia listed in M12-667 that was identified as an on-treatment event for subject (b) (6). A case narrative was requested and received from the Applicant on January 29, 2018. This subject was a 45-year-old white female at the time of entry into the pivotal study M12-665. She received placebo in the pivotal study for 169 days, followed by elagolix 200 mg BID for an additional 169 days in extension Study M12-667. She had a normal endometrial biopsy in the pivotal study, M12-665. The subject had normal biopsy findings of proliferative endometrium at the end of Study M12-665 and benign endometrium findings with scant material at the end of extension Study M12-667. Endometrial thickness at the time of the adverse event, day 190, was 11.6 mm. Endometrial biopsy results for this subject showed scant fragments of benign endometrium on day 167. The Applicant concluded the adverse event was “physiologic;” the event should have been termed “endometrial hypertrophy” rather than hyperplasia.

We concur with the Applicant’s assessment that this case event should have been termed endometrial hypertrophy.

8.2.5.6. Uterine Bleeding

Uterine bleeding was recorded by subjects in their daily e-Diary. Subject recorded "yes" or "no" for uterine bleeding in the last 24 hours, then if yes, rated any bleeding intensity as spotting, light, medium, or heavy.

The mean number of bleeding or spotting days at month 6 was 5.9 days for placebo, 5.0 days for elagolix 150 mg QD, and 3.3 days for elagolix 200 mg BID. The number of subjects who reported any bleeding/spotting days in the elagolix 200 mg BID group markedly decreased after month 1.

Bleeding intensity evaluation showed that elagolix reduced the mean number of days relative to placebo in all bleeding categories including spotting, light, medium, and heavy bleeding throughout the 6-month treatment period, as shown in Table 86. The number of days with no bleeding increased particularly for the 200 mg BID dosage.

Table 86. Mean Bleeding Intensity Scores Based on 28-Day Intervals During the Treatment Period (Phase 3 Endometriosis Controlled Analysis Set)

Study Days	Placebo		Elagolix 150 mg QD		Elagolix 200 mg BID	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
-28 to -1 (Baseline)	626	2.6 (0.63)	405	2.6 (0.65)	423	2.5 (0.66)
1 to 28 (Month 1)	580	2.4 (0.64)	362	2.0 (0.71)	362	1.8 (0.66)
29 to 56 (Month 2)	556	2.4 (0.67)	263	2.1 (0.78)	94	1.9 (0.88)
57 to 84 (Month 3)	527	2.4 (0.64)	250	2.2 (0.80)	81	2.0 (0.84)
85 to 112 (Month 4)	497	2.4 (0.64)	234	2.2 (0.73)	86	1.8 (0.78)
113 to 140 (Month 5)	474	2.4 (0.63)	235	2.2 (0.76)	72	2.0 (0.78)
141 to 168 (Month 6)	423	2.3 (0.65)	246	2.0 (0.77)	108	1.8 (0.87)

Source: Reproduced from Integrated Summary of Safety; Table 100; page 361 of 5658
 Note: Bleeding intensity scores ranged from 1 to 4, where 1 = spotting, 2 = light, 3 = medium and 4 = heavy

With regard to absence of menses, the Applicant stated the following in the clinical overview: "Given that the absence of menses is not the same as the absence of ovulation, and the proposed contraindications associated with pregnancy, patients will be informed on how to watch for other signs of pregnancy such as breast tenderness, weight gain, and nausea through the patient information leaflet as well as through encounters with health care professionals, informed by the proposed prescribing information."

Appropriate labeling (a Warning and Precaution for health care providers and information in the medication guide for patients) will be needed to address this situation. Specific bleeding adverse events such as amenorrhea, metrorrhagia and menorrhagia will be compared against placebo in the following section.

8.2.5.7. Other Genital and Breast Adverse Events

Selected preferred terms from the reproductive system and breast disorders SOC are shown in Table 87 below.

Table 87. Number and Percentage of Subjects with Treatment-Emergent Adverse Events – Reproductive System and Breast Disorders SOC (Phase 3 Endometriosis Controlled Analysis Set)

System Organ Class/ MedDRA 19.1 Preferred Term	Placebo (N = 734) n (%)	Elagolix		Overall (N = 952) n (%)
		150 mg QD (N = 475) n (%)	200 mg BID (N = 477) n (%)	
Amenorrhea	2 (0.3)	19 (4.0)	34 (7.1)	53 (5.6)
Atrophic vulvovaginitis	0	0	1 (0.2)	1 (0.1)
Breast cyst	2 (0.3)	1 (0.2)	5 (1.0)	6 (0.6)
Breast tenderness	10 (1.4)	2 (0.4)	3 (0.6)	5 (0.5)
Dysmenorrhea	11 (1.5)	5 (1.1)	3 (0.6)	8 (0.8)
Dyspareunia	3 (0.4)	2 (0.4)	5 (1.0)	7 (0.7)
Endometriosis	17 (2.3)	13 (2.7)	7 (1.5)	20 (2.1)
Fibrocystic breast disease	1 (0.1)	0	2 (0.4)	2 (0.2)
Menorrhagia	10 (1.4)	8 (1.7)	4 (0.8)	12 (1.3)
Menstruation irregular	1 (0.1)	1 (0.2)	2 (0.4)	3 (0.3)
Metrorrhagia	0	3 (0.6)	5 (1.0)	8 (0.8)
Ovarian cyst	19 (2.6)	7 (1.5)	2 (0.4)	9 (0.9)
Pelvic pain	22 (3.0)	12 (2.5)	12 (2.5)	24 (2.5)
Sexual dysfunction	0	0	3 (0.6)	3 (0.3)
Uterine hemorrhage	1 (0.1)	1 (0.2)	0	1 (0.1)
Uterine polyp	1 (0.1)	6 (1.3)	1 (0.2)	7 (0.7)
Vaginal discharge	3 (0.4)	5 (1.1)	0	5 (0.5)
Vaginal hemorrhage	3 (0.4)	10 (2.1)	9 (1.9)	19 (2.0)
Vulvovaginal dryness	5 (0.7)	7 (1.5)	11 (2.3)	18 (1.9)

Source Table 2.1_1.2.1, ISS, pages 977-9 of 5658

BID = twice daily, QD = once daily, SOC = system organ class

The amenorrhea findings are expected due to the mechanism of action for elagolix. Although there was only one event of atrophic vulvovaginitis, there appears to be a slight dose-related effect regarding vulvovaginal dryness. Dysmenorrhea, endometriosis and pelvic pain events are consistent with the study population. Dyspareunia is somewhat more difficult to judge since only deep dyspareunia is related to endometriosis. The adverse event percentages for menorrhagia and metrorrhagia seem to correspond to the mechanism of action for elagolix. It is difficult to assess the vaginal hemorrhage percentages without additional information on quantity and timing in the cycle. The information on uterine bleeding in the previous section based on diary information may be somewhat more reliable because of a shorter recall. It is very unlikely that the percentage for uterine polyps correlates at all with the lower dose elagolix.

8.2.6. Safety Analyses by Demographic Subgroups

Endometriosis is a condition affecting premenopausal women and the clinical development for elagolix specifically studied this group beginning at age 18. As opposed to uterine fibroids, endometriosis is more common in the Caucasian population compared to the African American

population. Although endometriosis is sometimes diagnosed in late adolescence, the number with moderate to severe disease would be very small. There did not appear to be any elagolix safety signals indicating demographic influence (at least for non-bone loss safety).

8.2.7. Specific Safety Studies/Clinical Trials

Bone Mineral Density (BMD)

Elagolix reduces estrogen in a dose-dependent manner. Declines in estrogen levels are associated with an increase in bone resorption that may exceed bone formation and can result in bone loss. Therefore, elagolix may have a negative impact on bone health. Accordingly, changes in BMD during treatment as well as post-treatment were a safety endpoint of interest.

BMD Study Protocol

In the placebo-controlled pivotal trials M12-665 and M12-671, measurements of BMD were performed in all subjects at baseline and at month 6. Subjects who discontinued study drug prematurely were required to have a DXA scan at the Premature Discontinuation visit, unless they discontinued prior to month 3. The month 6 BMD assessment was obtained between study days 141 and 196, inclusive, and had to be no more than 28 days after the last dose of study drug; a minimum exposure to study drug of 140 days was also required. Therefore, subjects who discontinued study drug prematurely, but met the above month 6 BMD inclusion criteria, were included in the BMD analysis. Note that the inclusion of subjects with less than 6 months of elagolix exposure at the month 6 BMD analysis, may underestimate the decline in BMD on therapy. A repeat DXA scan was performed if the subject had $\geq 5\%$ decline in BMD at the lumbar spine or total hip. The lower of the two measurements was used for analysis. A central imaging contractor ((b) (6) for trials M12-665 and M12-667 and (b) (6) for trials M12-671 and M12-821) coordinated the longitudinal calibration of scanners and performed treatment-blinded readings. A correction factor, based on site-specific calibration data, was applied to all submitted BMD data. Subjects were counseled at every visit on the importance of taking calcium 500 to 1000 mg and vitamin D 400 IU daily.

The BMD exclusion criterion for participation in the extension trials was bone loss of $\geq 8\%$ at any anatomic site during the pivotal trial. Subjects who did not enter the extension trials (e.g., those who discontinued investigational drug, declined participation, or did not qualify), entered the PTFU for up to 12 months.

DXA scans for BMD assessment were performed at month 6 of the extension trials according to the procedures described above for the pivotal trials. In addition, subjects who had $\geq 5\%$ and $< 8\%$ decline in BMD at any anatomic site after 6 months of treatment in the pivotal trials were required to have DXA scans in duplicate at month 3 of the extension trial and discontinue the study if they had a decline in BMD of $\geq 8\%$ at any anatomic site. At the end of the 6-month extension trial treatment period, subjects entered the PTFU period as described below.

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Note that lack of a control arm during the extension study limits the interpretation of changes at one year of treatment since younger subjects (typically < 30 years of age), who have not yet attained peak bone mass, would be expected to experience an increase in BMD over time.

Post-Treatment Follow Up Period:

Subjects could enter the PTFU directly from the pivotal placebo-controlled Phase 3 trials or from their extension trials. For the pivotal trials and extension trial M12-667, subjects with bone loss of > 1.5% at the spine and/or > 2.5% at the total hip at month 6 of treatment who entered the PTFU period were required to have a DXA scan at PTFU month 6. In trial M12-821, all subjects were required to enter the PTFU period. DXA scans obtained between days 141 and 196 after the last dose of elagolix were included in the PTFU month 6 BMD analysis. After completing a minimum of 6 months in the PTFU period, a subject was considered to have completed the study if her menses had returned and she demonstrated adequate bone recovery, which was defined as $\leq 1.5\%$ bone loss in the spine and $\leq 2.5\%$ bone loss in the total hip compared with pretreatment baseline. All other subjects continued to return for visits through PTFU month 12, until return to menses and adequate bone recovery (if applicable) had been demonstrated. DXA scans were performed again at month 12. DXA scans obtained > 308 days after the last dose of elagolix were included in the PTFU month 12 BMD analysis. Subjects who had $\geq 3\%$ bone loss at any site at the end of the study (month 12 of the PTFU period) were to be referred to a bone specialist. Subjects were permitted to resume medications on the prohibited medication list (see Table 88) after 3 months into the PTFU period.

Table 88. Prohibited Medications During Elagolix Treatment and First 3 Months of PTFU Period

Prohibited during the Washout, Screening and Treatment Periods and during the first 3 months of the PTFU Period	
Hormonal medications and nonhormonal estrogen supplements, such as:	GnRH agonist (leuprolide acetate (Lupron [®]), nafarelin acetate (Synarel [®]), goserelin acetate (Zoladex [®]) GnRH antagonists (other than elagolix) Danazol (Danocrine [®] , Cyclomen [®]) Medroxyprogesterone acetate (Depo-Provera [®] , Provera [®]) Oral contraceptives Other progestins (oral, vaginal, IUDs, implantable) Levonorgestrel (except emergency contraception, i.e., levonorgestrel 1.5 mg) Spironolactone Mifepristone Testosterone preparations Glucocorticoids, oral or injectable Tamoxifen Bromocriptine (Parlodel [®]) Cabergoline (Dostinex [®]) Raloxifene (Evista [®]) Aromatase inhibitors [e.g., anastrozole (Arimidex [®]), exemestane (Aromasin [®]), letrozole (Femara [®])] Natural estrogen preparations (e.g., soy-containing supplements, black cohosh)
Prohibited during Screening and Treatment Periods and during the first 3 months of the PTFU Period	
Cytochrome P450 (CYP) inducers, such as:	St. John's Wort Rifabutin Rifampin Carbamazepine Phenytoin Dexamethasone Phenobarbital

GnRH = gonadotropin-releasing hormone, IUD = intrauterine device, PTFU = post-treatment follow-up

Most of these prohibited drugs that subjects could resume 3 months into the PTFU could impact BMD results. The Applicant was asked to also analyze the BMD data during the PTFU period excluding subjects who took medications that could impact BMD.

Subjects:

Key exclusion criteria with respect to bone health included diagnosis of or treatment for osteoporosis, baseline DXA screening BMD Z-score ≤ -1.5 at any site [lumbar spine (L1-4), total hip or femoral neck], underlying conditions that would interfere with obtaining an adequate BMD measurement, underlying conditions associated with bone loss such as hyperparathyroidism, anorexia nervosa or glucocorticoid excess, known bone disease such as osteomalacia or osteogenesis imperfecta, low trauma spine or hip fracture, pathologic fracture, or disturbances in calcium or phosphate. Women who had a decline in BMD from baseline of $\geq 8\%$ at any site were excluded from entering the extension trials.

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Bone Safety Endpoints of Interest:

Change in BMD from baseline to treatment month 6 and 12.

Change in BMD during post-treatment for up to 12 months.

Fracture was an adverse event of special interest, and was further evaluated with the use of follow-up questionnaires.

Statistical Analysis for BMD Endpoints:

In the pivotal controlled trials, mean percent changes from baseline was summarized for each treatment group with descriptive statistics and analyzed using a one-way ANOVA, with treatment group as the main effect. Comparisons between each elagolix dose group and placebo group were performed using Fisher's exact test. Descriptive statistics were used to summarize changes in BMD according to treatment group for the extension trials. A categorical analysis of changes in BMD from baseline on treatment and from end of treatment to PTFU months 6 and 12 were also done. A categorical summary of Z-scores and T-scores was also provided.

Results

Baseline characteristics of the subjects included in the BMD analyses are shown in Table 89.

Table 89. Baseline Characteristics of Subjects Who Participated in the BMD Analysis

	M12-665 (N = 640)		M12-667 (N = 385)		M12-671 (N = 628)		M12-821 (N = 408)	
	Mean (SD)	Range (min, max)	Mean (SD)	Range (min, max)	Mean (SD)	Range (min, max)	Mean (SD)	Range (min, max)
Age, yrs	32 (6.3)	18, 48	32 (6.2)	19, 48	33 (6.8)	18, 49	34 (6.9)	18, 49
BMI, kg/m ²	28* (6.3)	17, 53	28** (6.4)	17, 53	27*** (6.7)	16, 54	27 ^a (6.6)	16, 48
BMD Z-score ^b								
Lumbar spine	0.5 (1.0)	-1.7, 4.4	0.6 (1.0)	-1.6, 4.5	0.4 (1.0)	-1.4, 4.0	0.4 (1.0)	-1.4, 4.0
Total hip	0.4 (0.9)	-1.4, 3.8	0.5 (0.9)	-1.3, 4.5	0.3 (0.9)	-1.5, 4.1	0.4 (0.9)	-1.4, 3.0
Femoral neck	0.3 (0.9)	-1.5, 4.7	0.3 (0.9)	-1.6, 3.9	0.4 (1.0)	-1.4, 4.7	0.4 (1.0)	-1.4, 3.4
	Number	%	Number	%	Number	%	Number	%
Race								
Caucasian	575	88.5%	350	89.3%	564	89.8%	372	91.2%
Black	48	7.4%	33	8.4%	52	8.3%	31	7.6%
Other	27	4.1%	9	2.3%	12	1.9%	5	1.2%
Current smoker	166	25.5%	101	25.8%	133	21.2%	80	19.6%
Current drinker	497	76.5%	307	78.3%	389	62.3%	267	65.4%
	Source: Tables 665_3.1, 665_3.2, 665_3.3, 665_4.20.3.1.99		Source: Tables 667_3.1, 667_3.2, 667_3.3, 667_4.20.3.1.99		Source: Tables 671_3.1, 671_3.2, 671_3.3, 671_4.20.3.1.99		Source: Tables 821_3.1, 821_3.2, 821_3.3, 821_4.20.3.1.99	

^a missing information for 1 subject in PBO/Ela 200 group

^b Data excludes subjects who switched DXA machine manufacturers

* missing information for 2 subjects in the Ela 200 group

** missing information for 1 subject in the Ela/Ela 200 group

*** missing information for 2 subjects in placebo, 1 in Ela 150 and 1 in Ela 200 groups

Subject Disposition

The disposition of subjects in each study as it pertains to the BMD analyses is presented in Table 90 and Table 91 below. A small number of subjects ($\leq 1\%$ of subjects in each trial arm for study M12-665, $\leq 2\%$ in M12-667, and 0 subjects in studies M12-671 and M12-821) had DXA scans performed on machines from different manufacturers (GE Lunar versus Hologic) during the trial. Because machines were not cross-calibrated, these subjects were excluded from the BMD analyses, unless otherwise specified. Two percent of subjects included the PTFU month 6 BMD analysis and 0 to 1% of subjects included in the PTFU month 12 BMD analysis for each study had a DXA scan at that time point that was not required according to the protocol.

In study M12-665, 23 subjects (3 (1%) receiving placebo, 5 (2%) receiving elagolix 150 mg QD and 15 (6%) receiving elagolix 200 mg BID) were ineligible to enter the extension trials due to bone loss $\geq 8\%$. In study M12-671, 11 subjects (none receiving placebo, 1 ($< 1\%$) receiving elagolix 150 mg QD and 10 (4%) receiving elagolix 200 mg BID) were ineligible to enter the extension trials due to bone loss $\geq 8\%$. In extension trial M12-667, seven subjects (one (1%) in the elagolix/elagolix 150 QD group and six (4%) in the elagolix/elagolix 200 mg BID group) discontinued the study drug early due to bone loss. In extension trial M12-821, four subjects (3%), all from the elagolix/elagolix 200 mg BID group, discontinued study drug early due to bone loss. The mean age of subjects in each study with $\geq 8\%$ decline in BMD did not differ from study subjects as a whole. No subject discontinued the study during treatment or the PTFU period due to fracture.

Table 90. Subject Disposition for Pivotal Trial M12-665 and Extension Trial M12-667^a

	Placebo N (%)	Elagolix 150 mg QD N (%)	Elagolix 200 mg BID N (%)	Total N (%)
Trial M12-665: Treatment Period				
Randomized and treated	374	249	248	871
Discontinued treatment	100 (27)	53 (21)	65 (26)	218 (25)
Discontinued due to bone loss or fracture	0	0	0	0
Completed month 6 DXA scan*	282 (75)	186 (75)	182 (73)	650 (75)
Ineligible to Enter Extension based on BMD loss $> 8\%$	3 (1)	5 (2)	15 (6)	23 (3)
Trial M12-665: PTFU Period				
Entered PTFU period	68 (18)	48 (19)	51 (21)	167 (19)
Completed PTFU month 6 DXA scan*	16 (4)	16 (6)	30 (12)	62 (7)
Met stop criteria/completed PTFU month 6 ^b	46 (12)	26 (10)	18 (7)**	90 (10)
Completed PTFU month 12 DXA scan*	3 (1)	5 (2)	21 (8)	28 (3)
Premature discontinuation	20 (5)	17 (7)	14 (6)	51 (6)
Completed PTFU month 12	2 (1)	5 (2)	19 (13)	26 (3)

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	Placebo N (%)		Elagolix 150 mg QD N (%)	Elagolix 200 mg BID N (%)	Total N (%)
Trial M12-667 Extension Treatment Period					
Entered Extension Trial and treated	217		149	138	504
	150 mg QD N=108	200 mg BID N=109			
Discontinued treatment	21 (19)	26 (24)	33 (22)	28 (20)	47 (9)
Discontinued due to bone loss	0	0	1 (1)	6 (4)	7 (1)
Completed month 12 DXA scan*	86 (80)	84 (77)	114 (77)	108 (78)	392 (78)
Trial M12-667: PTFU Period					
Entered PTFU period	86 (80)	87 (80)	126 (85)	118 (86)	417 (83)
Completed PTFU month 6 DXA scan*	29 (27)	49 (45)	45 (30)	84 (61)	207 (41)
Met stop criteria at month 6 follow-up ^b	54 (50)	48 (44)	75 (50)	33 (24)	210 (42)
Premature Discontinuation	20 (19)	20 (18)	29 (19)	35 (25)	104 (21)
Early discontinuation due to meeting stop criteria ^b	1 (0.1)	0	0	0	1 (0.2)
Completed PTFU month 12 DXA scan*	14 (13)	25 (23)	28 (19)	64 (46)	131 (26)
Completed month 12 follow-up	12 (11)	19 (17)	22 (15)	50 (36)	103 (20)

Source: M12-665 Study report Table 12, age 263, CSR Table 12.1__1.2.2, 14.4__1.1, 14.1__1.3.1, 14.3__4.20.8.1 Table 14 page 268, CSR Tables 14.1__1.1, 14.2__1.3.1, 14.1__1.3.2, Study M12-667 Table 11, CSR Table 14.1__1.1, Table 14.1__1.2.2, 14.3__4.20.8.1, 14.3__4.20.8.2

^a Percentages are of those subjects treated in each study phase, pivotal and then extension

^b Stop criteria at PTFU month 6 was defined having had a PTFU visit month 6, return of menses and BMD loss $\leq 1.5\%$ for the spine and $\leq 2.5\%$ for the total hip.

* Includes subjects who discontinued study drug prematurely, but met criteria for inclusion in designated BMD analysis

** nominal P < 0.001 vs. placebo using Fisher's Exact Test.

Table 91. Subject Disposition for Pivotal Trial M12-671 and Extension Trial M12-821^a

	Placebo		Elagolix 150 mg QD	Elagolix 200 mg BID	Total
	N (%)		N (%)	N (%)	N (%)
Trial M12-671: Treatment Period					
Randomized and treated	360		226	229	815
Discontinued treatment	90 (25)		48 (21)	45 (20)	183 (23)
Discontinued due to bone loss or fracture	0		0	0	0
Completed month 6 DXA scan*	271 (75)		174 (77)	183 (80)	628 (77)
Ineligible to Enter Extension based on BMD loss $\geq$ 8%	0		1 (0.4)	10 (4)**	11 (1)
Trial M12-671: PTFU Period					
Entered PTFU period	61 (17)		40 (18)	54 (24)	155 (19)
Completed PTFU month 6 DXA scan*	16 (4)		15 (7)	25 (11)	56 (7)
Met stop criteria/completed PTFU month 6 ^b	42 (12)		24 (11)	18 (8)	84 (10)
Completed PTFU month 12 DXA scan*	0		4 (2)	17 (7)	21 (3)
Premature discontinuation	18 (5)		12 (5)	20 (9)	50 (6)
Completed PTFU month 12	0		4 (2)	15 (7)	19 (2)
Trial M12-821 Extension Treatment Period					
Entered Extension Trial and treated	213		142	140	495
	150 mg N=102	200 mg N=111			
Discontinued treatment	20 (20)	12 (11)	22 (16)	28 (20)	82 (17)
Discontinued due to bone loss	0	0	0	4 (3)	4 (1)
Completed month 12 DXA scan*	78 (77)	100 (90)	121 (84)	109 (78)	408 (82)
Trial M12-821: PTFU Period					
Entered PTFU period	85 (83)	105 (95)	125 (88)	122 (87)	437 (88)
Completed PTFU month 6 DXA scan*	62 (61)	79 (71)	84 (82)	90 (64)	315 (64)
Met stop criteria at PTFU month 6 ^b	58 (57)	44 (40)	64 (46)	36 (26)	202 (41)
Premature Discontinuation	12 (12)	24 (22)	29 (20)	27 (19)	92 (19)
Early discontinuation due to meeting stop criteria ^b	0	0	0	0	0
Completed PTFU month 12 DXA scan*	16 (16)	36 (32)	31 (22)	60 (43)	143 (29)

Source: M12-671 Study report Tables 12 and 13, CSR Table 14.4_1.1, Table 14.1_1.2.2, Table 14.1_6.1.2.1, 14.3_4.20.8.1, M12-821 CSR Table 11, Table 12, Table 14.1_1.1, Table 14.1_1.2.2, Table 14.1_1.3.1, 14.1_1.3.2, 14.3_4.20.8.1, 14.3_4.20.8.2

No subject switched DXA machine manufacturers during these trials.

^a Percentages are of those subjects treated in each study phase, pivotal and then extension.

^b Stop criteria at PTFU month 6 was defined having had a PTFU visit month 6, return of menses and BMD loss $\leq$ 1.5% for the spine and $\leq$ 2.5% for the total hip.

* Includes subjects who discontinued study drug prematurely, but met criteria for inclusion in BMD analysis

** nominal P < 0.002 vs. placebo, nominal P < 0.01 for difference from placebo using Fisher's exact test.

The PTFU protocol selected for subjects with persistent declines in BMD from baseline and the stop criteria used did not allow for assessment of full recovery of BMD.

Changes in Bone Mineral Density on Treatment

As shown in Table 92 below, subjects who received placebo for 6 months in both pivotal studies had a modest increase in BMD at the lumbar spine and total hip. Subjects who received elagolix had a significant decline in BMD at all sites as compared to placebo treated subjects; the decline was greatest at the spine in the elagolix 200 mg BID group.

Table 92. Change in Bone Mineral Density at Month 6 of Treatment

	M12-665 ^a			M12-671 ^b		
	Placebo ^c	Elagolix 150 mg QD	Elagolix 200 mg BID	Placebo ^c	Elagolix 150 mg QD	Elagolix 200 mg BID
Lumbar Spine						
N	277	183	180	271	174	183
% change	0.51	-0.34	-2.57	0.56	-0.72	-2.49
Trt diff		-0.85	-3.08		-1.28	-3.04
95% CI		-1.34, -0.35	-3.58, -2.59		-1.75, -0.80	-3.51, -2.58
P-value ^d		0.001	< 0.001		< 0.001	< 0.001
Total Hip						
N	275	182	180	271	172	182
% change	0.21	-0.31	-1.53	0.58	-0.47	-1.58
Trt diff		-0.53	-1.75		-1.05	-2.16
95% CI		-0.91, -0.14	-2.14, -1.36		-1.46, -0.64	-2.57, -1.76
P-value		0.008	< 0.001		< 0.001	< 0.001
Femoral Neck						
N	275	182	180	271	172	182
% change	0.01	-0.45	-1.89	0.31	-0.35	-1.42
Trt diff		-0.46	-1.9		-0.66	-1.73
95% CI		-1.06, -0.14	-2.49, -1.30		-1.23	-2.28, -1.17
P-value		0.132	< 0.001		0.021	< 0.001

Trt diff = treatment difference compared to placebo, CI = confidence interval, BID = twice daily, QD = once daily

^a Source: Trial M12-665 CSR Table 14.3 4.20.1.2. One-way ANOVA was used to compare difference between treatment groups in baseline and percent mean change from baseline in study M12-665

^b Source: Trial M12-671 CSR Table 14.3 4.20.1.2. One-way ANOVA was used to compare difference between treatment groups in baseline and percent mean change from baseline in study M12-671 Placebo shows change from baseline

^c Placebo shows change from baseline

^d nominal P-value, compared to placebo

Declines in bone mineral density were most prominent at the spine, a site comprised of predominantly trabecular bone, and is consistent with bone loss associated with the decline in estrogen levels. Overall, in the 6-month placebo-controlled trials combined, subjects treated with elagolix 150 mg QD had a mean treatment difference at the lumbar spine of -1.07% (95% CI -1.41, -0.73) and subjects treated with elagolix 200 mg BID group had a mean treatment difference of -3.06% (95% CI -3.40, -2.72) (Source: ISS Table 5.1__1.2)

To evaluate the effects of elagolix on BMD for up to 12 months the results for each pivotal trial together with its corresponding extension study are presented in Table 93. Bone loss was not only related to dose, but also appeared to continue with increasing duration of use.

Table 93. Mean Percent Change in BMD from Baseline at Month 6 and Month 12 of Elagolix Treatment

	M12-665 and M12-667				M12-671 and M12-821			
	Elagolix 150 mg QD	PBO/Ela 150 mg QD	Elagolix 200 mg BID	PBO/Ela 200 mg BID	Elagolix 150 mg QD	PBO/Ela 150 mg QD	Elagolix 200 mg QD	PBO/Ela 200 mg QD
6 months elagolix treatment								
Lumbar Spine % (95% CI)	N = 183 -0.34 (-0.72, 0.05)	N = 86 -1.13 (-1.76, -0.50)	N = 180 -2.57 (-2.96, -2.19)	N = 82 -2.51 (-3.16, -1.87)	N = 174 -0.72 (-1.09, -0.35)	N = 78 -1.15 (-1.84, -0.47)	N = 183 -2.49 (-2.85, -2.13)	N = 100 -2.62 (-3.23, -2.02)
Total Hip % (95% CI)	N = 182 -0.31 (-0.61, -0.01)	N = 86 -0.33 (-0.84, 0.19)	N = 180 -1.53 (-1.84, -1.23)	N = 82 -1.36 (-1.89, -0.83)	N = 172 -0.47 (-0.79, -0.15)	N = 77 -0.41 (-0.99, 0.17)	N = 182 -1.58 (-1.90, -1.27)	N = 99 -1.76 (-2.27, -1.25)
Femoral Neck % (95% CI)	N = 182 -0.45 (-0.91, 0.01)	N = 86 -0.50 (-1.26, 0.26)	N = 180 -1.89 (-2.35, -1.42)	N = 82 -0.93 (-1.71, -0.15)	N = 172 -0.35 (-0.79, 0.09)	N = 77 -0.59 (-1.36, 0.17)	N = 182 -1.42 (-1.84, -0.99)	N = 99 -1.43 (-2.10, -0.76)
12 months elagolix treatment								
Lumbar Spine % (95% CI)	N = 112 -0.77 (-1.32, -0.22)		N = 105 -3.50 (-4.07, -2.93)		N = 121 -1.10 (-1.65, -0.55)		N = 109 -3.91 (-4.49, -3.33)	
Total Hip % (95% CI)	N = 112 -0.66 (-1.11, -0.20)		N = 104 -2.89 (-3.36, -2.42)		N = 121 -0.81 (-1.27, -0.35)		N = 108 -2.56 (-3.05, -2.07)	
Femoral Neck % (95% CI)	N = 112 -0.88 (-1.54, -0.21)		N = 104 -2.57 (-3.26, -1.88)		N = 121 -0.87 (-1.48, -0.26)		N = 108 -2.27 (-2.91, -1.62)	

Source CSR Study M12-665 Table 14.3__4.20.1.2 and M12-667 Table 14.3__4.20.1.2

Baseline BMD was defined as pretreatment baseline for subjects on continuous treatment through trials M12-665 and M12-667, and as M12-665 month 6 BMD for subjects on placebo during trial M12-665.

Source CSR Study M12-671 Table 14.3__4.20.1.2 and M12-821 Table 14.3__4.20.1.2

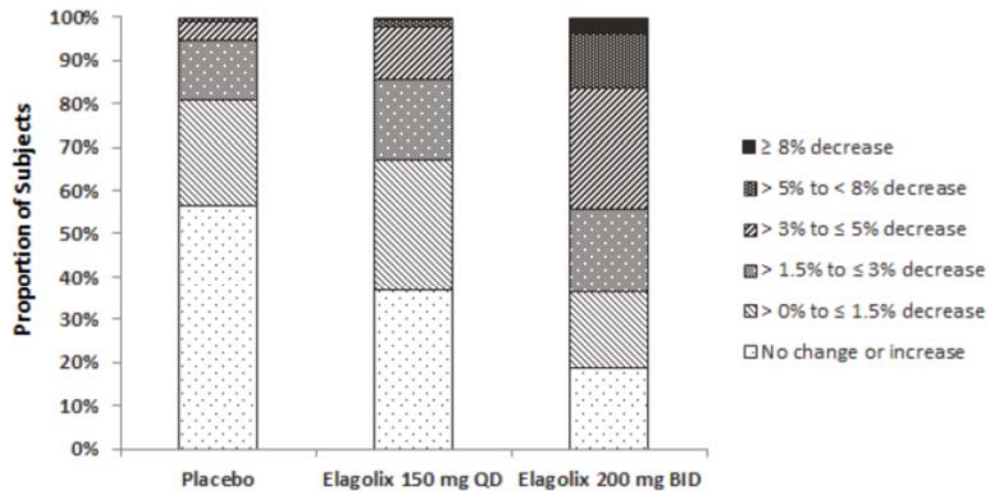
Baseline BMD was defined as pretreatment baseline for subjects on continuous treatment through trials M12-671 and M12-821, and as M12-671 month 6 BMD for subjects on placebo during trial M12-671.

BID = twice daily, BMD = bone mineral density, CI = confidence interval, QD = once daily

Categorical Analysis of Percent Change in BMD

The Applicant also presented the distribution of percent change in BMD according to categories of bone loss for each study, as requested by FDA. Differences in patterns of bone loss began to emerge by month 6 in both treatment arms. Figure 18 and Figure 19 illustrate changes in the distribution of categorical bone loss at the spine for study M12-671 and its extension M12-821. Higher doses and longer duration of treatment was associated with a greater proportion of subjects having declines in BMD and more subjects with $\geq 5\%$ decline in BMD.

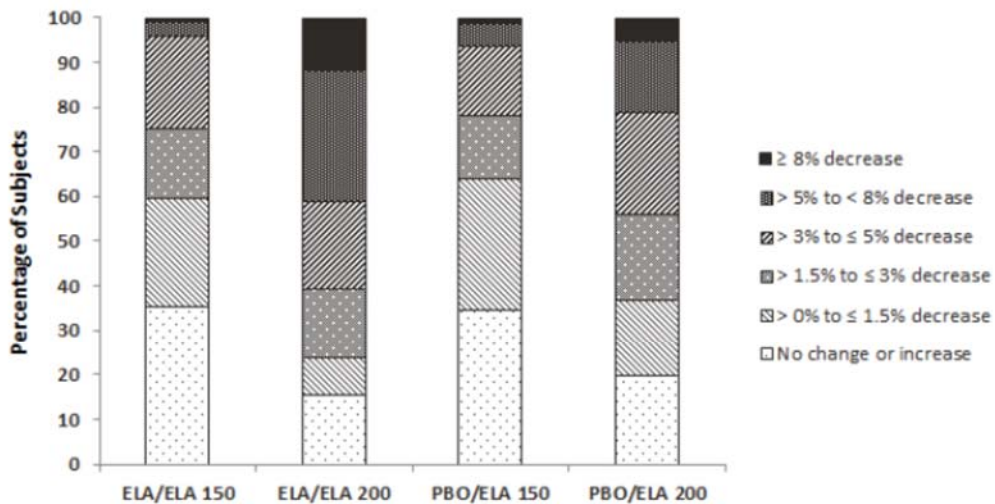
Figure 18. Categorical Summary of Percent Change from Baseline to Month 6 of Treatment for Lumbar Spine BMD in Study M12-671



Cross reference: [Table 14.3_4.20.2.1](#)

Source: M12-671 CSR Figure 21

Figure 19. Categorical Summary of Percent Change from Baseline to Month 12 of Treatment for Lumbar Spine BMD in Extension Study M12-821



ELA/ELA = Elagolix in pivotal Study M12-671; elagolix (same dosage) in this extension Study M12-821.

PBO/ELA = Placebo in pivotal Study M12-671; elagolix in this extension Study M12-821.

Baseline = last value prior to the first dose of elagolix in Study M12-671 for ELA/ELA groups; end of PBO treatment in Study M12-671 for PBO/ELA groups.

Cross reference: [Table 14.3_4.20.2.1](#)

Source: M12-821 CSR Figure 31

During the pivotal trials combined, a decline in BMD of $\geq 8\%$ at any anatomic site occurred in 2 (0.4%) subjects in the placebo arm, 5 (1%) in the elagolix 150 mg QD arm and 24 (6%) in the elagolix 200 mg BID arm. During the extension studies combined, 12 (5%) additional patients

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receiving elagolix 150 mg QD and 51 (21%) additional patients receiving elagolix 200 mg BID had bone loss $\geq 8\%$ at any site compared to pre-treatment baseline.

Advancing age did not appear to be associated with greater bone loss. Lower BMI, however, was associated with greater bone loss in subjects treated with elagolix 200 mg BID. The percentage of subjects with a decrease in BMD of $> 5\%$ to $< 8\%$ and $\geq 8\%$ was higher in the lower BMI subsets ($< 25 \text{ kg/m}^2$ and $25 - < 30 \text{ kg/m}^2$) in each of the three anatomic locations at month 6 of treatment and higher in the lowest BMI subset ($< 25 \text{ kg/m}^2$) at month 12 (ISS Tables 90, Cross reference: Table 5.1__18.1, Table 5.1__19.1, Table 5.1__20.1, Table 5.1__21.1; Table 91, Cross reference: Table 5.2__18, Table 5.2__19, Table 5.2__20, Table 5.2__21; treatment (ISS Table 92, Cross reference: Table 5.1__25.1, Table 5.1__26.1, Table 5.1__27.1; ISS Table 93, Cross reference: Table 5.2__25, Table 5.2__26, Table 5.2__27).

The Applicant stated that

(b) (4)

We disagree with the Applicant's interpretation of clinically meaningful bone loss. Decline in BMD at a time when subjects in the placebo arm were gaining BMD is clinically important. A decline in BMD of $\geq 8\%$ over 6-12 months is clearly accelerated. However, the potential impact of bone loss in premenopausal women, with respect to lack of attainment of peak bone density and fracture risk later in life is uncertain.

Z-score Analysis

An analysis of categorical change in Z-score was also performed. Subjects were required to have a Z-score > -1.5 in order to be eligible to participate in the study, although seven Z-score measurements were actually ≤ -1.5 at entrance into the two pivotal trials. At the spine, the site of greatest bone loss, 94% of subjects in each active drug treatment arm had a Z-score > -1.0 at baseline. There was no change in this percentage after 6 and 12 months of treatment with elagolix 150 mg QD, whereas the percentage of subjects with a Z-score > -1.0 declined to 89% after 6 months of elagolix 200 mg BID, and to 83% at 12 months. Correspondingly, the proportion of subjects with a Z-score in the range of ≤ -1.5 to > -2.0 increased from 0.7% (2 subjects) at baseline to 4.6% after 12 months of elagolix 200 mg BID. One subject in this treatment arm had a Z-score ≤ -2.0 at the spine (Source: ISS Table 83, Table 5.2__5.1).

The Z-score is a measure of the number of standard deviations above or below the age-matched mean for the reference population. In the clinical setting, the International Society for Clinical Densitometry recommends using the Z-score to interpret BMD in pre-menopausal women. A Z-score between -2.0 and $+2.0$ is within the expected range for age, and a Z-score ≤ -2.0 is below the expected range for age. The relationship between Z-score and fracture risk in the premenopausal women is not robust. Z-scores should not be used to predict fracture risk in

the manner that T-scores are used for postmenopausal women. In this study, over 90% of subjects had Z-scores > -1.0 at baseline. The Z-score at the end of treatment is dependent not only on bone loss, but also baseline BMD. Therefore, it is not unexpected that Z-scores for all but one subject remained within the expected range for age despite significant bone loss. Z-scores or change in Z-score categories do not inform risk for bone loss or recommendations for duration of treatment with elagolix. (b) (4)

Protocol violation: Systemic Glucocorticoid Use

Although systemic glucocorticoids were prohibited during the treatment phase and the first 3 months of the PTFU period, 6.6% of subjects in trial M12- 665 and 3.2% of subjects in trial M12-671 received systemic glucocorticoids while they were on elagolix treatment. In the extension trials, 5% of subjects in trial M12-667 and 4.2% of subjects in trial M12-821 received systemic glucocorticoids while on elagolix. Systemic glucocorticoids were defined as glucocorticoids received by oral, intravenous or intra-articular routes. Duration of use was less than 1 month for all but seven subjects. These seven subjects used systemic glucocorticoids for 1 to < 3 months. No subject used glucocorticoids for 3 months or more.

The use of prednisone 5 mg daily or more (or its equivalent) for ≥ 3 months is a risk factor for bone loss and fracture. The small number of subjects on elagolix treatment receiving glucocorticoids and the short duration of glucocorticoid use that occurred in these studies does not allow for meaningful interpretation of the impact on bone loss from concomitant elagolix and glucocorticoid use.

Calcium and Vitamin D Supplementation

Subjects were reminded to take calcium and vitamin D at each visit and intake was recorded. Overall, 83% of subjects included in the 6-month controlled BMD analysis and 86% of subjects included in the 12-month extension BMD analysis took one or both of these supplements. A post-hoc analysis suggested that after 12 months of treatment, the mean percent change in lumbar spine BMD from pre-treatment baseline for the Ela/Ela 150 mg QD subjects that did and did not take supplements was -0.78 (95% CI -1.23 to -0.33) as compared to -1.43 (95% CI -2.59 to -0.28), respectively. For the Ela/Ela 200 mg BID subjects that took supplements, mean percent change in lumbar spine BMD was -3.69 (95% CI -4.16 to -3.22) as compared to -4.17 (95% CI -5.34 to -3.00) for those that did not. However, confidence intervals were overlapping. (Source: ISS Table 5.2_1.1.99.1 and Table 5.2_1.1.99.2 from IR response 1/29/18).

This analysis has several other limitations including that it is a post-hoc analysis, subjects were not randomized to calcium/vitamin D versus “no supplementation,” and the number of subjects included in the “no supplementation” group is small. Furthermore, subjects who complied with recommendations for supplementation may have had other healthy lifestyle habits that may have benefited skeletal health. Although the results are inconclusive and calcium and vitamin D supplementation was not formally studied, it is reasonable to recommend adequate calcium

and vitamin D intake in labeling. This recommendation is consistent with the conduct of the study, standard preventative health measures, and standard recommendations for patients with risk factors for bone loss.

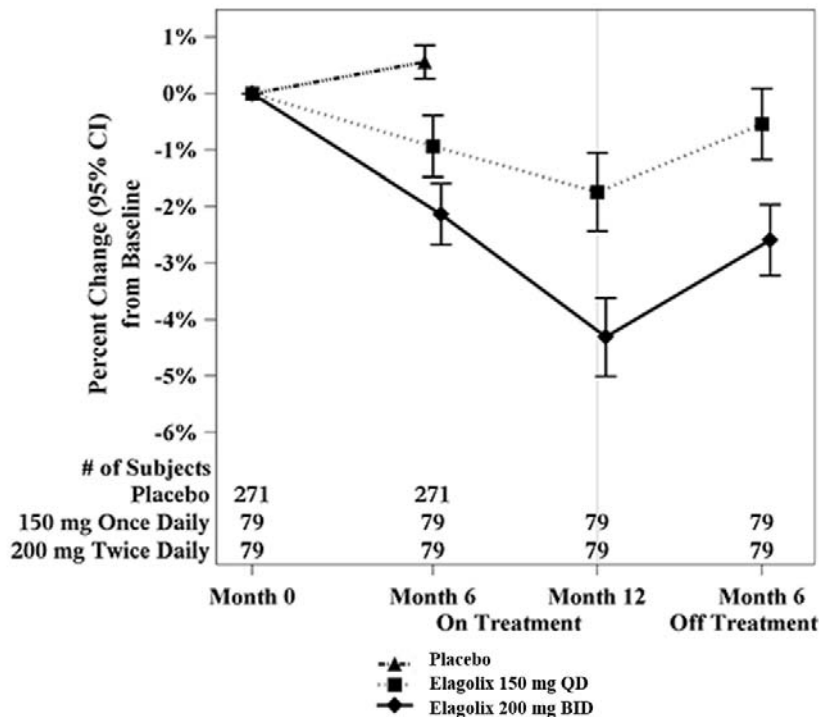
Post Treatment Follow-up Period

Pivotal Trials

Extension Trials

In extension study M12-667, the criteria for BMD monitoring during the PTFU period after 12 months of investigational drug was the same as those described above for the pivotal trials. For study M12-821, however, all subjects were required to have a PTFU month 6 DXA scan regardless of change in BMD after 12 months of investigational drug. The data for this group at PTFU month 6 is therefore more complete, and more representative of the entire cohort. Subsequently, only those subjects with persistent bone loss as defined for the pivotal trials above were required to have a PTFU month 12 scan. Mean percent change from pre-treatment baseline in lumbar spine BMD during 12 months of elagolix treatment and PTFU month 6 is shown in Figure 20 for subjects from studies M12-671 and M12-821 who had a DXA scan performed at all four timepoints. Change in BMD during the first 6 months of study M12-671 is also shown for placebo treated subjects.

Figure 20. Mean Percent Change from Baseline in Lumbar Spine BMD During 12 Months of Elagolix Treatment and 6 Months Post Treatment for Subjects from Study M12-671 and M12-821

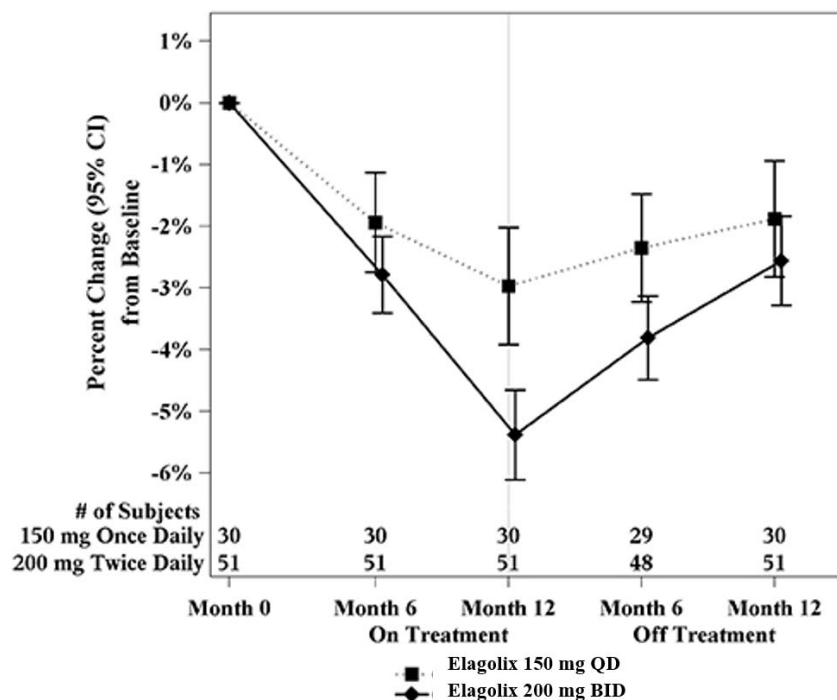


Source: M12-671 Table 14.3__4.20.1.2, and ISS Table 5.2__9.1.2.
 BID = twice daily, CI = confidence interval, QD = once daily
 Data shown for months 0 and 6 are from pivotal controlled trial M12-671. Data shown for month12 and PTFU (off-treatment) month 6 are from extension trial M12-821.

As discussed above, gains in BMD were seen in the placebo group over 6 months, while declines in BMD in a dose-dependent manner were observed for subjects receiving elagolix. At PTFU month 6, partial recovery of BMD was seen at the lumbar spine.

Mean percent change from baseline BMD at the lumbar spine is shown in Figure 21 for the subset of subjects who completed 12 months of elagolix treatment and had a PTFU month 12 DXA scan in extension study M12-821. Partial recovery in this subset of subjects was seen during 12 months of PTFU.

Figure 21. Mean Percent Change from Baseline in Lumbar Spine BMD During 12 Months of Elagolix Treatment and 12 Months Post Treatment for Subjects from Studies M12-671 and M12-821



Source: M12-671 Table 14.3_4.20.1.2 and ISS Table 5.2_9.2.2.

BID = twice daily, CI = confidence interval, QD = once daily

Data shown for months 0 and 6 are from pivotal controlled trial M12-671. Data shown for month 12 and PTFU (off-treatment) month 6 and 12 are from extension trial M12-821.

Clinicians should be informed of the risk of decline in BMD while on elagolix and that BMD loss may not be completely reversible after stopping elagolix and should be advised to consider monitoring BMD in patients with risk factors for bone loss. Whether ongoing or complete recovery would occur in either group beyond 12 months after stopping treatment is unknown.

Categorical Changes in BMD Post Treatment

In the extension trials, the percent recovery was assessed for subjects with BMD decreases from pre-treatment baseline to the final treatment value. The Applicant calculated percent recovery using the following formula: $100 \times (\% \text{ change from baseline to final treatment}) - (\%$

change from baseline to PTFU visit)/ (% change from baseline to final treatment). A negative value indicates that BMD declined off treatment.

Extension study M12-821 provides the most complete dataset to examine changes in BMD within the first 6 months post-treatment because all subjects were required to have a BMD at that timepoint (Source: M12-821 CSR Table 125). Twenty-three percent (14/60) of the subjects who entered extension study M12-821 were treated with elagolix 150 mg QD for up to 12 months, experienced a decrease in BMD from pre-treatment baseline to final BMD at the lumbar spine, and had a full recovery (> 100%) at PTFU month 6. For the group treated with elagolix 200 mg BID for a total of 12 months and experienced bone loss at the lumbar spine, full recovery (> 100%) was seen in 12% (9/74) of subjects at PTFU month 6.

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both extension trials, ongoing declines in BMD were seen in a small subset of subjects during the PTFU period. In response to an Information Request, the Applicant provided an analysis of all subjects with a decline in lumbar spine BMD from final BMD in the extension studies during the PTFU period, including those who had DXA scans on machines from different manufacturers. Approximately 86% of these 118 subjects had a decline of $\leq 3\%$, a range considered to be within the variability of the DXA measurement. Of those with > 3% decline in lumbar spine BMD (approximately 3% of the population with PTFU BMD data), the majority had at least 1 potential clinical risk factor or technical factor identified that might have contributed to the observed change in BMD. It is also noteworthy that, according to the Applicant, 6% of placebo-treated subjects in the pivotal trials had >3% decline in BMD from baseline to treatment month 6, suggesting background variability in the DXA measurements.

The PK and PD properties of elagolix do not support ongoing bone loss after discontinuation of elagolix. The half-life of elagolix is 4 to 6 hours and the drug is completely eliminated from plasma within 24 to 30 hours. Estradiol levels begin to rise within 48 hours of drug discontinuation and menses resume within 6 months of drug discontinuation for at least 95% of subjects treated for 6 months, suggesting normalization of estradiol levels. In addition, nonclinical studies did not demonstrate any off-target adverse bone effects. The potential confounding clinical and technical factors these subjects had, the PK and PD properties of elagolix, and the observed bone loss in placebo-treated subjects in the pivotal trials, suggest that factors other than prior elagolix treatment are responsible for the observed decline in BMD during post-treatment follow-up.

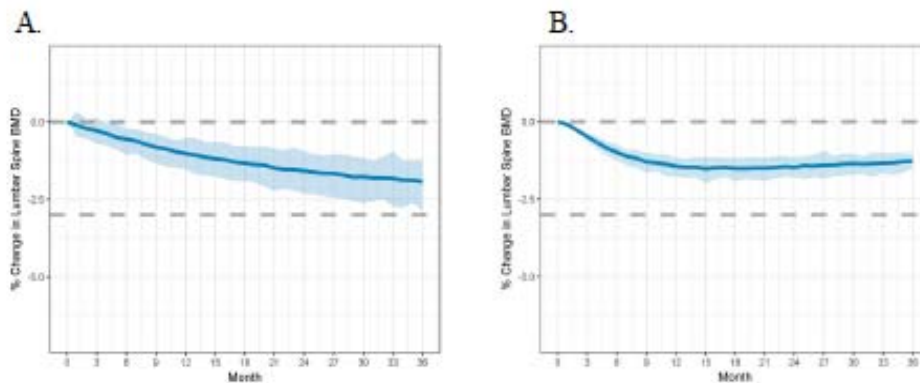
After PTFU month 3, subjects were permitted to take medications on the list of prohibited medications (Table 88). With one exception, the most commonly used medications were glucocorticoids. In study M12-821, the most commonly used medication for the Placebo/elagolix 150 mg QD arm was combination oral contraceptives which was used by 3/9 subjects who took a prohibited medication. In response to an Information Request, the Applicant re-calculated mean percent change in BMD excluding subjects who took “prohibited” medications that could impact BMD. The numbers of subjects included in this analysis was too small to draw conclusions. However, use of medications associated with bone loss was a

potential explanation for >3% decline in lumbar spine BMD off treatment for some of the subjects in the analysis described above.

Bone Mineral Density Simulation Modeling

The Applicant only has BMD data for 12 months of treatment with elagolix and proposed simulation modeling to predict changes in lumbar spine BMD with elagolix treatment beyond 12 months. At the late cycle meeting held on February 12, 2018, we requested simulations predicting what would happen with up to 36 months of elagolix treatment. BMD changes upon continuous dosing with elagolix 150 mg QD or 200 mg BID for 36 months were predicted using two approaches: Indirect response exposure-BMD model (R&D/17/0090 (Module 5, Section 5.3.4)) and quantitative systems pharmacology estradiol-BMD model (R&D/17/0097 (Module 5, Section 5.3.5.4)). Simulations of BMD changes based on the indirect response model were performed using 100 trials of 100 subjects each, and results from the simulations were summarized as mean (95% CI) across the 100 simulated trials. The estradiol-BMD quantitative systems pharmacology model predictions for BMD changes over time were obtained using individual estradiol levels at month 6 from subjects treated with elagolix 150 mg QD or 200 mg BID for at least 6 months in Phase 3 studies (N = 1011), as input into the model. Means (95% CI) for the simulation results were calculated across 100 subsets of the individual simulations by random sampling. Results predicting changes in lumbar spine BMD with treatment at each dose of elagolix are shown in Figure 22, Table 94, Figure 23, and Table 95 below.

Figure 22. Simulation of Percent Change from Baseline in Lumbar Spine BMD Following Treatment with Elagolix 150 mg QD for 36 Months (A. Indirect Response Model; B: QSP Model)



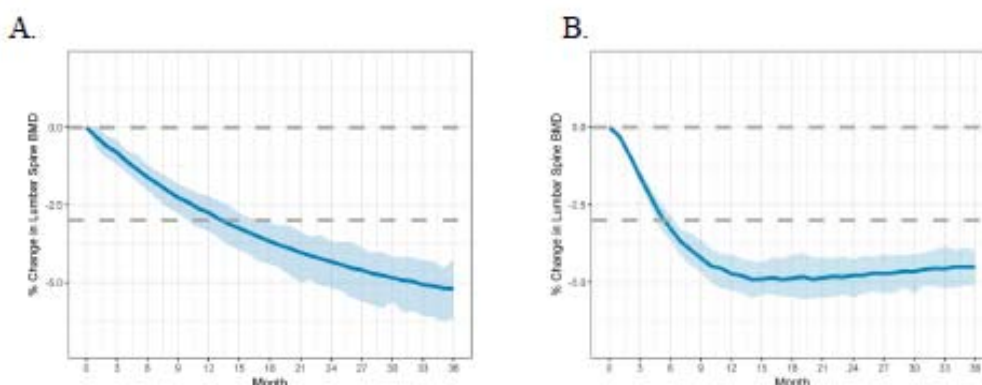
BMD = bone mineral density, QSP = quantitative systems pharmacology

Table 94. Summary Statistics of Predicted Percent Change from Baseline in Lumbar Spine BMD Following Treatment with Elagolix 150 mg QD for 36 Months

Dosing Regimen	Month	% Change from Baseline in Lumbar Spine BMD			
		Indirect Response Model		QSP Model	
		Mean	95% CI	Mean	95% CI
150 mg QD	6	-0.6	-1.1 -- -0.2	-0.9	-1.2 -- -0.7
	12	-1.1	-1.5 -- -0.5	-1.4	-1.8 -- -1.2
	24	-1.6	-2.3 -- -0.9	-1.5	-1.8 -- -1.2
	36	-1.9	-2.9 -- -1.2	-1.3	-1.5 -- -1.0

BMD = bone mineral density, CI = confidence interval, QD = once daily, QSP = quantitative systems pharmacology

Figure 23. Simulation of Percent Change from Baseline in Lumbar Spine BMD Following Treatment with Elagolix 200 mg BID for 36 Months (A. Indirect Response Model; B: QSP Model)



BID = twice daily, BMD = bone mineral density, QSP = quantitative systems pharmacology

Table 95. Summary Statistics of Predicted Percent Change from Baseline in Lumbar Spine BMD Following Treatment with Elagolix 200 mg BID for 36 Months

Dosing Regimen	Month	% Change from Baseline in Lumbar Spine BMD			
		Indirect Response Model		QSP Model	
		Mean	95% CI	Mean	95% CI
200 mg BID	6	-1.6	-2.0 -- -1.2	-3.3	-3.6 -- -2.9
	12	-2.7	-3.3 -- -2.2	-4.7	-5.3 -- -4.1
	24	-4.3	-5.2 -- -3.7	-4.8	-5.5 -- -4.2
	36	-5.2	-6.2 -- -4.3	-4.5	-5.1 -- -3.9

BID = twice daily, BMD = bone mineral density, QSP = quantitative systems pharmacology

The indirect response exposure-BMD model appears to more closely parallel the pattern of change in BMD observed during the clinical trials. Specifically, bone loss in this model is associated with dose and duration of elagolix treatment without evidence of a plateau. In contrast, the quantitative systems pharmacology estradiol-BMD model shows a plateau to a slight increase in BMD with ongoing use which was not demonstrated in the clinical trials. The

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magnitude of bone loss at month 12 seen at the 150 mg QD dose with the indirect model is comparable to that observed in the clinical trials but at the 200 mg BID dose, the model appears to underestimate bone loss. This discrepancy in how the model performs at different doses raises concerns about its overall predictive ability. Another major limitation of these data is the lack of a simulated control group to predict gains in BMD during this time as was demonstrated in the pivotal trials over 6 months. This information would better inform risk. In addition, the model has not been validated in other populations of treated subjects. In summary, these simulations have important limitations and should not be used to reliably assess bone loss when elagolix is used beyond 12 months.

Fractures

Fractures were an adverse event of special interest. A total of 21 fractures occurred in 20 subjects in all four studies combined. Eleven fractures involved fingers, toes and feet. Three fractures (one arm (both radius and ulna), sternum and tibia) were the result of motor vehicle accidents. Two subjects experienced ankle fractures. Fractures at other sites occurred in 5 subjects and are summarized in Table 96 below. Fracture did not lead to discontinuation of study drug in any of the cases.

Table 96. Subjects With Fractures Excluding Those Caused by a Motor Vehicle Accident

Study	Subject ID	Age, Race	Wt (kg)	Treatment	Location	Cause	Study Day Event	Study Period of BMD	%change in BMD from baseline ^a		
									Spine	Total Hip	Femoral Neck
M12-665	(b) (6)	24, Wh	86	PBO	Right elbow	Fell while running	27		N/A	N/A	N/A
M12-671	(b) (6)	20, Wh	81	150 mg QD	Coccyx	Not provided	48	M6	1.02	-0.44	-1.45
								PTFU M6	-	-	-
								PTFU M12	-	-	-
M12-671	(b) (6)	43, Wh	64	150 mg QD	Left rib fracture	Not provided	234	M6	-0.63	-0.87	-2.01
								PTFU M6	-0.34	-0.62	0.22
								PTFU M12	-	-	
M12-821	(b) (6)	33, Bl	148	PBO/Ela 200 mg BID	Osteo-chondral fracture	Not provided	PTFU d 315	M12-671 Final	-2.16	-3.41	-5.36
								M12-821 M3-6	-0.12	-1.9	9.5
								PTFU M6	1.07	-2.71	-1.84
								PTFU M 7-12	5.17	-11.68	-6.81
M12-821	(b) (6)	31, Wh	87	PBO/Ela 200 mg BID	Lower leg	Fall from standing height	PTFU d 120	M12-671 Final	7.27	0.27	-1.19
								M12-821 M3-6	-9.45	-1.06	-0.68
								PTFU M6	-6.77	-0.82	0.24
								PTFU M 7-12	-	-	-

Source: M12-665 CSR Table 112 and Appendix Table 16.2__7.1; M12-667 CSR Table 131 and Appendix Table 16.2__7.1; M12-671 CSR Table 113 and Appendix Table 16.2__7.1; M12-821 CSR Table 131, Appendix Table 16.2__7.1
 MVA = motor vehicle accident, PBO = placebo, M = month, BID = twice daily, QD = once daily, d = day, Wh = white race, Bl = black race
^a Baseline is defined as pre-treatment baseline for studies M12-665 and M12-671 and end of pivotal study for subjects in M12-667 and M12-821 who were treated with placebo in M12-665 and M12-667.

Fragility fracture is defined as a fracture that results from a simple fall from a standing height or less, and excludes hands, feet, fingers, toes, face and skull. It is controversial as to whether ankle fractures are considered fragility fractures. Of the fractures described above, insufficient information is provided to determine if the fractures experienced by subjects (b) (6) (coccyx), (b) (6) (rib) and (b) (6) (lower leg) were fragility fractures. All 3 subjects experienced bone loss on treatment, although the decline in BMD was minimal for the first subject. From the information provided, it is not possible to determine whether accelerated bone loss increased the risk for fracture.

Conclusions and Recommendations Related to Bone Safety

Elagolix treatment for women with moderate to severe EAP is associated with declines in BMD at all anatomic sites as measured by DXA and seems to be related to both dose and duration of

treatment. The decline in BMD was detected as early as 6 months of treatment and appeared to be continuous for subjects treated with both doses, without evidence of a plateau during the 12 months of treatment studied. Conversely, subjects in the placebo group had gains in BMD over 6 months studied, as expected in premenopausal women, some of who may not yet have attained peak bone density. Recovery of bone loss was variable in the PTFU period. Partial recovery was observed for the majority of subjects assessed at PTFU month 6.

The study population had a BMD within the expected range for age as assessed by Z-score. Despite bone loss, the BMD of all but one participant remained within the expected range for age. In contrast to T-score which is used to estimate fracture risk in postmenopausal women, the relationship between Z-score and fracture risk is not robust, and Z-scores should not be used to diagnose osteoporosis. Changes in Z-scores do not sufficiently inform risk and should not be relied upon to interpret the impact of elagolix treatment on bone loss. (b) (4)

Other approved hormonal therapies associated with declines in BMD in premenopausal women include GnRH agonists (e.g., leuprolide) for endometriosis and uterine fibroids and depomedroxyprogesterone acetate (DMPA) for contraception. The duration of use for each of these therapies is limited in order to limit bone loss. In the case of leuprolide, treatment for endometriosis is limited to 6 months in the initial treatment course; an additional 6-month course can be administered only with norethindrone add-back therapy. In the clinical trial, leuprolide alone was associated with a mean percent change from baseline in spine BMD (the site of greatest bone loss) of -3.2% (95% CI -3.8, -2.6) after 6 months of treatment. In the case of DMPA for contraception in adolescents, bone loss as well as recovery was examined. Examination of the data according to duration of use for at least 2 years demonstrated mean percent changes from baseline BMD of -0.9%, -1.5% and -1.6% at the spine, total hip and femoral neck respectively. Full recovery was seen at the spine at 12 months and at the total hip and femoral neck at 18 months. Use for longer than 2 years resulted in greater bone loss and incomplete recovery at the total hip and femoral neck after 5 years post-treatment. Data are limited in that only a subset of subjects were monitored during recovery to inform these results. Nonetheless, DMPA has a boxed warning regarding the risk for decrease in BMD and incomplete recovery and the recommendation to limit its use to no more than 2 years. The degree of bone loss at the lumbar spine observed with elagolix 200 mg BID over 6 months is no more than that seen in the studies of leuprolide over 6 months, and bone loss with elagolix 150 mg BID over 12 months is much less. Consistent with the labeling for leuprolide, it is reasonable to mitigate the risk of bone loss by limiting the duration of treatment of elagolix 200 mg BID to no more than 6 months, and, assuming ongoing linear bone loss of under 1% per year, to limit treatment with elagolix 150 mg QD to no more than 24 months.

Simulation modeling of changes in BMD were not validated and therefore, should not be relied upon to inform the duration of treatment.

Data available from the elagolix clinical trials are insufficient to determine whether elagolix increases the risk for fracture. It is uncertain as to whether rapid bone loss increases the risk

for fracture. Three subjects who had fractures at sites where fragility fractures occur experienced bone loss. However, the circumstances surrounding their fractures were not documented and the fracture event rates were very low, precluding definitive conclusions.

In summary, elagolix treatment was associated with dose and duration dependent declines in BMD, without evidence of a plateau over 12 months. Additionally, recovery of bone loss over 6 to 12 months off treatment was incomplete. The label should reflect the observed declines in BMD with elagolix treatment and lack of complete recovery. Additionally, limiting the duration of elagolix treatment is recommended. Taking into consideration the extent of decline in BMD with other therapies approved for use in premenopausal women, the duration of use for elagolix 200 mg BID should be limited to 6 months. Assuming the rate of bone loss observed over 12 months in the clinical trials for the elagolix 150 mg QD dose remains relatively constant, treatment with this dose for up to 24 months seems reasonable in women who respond to and require ongoing treatment for endometriosis. The effects of elagolix-associated changes in BMD on long-term bone health and future fracture risk are unknown. Assessment of BMD during treatment and/or post-treatment should be considered for patients with risk factors for bone loss. Although the effect of supplementation with calcium and vitamin D was not formally investigated, such supplementation may be beneficial.

8.2.8. Additional Safety Explorations

8.2.8.1. Human Carcinogenicity or Tumor Development

There is no evidence of human carcinogenicity in the elagolix development program.

8.2.8.2. Pediatrics and Assessment of Effects on Growth

Endometriosis is not seen in girls before age 11 years of age or in boys. It is extremely rare in premenarchal girls older than 11 years of age; fewer than 10 case reports have been documented in the literature.⁷ Occurrence of endometriosis in postmenarchal adolescents is very rare, in part attributed to the fact that definitive diagnosis by direct laparoscopic visualization and biopsy is rarely performed in adolescents. Because no adolescents were enrolled in the clinical program, the effect of elagolix on growth was not assessed.

8.2.8.3. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no evidence for acute overdose, drug abuse potential, withdrawal or rebound for elagolix in the clinical trials.

The Controlled Substance Staff evaluated the submitted studies that contained data pertinent to an abuse assessment and agreed with the Applicant that “elagolix does not cross the blood

⁷ Marsh, EE, and Laufer MR, 2005, Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly, *Fertil Steril*, 83(3):758-760.

brain barrier, does not produce overt behaviors indicative of central nervous system activity in animal and does not produce a pattern of abuse-related adverse events in clinical studies with elagolix.” In a review dated May 2, 2018, the Controlled Substance Staff concluded that elagolix is unlikely to have abuse potential [REDACTED] (b) (4)

8.2.9. Safety in the Postmarket Setting

8.2.9.1. Safety Concerns Identified Through Postmarket Experience

Elagolix has not been marketed in any other country.

8.2.9.2. Expectations on Safety in the Postmarket Setting

It is possible that elagolix 200 mg BID could be used off-label for treatment of heavy bleeding with uterine fibroids but the patients would be at risk for bone loss if the drug is used longer than 6 months. [REDACTED] (b) (4)

[REDACTED] It is also possible that clinicians may add their own add-back hormone regimen to elagolix in a postmarket setting.

It is not anticipated that elagolix will be used in postmenopausal patients since endometriosis and uterine fibroids present problems primarily in the premenopausal age range.

8.2.10. Integrated Assessment of Safety

As of June 19, 2017, a total of 3611 subjects have received elagolix in the clinical studies included in this submission. Among these, 1557 subjects received elagolix for at least 6 months and 425 subjects received elagolix for at least 12 months, where each month reflects a 28-day period to coincide with the typical duration of a menstrual cycle. These numbers include subjects across the clinical development programs for both endometriosis and uterine fibroids who received elagolix alone or in combination with various forms of hormonal add-back therapy (i.e., from Phase 2 uterine fibroids studies) and other drugs.

In Phase 3 clinical studies, 685 women with endometriosis have received elagolix 150 mg QD, and 697 women with endometriosis have received elagolix 200 mg BID.

The principal safety concerns for elagolix in the endometriosis population includes the following:

- Bone loss

The effect of elagolix on BMD was assessed by DXA in the Phase 3 program. BMD changes observed in the femoral neck and hip were typically less than those at the lumbar spine. In the

two placebo-controlled trials, lumbar spine BMD increased in placebo-treated subjects by 0.5% on average after 6 months because many subjects, who were young women, had not attained peak bone mass when treatment commenced. In contrast, in Studies 665 and 671, subjects treated with elagolix 150 mg QD lost BMD at the lumbar spine by 0.3 and 0.7% on average, respectively. Thus, compared to placebo subjects who gained bone, those who received elagolix 150 mg QD for 6 months experienced a loss of 0.8 and 1.3% in lumbar spine BMD on average, in Studies 665 and 671, respectively. BMD was further assessed in subjects who enrolled in the extension trials (approximately 60% of those who were randomized to begin treatment). In these subjects, mean lumbar BMD loss was approximately 1% after 12 months of treatment with elagolix 150 mg QD. These 12-month data are uncontrolled because the extension period did not include a placebo arm.

The adverse effect on BMD of elagolix 200 mg BID was more pronounced. Subjects treated for 6 months in the placebo-controlled trials experienced a mean 3.1% decrease in lumbar BMD compared to placebo-treated subjects. Among subjects who enrolled in the extension trials (again, approximately 60% of those who were randomized and started treatment with elagolix 200 mg BID), a mean BMD loss of 3.5 and 3.9% were observed in Studies 665 and 671, respectively.

Partial recovery was seen in subjects treated with elagolix who had follow-up BMD measurements during the PTFU period up to 12 months off therapy.

- Elevations in hepatic enzymes

No subjects met the criteria for Hy's law (i.e., no subject had AST and/or ALT at or more than three times the upper limit of normal (ULN) and total bilirubin at or more than twice the ULN) at any time point during elagolix treatment. However, our review identified a subject whose liver tests nearly met the Hy's law criteria, triggering a detailed review for hepatotoxicity. In response to our request, the Applicant eventually obtained the subject's medical records and confirmed a history of acute viral hepatitis A. Refer to section 8.2.4.6 for details of this case.

In placebo-controlled clinical trials (Studies 665 and 671), dose-dependent elevations of serum ALT at least three times the ULN were noted with treatment with elagolix: 0.1% (1 in 696) in the placebo group, 0.2% (1 in 450) in the 150 mg QD group, and 1.1% (5 in 443) in the 200 mg BID group.

One subject with a history of alcoholism and cirrhosis of the liver died 21 days after receiving a single-dose of elagolix 150 mg in Study M12-662 (pharmacokinetic study in subjects with hepatic impairment). The subject was found with bleeding noted near her nose and mouth, but the death was unwitnessed and autopsy was not performed. The death certificate lists chronic alcohol abuse with alcoholic cirrhosis as causes of death. Because the half-life of elagolix was less than 7 hours, the investigator and the Applicant judged the death as probably not related to elagolix. Compared to women with normal hepatic function, exposure of elagolix is

increased 7-fold in subjects with severe hepatic impairment so use in this population will be contraindicated.

- Suicidal ideation, behavior and exacerbation of mood disorders

In placebo-controlled trials (Studies 665 and 671), treatment with elagolix was associated with adverse mood changes, particularly in patients with a history of depression (Table 97).

Table 97. Adverse Reactions Related to Suicidality and Mood Changes in Studies 665 and 671

Adverse Reactions	Placebo (N = 734), n (%)	Elagolix 150 mg QD (N = 475), n (%)	Elagolix 200 mg BID (N = 477), n (%)
Completed suicide	0 (0)	1 (0.2)	0 (0)
Suicidal ideation	0 (0)	1 (0.2)	1 (0.2)
Depressed mood, depression, depressive symptom and/or tearfulness	17 (2.3)	13 (2.7)	29 (6.1)
Mood altered and/or mood swings	25 (3.4)	27 (5.7)	25 (5.2)

Note: Subjects may have reported more than one adverse reaction.
BID = twice daily, QD = once daily

There has been one completed suicide and four patients with suicidal ideation among elagolix-treated patients in the Phase 2/3 endometriosis program. These cases are summarized below. In all three cases it is not possible to exclude drug causality.

One of the two deaths in the elagolix clinical program occurred in a subject who had received elagolix 150 mg QD for 31 days who died from suicide 2 days after the last dose of study drug in a Phase 3 endometriosis study (Study 671). The investigator assessed the death as having no reasonable possibility of being related to study drug and was likely due to multiple life stressors.

One subject receiving elagolix 150 mg QD in Study 665 reported suicidal ideation beginning on study day 113. Her past medical history indicated postpartum depression and depression. The study drug was permanently discontinued two days after the events. By the time the subject was evaluated by a mental health professional 23 days after stopping treatment, her depression and suicidal ideation had resolved.

A subject receiving 200 mg in Study 671 reported suicidal ideation and worsening depression and anxiety 12 days after starting treatment. Citalopram once daily was added to manage depression, in addition to continuing alprazolam. She was not evaluated by a mental health provider and was continued on elagolix. Two months later (on Study day 71), her suicidal ideation, mood swing, and agitation recurred; her citalopram was increased from once daily to twice daily. On study day 84, elagolix was permanently discontinued after a consultation with her primary care physician. The events of agitation and suicidal ideation were considered resolved on study day 111.

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Additionally, a subject in an extension trial reported suicidal ideation after receiving elagolix 150 mg QD for 212 days (183 days in Study 665 and 29 more days in extension trial Study 667). The subject had a prior history of premenstrual dysphoric disorder. She declined a psychiatric referral and was treated with fluoxetine and elagolix was not interrupted due to these events. The suicidal ideation resolved 21 days after onset.

Further, suicidal ideation was also reported by a subject who received elagolix 75 mg BID for 24 weeks in a Phase 2 trial. Her past medical history included depression, two suicide attempts, bipolar disorder, and anxiety. The subject was able to complete the study despite being hospitalized for psychiatric treatment.

The totality of data from the clinical program indicate that treatment with elagolix is associated with adverse mood changes in women, particularly those with pre-existing mood disorders.

- Change in menstrual bleeding pattern which may reduce the ability to recognize pregnancy

In subjects who reported menstrual bleeding, treatment with elagolix resulted in a dose-dependent reduction in the mean number of days of bleeding/spotting, bleeding intensity, and bleeding duration. A dose-dependent increase in the percentage of women with amenorrhea (defined as no bleeding or spotting in a 56-day interval) was also observed. In Studies 665 and 671, the incidence of amenorrhea during the 6-month treatment ranged from 6-17% in subjects treated with elagolix 150 mg QD and 13-52% in those treated with elagolix 200 mg BID compared to less than 1% with placebo.

However, ovulation can still occur during treatment with elagolix. Of more than 3500 women (of whom more than 2000 had endometriosis and are presumed to have more difficulty achieving pregnancy) treated with elagolix for up to 12 months, 49 women (1.4%) became pregnant either while receiving elagolix treatment or within 30 days after stopping treatment. The annualized on-treatment pregnancy rates among subjects with up to 12 months of treatment exposure in the elagolix Phase 3 endometriosis clinical development program are 4.8% for placebo, 4.1% for elagolix 150 mg QD, and 2.7% for elagolix 200 mg BID.

- Effects on lipid parameters

Dose-dependent increases in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides were noted during treatment with elagolix.

In Studies 665 and 671, 10 to 27% of subjects with mildly elevated LDL-C (130 to 159 mg/dL) at baseline developed LDL-C levels $\geq$ 190 mg/dL during treatment. Three percent to 7% of subjects with mildly elevated triglycerides (150 to 300 mg/dL) at baseline developed increases to between 500 to 1000 mg/dL during treatment.

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Lipid increases occurred within 1 to 2 months after starting elagolix and remained stable thereafter over 12 months of treatment, declining after elagolix was stopped.

Other side effects that are expected with the hypoestrogenic state and were reported in the clinical program, included hot flushes and night sweats.

In summary, the severity and frequency of overall safety findings are not at a level that would preclude approval of elagolix. These safety issues can be mitigated with labeling alone, without the need for Risk Evaluation and Mitigation Strategies. Some require further study and surveillance in the postmarketing setting.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There were no statistical issues. The Applicant followed the prespecified statistical analysis plan and, from the statistical perspective, demonstrated the effectiveness of both proposed elagolix doses for the management of endometriosis with associated moderate to severe pain.

Elagolix 200 mg BID also demonstrated statistically significant reduction from baseline in dyspareunia compared to placebo, whereas elagolix 150 mg QD did not.

8.4. Conclusions and Recommendations

Elagolix is a first-in-class, GnRH antagonist proposed for the management of endometriosis with associated moderate to severe pain. It will also be the only marketed oral therapy for moderate to severe pain associated with endometriosis. Both elagolix 150 mg QD and 200 mg BID have been convincingly shown, in confirmatory placebo-controlled clinical trials, to increase the proportion of patients who reported a reduction in both dysmenorrhea and non-menstrual pelvic pain 3 months into treatment. Although the Applicant claims that treatment benefit was maintained into the blinded extension trials through 12 months of total treatment, sustained effect in reducing dysmenorrhea and non-menstrual pelvic pain cannot be ascertained because there are no controlled data beyond 6 months. The 200 mg BID dose, but not the 150 mg QD dose, also reduced dyspareunia, a symptom that can be distressing to women due to potential impact on their personal relationship.

There was consensus among all disciplines of the review team regarding the approvability of this application. Because of its mechanism of action, the safety profile of elagolix is generally consistent with agents that induce hypoestrogenism. There is also agreement among the review team that the risks can be mitigated with labeling alone. Among the safety issues

identified, bone loss is of the greatest concern, given the likelihood of chronic use of elagolix to delay or prevent surgery in women with endometriosis. The dose- and duration- dependent declines in BMD occurred during the time when some women were still accruing bone. Compared to subjects receiving placebo, those receiving elagolix 200 mg BID for 6 months had approximately 3% decrease in their lumbar BMD. This degree of bone loss is comparable to that observed in women treated with leuprolide after 6 months of injections for endometriosis. Therefore, the duration of use for elagolix 200 mg BID will be limited to 6 months consistent with the approach taken with leuprolide. Compared to subjects receiving placebo, those who were treated with elagolix 150 mg QD for 6 months experienced approximately a 1% mean reduction in lumbar spine BMD, and those who entered blinded extension trials continued to experience reduction in BMD. Based on the rate of bone loss over 12 months with 150 mg QD, we anticipate bone loss over 24 months with this dose being less or comparable to that seen with 200 mg BID for 6 months, supporting a treatment duration limitation of 24 months for the 150 mg QD regimen. For women who are close to menopause or who wish to delay surgical therapy, 6 to 24 months of treatment may offer benefit that offsets the concern with bone loss. Note that these duration limits are for women with normal liver function or mild hepatic impairment. For reasons explained in the clinical pharmacology section, there are different recommendations for women with more severe hepatic impairment and in the setting of certain drug-drug interactions. Consideration should be given to assessing BMD in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss.

Other important safety issues, such as suicidality and exacerbation of mood disorders, changes in menstrual bleeding patterns that may reduce the ability to timely recognize pregnancy in women taking elagolix (and of child-bearing potential), and dose-related elevations in hepatic enzyme elevations will be described in the Warnings and Precautions sections of product labeling. The lipid effects will be described in the Adverse Reactions section of the label.

9. Advisory Committee Meeting and Other External Consultations

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

10. Pediatrics

The Applicant sought a full waiver from the requirements to obtain pediatric data under the Pediatric Research Equity Act. Reasons provided by the Applicant to justify a full waiver included:

- Boys are not affected by endometriosis.
- Endometriosis does not occur in premenarchal girls.
- Definitive diagnosis of endometriosis in postmenarchal girls younger than age 17 is rare because the symptoms of presumptive endometriosis are generally treated empirically with nonsteroidal anti-inflammatory drugs and/or combined hormonal contraceptives; diagnostic laparoscopy is often avoided or delayed until adulthood. Therefore, the potential pediatric population eligible for treatment with elagolix is limited, rendering a clinical trial with elagolix in this population infeasible.

The Division agreed with the Applicant's rationale; the Applicant submitted an agreed-upon initial Pediatric Study Plan under IND 064802 on January 5, 2017.

This application was discussed with the Pediatric Research Committee on January 31, 2018. The Pediatric Research Committee agreed with the Division to grant the full waiver as per the initial Pediatric Study Plan. The final Pediatric Research Committee decision is documented in the Meeting Minutes dated February 22, 2018.

11. Labeling Recommendations

11.1. Prescribing Information

The proposed proprietary name, Orilissa, is determined by the Division of Medication Error Prevention and Analysis to be acceptable.

Table 98 compares key aspects of the Prescribing Information (PI) first submitted by the Applicant and the approved PI:

Table 98. Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling ^a
Section 1	Indicated for the management of endometriosis with associated pain.	Limited the target population to patients with moderate to severe pain
Section 2.2	150 mg once daily regimen is recommended in women with moderate hepatic impairment (Child-Pugh B).	Limited the duration of treatment with TRADENAME 150 mg once daily to 6 months in women with moderate hepatic impairment (Child-Pugh B)
Section 2.2		Limited the duration of treatment

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		to 6 months with 200 mg twice daily regimen and to 24 months with 150 mg daily regimen
Section 4	Contraindications: Pregnancy and severe hepatic impairment	Also contraindicated in women with: • Known osteoporosis • Strong organic anion transporting polypeptide (OATP) 1B1 inhibitors
Section 5		Significant revisions, including: • Strengthening warnings regarding effect on BMD ^{(b) (4)} • Added longitudinal data to describe decreased BMD • Added suicidality and mood disorders • Added liver test abnormalities • Revised information on concomitant use of hormonal contraceptives (combination or progestin-only) • Moved lactation data to Section 8.2
Section 6		• Elaborated on adverse reactions described in Section 5 • Added information on changes in low-density lipoprotein cholesterol and triglycerides
Section 7.2	^{(b) (4)}	Concomitant use of 200 mg BID and strong CYP3A inhibitors for more than 1 month is not recommended. Concomitant use of 150 mg QD and strong CYP3A inhibitors should be limited to 6 months.
Section 7.2	Concomitant use of 200 mg BID and potent OATP1B1 inhibitors is ^{(b) (4)}	Concomitant use of both doses and potent OATP1B1 inhibitors ^{(b) (4)}
^{(b) (4)}		Deleted.
Section 8.1		Deleted language suggesting ^{(b) (4)} to pregnancy ^{(b) (4)}
Section 12.3	^{(b) (4)}	^{(b) (4)}
Section 12.3		Revised significantly the PK data in Tables ^{(b) (4)}
Section 12.3	^{(b) (4)}	Deleted.
Section 12.5		Added the effect of OATP1B1 transporter genotype on the exposure of elagolix

Section 14	(b) (4) Deleted all secondary endpoints that were not adequately supported for labeling. Added enrollment criteria defining moderate to severe pain associated with endometriosis Described data on use of opioid rescue and stated that (b) (4)

* Information reflects high-level changes and not direct quotations.

11.2. Patient Labeling

The Patient Labeling team and the 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 consistency and that the materials are truthful and not misleading. Agreement has been reached with the Applicant and there are no outstanding issues. Please see separate consult in DARRTS, dated July 5, 2018, for further details.

11.3. Carton and Container Labeling

Reviewers in the Division of Medication Error Prevention and Analysis and Office of Product Quality collaborated with the core review disciplines on the review of carton and container labeling. Agreement has been reached and there are no outstanding issues from the medication error perspective. Please see the separate consults in DARRTS and Panorama, respectively, for further details.

12. Risk Evaluation and Mitigation Strategies

12.1. Safety Issue(s) that Warrant Consideration of a Risk Evaluation and Mitigation Strategy

The review team, including the Division of Risk Management in the Office of Surveillance and Epidemiology, and the Applicant agree that the potential risks of elagolix can be adequately managed in the postmarket setting through product labeling alone, and that a REMS is not necessary to ensure that the drug's benefits will outweigh the risks.

Please see the separate consult from the Division of Risk Management, dated July 23, 2018 in DARRTS, for complete details.

12.2. Conditions of Use to Address Safety Issue(s)

None.

12.3. Recommendations on Risk Evaluation and Mitigation Strategies

Not applicable; there are no safety concerns for which a risk evaluation and mitigation strategy is necessary to ensure safe use.

13. Postmarketing Requirements and Commitments

The Division has requested three postmarketing requirements (PMRs) and one postmarketing commitment (PMC).

As a GnRH receptor antagonist, elagolix may cause a decrease in progesterone production in early pregnancy and in turn increase the risk for pregnancy complications. Although elagolix inhibits ovulation in a dose-dependent manner, neither proposed dosing regimen suppressed ovulation enough for the drug to be considered an acceptable alternative for contraception. As discussed in section 8.2.5.4, there were 49 reported pregnancies in women treated with elagolix to date (47 in the endometriosis program and 2 in the fibroid program) where hormonal contraceptives were prohibited. Of the 49 pregnancies, 15 resulted in elective abortions, 5 resulted in spontaneous abortions, 6 were lost to follow-up, and 23 were carried to term. Among the 23 pregnancies that were carried to term, 2 subjects delivered infants with congenital anomalies (cleft palate and tracheo-esophageal fistula). These data were too limited to draw definitive conclusions regarding the effect of elagolix on pregnancy outcomes. Because endometriosis occurs in women of reproductive age in whom pregnancy may become more likely when symptoms of endometriosis abate, meaningful data on outcomes of pregnancies exposed to elagolix are needed to further inform safety post-approval. The Applicant is required and has agreed to conduct:

- PMR 1: a prospective pregnancy registry study to evaluate [REDACTED] (b) (4) and maternal and fetal/neonatal outcomes
- PMR 2: a pharmacoepidemiologic surveillance study [REDACTED] (b) (4) to evaluate pregnancy-related outcomes

We are also requiring the following drug-drug interaction trial (see the rationale for this trial in Clinical Pharmacology section 6.3.2.4):

- PMR 3: a drug-drug interaction study to assess the PK, safety, and tolerability of the coadministration of a combined oral contraceptive (containing ethinyl estradiol and levonorgestrel) with elagolix 200 mg BID [REDACTED] (b) (4)

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Because endometriotic lesions are estrogen-dependent, concomitant use of elagolix and estrogen-containing hormonal contraceptives is expected to reduce elagolix's effectiveness in managing pain. For this reason, all hormonal contraceptives (estrogen-containing and progestin-only) were prohibited in the clinical program. Thus, the extent to which the effectiveness of elagolix may be reduced during co-administration with estrogen-containing contraceptive is unknown. However, given the uncertainty surrounding pregnancies exposed to elagolix and the need for effective contraceptive methods other than permanent sterilization or barrier methods/spermicides, such information would help patients with endometriosis and providers make informed choices as to the treatment options. The Applicant has agreed to conduct:

- PMC 1: a clinical trial in women taking elagolix and a combined hormonal contraceptive to assess the efficacy of elagolix (b) (4) and the efficacy of the combined hormonal contraceptive (b) (4)

Synopses of these PMRs and the PMC and associated milestones were submitted by the Applicant on April 17, 2018. Protocol comments were conveyed to the Applicant on June 6, 2018. These protocols will be finalized after approval.

14. Appendices

14.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): Studies 665, 671, 667, 821

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 151		
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): 5		
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: <u>N/A</u> Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in Sponsor of covered study: <u>N/A</u>		
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)

14.2. Nonclinical Pharmacology/Toxicology

Refer to the nonclinical review in DARRTS on May 10, 2018.

14.3. Office of Clinical Pharmacology Appendices

Refer to the clinical pharmacology review in DARRTS.

14.4. Hypersensitivity Reactions Observed in Phase 1 or 2 Studies

Table 99. Hypersensitivity Reactions Observed in Phase 1 or 2 Studies

Study	SID Age	AE	Study Day of AE	Dose (mg)	Notes ^a
Phase 1 studies					
NBI-56418-0503	(b) (6) 35 yr	Drug hypersensitivity (allergic rash) Maculopapular across chest, abdomen and upper back	3	150 QD	Discontinuation
NBI-56418-0503	(b) (6) 24 yr	Rash	7	150 QD	Discontinuation
M12-790	(b) (6) 44 yr	Rash localized Day 1 Progression reported on Day 6	1 and 6	200 BID	Discontinuation (last dose day 5)
Phase 2 studies					
NBI-56418-0504	(b) (6) 19 yr	Diffuse rash	4	50 BID	Pruritic, raised rash occurred after morning dose. Evening dose skipped and rash subsided. Next morning subject took another dose and the rash re-appeared
NBI-56418-0603	(b) (6) 22 yr	Macular rash	5	75 BID	Investigator felt probably related
NBI-56418-0702	(b) (6) 25 yr	Pruritus	20	150 QD	Possibly related, appears to subject to correlate with hot flushes
NBI-56418-0702	(b) (6) 36 yr	Rash	31	150 QD	Possibly related
NBI-56418-0703	(b) (6) 32 yr	Rash	2	250 QD	Discontinuation due to event
Additional Phase 3 study cases (not severe or resulting in discontinuation)					
M12-665	(b) (6)	Rash on face and neck	3	200 BID	Study drug not interrupted, AE duration = 4, Possibly new shampoo, Dermatology not seen
M12-665	(b) (6) 26 yr	Pruritus intermittent itching around breasts	56	200 BID	Study drug not interrupted, AE duration = ongoing, Dermatology not seen
M12-665	(b) (6) 23 yr	Rash on breasts	3 & 50	200 BID	Study drug not interrupted, AE duration = ~8 (both), Dermatology not seen

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Study	SID Age	AE	Study Day of AE	Dose (mg)	Notes ^a
M12-665	(b) (6) 30 yr	Rash on upper back (raised, pruritic)	90	150 QD	Study drug interrupted but no occurrence with rechallenge, AE duration = 5, Dermatology not consulted
M12-665	(b) (6) 26 yr	Rash on neck (pruritic, raised, scaling)	29	200 BID	Study drug not interrupted, AE duration = 70, Treated = triamcinolone, Dermatology not consulted
M12-665	(b) (6) 34 yr	Erythema between breasts Neck rash	85 x 3 days 162 ongoing	200 BID	Study drug not interrupted for either event, Erythema Rx = clotrimazole, Rash Rx = benzocaine, Dermatology not consulted
M12-665	(b) (6)	Photosensitivity	125	200 BID	Study drug not interrupted, AE duration = 1, Dermatology not consulted
M12-665	(b) (6) 31 yr	Eczema (perineal)	82	150 QD	Study drug not interrupted, AE duration = ongoing, Rx = metronidazole, Replens, diphenhydramine, and clobetasol, Dermatology not consulted
M12-671	(b) (6) 28 yr	Facia rash	19	200 BID	Study drug not interrupted, AE duration = 5, Rx = diphenhydramine and fexofenadine, Dermatology not consulted
M12-671	(b) (6) 41 yr	Eczema exacerbation	15	200 BID	Study drug not interrupted, AE duration = 137, Rx = methylprednisolone, Dermatology not consulted
M12-671	(b) (6) 29 yr	Macular rash x 2	112 x 1 day 198 x ongoing	150 QD	Study drug not interrupted for either event, Rx = none reported, Dermatology not consulted

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Study	SID Age	AE	Study Day of AE	Dose (mg)	Notes ^a
M12-671	(b) (6) 29 yr	Mild urticaria and localized rash right buttock	152	150 QD	Study drug not interrupted, AE duration = 3, Rx = diphenhydramine, Dermatology not consulted
M12-671	(b) (6) 37 yr	Maculo-papular rash (intermittent on left cheek)	24	200 BID	Subject discontinued due to another AE (depressed mood) not because of rash, AE duration = 143, Dermatology not consulted
M12-671	(b) (6) 36 yr	Mild popular rash with pruritus (face, neck, upper limbs)	22	150 QD	Study drug not interrupted, AE duration = 13, Rx = none reported, Dermatology not consulted
M12-671	(b) (6) 33 yr	Mild rash on arms, intermittent with pruritus	1	150 QD	Study drug not interrupted, AE duration = 15, Rx = none reported, Dermatology not consulted
M12-671	(b) (6) 43 yr	Intermittent atopic dermatitis localized to hands and eyelids	46	200 BID	Study drug not interrupted, AE duration = 123, Dermatologist seen with treatment of belosalic and hydrocortisone eye drops
M12-671	(b) (6) 18 yr	Neck rash	10	200 BID	Study drug not interrupted, AE duration = 26, Rx = hydrocortisone cream and pawpaw ointment, Dermatology not consulted
M12-671	(b) (6) 29 yr	Face and neck rash (further described as nodule)	20	150 QD	Study drug not interrupted, AE duration = 10, Dermatologist Rx = topical azelaic acid and BenzaClin
M12-671	(b) (6) 30 yr	Pustular rash on arms, neck, abdomen (Recent viral illness)	2	150 QD	Study drug not interrupted, AE duration = 5, Rx = none reported, Dermatology not consulted

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Study	SID Age	AE	Study Day of AE	Dose (mg)	Notes ^a
M12-667	(b) (6) 28 yr	Intermittent photosensitivity (sun burn with minimal exposure)	31 of ext	150 QD	Study drug not interrupted, AE duration = 56, Rx = none reported, Dermatology not consulted
M12-821	(b) (6) 31 yr	Facial papular rash with itching	84 of ext	200 BID	Study drug not interrupted, AE duration = 121, Rx = hydrocortisone cream, Dermatology not consulted
M12-821	(b) (6) 21 yr	Facial eczema	102 of ext	150 QD	Study drug not interrupted, AE duration = 22, Rx = topical epaderm, Dermatology not consulted
M12-821	(b) (6) 23 yr	Maculo-papular rash on upper limbs	132 of ext	200 BID	Study drug not interrupted, AE duration = 3, Rx = rupatadine, Dermatology not consulted
M12-821	(b) (6) 42 yr	Generalized intermittent urticarial rash with pruritus	15 of ext	150 QD	Study drug not interrupted, AE duration = 159, Investigator also considered the event as psychosomatic, Rx = none, Dermatology not consulted
M12-821	(b) (6) 44 yr	Facial eczema	87 of ext	200 BID	Study drug not interrupted, AE duration = 63, Rx = none, Dermatology not consulted

Source: Individual narratives found in Study Case Reports

AE = adverse event, BID = twice daily, QD = once daily, Rx = prescription, ext = extension trial

^a All durations given in days

14.5. Clinical and Statistical Appendices

14.5.1. Analgesic Use

For each class of rescue analgesics (NSAIDs and Narcotics), analgesic use for each defined monthly period was based on the average pill count. For months 2 through 6, the average pill count for each class of analgesics was calculated by dividing the total pill count for the corresponding class of analgesic by the length of the window, which was in general equal to 35, but may be shorter for a subject who prematurely discontinued prior to study day 36. The total pill count was the sum of the number of pills within the corresponding class of the

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rescue analgesic as specified previously, reported in the e-Diary over the 35 calendar days preceding the time point of interest, e.g., months 3 and 6, etc. For the month 1 analysis, the averaging was done over the time period since randomization (beginning at study day 2) and until the reference study day (inclusive), but not exceeding 35 days. For each class of rescue analgesic, if no analgesic use was reported for a period of interest, but e-Diary information was available for the corresponding time period, then the average pill count for the corresponding class of rescue analgesic use was set to 0 (zero). The evaluation of increased analgesic use was determined per the specification in Table 100.

Responder analysis at the End-of-Treatment was based on observed data, except for subjects who prematurely discontinued before month 3. Subjects who prematurely discontinued before month 3 and had missing data corresponding to rescue analgesic use for both classes of rescue analgesic medication had their analgesic use carried forward (LOCF) from the previous time point when both monthly average pain score and analgesic use were observed.

Table 100. Analgesic Change During Treatment Period

Use of No Analgesics at Baseline		
Analgesic Used at Baseline	Analgesic Dose Status at End of Time Window	Responder Status*
None	None	Responder
	Narcotic analgesic and/or Naproxen is started	Non-responder
Use of Only Naproxen at Baseline		
Analgesic Used at Baseline	Analgesic Dose Status at End of Time Window	Responder Status*
Naproxen	Dose stopped, decreases, or is stable (increases by less than 15%)	Responder
	Dose increases by 15% or more	Non-responder
	Narcotic analgesic is substituted or added	Non-responder
Use of Only Narcotic Analgesic at Baseline		
Analgesic Used at Baseline	Analgesic Dose Status at End of Time Window	Responder Status*
Narcotic analgesic	Dose stopped, decreases, or is stable (increases by less than 15%)	Responder
	Dose stopped and Naproxen substituted (any dose)	Responder
	Dose decreases and Naproxen added (any dose)	Responder
	Dose stable (increases by less than 15%) and Naproxen added (any dose)	Non-responder
	Dose increases by 15% or more	Non-responder

(Continued)

Table 100. (continued) Analgesic Change During Treatment Period

Use of Naproxen + Narcotic Analgesics at Baseline		
Analgesic Used at Baseline	Analgesic Dose Status at End of Time Window	Responder Status*
Naproxen + Narcotic analgesic	Naproxen use stops + Narcotic analgesic use stops, decreases, or is stable**	Responder
	Naproxen use stops + Narcotic analgesic dose increases by 15% or more	Non-responder
	Naproxen dose decreases + Narcotic analgesic use stops, decreases, or is stable**	Responder
	Naproxen dose decreases + Narcotic analgesic dose increases by 15% or more	Non-responder
	Naproxen dose stable + Narcotic analgesic use stops, decreases, or is stable**	Responder
	Naproxen dose stable + Narcotic analgesic dose increases by 15% or more	Non-responder
	Naproxen dose increases by 15% or more + Narcotic analgesic use stops	Responder
	Naproxen dose increases by 15% or more + Narcotic analgesic dose decreases	Responder
	Naproxen dose increases by 15% or more + Narcotic analgesic dose is stable**	Non-responder
	Naproxen dose increases by 15% or more + Narcotic analgesic dose increases by 15% or more	Non-responder

* Responder = Defined as a subject who meets the protocol-specified pain score criteria for no increase in analgesic use.

** Stable = Dose is the same as the screening dose or increases by less than 15% of the screening dose.

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
07/23/2018

HYLTON V JOFFE
07/23/2018

VICTOR CRENTSIL
07/23/2018

Office of Clinical Pharmacology Review- Appendices

NDA or BLA Number	210450
Link to EDR	\\CDSESUB1\evsprod\NDA210450\210450.enx
Submission Date	August 23, 2017 (SDN001), November 15, 2017 (SDN007), February 20, 2018 (SDN24), April 17, 2018 (SDN039), June 15, 2018 (SDN043), July 10, 2018 (SDN046), July 13, 2018 (SDN048)
Submission Type	Priority
Brand Name	Orilissa™
Generic Name	Elagolix sodium
Dosage Form and Strength	Tablet, 150 mg and 200 mg
Route of Administration	Oral administration
Proposed Indication	Management of endometriosis with associated moderate to severe pain
Applicant	Abbvie Inc.
Associated IND	IND 064802
OCP Review Team	Peng Zou, PhD; Da Zhang, PhD; Doanh Tran, PhD; Fang Li, PhD; Jingyu Yu, PhD; Nan Zheng, PhD; Oluseyi Adeniyi, PhD; Christian Grimstein, PhD
OCP Final Signatory	Gil Burckart, PharmD Associate Director Office of Clinical Pharmacology

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Note: This document contains the appendices to the Clinical Pharmacology review.

APPENDICES

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 by AbbVie or Neurocrine Biosciences Inc. (NBI) for the quantitative determination of elagolix and its two metabolites (NBI-61962 [A-1323217] and NBI-54048 [A-1298847]) in human plasma or urine. The validation reports for each method and analytical study reports for each PK study were submitted.

Two method validation reports (Report #: R&D/11/991 and R&D/11/992) and one stability update validation report (Report #: R&D/17/0277) were submitted to support the bioanalysis of elagolix and metabolites in plasma samples in Phase 1 and Phase 3 studies conducted by AbbVie. A salt-assisted protein precipitation extraction method for the determination of elagolix was employed for plasma samples. Separation was conducted on a Zorbax SB-C18 5 μ m 2.1 $\times$ 50 mm column. The mobile phase consisted of a 50:50 (v/v) mixture of acetonitrile: water containing 10 mM ammonium acetate and 0.1% acetic acid, at an isocratic flow rate of 0.6 mL/min, with a total run time of 3.5 minutes. The same HPLC conditions were employed in Methods R&D/11/991 and R&D/11/992 but there was a difference in mass spectrometer parameters. To determine the two elagolix metabolites A-1323217 and A-1298847, two MRM scan ion transitions m/z 618 $\rightarrow$ 515 and m/z 546 $\rightarrow$ 177 were added to the Method R&D/11/992. The method validation parameters for Methods R&D/11/991 and R&D/11/992 are summarized in **Table 1-1**. In the stability update validation Report R&D/17/0277, the storage stability period for Method R&D/11/991 was extended. The updated validation report also included the qualification of API4000 mass spectrometer and a change of acetic acid content in the mobile phase from 0.1% to 0.2%. The revised method was re-validated for linearity of standard curve, assay accuracy and precision, selectivity, matrix effect and dilution effect and the results met requirements. The established frozen storage stability and run storage stability covered the corresponding study period and sample analysis period.

Table 1-1. Validation Parameters for Methods R&D/11/991 and R&D/11/992

Analytical Methods	R&D/11/991	R&D/11/992
Standard Curve	Curve A: 0.101 – 196 ng/mL, $r^2 \geq 0.990$ Curve B: 1.57 - 2460 ng/mL, $r^2 \geq 0.992$	Elagolix: 0.151 – 196 ng/mL, $r^2 \geq 0.997$ A-1298847: 0.146 – 190 ng/mL, $r^2 \geq 0.998$ A-1323217: 0.148 – 193 ng/mL, $r^2 \geq 0.998$
Accuracy	Curve A: -12.3% to 5.1% Curve B: -10.7% to 3.9%	Elagolix: -7.5% to 1.1% A-1298847: -2.0% to -1.5% A-1323217: 0.9% to 4.3%
Carry-Over	The peak area of the blank sample without IS injected following the highest standard was 3.6% of the analyte peak area of the LLOQ calibration standard.	N.A.
Intra-Run Precision	Curve A: 2.1-5.4% (LLOQ); 1.2-3.1% (ULOQ) Curve B: 2.0-15.3% (LLOQ); 0.6-2.4% (ULOQ)	Elagolix: 2.5-4.6% % (LLOQ); 0.8-1.6% (ULOQ) A-1298847: 5.8-6.7% % (LLOQ); 0.5-1.2% (ULOQ) A-1323217: 4.9-6.5% % (LLOQ); 0.9-2.3% (ULOQ)
Inter-Run Precision	Curve A: 4.4% (LLOQ), 2.6% (ULOQ), and $\leq 3.2%$ (QC) Curve B: 11.4% (LLOQ), 2.7% (ULOQ), and $\leq 2.7%$ (QC)	Elagolix: 3.8% (LLOQ), 2.1% (ULOQ), and $\leq 2.8%$ (QC) A-1298847: 6.2% (LLOQ), 0.9% (ULOQ), and $\leq 3.0%$ (QC)

		A-1323217: 8.9% (LLOQ), 1.9% (ULOQ), and ≤ 5.4% (QC)
Dilution Effects	Dilution factor 10: mean bias = -17%	Dilution factor 10: Elagolix: -1.4% A-1298847: -9.2% A-1323217: 2.7%
Selectivity	100% of blank samples had peak areas < 20% of that of the LLOQ	100% of blank samples had peak areas < 20% of that of the LLOQ
Matrix Effects	Mean bias between 0.1% and 12.8%	Elagolix: -4.2% to -1.0% A-1298847: -5.5% to 2.8% A-1323217: 6.5% to 10.2%
Extraction Recovery	54.0 - 59.3%	Elagolix: 48.6 – 56.5% A-1298847: 54.6 – 70.7% A-1323217: 42.6 – 48.4%
Freeze Thaw Stability	7 freeze/thaw cycles, mean bias -8.8% to 2.9%	5 freeze/thaw cycles, mean bias (-20 °C): Elagolix: -8.7% to -2.1% A-1298847: -6.4% to -2.0% A-1323217: -3.8% to -1.9%
Long-Term Storage Stability	Original: -70°C: ≥ 377 days; -20°C: ≥ 299 days Extended in Report R&D/17/0277: -70°C: ≥ 555 days; -20°C: ≥ 477 days	-70°C: ≥ 398 days for elagolix and two metabolites -20°C: ≥ 398 days for elagolix and A-1323217; ≥ 168 days for A-1298847
Run-Storage Stability	≥ 264 hours at 4°C in an autosampler ≥ 93 hours at 10°C in a polypropylene plate	≥ 97 hours at 4°C in an autosampler
Incurred Sample Reanalysis (acceptance criteria: 2/3 of repeated samples within ± 20% of mean result)	Study M12-653 as an example: Difference between -83.2% and 65.0%; 177/180 of the repeats met the acceptance criteria	Study M12-662 as an example: Elagolix: difference between -43.6% and 22.4%, 41/44 of the repeats met the acceptance criteria; A-1298847: between -29.6% and 111.6%, 34/44 of the repeats met the acceptance criteria; A-1323217: between -25.6% and 22.0%, 48/52 of the repeats met the acceptance criteria

PD Assays:

LC-MS/MS bioanalytical methods using liquid-liquid extraction were validated for quantitation of estradiol and progesterone in serum samples from AbbVie's clinical studies using isotope labeled internal standards. Three method validation reports (Report #: R&D/11/124, R&D/17/0279, and R&D/17/0280) and one stability update validation report (Report #: R&D/17/0281) were submitted to support the bioanalysis of estradiol and progesterone in serum samples in Phase 1 and Phase 3 studies conducted by AbbVie.

For quantitation of estradiol, the serum extracts were evaporated, derivatized with dansyl chloride and separated on a Phenomenex Kinetex 2.6 µm C18 100 Å 50 × 2.1 mm column coupled with a Waters Xbridge C18 5 µm 2.1 × 10 mm guard column. The mobile phase consisted of a 75:25:0.1 (by volume) mixture of acetonitrile: water: formic acid at an isocratic flow rate of 0.6 mL/min, with a total run time of 2.0 minutes. Analysis was performed on an ABSciex mass spectrometer with a Turbo Ion Spray interface; the dansyl derivatives were detected in the MRM mode at m/z 506.2 → 171.1 for estradiol and at m/z 509.0 → 171.1 for estradiol-d3 (the internal standard for estradiol). Similarly, for progesterone quantitation, the reconstituted extracts were separated on a Phenomenex Kinetex 2.6 µm C18 100 Å 2.1 × 50 mm column coupled with a Waters Xbridge C18 5 µm 2.1 × 10 mm guard column. The mobile phase consisted of a 50:5:45 (by volume) mixture of acetonitrile: methanol:(water with 2 mM ammonium formate) at an isocratic flow rate of 0.4 mL/min, with a total run time of 3.0 minutes. Detection was performed in the MRM mode at m/z 315.3 → 109 for progesterone and at m/z 324.4 → 113 for

progesterone-d9. The method validation parameters for estradiol and progesterone are summarized in **Table 1-2**. The established frozen storage stability and run storage stability covered the corresponding study period and sample analysis period.

Table 1-2. Method Validation Parameters for Estradiol and Progesterone

Analytes	Estradiol	Progesterone
Standard Curve	Curve A: 3.0 – 319 pg/mL, $r^2 \geq 0.997$ Curve B: 11.2 – 320 pg/mL, $r^2 \geq 0.996$	0.116 – 58.2 ng/mL, $r^2 \geq 0.997$
Accuracy	Curve A: -0.8% to 1.8% Curve B: -9.0% to 4.4%	Stripped serum: -0.6% to 3.9% Normal serum: -0.8% to 9.1%
Carry-Over	The peak area of the blank sample without IS injected following the highest standard was 0% of the analyte peak area of the LLOQ calibration standard.	The peak area of the blank sample without IS injected following the highest standard was 8.3% of the analyte peak area of the LLOQ calibration standard.
Intra-Run Precision	Curve A: 8.8-13.9% (LLOQ); 0.8-3.4% (ULOQ) Curve B: 4.2% (LLOQ); 3.9 – 8.8% (QC)	Stripped serum: $\leq 11.8\%$ (QC) Normal serum: $\leq 2.1\%$ (QC)
Inter-Run Precision	Curve A: 13% (LLOQ), 3.4% (ULOQ), and $\leq 9.4\%$ (QC) Curve B: 4.2% (LLOQ) and $\leq 8.8\%$ (QC)	Stripped serum: $\leq 6.2\%$ (QC) Normal serum: $\leq 2.1\%$ (QC)
Dilution Effects	Dilution factor 10: mean bias between -11.4% and 8.6%	Dilution factor 10: mean bias -7.1%
Selectivity	Endogenous levels were observed for β -estradiol	100% of blank samples had peak areas less than 20% of the average peak area of the LLOQ without IS
Matrix Effects	Mean bias between -1.0% and 5.5%	Mean bias between -3.0% and 5.1%
Extraction Recovery	110.8 – 123.6%	93.8 – 106.0%
Freeze Thaw Stability	-20 °C: 6 freeze/thaw cycles, mean bias -5.7% to -0.7%; -70 °C: 6 freeze/thaw cycles, mean bias 5.9% to 10.4%	-20 °C: 4 freeze/thaw cycles, mean bias -3.3% to 9.6%; -70 °C: 5 freeze/thaw cycles, mean bias -5.3% to 5.2%
Long-Term Storage Stability	-70°C: ≥ 102 days; -20°C: ≥ 1016 days	≥ 1044 days stored at -20°C
Run-Storage Stability	≥ 196 hours at 10°C in an autosampler or a polypropylene plate	≥ 205 hours at 10°C in an autosampler or a polypropylene plate

Assays for DDI Studies:

LC-MS/MS methods were also developed and validated for the quantitative determination of other drugs administered in drug interaction studies. The drugs and their method validation reports were submitted.

2. Clinical BA/BE Assessments

Seven bioavailability/bioequivalence (BA/BE) studies were submitted in this NDA, including Studies NBI-56418-0404, NBI-56418-0506, NBI-56418-0701, M14-731, M15-817, M13-995, and M12-653. The formulations tested in Studies NBI-56418-0701 and M14-731 were different from Phase 3 formulations and were not selected for further development. The formulations tested in Studies NBI-56418-0404 and NBI-56418-0506 were developed by NBI and were evaluated in six early-stage Phase 1 studies and one Phase 2 study conducted by NBI. These formulations were not tested in the studies conducted by AbbVie. Therefore, the four BA/BE studies are not reviewed and only three studies (M15-817, M13-995, and M12-653) are reviewed. Study M15-817 is the pivotal BE study which bridges the commercial formulation ((b) (4) 200 mg light orange) and one Phase 3 formulation ((b) (4) formulation). Study M13-995 was used to bridge two Phase 3 formulations ((b) (4) formulation and (b) (4) formulation). A (b) (4)

(b) (4) formulation (50 mg/tablet and 150 mg/tablet) was used in 16 Phase 1 studies conducted by AbbVie. Study M12-653 was conducted to bridge the Phase 3 (b) (4) formulation and the (b) (4) formulation.

On Oct 20, 2017, 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 Applicant’s BE clinical study site and bioanalytical site for Study M15-817 and Study M13-995. Both BE studies were conducted at AbbVie Clinical Pharmacology Research Unit and bioanalysis was performed at AbbVie Drug Analysis Department. In the consult report dated Nov 7, 2017, OSIS recommended accepting data without an on-site inspection because an inspection was not needed at that time based on previous inspectional outcome.

2.1 Study M15-817 (Pivotal BE and food effects)

Title: *A Bioequivalence and Food Effect Study of Elagolix Tablets in Healthy Premenopausal Female Subjects*

Objectives:

- to assess the BE of a single dose of one elagolix 200 mg IR tablet of test formulation (commercial formulation, (b) (4) light orange) with that of two elagolix 100 mg IR tablets of the reference formulation (Phase 3 formulation, (b) (4)) under fasting conditions;
- to assess the potential effects of food on the PK of the test elagolix IR tablet formulation ((b) (4) light orange)

Study Design:

This was a Phase 1, single-dose, open-label, randomized, six-sequence, three-period, complete crossover study designed to assess the bioequivalence of two elagolix tablet formulations and the effect of food on the test formulation. 54 healthy premenopausal female subjects were randomly assigned to one of six groups as outlined in **Table 2.1-1**.

Table 2.1-1. Sequence Groups in Study M15-817

Sequence Group	Number of Subjects	Regimens		
		Period 1	Period 2	Period 3
1	9	A	B	C
2	9	B	C	A
3	9	C	A	B
4	9	A	C	B
5	9	B	A	C
6	9	C	B	A

Regimen A Single dose of one elagolix 200 mg IR tablet (b) (4) light orange) administered under fasting conditions (test).

Regimen B Single dose of two elagolix 100 mg IR tablets (b) (4) administered under fasting conditions (reference).

Regimen C Single dose of one elagolix 200 mg test IR tablet (b) (4) light orange) administered approximately 30 minutes after starting a high-fat meal

Blood samples for elagolix assay were collected prior to dosing (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30 and 36 hours after dosing on Day 1 in each study period.

PK Results:

All subjects (N = 54) who completed the study were included in the PK and safety analyses. For the two one-sided test based on the analysis of log-transformed C_{max} , AUC_t and $AUC_{0-\infty}$, the point estimates and the corresponding 90% confidence intervals of relative bioavailability calculated by the Applicant are presented in **Table 2.1-2**. Per the Applicant's analysis, the elagolix 200 mg IR tablet ((b) (4) light orange formulation) was bioequivalent to two elagolix 100 mg IR tablets ((b) (4) formulation). This reviewer did BE analysis using the same individual subject PK parameter dataset and the results are shown in **Table 2.1-2**. Although the geometric means of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of both test and reference formulations calculated by this reviewer are lower than that submitted by the Applicant, both the Applicant's and this reviewer's calculations showed that the two formulations are bioequivalent.

Table 2.1-2. Bioequivalence Assessment for Elagolix (Study M15-817)

Parameter	Least Squares Geometric Means		% Test/Ref Ratio (90% CI)
	Regimen A [Test]	Regimen B [Ref]	
	The Applicant's Calculation		
C_{max} (ng/mL)	689	734	93.8 (85.2 – 103.2)
AUC_{0-t} (ng•h/mL)	1859	1903	97.7 (93.6 – 102.0)
$AUC_{0-\infty}$ (ng•h/mL)	1865	1908	97.7 (93.6 – 102.0)
	The Reviewer's Calculation		
C_{max} (ng/mL)	641	672	95.3 (87.3 – 104.1)
AUC_{0-t} (ng•h/mL)	1695	1714	98.9 (94.5 – 103.5)
$AUC_{0-\infty}$ (ng•h/mL)	1700	1718	99.0 (94.6 – 103.6)

Regimen A: One elagolix 200 mg IR tablet (commercial (b) (4) light orange) administered under fasting conditions (test); Regimen B: Two elagolix 100 mg IR tablets (Phase 3 (b) (4)) administered under fasting conditions (reference)

The effects of food on the pharmacokinetics of the commercial (b) (4) light orange formulation were shown in **Table 2.1-3**. The Applicant's analysis showed that, under high-fat meal conditions, the elagolix (b) (4) light orange formulation 200 mg IR tablet had a lower exposure relative to fasted conditions; with a decrease of 36% and 24% in C_{max} and $AUC_{0-\infty}$, respectively. However, this reviewer's analysis showed a decrease of 38% and 26% in C_{max} and $AUC_{0-\infty}$, respectively.

Table 2.1-3. Food Effects on the PK parameters of Elagolix Commercial Formulation 200 mg Tablet (Study M15-817)

Parameter	Least Squares Geometric Means		% Test/Ref Ratio (90% CI)
	Regimen C [Test]	Regimen A [Ref]	
	The Applicant's Calculation		
C_{max} (ng/mL)	437	689	63.5 (53.2 – 75.9)
AUC_{0-t} (ng•h/mL)	1401	1859	75.4 (69.4 – 81.8)
$AUC_{0-\infty}$ (ng•h/mL)	1412	1865	75.7 (69.8 – 82.1)
	The Reviewer's Calculation		
C_{max} (ng/mL)	397	641	61.9 (53.8 – 71.2)
AUC_{0-t} (ng•h/mL)	1243	1695	73.3 (68.5 – 78.5)
$AUC_{0-\infty}$ (ng•h/mL)	1253	1700	73.7 (68.8 – 78.8)

Regimen A: One elagolix 200 mg IR tablet ((b) (4) light orange) administered under fasting conditions (reference)
Regimen C: One elagolix 200 mg IR tablet ((b) (4) light orange) administered under fed conditions (test)

Reviewer's Comments:

- There are slight differences between the Applicant's and this reviewer's analyses. The slight differences do not affect the conclusion that the commercial (b) (4) light orange formulation (200 mg tablet) and Phase 3 (b) (4) formulation (two 100 mg tablets) are bioequivalent.
- For food effect calculations, the Applicant's analysis showed food intake decreased C_{max} and $AUC_{0-\infty}$ of elagolix by 36% and 24%, respectively. However, this reviewer's analysis showed a decrease of 38% and 26% in C_{max} and $AUC_{0-\infty}$, respectively. In the USPI submitted by the Applicant on July 13, 2018, the Applicant stated that an unstructured variance-covariance (UN) structure was used in their statistical analysis. In contrast, this reviewer used a variance component (VC) structure in statistical analysis, which may explain the slight difference between the Applicant's and this reviewer's analyses. The Applicant justified the use of UN structure by comparing the Akaike's information criterion (AIC) and Bayesian information criterion (BIC) values generated from the two structures. According to the Applicant's data in the table below, UN structure resulted in lower AIC and BIC values than the VC structure. This reviewer agrees with the Applicant that it is appropriate to use UN structure in the relative BA analysis.

	Model 1 (VC)		Model 2 (UN)	
	AIC	BIC	AIC	BIC
C_{max}	276.4	278.4	254.1	266.0
AUC_t	217.8	219.8	122.4	134.3
AUC_{inf}	217.4	219.4	121.7	133.6

- The Applicant's exposure-response analyses and simulations showed that 24% decrease of elagolix exposure under fed conditions did not have a clinically meaningful impact on DYS and NMPP responder rates. This reviewer agrees that 24% decrease of elagolix exposure is not expected to have a clinically meaningful impact on the efficacy. Elagolix can be orally administered without regard to meals and no dose adjustment was recommended under fed conditions.
- This reviewer assessed the effects of study sequence on the PK parameters of elagolix. As shown in **Table 2.1-4**, study sequence had no obvious effects on the C_{max} or T_{max} of elagolix. However, a decreasing trend in AUC was observed under fasting conditions (Regimen A and B) and an increasing trend in AUC was observed under fed conditions (Regimen C). Both the decreasing trend in AUC under fasting conditions and the increasing trend in AUC under fed conditions were not observed in BA/BE Study M13-995 (refer to Section 4.2.2, **Table 2.2-3**), indicating that a consistent study sequence-dependent increase or decrease in elagolix AUC is not expected.

Table 2.1-4. The Effects of Study Sequence on the Pharmacokinetics of Elagolix (Study M15-817)

Formulations	Period	AUC_{0-t} (ng*h/mL)	AUC_{0-} $_{inf}$ (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)
Regimen A	1	2015.2 ± 957.8	2019.6 ± 958.0	723.5 ± 370.0	1.42 ± 0.69
	2	1946.2 ± 1045.0	1953.1 ± 1046.5	733.0 ± 408.9	1.26 ± 0.60
	3	1776.5 ± 912.1	1780.2 ± 913.1	757.9 ± 493.3	1.10 ± 0.31
Regimen B	1	2098.1 ± 873.8	2100.6 ± 874.5	820.8 ± 370.2	1.21 ± 0.57
	2	2027.4 ± 904.0	2033.1 ± 904.7	800.5 ± 424.1	1.14 ± 0.52
	3	1558.8 ± 707.8	1563.0 ± 708.4	610.4 ± 209.2	1.19 ± 0.41

Regimen C	1	1307.0 ± 727.6	1317.0 ± 730.4	550.8 ± 375.9	2.00 ± 0.89
	2	1355.3 ± 690.9	1363.0 ± 693.7	459.1 ± 342.6	2.51 ± 1.39
	3	1550.8 ± 638.6	1561.4 ± 639.0	484.7 ± 303.0	2.86 ± 1.35

Safety Results:

No clinically significant vital signs, ECG or laboratory measurements were observed during the study. No deaths, serious adverse events or other significant adverse events were reported during the study. The proportions of subjects who reported at least one treatment-emergent adverse were similar among the regimens (**Table 2.1-5**).

Table 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	4/54 (7%)	4/54 (7%)	5/54 (9%)

2.2 Study M13-995 (BE)

Title: *A Comparative Bioavailability and Food Effect Study of Elagolix Tablets in Healthy Premenopausal Females*

Objectives:

- To assess BE of single doses of one 200 mg test IR tablet of elagolix ((b) (4) formulation used in one Phase 3 study) with that of two 100 mg reference IR tablets ((b) (4) formulation used in three Phase 3 studies) under fasting conditions.
- To assess BE of single doses of one 200 mg ((b) (4) tablet formulation of elagolix to one 200 mg IR tablet ((b) (4) formulation of elagolix under fasting conditions.
- To assess the potential effects of a high fat meal on the pharmacokinetics of the ((b) (4) tablet formulation of elagolix.

Study Design:

This Phase 1, single-dose, open-label study was conducted in 23 healthy premenopausal females according to a four-period, randomized, crossover design. Enrolled subjects were randomly assigned to one of four groups as outlined in **Table 2.2-1**.

Table 2.2-1. Sequence Groups in Study M13-995

Sequence Group	Subjects	Regimens			
		Period 1	Period 2	Period 3	Period 4
I	102, 108, 110, 116, 119	A	B	D	C
II	104, 107, 112, 114, 118, 123	B	C	A	D
III	103, 106, 109, 115, 120, 122	C	D	B	A
IV	101, 105, 111, 113, 117, 121	D	A	C	B

Regimen A: One 200 mg elagolix IR tablet ((b) (4) formulation) administered under fasting conditions (test).

Regimen B: Two 100 mg elagolix IR tablets ((b) (4) formulation) administered under fasting conditions (reference).

Regimen C: One 200 mg elagolix (b) (4) tablet administered under fasting conditions (test).

Regimen D: One 200 mg elagolix (b) (4) tablet administered under high fat conditions (test).

Blood samples for elagolix assay were collected by venipuncture prior to dosing (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing in each study period.

Since the (b) (4) formulation was not selected for further development, the PK and safety data of Regimen C and D are not reviewed.

PK Results:

All the subjects (N = 23) completed all four periods of the study and were included in the PK and safety analyses. For the analysis of log-transformed C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$, the 90% confidence intervals and the corresponding point estimates are shown in **Table 2.2-2**. Both the Applicant's and this reviewer's calculations showed that the 90% confidence intervals with respect to elagolix C_{max} and AUCs were within the 80 - 125% range following administration of the single, 200 mg IR tablet (Regimen A, test) relative to the 2 × 100 mg IR tablet formulation (Regimen B, reference). The two Phase 3 study formulations, one 200 mg tablet of (b) (4) formulation and two tablets of (b) (4) formulation are bioequivalent.

Table 2.2-2. Bioequivalence Assessment for Elagolix (Study M13-995)

Parameter	Least Squares Geometric Means		% Test/Ref Ratio (90% CI)
	Regimen A [Test]	Regimen B [Ref]	
The Applicant's Calculation			
C_{max} (ng/mL)	784.3	800.2	98.0 (87.6 – 109.6)
AUC_{0-t} (ng•h/mL)	2060.5	2212.3	93.1 (86.3 – 100.5)
$AUC_{0-\infty}$ (ng•h/mL)	2066.8	2219.2	93.1 (86.3 – 100.5)
The Reviewer's Calculation			
C_{max} (ng/mL)	788.8	808.9	97.5 (89.2 – 106.6)
AUC_{0-t} (ng•h/mL)	2062.6	2223.4	92.8 (87.3 – 98.5)
$AUC_{0-\infty}$ (ng•h/mL)	2068.7	2230.3	92.8 (87.3 – 98.5)

Reviewer's Comments:

This reviewer assessed the effects of study sequence on the PK parameters of elagolix in Study M13-995. As shown in **Table 2.2-3**, for all the four regimens, study sequence had no obvious effects on the AUCs or C_{max} of elagolix. Different from the finding in Study M15-817, a decreasing trend in AUC under fasting conditions was not observed (Regimen A, B and C). An increasing trend in AUC under fed conditions was not observed (Regimen D).

Table 2.2-3. The Effects of Study Sequence on the Pharmacokinetics of Elagolix

Formulations	Period	AUC _{0-t} (ng*h/mL)	AUC _{0-inf} (ng*h/mL)	C _{max} (ng/mL)
Regimen A	1	2108.3 ± 779.1	2116.6 ± 783.3	751.6 ± 316.6
	2	1665.8 ± 605.3	1670.9 ± 605.6	638.3 ± 165.0
	3	2420.7 ± 1070.0	2427.2 ± 1070.5	920.2 ± 319.0
	4	2630.3 ± 759.5	2634.9 ± 759.6	1053.8 ± 384.4
Regimen B	1	2737.3 ± 1178.4	2747.0 ± 1176.8	1086.0 ± 579.6
	2	2170.2 ± 736.8	2178.8 ± 741.0	745.4 ± 243.2
	3	2693.0 ± 868.6	2697.9 ± 868.4	943.0 ± 384.5
	4	1899.5 ± 724.2	1903.5 ± 723.5	720.7 ± 270.8
Regimen C	1	2596.0 ± 964.2	2602.6 ± 964.1	996.0 ± 301.1
	2	2467.6 ± 1251.6	2475.2 ± 1250.4	932.0 ± 442.2
	3	1830.1 ± 740.7	1834.9 ± 742.3	761.0 ± 244.4
	4	1940.7 ± 552.4	1950.9 ± 556.8	737.8 ± 179.2
Regimen D	1	1530.2 ± 718.9	1540.4 ± 720.4	571.2 ± 321.4
	2	1550.7 ± 559.0	1560.7 ± 555.0	468.5 ± 233.5
	3	1307.7 ± 435.7	1322.5 ± 437.3	505.8 ± 329.2
	4	1324.6 ± 741.7	1345.2 ± 736.7	414.0 ± 361.1

Safety Results:

The proportion of subjects reporting at least one treatment-emergent adverse event were 3/23 (13.0%) in Regimen A, 1/23 (4.3%) in Regimen C, and 1/23 (4.3%) in the Regimen D. No adverse events were experienced by any subjects in Regimen B. No clinically significant vital signs, ECG or changes in laboratory measurements were observed during the study. No deaths, serious adverse events or other significant adverse events were reported during the study.

2.3 Study M12-653

Title: *A Comparative Bioavailability Study of Elagolix Tablets in Healthy Premenopausal Females*

Objectives:

- To assess the relative bioavailability of single doses of two test tablet formulations of elagolix with that of the reference IR tablet (Phase 1 ^{(b) (4)} formulation) at a 150 mg dose under fasting conditions.
- To assess the potential effects of a high fat meal on the pharmacokinetics of two test tablet formulations of elagolix.

Study Design:

This Phase 1, single-dose, open-label study was conducted according to a two-part (Part 1: 3-period, complete crossover; Part 2: 1-period, parallel), randomized design. 24 healthy premenopausal female subjects participated in both parts of the study and were randomly assigned in equal numbers to twelve sequences as shown in **Table 2.3-1**.

Table 2.3-1. Sequence Groups in Study M12-653

Sequence	Subject Numbers	Period 1	Period 2	Period 3	Period 4
I	(b) (6)	A	B	C	D
II	(b) (6)	B	C	A	D
III	(b) (6)	C	A	B	D
IV	(b) (6)	A	C	B	D
V	(b) (6)	B	A	C	D
VI	(b) (6)	C	B	A	D
VII	(b) (6)	A	B	C	E
VIII	(b) (6)	B	C	A	E
IX	(b) (6)	C	A	B	E
X	(b) (6)	A	C	B	E
XI	(b) (6)	B	A	C	E
XII	(b) (6)	C	B	A	E

In Part 1 (Periods 1, 2, and 3), study drug was administered in the morning on Study Day 1 of each period as follows:

- Regimen A One 150 mg elagolix IR tablet (Formulation A, (b) (4) formulation) administered under fasting conditions (test) (Note: Formulation A was not selected for further development)
- Regimen B One 150 mg elagolix IR tablet (Formulation B, (b) (4) formulation) administered under fasting conditions (test) (Note: Formulation B is the (b) (4) formulation used in three Phase 3 studies)
- Regimen C One 150 mg elagolix IR tablet (Formulation C, (b) (4) formulation) administered under fasting conditions (reference) (Note: Formulation C is the (b) (4) formulation used in eleven Phase 1 studies conducted by (b) (4))

In Part 2 (Period 4), study drug was administered in the morning of Study Day 1 after consuming a high-fat meal as follows:

- Regimen D One 150 mg elagolix IR tablet (Formulation A, (b) (4) formulation) administered approximately 30 minutes after a high-fat meal (test)
- Regimen E One 150 mg elagolix IR tablet (Formulation B, (b) (4) formulation) administered approximately 30 minutes after a high-fat meal (test)

Since Formulation A was not selected for further development, the PK and safety data of Regimen A and D are not reviewed.

PK Results:

For Part 1 of the study, the data of all 24 subjects enrolled in the study were included in the BE assessment. In Part 2, Subjects (b) (6) and (b) (6) did not receive test Regimen E ((b) (4) formulation) and data from 10 subjects were included in the food effect assessment for (b) (4) formulation. Subject (b) (6) had missing pharmacokinetic assay results at 2 hours post dose for Regimen B, at 0.5, 0.75 and 1.5 hours post dose for Regimen C. Subject (b) (6) was excluded from the BE analysis between Formulation B and C. The BE analysis results for (b) (4) formulation (Regimen B, test) and (b) (4) formulation (Regimen C, reference) are shown in **Table 2.3-2**. The 90% confidence intervals with respect to elagolix C_{max} and AUCs were within the 80 - 125% range following administration of one 150 mg (b) (4) formulation tablet (Regimen B,

test) relative to one 150 mg (b) (4) formulation tablet (Regimen C, reference). The (b) (4) formulation used in Phase 3 studies and the (b) (4) formulation used in Phase 1 studies are bioequivalent.

The effects of food on the PK of (b) (4) formulation were shown in **Table 2.3-2**. Under high-fat meal conditions, the elagolix (b) (4) formulation 150 mg IR tablet had a lower exposure relative to fasted conditions; with a decrease of 34% and 25% in C_{max} and $AUC_{0-\infty}$, respectively. Similar food effects were observed with the commercial (b) (4) light orange formulation in Study M15-817 (a decrease of 36% and 24% in C_{max} and $AUC_{0-\infty}$ under fed conditions, respectively).

Table 2.3-2. Bioequivalence and Food Effect Assessment for Elagolix (Study M12-653)

Parameter	Least Squares Geometric Means		% Test/Ref Ratio (90% CI)
	Regimen B [Test]	Regimen C [Ref]	
BE Assessment¹			
C_{max} (ng/mL)	465.9	468.5	99.4 (88.1 – 112.2)
AUC_{0-t} (ng•h/mL)	1196.2	1158.7	103.2 (97.5 – 109.3)
$AUC_{0-\infty}$ (ng•h/mL)	1205.0	1168.1	103.2 (97.5 – 109.2)
Food Effect Assessment²	Regimen E [Test]	Regimen B [Ref]	
C_{max} (ng/mL)	366.2	550.4	66.5 (49.7 – 89.0)
AUC_{0-t} (ng•h/mL)	1087.2	1452.6	74.8 (62.5 – 89.6)
$AUC_{0-\infty}$ (ng•h/mL)	1097.6	1461.3	75.1 (62.8 – 89.8)

1. Subject (b) (6) was excluded from the analysis.
2. Subjects (b) (6) and (b) (6) were not included in the analysis.

Safety Results:

The proportion of subjects reporting at least one treatment-emergent adverse event were 4/23 (17.4%) in Regimen B, 5/23 (21.7%) in Regimen C, and 1/10 (10%) in the Regimen E. No clinically significant vital signs, ECG or changes in laboratory measurements attributed to elagolix were observed during the study. No deaths or serious adverse events were reported during the study. One subject was prematurely discontinued from the study prior to dosing on Study Day 1 in Period 3 due to an adverse event of trichomoniasis.

3. Clinical PK and/or PD Assessments

In addition to the BA/BE, DDI and QT studies, AbbVie conducted six Phase 1 PK/PD studies and four Phase 3 studies while NBI conducted five Phase 1 PK/PD studies and six Phase 2 studies (**Table 3.1**). In the Phase 2 and Phase 3 studies, PK and PD samples were sparsely collected. The formulations used in NBI's five Phase 1 studies were either (b) (4) tablets, which were different from the formulations used in AbbVie's Phase 1 and Phase 3 studies. Therefore, only AbbVie's Phase 1 studies and NBI's mass balance study (NBI-56418-0601) are individually reviewed.

Table 3.1. Clinical PK/PD Studies Submitted in the NDA (BA/BE, DDI and QT studies excluded)

Study Number	Study Population	Study Formulations	Dose Regimens	Descriptions
Studies Conducted by AbbVie				

M13-784	Healthy	(b) (4)	150 mg	Single dose 600 mg and 900 mg	SAD
M12-790	Healthy	(b) (4)	50 and 150 mg	150 mg QD, 100-400 mg BID	MAD
M12-654	Healthy	(b) (4)	50 and 150 mg	150 mg QD, 200 mg BID	Multi-dose PK/PD in Japanese and Chinese females
M12-673	Healthy	(b) (4)	50 and 150 mg	100-200 mg QD, 100-300 mg BID	Ovarian activity and ovulation
M12-662	Patients	(b) (4)	150 mg	Single dose 150 mg	Hepatic impairment
M12-655	Patients	(b) (4)	50 and 150 mg	Single dose 200 mg	Renal impairment
M12-665	Patients	(b) (4)	100 and 150 mg	150 mg QD and 200 mg BID	Pivotal Phase 3
M12-671	Patients	(b) (4)	100 and 150 mg	150 mg QD and 200 mg BID	Pivotal Phase 3
M12-667	Patients	(b) (4)	100 and 150 mg	150 mg QD and 200 mg BID	Extended Phase 3
M12-821	Patients	(b) (4)	150 and 200 mg	150 mg QD and 200 mg BID	Extended Phase 3
Studies Conducted by NBI					
NBI-56418-0401	Healthy	(b) (4)	solution	Single dose, 100 mg	Site of oral absorption
NBI-56418-0601	Healthy	(b) (4)	solution	Single dose, 150 mg	Mass balance
NBI-56418-0301	Healthy	(b) (4)	solution	Single dose, 25-400 mg Multi-dose, 50-200 mg QD and 100 mg BID	Single- and multi-dose PK/PD
NBI-56418-0405	Healthy	(b) (4)	solution	50 mg QD, 150 mg QD	Multi-dose PK/PD
NBI-56418-0503	Healthy	(b) (4)	25 mg	75 mg BID, 150 mg QD	Multi-dose PK/PD
NBI-56418-0501	Patients	(b) (4)	25 mg	75 mg QD, 150 mg QD	12-week Phase 2 efficacy/safety
NBI-56418-0504	Patients	(b) (4)	50 mg	50 mg BID, 100 mg BID	12-week Phase 2 efficacy/safety
NBI-56418-0603	Patients	(b) (4)	75 mg	75 mg BID, 150 mg QD	24-week Phase 2 efficacy/safety
NBI-56418-0702	Patients	(b) (4)	100 and 150 mg	150 mg QD, 250 mg QD	24-week Phase 2 efficacy/safety
NBI-56418-0703	Patients	(b) (4)	100 and 150 mg	150 mg QD, 250 mg QD	24-week Phase 2 efficacy/safety
NBI-56418-0901	Patients	(b) (4)	150 mg	150 mg QD	24-week Phase 2 efficacy/safety

3.1 Study M13-784 (SAD)

Title: *Assessment of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Doses of Elagolix in Healthy Premenopausal Female Volunteers*

Objectives:

- To assess the safety, tolerability and pharmacokinetics of single ascending doses of elagolix under fasting conditions in healthy premenopausal females.

- To assess the effect of elagolix on pharmacodynamics of hormones (estradiol [E2], progesterone [P], luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) in healthy premenopausal females.

Study Design:

This was a Phase 1, single-center, randomized, single ascending dose (SAD), double-blind, placebo-controlled study. The study consisted of two groups, 600 mg group (Group 1) and 900 mg group (Group 2) and 18 subjects were enrolled. Within each group, 6 subjects were randomized to receive elagolix and 3 subjects were randomized to receive matching placebo. Four 150 mg tablets (600 mg) or six 150 mg tablets (900 mg) of elagolix or matching placebo were administered on Study Day 1 after a 10-hour fast. Blood samples for the assay of elagolix were collected by venipuncture on Study Day 1 prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after dosing. Blood samples for the assay of hormones (E2, P, LH, and FSH) were obtained by venipuncture on Study Day 1 prior to dosing (0 hour) and at 2, 4, 8, 12, 24, 36 and 48 hours after dosing in each group, or upon premature discontinuation.

PK Results:

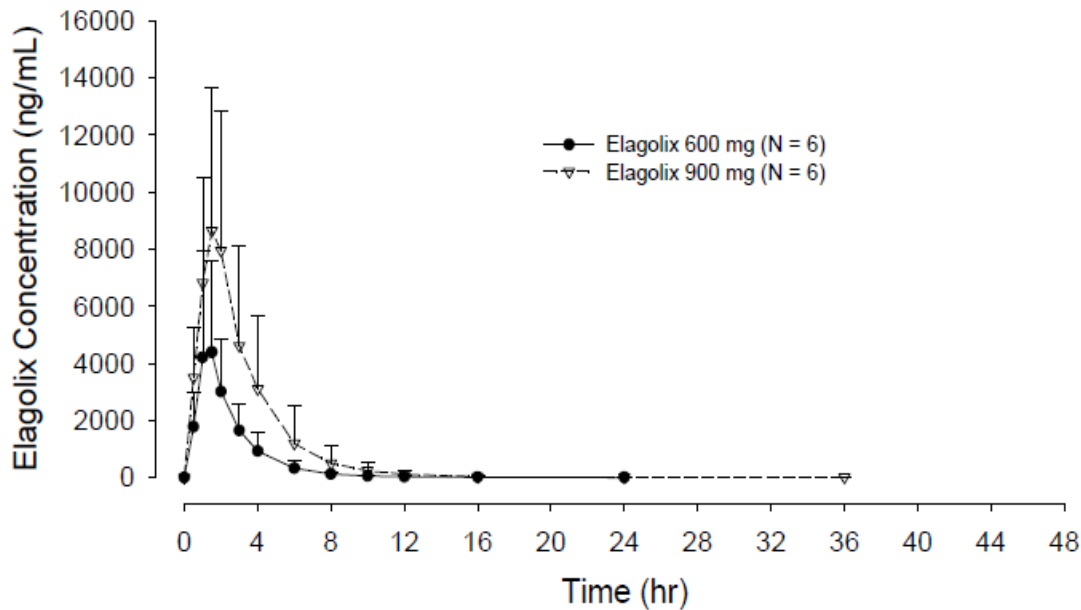


Figure 3.1-1. Mean + SD Plasma Concentration-Time Profiles of Single-Dose Elagolix (Study M13-784)

The mean ± SD plasma concentration-time profiles of single-dose elagolix are presented in **Figure 3.1-1** on a linear scale. The mean ± SD PK parameters of elagolix after administration of 600 and 900 mg of elagolix are shown in **Table 3.1-1**. Elagolix was characterized by a rapid absorption with a T_{max} of approximately 1 hour. After reaching C_{max} , elagolix concentrations declined in a biphasic fashion with an estimated $T_{1/2}$ of 3 to 5 hours. The mean dose-normalized C_{max} and AUC values of elagolix showed a greater than dose proportional increase in C_{max} and AUCs from 600 mg to 900 mg dose.

Table 3.1-1. Mean ± SD Pharmacokinetic Parameters of Single-Dose Elagolix (Study M13-784)

Pharmacokinetic Parameters (units)		Elagolix Single Dose Groups	
		600 mg (N = 6)	900 mg (N = 6)
C_{max}^a	(ng/mL)	5022 ± 3860	8992 ± 4901
T_{max}^a	(hr)	1.4 ± 0.4	1.2 ± 0.4
AUC_t^a	(ng•hr/mL)	11590 ± 7786	28934 ± 20695
AUC_{∞}^a	(ng•hr/mL)	11606 ± 7788	28952 ± 20696
AUC_{12}^a	(ng•hr/mL)	11471 ± 7683	28475 ± 20148
$t_{1/2}^b$	(hr)	2.67 ± 0.90	4.93 ± 2.55
CL/F^a	(L/h)	74.39 ± 43.80	39.20 ± 14.30
Vd_{β}/F^a	(L)	293.5 ± 119.1	309.2 ± 139.8
$C_{max}/Dose$	(ng/mL)/mg	8.37 ± 6.43	9.99 ± 5.45
$AUC_t/Dose$	(ng•hr/mL)/mg	19.32 ± 12.98	32.15 ± 22.99
$AUC_{\infty}/Dose$	(ng•hr/mL)/mg	19.34 ± 12.98	32.17 ± 23.00

a. Parameter not statistically compared between dose groups.

b. Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β .

PD Results:

Estradiol Suppression:

Mean + SD E2 hormone concentration-time profiles for single doses of elagolix 600 mg, 900 mg or placebo are presented in **Figure 3.1-2**. The mean ± SD E2 C_0 , C_{min} , T_{min} , and AUC_t after administration of elagolix 600 mg, elagolix 900 mg or placebo are shown in **Table 3.1-2**.

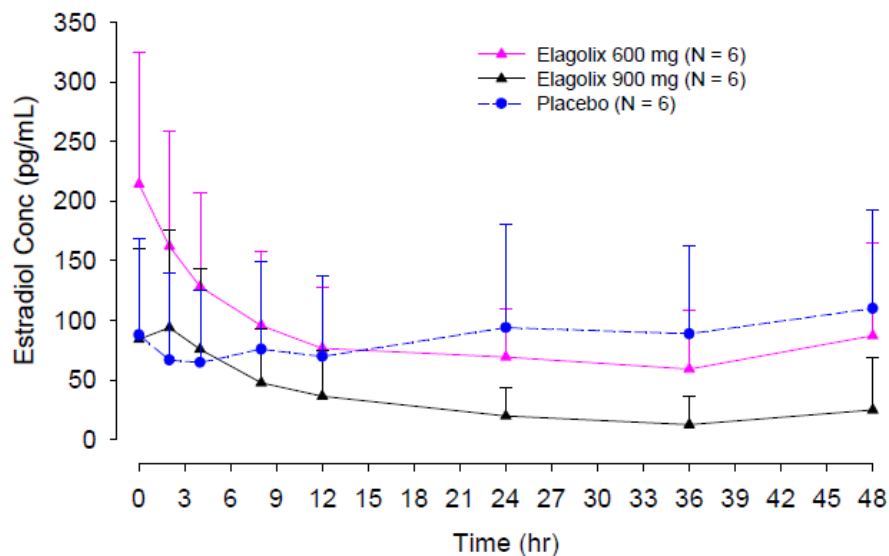


Figure 3.1-2. Mean + SD Estradiol (E2) Concentration-Time Profiles After Administration of Single Doses of Elagolix or Placebo (Study M13-784)

Table 3.1-2. Mean $\pm$ SD Estradiol (E2) PD Parameters After Administration of Single Doses of Elagolix or Placebo (Study M13-784)

Parameter (units)	E2		
	Elagolix 600 mg (N = 6)	Elagolix 900 mg (N = 6)	Placebo (N = 6)
C ₀ (pg/mL)	214 $\pm$ 110	84.0 $\pm$ 76.4	87.7 $\pm$ 80.4
C _{min} (pg/mL)	53.6 $\pm$ 40.3	8.7 $\pm$ 16.4	54.7 $\pm$ 67.7
T _{min} (hr)	34.0 $\pm$ 9.0	26.0 $\pm$ 14.0	5.0 $\pm$ 4.2
AUC _t (pg•hr/mL)	3848.1 $\pm$ 2602.3	1457.2 $\pm$ 1390.3	4124.8 $\pm$ 3602.0

The large difference in the average baseline estradiol level between 600 mg group and placebo group or 900 mg group precluded a valid comparison of 600 mg group with placebo group or 900 mg group. Compared to placebo group, estradiol suppression was observed in 900 mg group within 48 hours post-dose. The C_{min} of estradiol was determined as 26 $\pm$ 14 hour, indicating a 24-36 hour lag time of estradiol suppression compared to the T_{max} of elagolix (1.2 $\pm$ 0.4 hour).

Progesterone Suppression:

Mean + SD progesterone concentration-time profiles for single doses of elagolix 600 mg, 900 mg or placebo are presented in **Figure 3.1-3**. The average baseline progesterone levels were 35.3 nmol/L, 3.3 nmol/L, and 5.4 nmol/L for elagolix 600 mg, 900 mg, and placebo groups, which precluded a valid progesterone comparison of 600 mg group with placebo group. Considering the progesterone measurement variability and the slight differences in progesterone levels between 900 mg group and placebo group, we cannot draw a conclusion whether there was progesterone suppression within 48 hours after administration of a single dose of 900 mg elagolix.

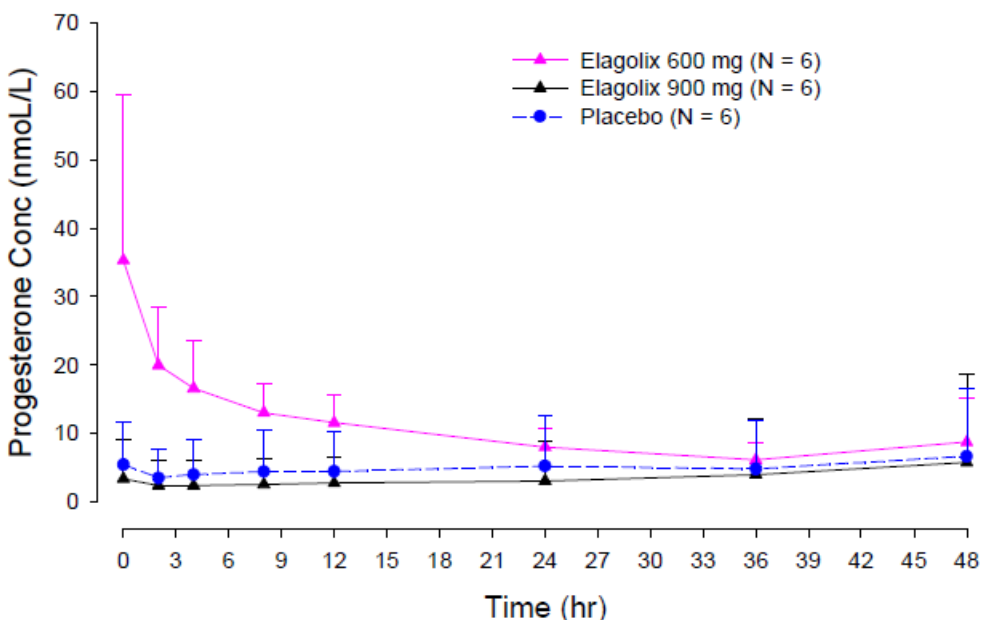


Figure 3.1-3. Mean + SD Progesterone (P) Concentration-Time Profiles After Administration of Single Doses of Elagolix or Placebo (Study M13-784)

Luteinizing Hormone (LH) Suppression:

As shown in **Figure 3.1-4**, compared to placebo group, LH appeared to be suppressed with administration of a single dose of 600 or 900 mg elagolix although dose-dependent suppression was not observed. A maximal suppression was observed at 12-18 hours post-dose.

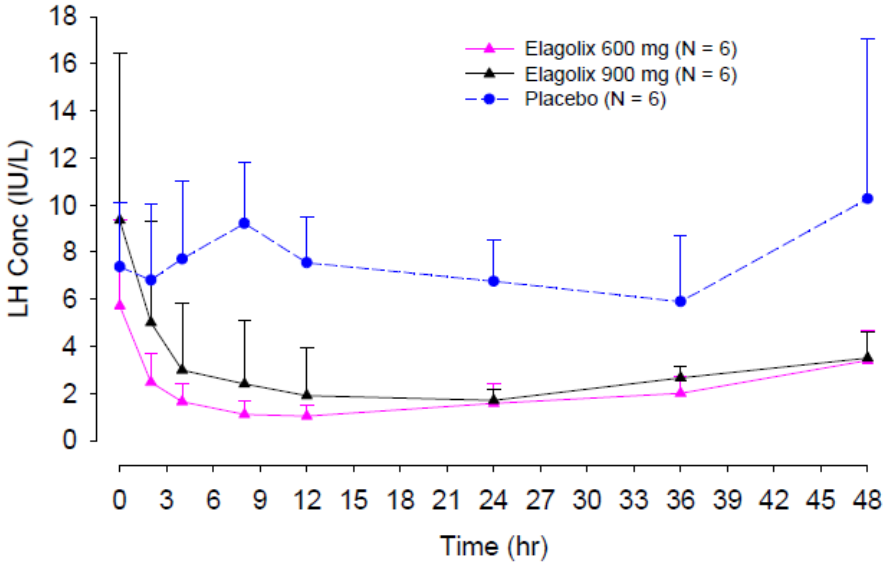


Figure 3.1-4. Mean + SD Luteinizing Hormone [LH] Concentration-Time Profiles After Administration of Single Doses of Elagolix or Placebo (Study M13-784)

Follicle-Stimulating Hormone (FSH) Suppression:

As shown in **Figure 3.1-5**, compared to placebo group, FSH appeared to be suppressed with administration of a single-dose of 600 or 900 mg elagolix, as FSH concentrations decreased from baseline for all subjects for both groups. A maximal suppression was observed at 12-24 hours post-dose.

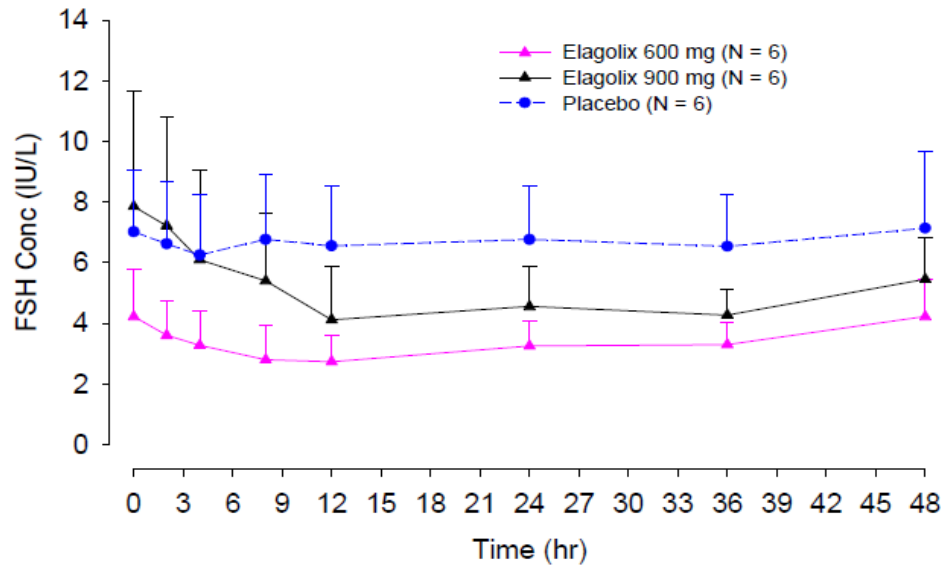


Figure 3.1-5. Mean + SD Follicle-Stimulating Hormone (FSH) Concentration-Time Profiles After Administration of Single Doses of Elagolix or Placebo (Study M13-784)

Reviewer's Comments:

- *In this study, subjects received elagolix or placebo at any timepoint during the menstrual cycle (between approximately 3 and 25 days after the date of their last menses with cycle durations ranging from 27 to 32 days), which resulted in a largely variable baseline hormone values. The single-dose hormone suppression findings are difficult to interpret in this study, since subjects were in different stages of the menstrual cycles when dosing began and large differences in baseline levels of hormones were observed among treatment groups and placebo group.*
- *Compared to placebo group, estradiol suppression was observed in 900 mg group within 48 hours post-dose.*
- *Compared to placebo group, a slight decrease in progesterone levels in elagolix 900 mg group. A valid conclusion on whether there was progesterone suppression after administration of a single dose of 900 mg elagolix cannot be drawn.*
- *Compared to placebo group, LH and FSH appeared to be suppressed with administration of a single dose of 600 or 900 mg elagolix although dose-dependent suppression was not observed.*

Safety Results:

One subject (1/6, 16.7%) in each of the elagolix 600 mg, 900 mg or placebo groups experienced a treatment-emergent adverse event. No clinically significant vital signs, ECG or changes in laboratory measurements attributed to elagolix were observed during the study. No clinically significant ECG abnormalities, including QTc findings up to a 900 mg single dose of elagolix. There was no apparent relationship between elagolix exposure and increase in QTcF. No deaths, other serious adverse events or discontinuations due to adverse events occurred during the study. No adverse events were reported as leading to elagolix discontinuation.

3.2 Study M12-790 (MAD)

Title: *Assessment of the Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Multiple Ascending Doses of Elagolix in Healthy Premenopausal Female Volunteers*

Objectives:

- To assess the safety, tolerability and pharmacokinetics of multiple ascending doses of elagolix under fasting conditions in healthy premenopausal females.
- To assess the effect of elagolix on pharmacodynamics of hormones (E2, P, LH and FSH) in healthy premenopausal females.

Study Design:

This Phase 1, single-center, randomized, placebo-controlled, multiple-ascending-dose, double-blind study was conducted according to a sequential design. The study consisted of five dose groups, 200 mg BID (Group 1), 300 mg BID (Group 2), 400 mg BID (Group 3), 150 mg QD (Group 4), and 100 mg BID (Group 5). 45 subjects were enrolled and randomly assigned to five groups. Within each group, subjects were randomly assigned in a 3:1 ratio to elagolix and matching placebo. Subjects received one of 5 dose regimens of elagolix or matching placebo for 21 consecutive days under fasting conditions. Serial blood samples for the assay of elagolix were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing on Study Days 1 and 21 in each group. An additional sample was collected at 36 and 48 hours after dosing on Study Day 21 (the afternoon of Study Day 22 and the morning of Study Day 23) in each group. In addition, trough samples were collected prior to the morning dose on Study Days 5, 7, 9, 15, 17, and 19 or upon premature discontinuation in each group. Blood samples for the assay of E2, P, LH, and FSH were collected at Screening, prior to dosing (0 hour) and at 2, 4, 6, 8, 10, 12, 16, and 24 hours after dosing on Study Days 1 and 21 in each group. An additional sample was collected at 30, 36, and 48 hours after dosing on Study Day 21 in each group. Additional

samples were collected prior to the morning dose (0 hour) on Study Days 3, 5, 7, 9, 11, 13, 15, 17, and 19 or upon premature discontinuation for the evaluation of hormones (E2, P, LH, and FSH).

PK Results:

The mean + SD plasma concentration-time profiles over a dosing interval of elagolix are presented in Figure 3.2-1 on a log-linear scale. The mean ± SD PK parameters of elagolix are shown in Table 3.2-1. Elagolix was characterized by a rapid absorption with a T_{max} of approximately 1 – 1.3 hour. After reaching C_{max} , elagolix concentrations declined in a biphasic fashion with an estimated $T_{1/2}$ of 4 to 6 hours.

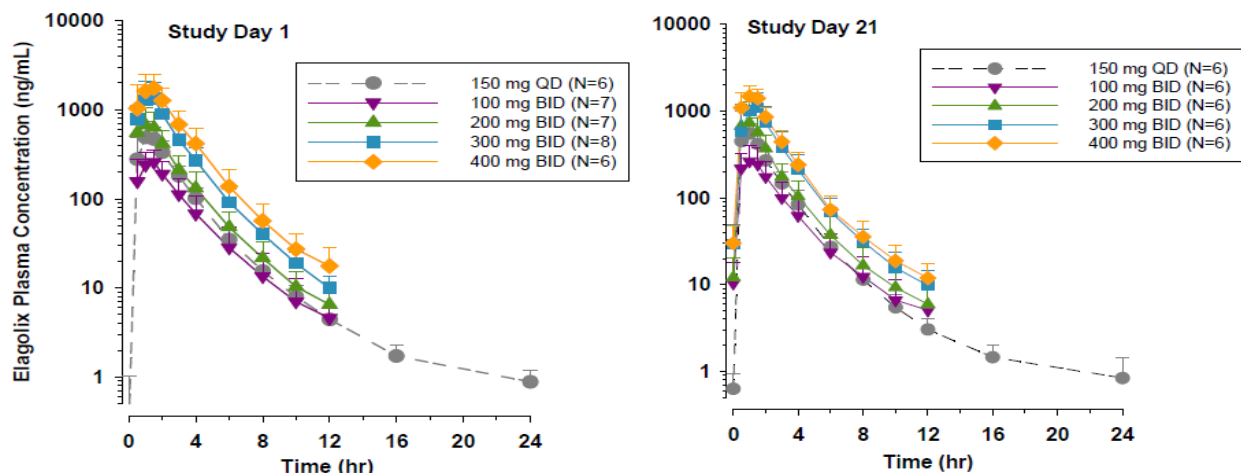


Figure 3.2-1. Mean + SD Elagolix Plasma Concentration-Time Profiles for a Dosing Interval (Study M12-790)

The mean ± SD dose-normalized C_{max} and AUC_{τ} were plotted against doses in Figure 3.2-2. On Day 1, both dose-normalized C_{max} and AUC_{τ} increased with dose. Elagolix showed an approximately dose-proportional increase in exposures from 100 mg BID to 200 mg BID and a more than dose-proportional increase from 200 mg BID to 400 mg BID. At steady state (Day 21), elagolix showed a dose-proportional increase in exposures (C_{max} and AUC_{τ}) from 100 mg BID to 400 mg BID.

The mean accumulation ratio was less than 1 among all elagolix doses, indicating no drug accumulation (Table 3.2-1). The mean accumulation ratios at high doses (0.78 for 300 mg BID and 0.84 for 400 mg BID) were lower than that at low doses (0.98 for 100 mg BID and 0.89 for 200 mg BID). Following multiple doses of 300 mg and 400 mg BID, the mean AUC_{τ} were 22% to 16% lower than those observed on Day 1.

To assess drug accumulation, the Applicant plotted mean predose concentrations (C_{trough}) of elagolix against study day (Figure 3.2-2). The data showed that a steady-state C_{trough} was likely achieved on Day 15 across all the four BID dose groups. It is unlikely that C_{trough} would further decrease beyond Day 22.

Table 3.2-1. Mean $\pm$ SD Pharmacokinetic Parameters of Elagolix (Study M12-790)

Pharmacokinetic Parameter (units)	100 mg BID N = 7	150 mg QD N = 6	200 mg BID N = 7	300 mg BID N = 8	400 mg BID N = 6
Study Day 1					
T _{max} (hr)	1.2 $\pm$ 0.4	1.3 $\pm$ 0.3	1.1 $\pm$ 0.3	1.2 $\pm$ 0.4	1.3 $\pm$ 0.5
C _{max} (ng/mL)	285 $\pm$ 89.2	507 $\pm$ 207	712 $\pm$ 362	1479 $\pm$ 740	1928 $\pm$ 783
AUC _{τ} (ng•hr/mL)	787 $\pm$ 288	1331 $\pm$ 487	1813 $\pm$ 876	3509 $\pm$ 1556	4918 $\pm$ 2070
C _{trough} (ng/mL) ^c	4.58 $\pm$ 4.67	0.88 $\pm$ 0.32	6.52 $\pm$ 3.20	9.97 $\pm$ 3.45	17.6 $\pm$ 10.3
C _{max} /Dose	2.85 $\pm$ 0.89	3.38 $\pm$ 1.38	3.56 $\pm$ 1.81	4.93 $\pm$ 2.47	4.82 $\pm$ 1.96
AUC _{τ} /Dose	7.87 $\pm$ 2.88	8.87 $\pm$ 3.25	9.07 $\pm$ 4.38	11.7 $\pm$ 5.19	12.3 $\pm$ 5.17
Study Day 21^a					
T _{max} (hr)	1.0 $\pm$ 0.4	0.9 $\pm$ 0.2	1.1 $\pm$ 0.4	1.2 $\pm$ 0.4	1.2 $\pm$ 0.4
C _{max} (ng/mL)	278 $\pm$ 131	574 $\pm$ 164	774 $\pm$ 530	1200 $\pm$ 544	1758 $\pm$ 308
AUC _{τ} (ng•hr/mL)	779 $\pm$ 373	1292 $\pm$ 403	1725 $\pm$ 990	2826 $\pm$ 1231	3716 $\pm$ 592
t _{1/2} (hr) ^b	4.65 $\pm$ 2.54	6.42 $\pm$ 3.20	4.29 $\pm$ 0.47	5.32 $\pm$ 1.52	5.62 $\pm$ 1.82
R _{ac} ^d	0.98 $\pm$ 0.15	0.98 $\pm$ 0.07	0.89 $\pm$ 0.17	0.78 $\pm$ 0.09	0.84 $\pm$ 0.29
C _{trough} (ng/mL) ^c	5.06 $\pm$ 4.25	0.84 $\pm$ 0.58	5.92 $\pm$ 4.05	9.78 $\pm$ 4.68	11.9 $\pm$ 5.52
CL/F (L/hr)	163 $\pm$ 91.1	123 $\pm$ 26.1	144 $\pm$ 61.5	126 $\pm$ 58.0	110 $\pm$ 16.6
Vd β /F (L)	1499 $\pm$ 1709	1674 $\pm$ 1570	881 $\pm$ 335	977 $\pm$ 327	1026 $\pm$ 512
C _{max} /Dose	2.78 $\pm$ 1.32	3.83 $\pm$ 1.09	3.87 $\pm$ 2.65	4.00 $\pm$ 1.81	4.40 $\pm$ 0.77
AUC _{τ} /Dose	7.79 $\pm$ 3.73	8.61 $\pm$ 2.68	8.62 $\pm$ 4.95	9.42 $\pm$ 4.10	9.29 $\pm$ 1.48

Note: AUC _{τ} where τ (tau) is the dosing interval (i.e., 12 hours for BID, 24 hours for QD).

- N = 6 on Study Day 21 for each of the dose groups.
- Presented as the harmonic mean, pseudo-standard deviation.
- C_{trough} is C₁₂ for BID dose groups and C₂₄ for the QD dose group.
- Accumulation ratio calculated as the ratio of Study Day 21 AUC _{τ} to Study Day 1 AUC _{τ} .

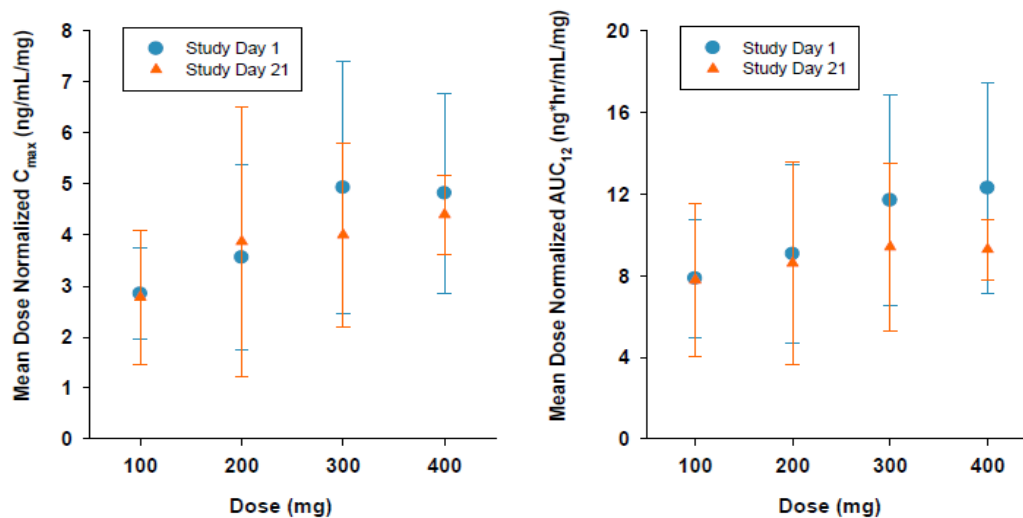


Figure 3.2-2. Mean $\pm$ SD Elagolix Dose Normalized C_{max} and AUC Following Multiple Doses of 100 to 400 mg BID

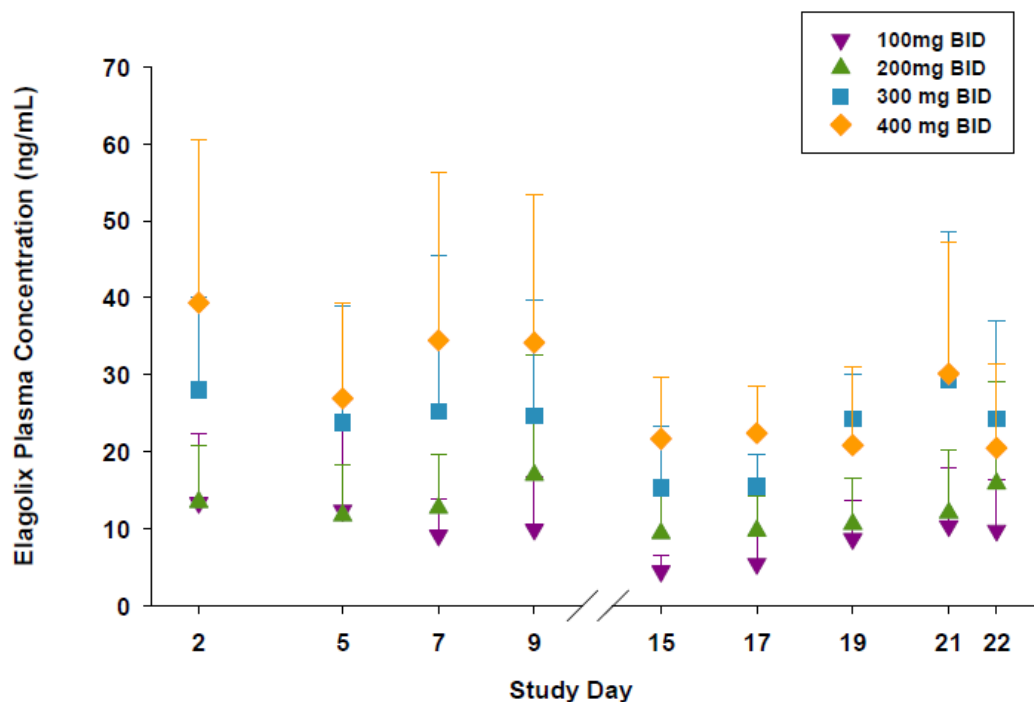


Figure 3.2-3. Mean + SD Plasma Elagolix Predose Concentrations (C_{trough}) Following BID Doses

Reviewer's Comments:

- The Applicant claimed that elagolix exhibits an approximately dose-proportional increase in exposures from 100 mg BID to 400 mg BID based on the PK data collected on Day 21 and Day 22. This reviewer agrees that elagolix showed a linear PK up to 400 mg BID at a steady state. However, for single-dose PK on Day 1, the approximate dose-proportionality was observed up to 200 mg only. In the dose range of 200 – 400 mg, single-dose showed a greater than dose proportional increase in C_{max} and AUC_t. Combined with the single-dose PK results from Study M13-784 (600 mg and 900 mg) and Study 12-661 (300 mg and 1200 mg), this reviewer concluded that single-dose elagolix showed a more than dose-proportional PK from 200 mg to 1200 mg.
- The different PK characteristics of single-dose and multi-dose elagolix probably can be explained by hepatic enzyme and/or transporter auto-induction by elagolix. Clinical DDI studies (Study M15-629 and Study NBI-56418-0502) showed that 150 mg QD and 300 mg QD elagolix induced hepatic metabolic enzyme CYP3A. Study M12-660 showed that elagolix is a substrate of CYP3A. Co-administration of 20 mg QD rosuvastatin with multiple-dose elagolix 300 mg BID resulted in a decrease of rosuvastatin AUC by 40% (Study M13-756), suggesting that elagolix is likely to be an inducer of hepatic transporters OATP1B1 and/or BCRP. Both in vitro and in vivo DDI data showed that elagolix is a substrate of OATP1B1. The auto-induction of CYP3A, OATP1B1 and/or BCRP may explain the low values of drug accumulation ratio ($R_{ac} < 1$) and the different characteristics of single-dose and multi-dose PK at high doses (> 200 mg).
- The continuous decrease in drug exposure caused by hepatic enzyme and/or transporter auto-induction might raise a potential concern on efficacy. The C_{trough} data collected between Day 1 and Day 22 (**Figure 3.2-3**) showed that a steady-state C_{trough} was achieved on Day 15, suggesting a maximal induction of CYP3A, OATP1B1 and/or BCRP was achieved in 2-3 weeks. The long-term elagolix treatment is not expected to compromise efficacy, which is further confirmed by Phase 3 efficacy data.

PD Results:

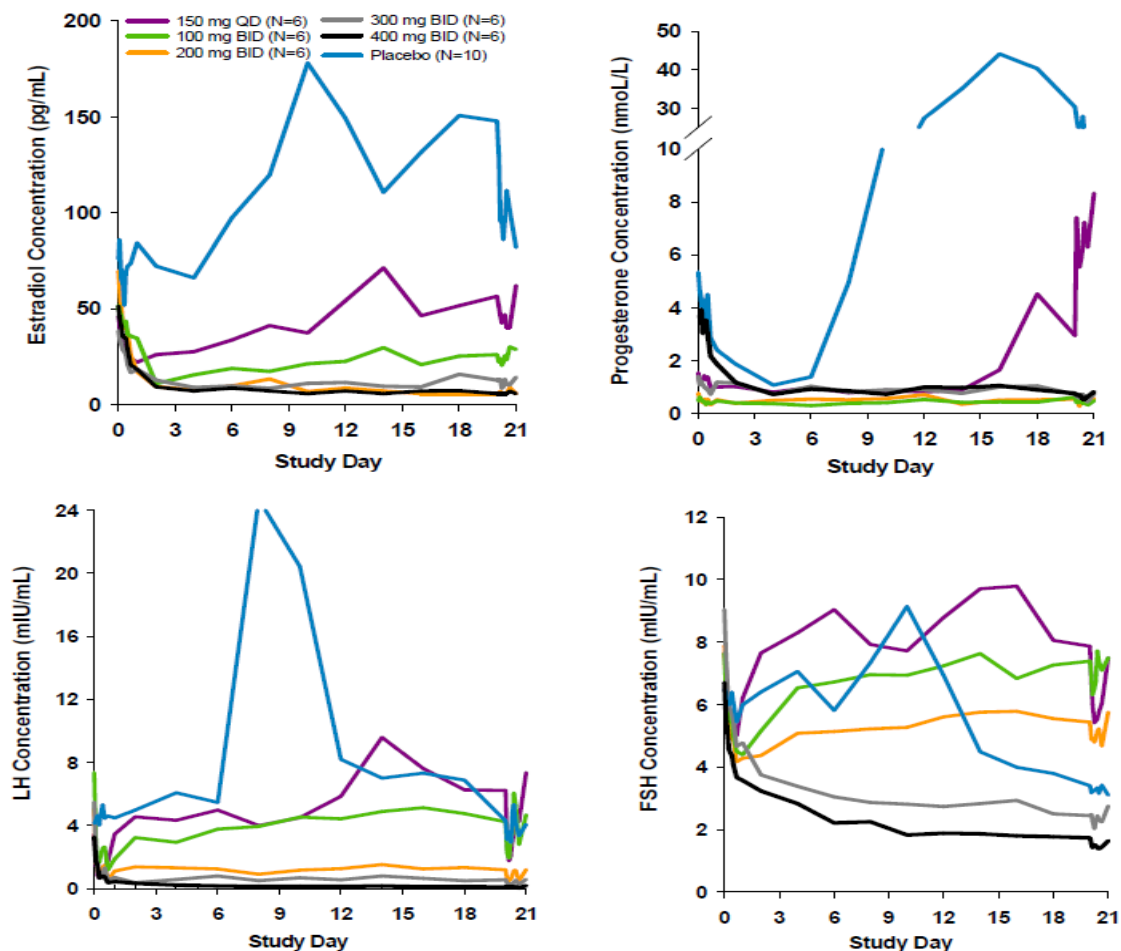


Figure 3.2-4. Mean Hormone Concentrations Following Multiple Doses of Placebo and Elagolix (Study M12-790)

Estradiol (E2):

As shown in **Figure 3.2-4** and **Table 3.2-2**, E2 suppression was observed within 6 hours of dosing and E2 concentrations were lower following elagolix administration compared to placebo. At the dose of 150 mg QD, E2 was partially suppressed. A nearly full suppression of E2 appeared to be achieved at doses of 200 mg BID and higher and a steady-state E2 suppression appeared to be achieved on Day 3. Following the last dose of elagolix on Day 21, E2 suppression was maintained for ≥ 12 hours in most subjects who received elagolix doses ≥ 200 mg BID.

An exposure-response analysis for E2 suppression was conducted at steady state using elagolix AUC_{0-24} on Study Day 21 and hormone AUC_{0-21d} for E2 (**Figure 3.2-5**). An elagolix AUC_{0-24} of approximately $0.63 \mu\text{g}\cdot\text{h}/\text{mL}$, corresponding to an elagolix daily dose of approximately 70 mg/day, was estimated to reduce E2 AUC_{0-21d} by 50% relative to placebo. Elagolix suppression of E2 appears to reach a maximum at doses of approximately 200 mg BID.

Table 3.2-2. Blood Concentrations of Unconjugated Estradiol (pg/mL) within 24 h postdose on Day 1

Dose Regimens		HOURS AFTER DOSING									
SUBJECT		0	2	4	6	8	10	12	16	24	
Placebo	MEAN	82.909	64.418	62.164	51.891	69.500	72.300	74.180	78.000	72.780	
	STD	83.902	59.046	48.828	33.783	54.128	59.554	72.463	69.859	67.597	
150 mg QD	MEAN	45.667	42.600	35.800	30.500	30.000	31.333	29.000	26.100	24.100	
	STD	21.510	20.526	21.557	18.163	16.757	16.046	14.381	18.677	16.387	
200 mg BID	MEAN	90.714	79.571	71.143	58.857	59.286	60.571	50.714	40.143	33.171	
	STD	57.728	49.467	55.508	52.550	52.671	55.512	40.194	40.151	34.932	

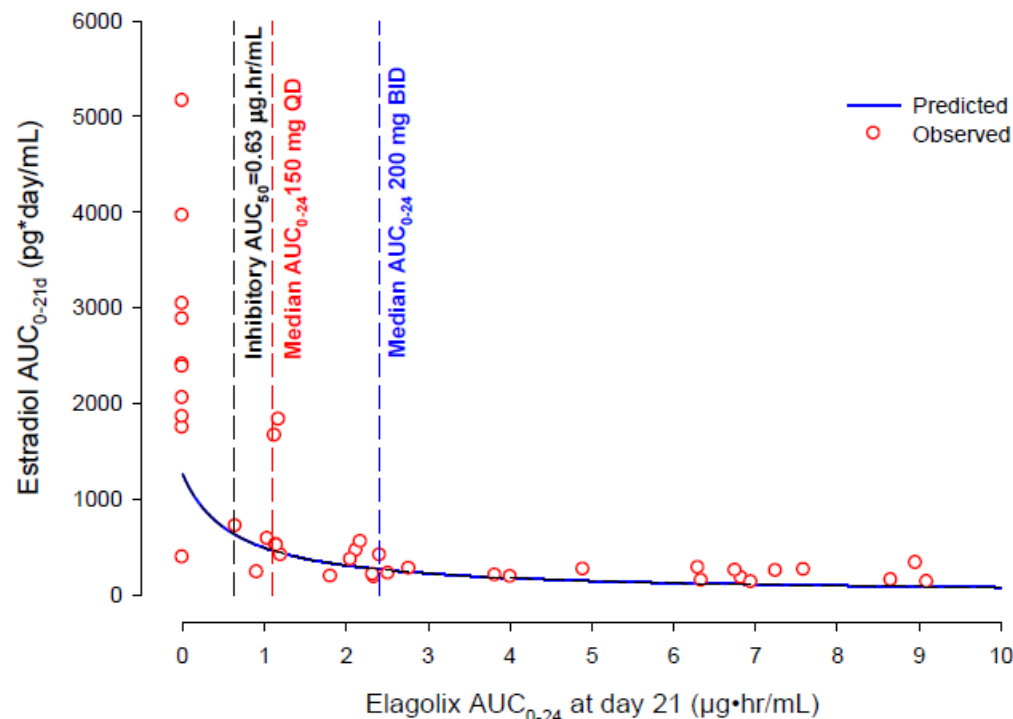


Figure 3.2-5. Elagolix Exposure-Response on Estradiol Suppression (Study M12-790)

Progesterone (P):

Anovulatory concentrations (< 5 nM) were observed in all subjects at elagolix doses of 100 mg BID (200 mg daily total) and above, and remained lower than 5 nM at 24 hours after the last dose on Study Day 21 (**Figure 3.2-4**). An increase in mean P concentrations for the 150 mg QD dose group on Day 17. Due to the very low baseline P levels in the 150 mg QD, 100 mg BID, 200 mg BID and 300 mg BID groups, it was difficult to detect the initiation of P suppression during Day 1 (**Figure 3.2-4** and **Table 3.2-3**). For the 400 mg BID group, P suppression was observed within 12 hours post dose and the maximal suppression was achieved on Day 4. Progesterone dose-response and exposure-response observed data could not be fit to an inhibitory model due to a steep dose-response and exposure-response relationship.

Table 3.2-3. Blood Concentrations of Progesterone (nM) within 24 h postdose on Day 1

Dose Regimens		HOURS AFTER DOSING								
SUBJECT		0	2	4	6	8	10	12	16	24
Placebo	MEAN	7.563	5.964	5.157	3.911	5.867	5.412	6.891	4.945	4.471
	STD	13.078	9.813	8.520	5.571	9.565	8.636	11.851	8.495	7.230
150 mg QD	MEAN	1.532	1.393	1.469	1.288	1.457	1.283	1.373	1.018	1.044
	STD	0.984	0.808	0.912	0.983	1.005	0.580	0.659	0.576	0.550
200 mg BID	MEAN	0.768	0.618	0.604	0.554	0.595	0.504	0.627	0.504	0.577
	STD	0.263	0.173	0.229	0.178	0.148	0.072	0.198	0.072	0.183

LH:

LH concentrations decreased in a dose dependent manner compared to placebo, with a maximal inhibition observed at doses of 300 mg BID and higher (**Figure 3.2-4**). For placebo subjects the LH surge was observed on around Day 9. LH suppression was observed in subjects at doses of 200 mg BID and above. LH was partially suppressed in 150 mg QD group. The blood LH concentrations measured on Day 1 indicated that LH suppression initialized within 4 hours post dose (**Table 3.2-4**). Suppression of LH was lost within 24 hours after the last dose of elagolix on Day 21 in the 200 mg BID group.

Table 3.2-4. Blood Concentrations of LH (IU/L) within 24 h postdose on Day 1

Dose Regimens		HOURS AFTER DOSING								
SUBJECT		0	2	4	6	8	10	12	16	24
Placebo	MEAN	3.945	3.755	4.000	3.864	4.990	4.550	4.380	3.760	4.340
	STD	2.087	2.211	2.051	2.266	2.265	2.491	2.569	2.108	2.309
150 mg QD	MEAN	3.450	2.000	0.840	0.683	0.833	1.150	1.400	1.733	3.467
	STD	0.660	0.596	0.270	0.331	0.216	0.704	0.620	1.001	1.015
200 mg BID	MEAN	6.857	3.071	1.857	1.514	1.457	1.871	2.014	0.900	1.643
	STD	5.281	3.055	1.882	1.785	1.536	1.455	1.535	0.963	1.508

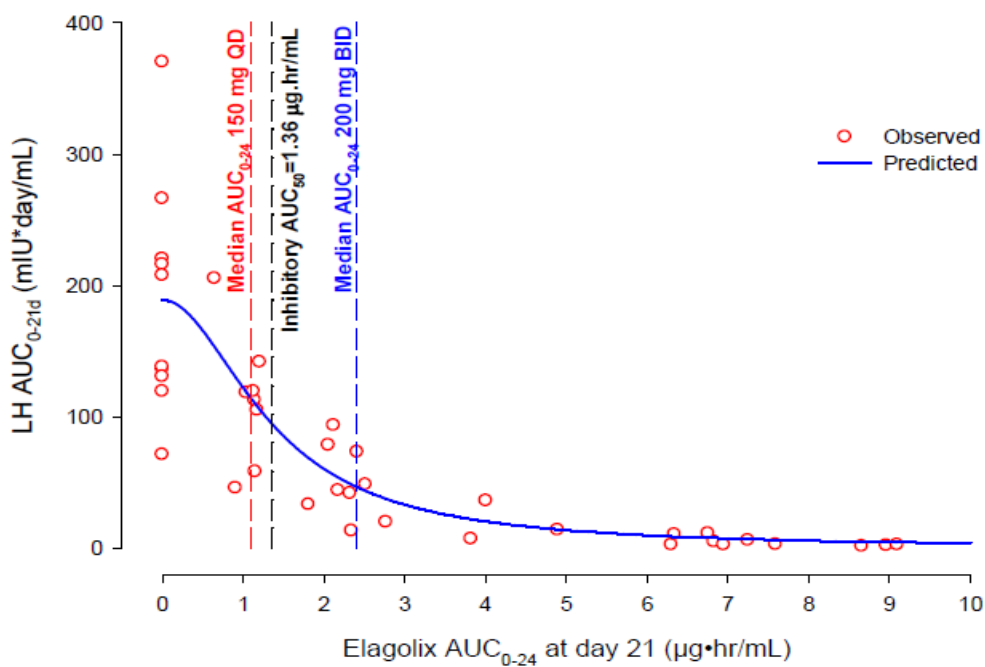


Figure 3.2-6. Elagolix Exposure-Response on LH Suppression (Study M12-790)

The exposure-response relationship for LH suppression were described using an inhibitory sigmoidal effect function (**Figure 3.2-6**). Elagolix AUC₀₋₂₄ of approximately 1.36 µg*h/mL, corresponding to an elagolix daily dose of approximately 188 mg/day, was estimated to reduce LH AUC_{0-21d} by 50% relative to placebo treatment. The effect of elagolix on LH suppression appears to reach a maximum at a dose of 300 mg BID.

FSH:

FSH suppression was found dependent on the dose of elagolix (**Figure 3.2-4**). An initial decline in mean FSH concentrations was observed within 4 hours post dose on Day 1 at an elagolix dose of 150 mg QD (**Table 3.2-5**). After the initial decline, mean FSH concentrations rebounded within 24 hours and remained higher than the placebo. At an elagolix dose of 200 mg BID, FSH suppression was observed and maintained through Day 21 (**Figure 3.2-4**). A maximal FSH inhibition was expected to be achieved at an elagolix dose at ≥400 mg BID compared to placebo. Suppression of FSH was lost at 24 to 36 hours after the last dose of elagolix on Day 21 at all doses evaluated in this study. An elagolix daily dose of approximately 622 mg/day is estimated to reduce FSH AUC_{0-21d} by 50% relative to placebo (**Figure 3.2-7**).

Table 3.2-5. Blood Concentrations of FSH (IU/L) within 24 h postdose on Day 1

Dose Regimens		HOURS AFTER DOSING									
SUBJECT		0	2	4	6	8	10	12	16	24	
Placebo	MEAN	5.918	5.727	5.518	5.482	5.460	5.660	5.510	5.080	5.350	
	STD	3.137	2.988	2.795	2.719	2.813	2.859	2.639	2.520	2.483	
150 mg QD	MEAN	7.650	7.220	6.400	5.483	5.167	5.417	5.283	5.000	6.200	
	STD	1.473	1.632	1.488	1.242	1.069	1.177	1.232	1.188	1.495	
200 mg BID	MEAN	8.000	6.757	5.986	5.714	5.329	5.143	5.157	4.386	4.614	
	STD	2.178	2.042	1.816	1.724	1.518	1.632	1.888	1.647	1.940	
400 mg BID	MEAN	6.700	5.667	5.133	4.567	4.450	4.383	4.083	3.667	3.567	
	STD	1.485	1.363	1.661	1.571	1.453	1.454	1.473	1.206	1.181	

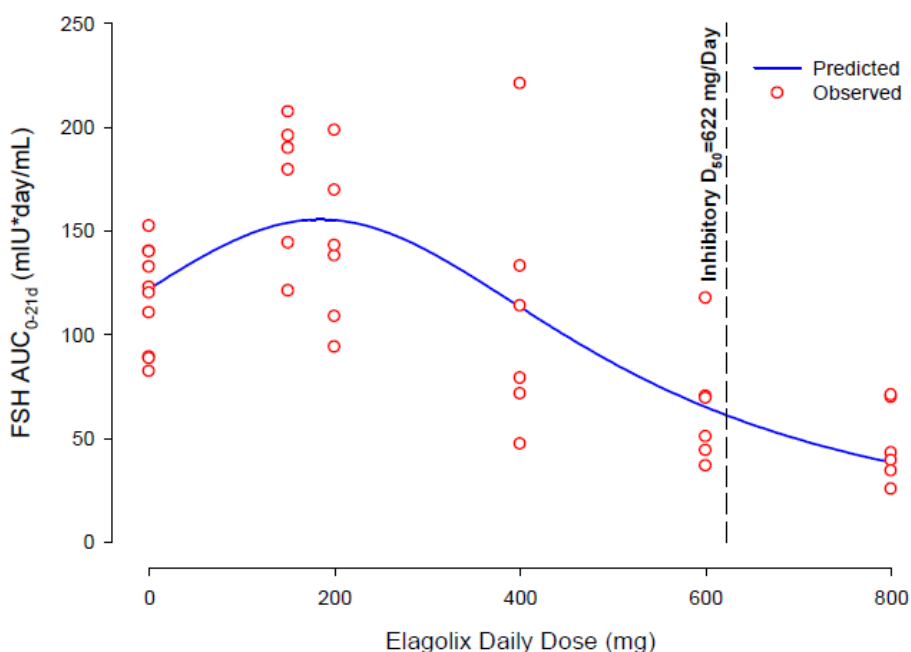


Figure 3.2-7. Elagolix Dose-Response on FSH Suppression (Study M12-790)

Reviewer's Comments:

- The PK/PD study showed that 21-day elagolix 150 mg QD treatment partially suppressed E2, P and LH but did not obviously suppress FSH compared to placebo. In contrast, 200 mg BID treatment caused a near maximal suppression of E2 and a partial suppression of LH and FSH. At doses of 100 mg BID (200 mg daily total) or greater, P concentrations remained at anovulatory levels below 5 nmol/L over the duration of the study.
- The suppression of LH and FSH was observed within 4 hours post dose on Day 1 while the suppression of LH and FSH was observed within 6-12 hours post dose on Day 1, which are similar with the findings in the SAD study (Study M13-784).
- After the last dose on Day 21, the suppression of the four hormones was maintained for 12 -36 hours.
- The exposure-response analysis on LH and E2 suppression may be confounded by dosing frequency.

Safety Results:

A total of 34 subjects received at least 1 dose of elagolix, and 11 subjects received placebo on at least one occasion during the study. Twenty-seven (27/34, 79%) subjects receiving elagolix and ten (10/11, 91%) receiving placebo reported at least one treatment emergent AE. Hot flush and headache were the most frequently reported adverse events across in the elagolix dose groups. No clinically relevant cardiac signals were identified, and no other clinically significant vital signs, physical examination findings, ECG measurements or changes in laboratory values were observed during the study. There were no deaths or other serious adverse events.

3.3 Study NBI56418-0601 (Mass balance)

Title: *A Phase I Study of the Pharmacokinetics and Mass Balance of [¹⁴C]NBI-56418 Administered Orally in Healthy Male Volunteers*

Objectives:

- To characterize the absorption, distribution, metabolism, excretion, and mass balance of a single 150 mg dose of [¹⁴C]NBI-56418 in healthy male subjects
- To evaluate the safety of NBI-56418

Study Design:

This was a Phase I, open-label, single dose study. On Study Day 1, [¹⁴C]NBI-56418 was administered to six healthy male subjects after an overnight fast (i.e., at least 8 hours). The study drug was administered as an oral solution containing 150 mg of NBI-56418 and 100 µCi of radioactivity. Both radioactivity and PK determinations were made on blood samples obtained 15 minutes before dosing; and at the following times after dosing: 15, 30, and 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours, and then every 24 hours thereafter until discharge from the research unit (up to Day 10 or until 90% of the administered radioactivity was recovered, whichever was sooner).

PK Results:

PK Measured by Radioanalysis:

As shown in **Figure 3.3-1**, maximum mean plasma radioactivity levels were observed at 45 minutes postdose, which then declined in a monoexponential fashion and were below the lower LOQ of the assay by approximately 6 to 16 hours postdose. The whole blood: plasma radioactivity ratios were 0.61 and 0.62 at 1.5 and 2.0 hours postdose, respectively, indicating drug-derived radioactivity partitions preferentially into the extracellular fraction of blood. The radioactivity-based whole blood and plasma mean PK parameters are summarized in **Table 3.3-1**.

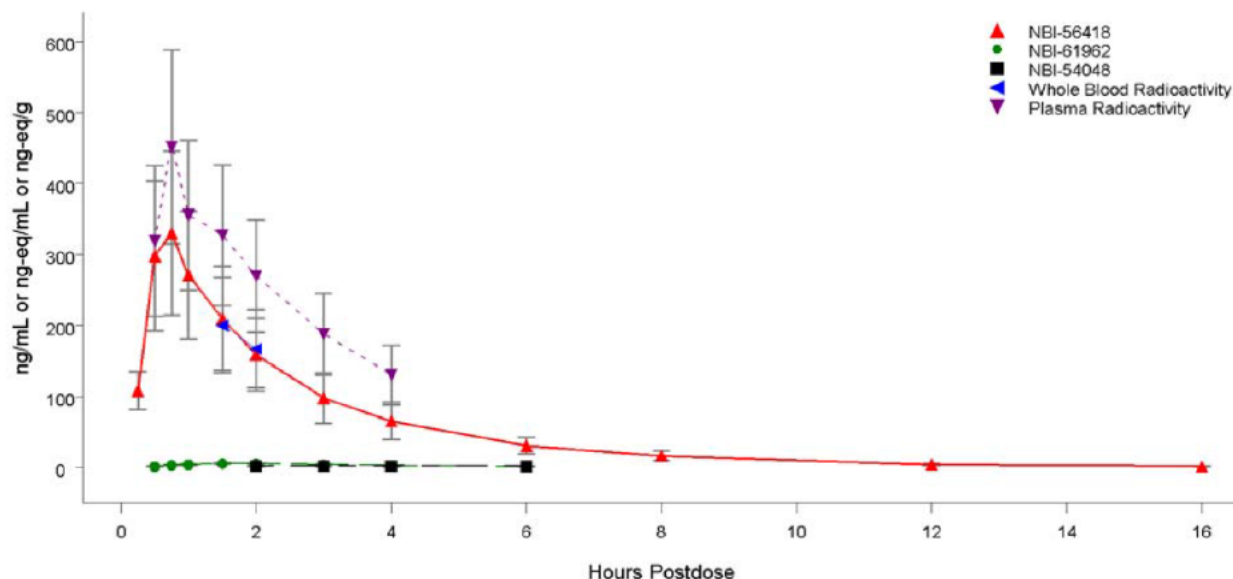


Figure 3.3-1. Mean ($\pm$ SEM) Plasma Concentration versus Time Profiles of NBI-56418, Metabolites NBI-61962 and NBI-54048, Plasma Radioactivity, and Whole Blood Radioactivity
Note: M3 or NBI-61962 is the O-demethyl metabolite and named A-1323217 in AbbVie’s studies. M6x or NBI-54048 is the N-dealkylated metabolite and named A-1298847 in AbbVie’s studies.

Table 3.3-1. Whole Blood and Plasma Radioactivity Pharmacokinetic Parameters

Parameter	Whole Blood Radioactivity (N=6)	Plasma Radioactivity (N=6)
C_{max} (ng-eq/g)		
Mean (SD)	294.78 (171.66) ^a	416.22 (290.67)
T_{max} (hr)		
Median (min, max)	0.75 (0.50, 1.50) ^a	0.75 (0.50, 2.00)
AUC₀₋₂₄ (ng-eq*hr/g)		
Mean (SD)	681.75 (738.62) ^a	1395.63 (1208.76)
AUC_{0-tlast} (ng-eq*hr/g)		
Mean (SD)	614.04 (713.32) ^a	1287.42 (1178.20)
AUC_{0-inf} (ng-eq*hr/g)		
Mean (SD)	1018.50 (820.75) ^b	1588.46 (1313.28)
t_{1/2} (hr)		
Mean (SD)	1.64 (0.45) ^b	2.97 (1.43)

Note: a n=5, b n=4; Two subjects (Subjects (b) (6) and (b) (6)) had non-measurable or very low blood radioactivity levels and therefore PK parameters could not be calculated for these subjects.

Recovery of Urine and Feces Radioactivity:

A mean total recovery of approximately 93% (range: 87.8% to 97.6%) of the administered dose (150 mg) of [14C]NBI-56418 was accounted for by the total amount of radioactivity contained in the urine and feces by approximately 9 days postdose (**Figure 3.3-2**). Approximately 90% of radioactivity was detected in the feces and approximately 2.9% of radioactivity in the urine. The majority (66.1%) of the radioactivity was excreted in the feces by Day 4.

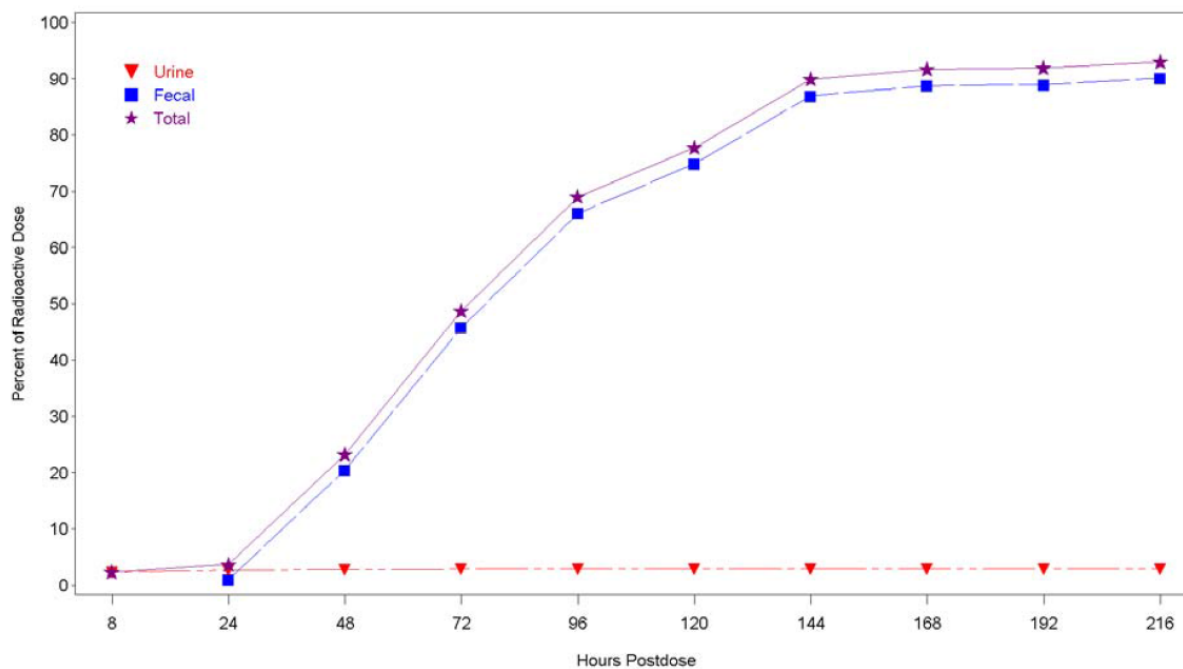


Figure 3.3-2. Mean Cumulative Recovery of Radioactivity in Urine and Feces

PK Measured by LC-MS/MS:

Table 3.3-2.

Parameter	Treatment Group		
	NBI-56418 (N=6)	Metabolite NBI-61962 (N=6)	Metabolite NBI-54048 (N=6)
C_{max} (ng/mL)			
Mean (SD)	350.75 (276.67)	5.80 (2.34)	2.03 (1.59) ^a
AUC₀₋₂₄ (ng*hr/mL)			
Mean (SD)	844.98 (711.50)	19.88 (9.90)	17.00 (17.33) ^a
AUC_{0-tlast} (ng*hr/mL)			
Mean (SD)	843.65 (712.33)	18.82 (9.38)	15.57 (16.71) ^a
AUC_{0-inf} (ng*hr/mL)			
Mean (SD)	846.71 (711.95)	20.49 (9.79)	27.82 (16.92) ^b
T_{max} (hr)			
Median (min, max)	0.75 (0.50, 2.00)	1.50 (1.50, 2.00)	3.00 (2.00, 4.00) ^a
t_{1/2} (hr)			
Mean (SD)	2.91 (1.15)	1.65 (0.23)	4.23 (0.37) ^b
CL/F (L/hr)			
Mean (SD)	264.36 (171.44)	N/A	N/A
V_z/F (L)			
Mean (SD)	1193.51 (969.37)	N/A	N/A

Note: M3 or NBI-61962 is the O-demethyl metabolite and named A-1323217 in AbbVie's studies. M6x or NBI-54048 is the N-dealkylated metabolite and named A-1298847 in AbbVie's studies.

The mean plasma NBI-56418 concentration peaked at 45 minutes postdose (approximately 350 ng/mL) and plasma NBI-56418 concentrations were below LOQ after approximately 16 to 24 hours postdose (**Figure 3.3-1**). Low levels of O-demethyl metabolite NBI-61962 were measured in plasma during 30 minutes to approximately 6 hours postdose; the mean $C_{\max}$ of approximately 5.8 ng/mL was observed at 1.5 hours postdose. Even lower concentrations of N-dealkylated metabolite NBI-54048 were measured in plasma during 2 to 6 hours postdose; the mean maximum concentration of NBI-54048 (2.0 ng/mL) was observed at 2 hours postdose.

Mean $C_{\max}$ values for the metabolites, NBI-61962 and NBI-54048, were approximately 1.7% and 0.6%, respectively, of the NBI-56418 mean $C_{\max}$ value. Similarly, the mean NBI-61962 and NBI-54048 $AUC_{0-\infty}$ values were approximately 2.4% and 3.3%, respectively, of the mean NBI-56418 $AUC_{0-\infty}$ value. The median $T_{\max}$ values for the metabolites NBI-61962 and NBI-54048 (1.5 and 3.0 hours, respectively) were higher than that for NBI-56418 (0.75 hours). The $t_{1/2}$ for NBI-61962 was approximately 1.6 hours, which was shorter than that of the parent drug NBI-56418 (2.9 hours) and NBI-54048 (4.2 hours).

Metabolite Profiling:

In the plasma, unchanged [14C]NBI-56418 was the major (>90%) component. All other metabolites were less than 10% of the radioactivity in the samples. Metabolites detected in this matrix included those formed by O-demethylation (NBI-61962), N-dealkylation (NBI-54048), glucuronidation, mono-oxidation, and/or lactam formation.

Urine radioactivity (which accounted for only 2.9% of the total radioactive dose) primarily consisted of unchanged [14C]NBI-56418 (approximately 90%), with minor to trace metabolites.

The radioactivity in the feces consisted of two major components, unchanged [14C]NBI-56418 and NBI-61962. On average, approximately 38% of the radioactive dose was eliminated as NBI-61962, 26% was unchanged NBI-56418, and the remainder was a combination of multiple minor metabolites formed by oxidative deamination, glucuronidation, oxidation, and/or lactam formation, and some unidentified metabolites. Totally, approximately 52% of the radioactive dose of NBI-56418 was excreted as metabolites.

Reviewer's Comments:

- *In both urine and feces, approximately 38.9% of the radioactive dose was eliminated as O-demethyl metabolite (M3 or NBI-61962). In vitro drug metabolism data showed that O-demethylation is contributed from CYP 3A4 (43%), 2D6 (52%) and 2C8 (5%). NBI-61962 was named A-1323217 in AbbVie's studies. The hepatic impairment study (Study M12-662) showed that the AUC values of A-1323217 in subjects with moderate hepatic impairment and subjects with severe hepatic impairment were approximately 5.5-fold and 17-fold, respectively, of AUC values from subjects with normal hepatic function.*
- *The formation of M6x (NBI-54048) through N-dealkylation pathway was mediated mainly by the CYP3A enzymes. M6x or NBI-54048 was named A-1298847 in AbbVie's studies. The exposure of NBI-54048 in subject with hepatic impairment was similar with that in subjects with normal hepatic function.*

Safety Results:

There were no deaths, serious, or severe AEs and no subject discontinued the study due to an AE. A total of six treatment emergent AEs were experienced by three of six subjects (50%). Two AEs (nightmares) were possibly related to study drug. There were no clinically important changes for vital signs, ECG, and physical examination findings.

3.4 Study M12-654 (Asian PK/PD)

Title: *A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Pharmacokinetics, Pharmacodynamics, and Tolerability of Multiple Doses of Elagolix in Adult Healthy Premenopausal Japanese and Han Chinese Females*

Objectives:

- To assess the safety, tolerability, and pharmacokinetics of multiple doses of elagolix under fasting conditions in healthy premenopausal Japanese and Han Chinese females
- To assess the effect of elagolix on pharmacodynamics of hormones (E2, P, LH, and FSH) in healthy premenopausal Japanese and Han Chinese females

Study Design:

This Phase 1, double-blind, multiple-dose, single-center study was conducted according to a 2-group, randomized, parallel design. Forty enrolled healthy subjects were randomly assigned to a single regimen for 7 days as shown in **Table 3.4-1**. Subjects began fasting for approximately 10 hours prior to the morning dose. For the BID evening dose, subjects began fasting approximately 2 hours prior to the evening dose. Subjects began dosing within 2 days following the start of their menstrual cycle.

Table 3.4-1. Number of Subjects in Each Dosing Group (Study M12-654)

Group	Female Population	Regimens			
		A: 150 mg QD	B: 200 mg BID	C: 150 mg QD Matching Placebo	D: 200 mg BID Matching Placebo
1	Japanese (N = 20)	8	8	2	2
2	Han Chinese (N = 20)	8	8	2	2

Blood samples for elagolix and metabolite assays were collected prior to dosing (0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the morning dose on Study Day 1; prior to dosing (0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 h after the morning dose on Study Day 7. Trough samples were collected prior to the morning dose on Study Days 3 – 6 or upon subject discontinuation.

Blood samples were obtained for assay of hormones at Screening and prior to morning dosing (0; E2, P, LH, and FSH) and at 2, 4, 6, 8, 10, 12, 16, and 24 hours after the morning dose (E2 and P only) on Study Day 1; prior to dose (0; E2, P, LH and FSH) and at 2, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after the morning dose (E2 and P only) on Study Day 7; prior to the morning dose on Study Days 3 – 6 (E2, P, LH and FSH), or upon premature discontinuation. LH and FSH were collected on Study Day 2 prior to the morning dose, and 24 and 48 hours after the morning dose on Study Day 7.

PK Results:

Elagolix:

As shown in **Figure 3.4-1**, the PK profiles of elagolix in Japanese and Han Chinese subjects are similar on both Day 1 and Day 7. The PK parameters of elagolix in Japanese and Han Chinese subjects are comparable (**Table 3.4-1**). For the 150 mg QD regimen, no drug accumulation was observed in Japanese and Han Chinese subjects. In contrast, for the 200 mg BID regimen, the mean R_{ac} on Day 7 was 0.84 and 0.79 in Japanese and Han Chinese subjects, respectively. A similar decrease in elagolix exposure was observed in White and Black subjects on Day 21 compared to that on Day 1 (Study M12-790). The decrease in elagolix exposure may be explained by the auto-induction of CYP3A, OATP1B1 and/or BCRP by high dose elagolix.

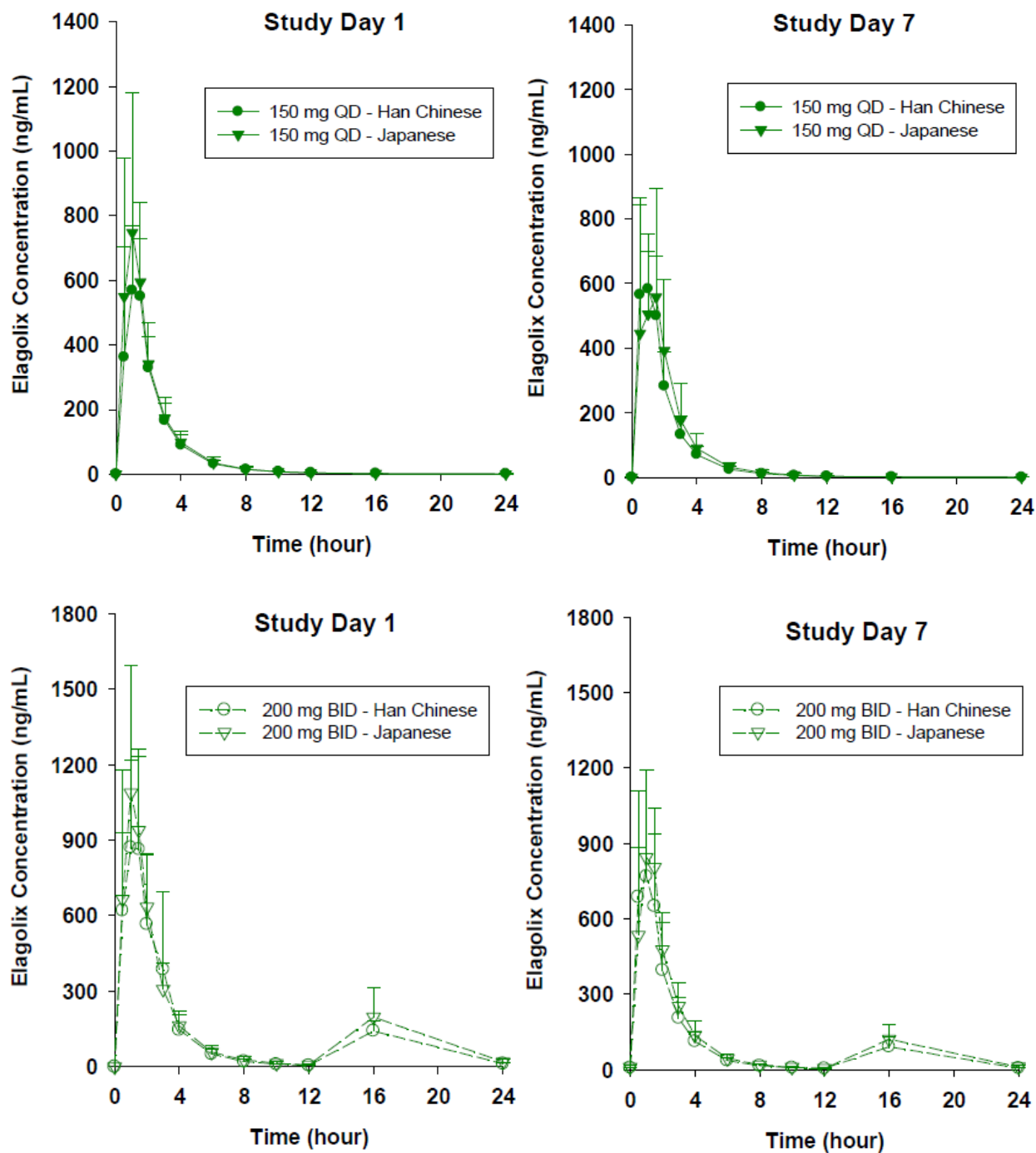


Figure 3.4-1. Mean + SD Elagolix Plasma Concentration-Time Profiles on Day 1 and Day 7 Following 150 mg QD and 200 mg BID Regimen

Table 3.4-1. Mean ± SD Pharmacokinetic Parameters of Elagolix on Day 1 and Day 7 Following Administration of the 150 mg QD and 200 mg BID Regimens

Dose Regimens	PK Parameters	Japanese N = 8	Han Chinese N = 8	Japanese N = 7	Han Chinese N = 8
150 mg QD		Day 1	Day 1	Day 7	Day 7
	T _{max} (h)	1.13 ± 0.23	1.13 ± 0.35	1.07 ± 0.53	0.75 ± 0.38
	C _{max} (ng/mL)	764 ± 423	634 ± 245	749 ± 128	711 ± 170
	AUC ₀₋₂₄ (ng*h/mL)	1650 ± 787	1416 ± 524	1490 ± 540	1378 ± 421
	T _{1/2} (h)	N.A.	N.A.	6.58 ± 4.18	9.80 ± 9.47
	CL/F (L/h)	N.A.	N.A.	110 ± 31.9	116 ± 28.6
	V _{dβ} /F (L)	N.A.	N.A.	1673 ± 1350	2452 ± 1567
	R _{ac}	N.A.	N.A.	0.99 ± 0.30	0.99 ± 0.11
	C _{max} /Dose (ng/mL/mg)	5.10 ± 2.82	4.23 ± 1.63	4.99 ± 2.19	4.74 ± 1.14
AUC/Dose (ng*h/mL/mg)	11.0 ± 5.25	9.44 ± 3.49	9.93 ± 3.60	9.18 ± 2.80	
200 mg BID		Japanese N = 8 Day 1	Han Chinese N = 8 Day 1	Japanese N = 8 Day 7	Han Chinese N = 6 Day 7
	T _{max} (h)	1.13 ± 0.23	1.13 ± 0.35	1.25 ± 0.27	0.84 ± 0.40
	C _{max} (ng/mL)	1140 ± 471	965 ± 391	929 ± 305	833 ± 376
	AUC ₀₋₁₂ (ng*h/mL)	2577 ± 933	2376 ± 1007	2059 ± 619	1851 ± 845
	T _{1/2} (h)	N.A.	N.A.	5.26 ± 1.04	7.04 ± 2.27
	CL/F (L/h)	N.A.	N.A.	105 ± 32.1	128 ± 56.3
	V _{dβ} /F (L)	N.A.	N.A.	809 ± 244	1347 ± 548
	R _{ac}	N.A.	N.A.	0.84 ± 0.22	0.79 ± 0.12
	C _{max} /Dose (ng/mL/mg)	5.70 ± 2.36	4.83 ± 1.95	4.65 ± 1.53	4.16 ± 1.88
AUC/Dose (ng*h/mL/mg)	12.9 ± 4.67	11.9 ± 5.04	10.3 ± 3.09	9.25 ± 4.22	

Metabolite A-1298847 (NBI-54048):

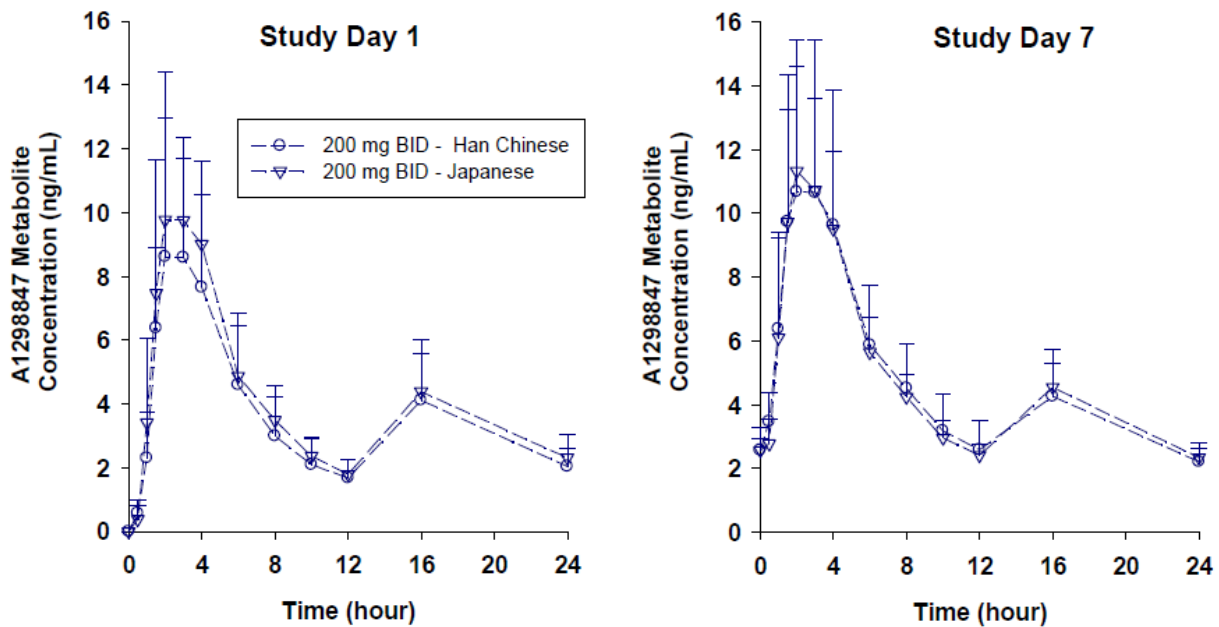


Figure 3.4-2. Mean + SD A-1298847 Plasma Concentration-Time Profiles on Day 1 and Day 7 Following 200 mg BID Regimen

A-1298847 is the N-dealkyl metabolite of elagolix. The PK profiles of A-1298847 in Japanese and Han Chinese subjects were similar (**Figure 3.4-2**) The PK parameters of A-1298847 in Japanese and Han Chinese subjects were comparable (**Table 3.4-2**). The mean accumulation ratio for A-1298847 in Japanese and Han Chinese subjects was 1.27 and 1.41 respectively.

Table 3.4-2. Mean $\pm$ SD Pharmacokinetic Parameters of A-1298847 on Day 1 and Day 7 Following Administration of the 150 mg QD and 200 mg BID Regimens

Dose Regimens	PK Parameters	Japanese N = 8	Han Chinese N = 8	Japanese N = 7	Han Chinese N = 8
150 mg QD		Day 1	Day 1	Day 7	Day 7
	T _{max} (h)	2.88 $\pm$ 0.83	2.56 $\pm$ 0.82	2.14 $\pm$ 0.63	2.69 $\pm$ 0.59
	C _{max} (ng/mL)	5.72 $\pm$ 2.76	5.29 $\pm$ 1.79	6.01 $\pm$ 2.19	6.95 $\pm$ 2.52
	AUC ₀₋₂₄ (ng*h/mL)	38.8 $\pm$ 16.6	36.3 $\pm$ 11.8	46.0 $\pm$ 11.0	49.9 $\pm$ 16.7
	T _{1/2} (h)	N.A.	N.A.	9.77 $\pm$ 4.18	10.5 $\pm$ 1.91
	R _{ac}	N.A.	N.A.	1.33 $\pm$ 0.35	1.38 $\pm$ 0.30
	C _{max} /Dose (ng/mL/mg)	0.04 $\pm$ 0.02	0.04 $\pm$ 0.01	0.04 $\pm$ 0.01	0.05 $\pm$ 0.02
AUC/Dose (ng*h/mL/mg)	0.26 $\pm$ 0.11	0.24 $\pm$ 0.08	0.31 $\pm$ 0.07	0.33 $\pm$ 0.11	
		Japanese N = 8	Han Chinese N = 8	Japanese N = 8	Han Chinese N = 6
200 mg BID		Day 1	Day 1	Day 7	Day 7
	T _{max} (h)	2.63 $\pm$ 0.74	2.50 $\pm$ 0.53	2.19 $\pm$ 0.53	2.58 $\pm$ 0.92
	C _{max} (ng/mL)	11.0 $\pm$ 4.12	9.27 $\pm$ 4.14	11.7 $\pm$ 3.20	10.9 $\pm$ 4.80
	AUC ₀₋₁₂ (ng*h/mL)	59.5 $\pm$ 19.2	52.2 $\pm$ 20.8	71.5 $\pm$ 15.5	73.2 $\pm$ 28.4
	T _{1/2} (h)	N.A.	N.A.	11.9 $\pm$ 3.50	12.8 $\pm$ 3.00
	R _{ac}	N.A.	N.A.	1.27 $\pm$ 0.41	1.41 $\pm$ 0.21
	C _{max} /Dose (ng/mL/mg)	0.05 $\pm$ 0.02	0.05 $\pm$ 0.02	0.06 $\pm$ 0.02	0.05 $\pm$ 0.02
AUC/Dose (ng*h/mL/mg)	0.30 $\pm$ 0.10	0.26 $\pm$ 0.10	0.36 $\pm$ 0.08	0.37 $\pm$ 0.14	

Reviewer's Comments:

- The formation of A-1298847 was catalyzed mainly by CYP3A enzymes. The induction of CYP3A enzymes by elagolix may partially explain the accumulation ratio for A-1298847 was more than 1 on Day 7.
- For the 150 mg QD regimen, the AUC ratio of A-1298847 and elagolix on Day 7 was 0.031 and 0.036 in Japanese and Han Chinese subjects, respectively. For the 200 mg BID regimen, the AUC ratio of A-1298847 and elagolix on Day 7 was 0.035 and 0.039 in Japanese and Han Chinese subjects, respectively. The AUC ratio of A-1298847 and elagolix slightly increased with the dose escalation of elagolix but the increase is not expected to have a clinically meaningful impact.

Metabolite A-1323217 (NBI-61962):

A-1323217 is the O-demethyl metabolite of elagolix. The PK profiles of A-1323217 in Japanese and Han Chinese subjects were similar (**Figure 3.4-3**) The PK parameters of A-1298847 in Japanese and Han Chinese subjects were comparable (**Table 3.4-3**). The mean accumulation ratio for A-1298847 in Japanese and Han Chinese subjects was 0.73 and 0.66, respectively.

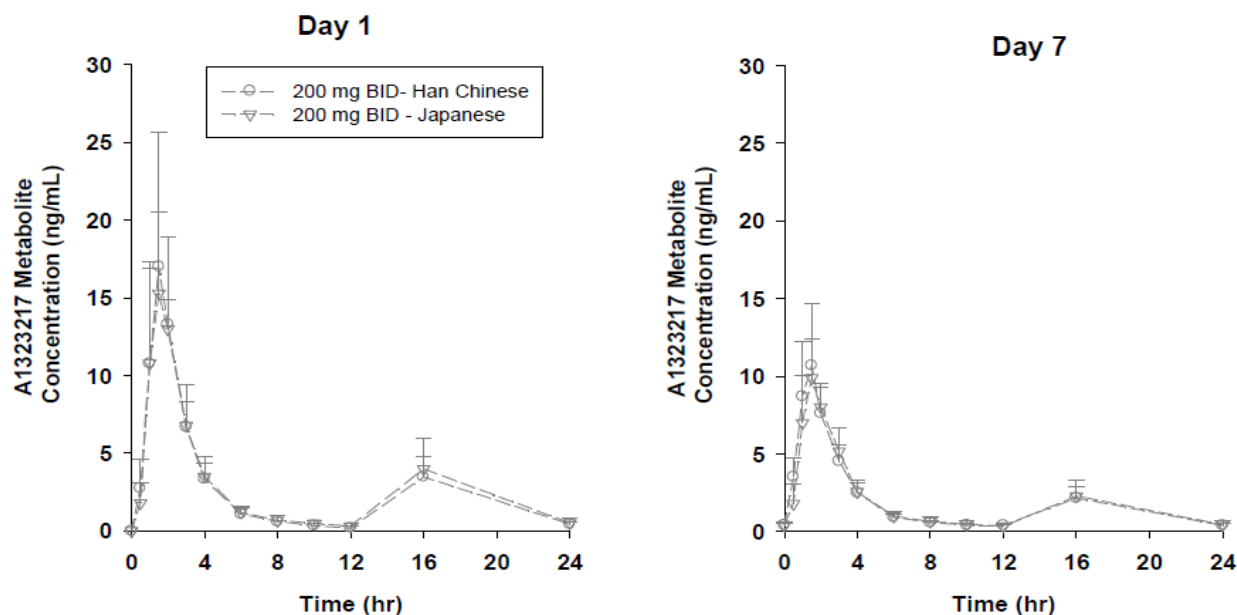


Figure 3.4-3. Mean + SD A-1323217 Plasma Concentration-Time Profiles on Day 1 and Day 7 Following 200 mg BID Regimen

Table 3.4-3. Mean ± SD Pharmacokinetic Parameters of A-1323217 on Day 1 and Day 7 Following Administration of the 150 mg QD and 200 mg BID Regimens

Dose Regimens	PK Parameters	Japanese N = 8	Han Chinese N = 8	Japanese N = 7	Han Chinese N = 8
150 mg QD		Day 1	Day 1	Day 7	Day 7
	T _{max} (h)	1.50 ± 0.00	1.75 ± 0.53	1.57 ± 0.19	1.56 ± 0.18
	C _{max} (ng/mL)	13.2 ± 6.90	9.69 ± 2.85	9.86 ± 2.96	8.82 ± 2.41
	AUC ₀₋₂₄ (ng*h/mL)	32.8 ± 16.6	26.6 ± 8.12	25.9 ± 7.76	23.1 ± 6.44
	T _{1/2} (h)	N.A.	N.A.	5.04 ± 2.46	3.42 ± 2.04
	R _{ac}	N.A.	N.A.	0.88 ± 0.24	0.88 ± 0.10
	C _{max} /Dose (ng/mL/mg)	0.09 ± 0.05	0.06 ± 0.02	0.07 ± 0.02	0.06 ± 0.02
AUC/Dose (ng*h/mL/mg)	0.22 ± 0.11	0.18 ± 0.05	0.17 ± 0.05	0.15 ± 0.04	
200 mg BID		Japanese N = 8 Day 1	Han Chinese N = 8 Day 1	Japanese N = 8 Day 7	Han Chinese N = 6 Day 7
	T _{max} (h)	1.69 ± 0.26	1.56 ± 0.18	1.50 ± 0.00	1.50 ± 0.32
	C _{max} (ng/mL)	16.1 ± 4.23	17.2 ± 8.51	9.89 ± 2.56	10.9 ± 3.60
	AUC ₀₋₁₂ (ng*h/mL)	40.6 ± 9.78	41.1 ± 17.6	28.9 ± 5.85	29.7 ± 6.23
	T _{1/2} (h)	N.A.	N.A.	6.57 ± 2.69	7.55 ± 3.74
	R _{ac}	N.A.	N.A.	0.73 ± 0.13	0.66 ± 0.11
	C _{max} /Dose (ng/mL/mg)	0.08 ± 0.02	0.09 ± 0.04	0.05 ± 0.01	0.05 ± 0.02
AUC/Dose (ng*h/mL/mg)	0.20 ± 0.05	0.21 ± 0.09	0.14 ± 0.03	0.15 ± 0.03	

Reviewer's Comments:

For the 150 mg QD regimen, the AUC ratio of A-1323217 and elagolix on Day 7 was 0.017 in both Japanese and Han Chinese subject. For the 200 mg BID regimen, the AUC ratio of A-1323217 and elagolix on Day 7 was 0.014 and 0.016 in Japanese and Han Chinese subjects, respectively. The AUC ratio of A-1323217 and elagolix slightly decreased with the increase of elagolix dose.

PD Results:

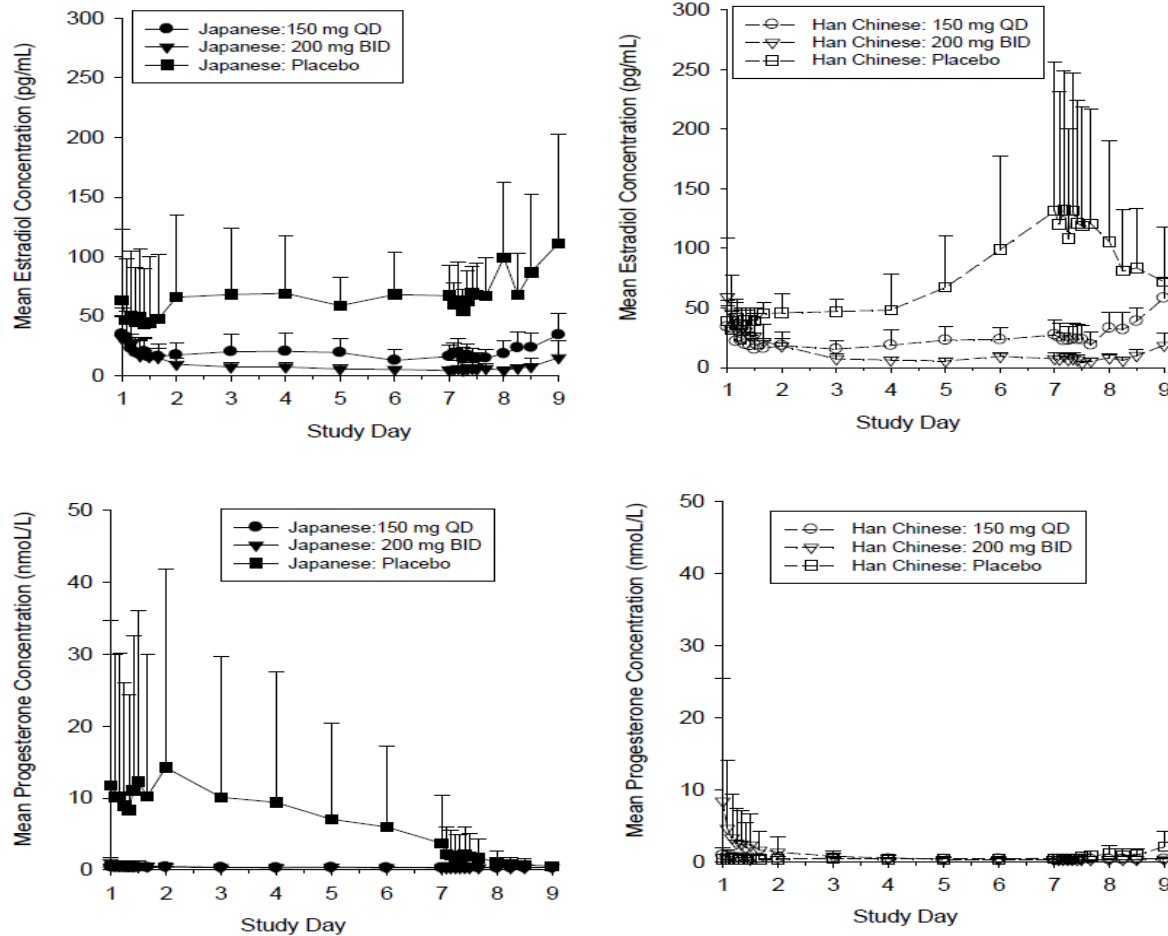


Figure 3.4-4. Mean + SD Estradiol and Progesterone Concentrations Following Multiple Doses of Elagolix and Placebo

As shown in **Figure 3.4-4**, dose-dependent suppression of estradiol was observed in both Japanese and Han Chinese subjects. Japanese and Han Chinese subjects appeared to have similar estradiol concentration time profiles for both 150 mg QD and 200 mg BID groups.

Anovulatory concentrations of progesterone (< 5 nM) were observed in all Japanese and Han Chinese subjects at elagolix doses of 150 mg QD and 200 mg BID, and remained lower than 5 nM at 24 hours after the last dose on Study Day 7. One Japanese subject (Subject ^(b)(6)) in placebo group had high progesterone concentrations beginning on Study Day 1 (> 32 nM) and remained above 5 nM through Study Day 7 which resulted in higher average progesterone concentrations in the placebo group.

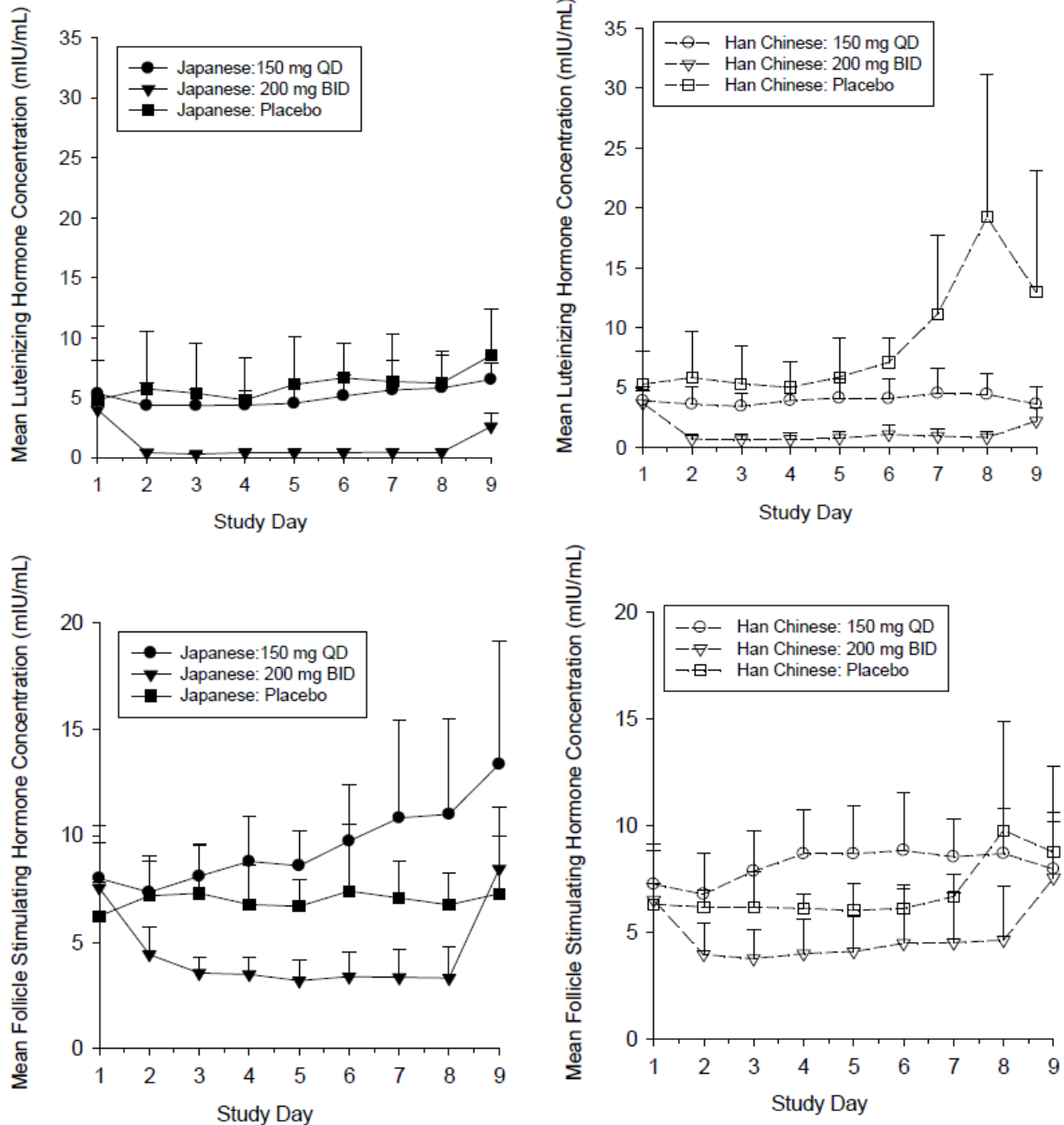


Figure 3.4-5. Mean + SD LH and FSH Concentrations Following Multiple Doses of Elagolix and Placebo

As shown in **Figure 3.4-5**, dose-dependent suppression of LH was observed in both Japanese and Han Chinese subjects. Japanese and Han Chinese subjects appeared to have similar LH concentration time profiles for both 150 mg QD and 200 mg BID groups.

The suppression of FSH was observed in both Japanese and Han Chinese subjects treated with the 200 mg BID regimen but not observed in both populations treated with 150 mg QD regimen. The mean FSH profile appeared to be similar between the Japanese and the Han Chinese subjects for at the 150 mg QD and 200 mg BID dose levels.

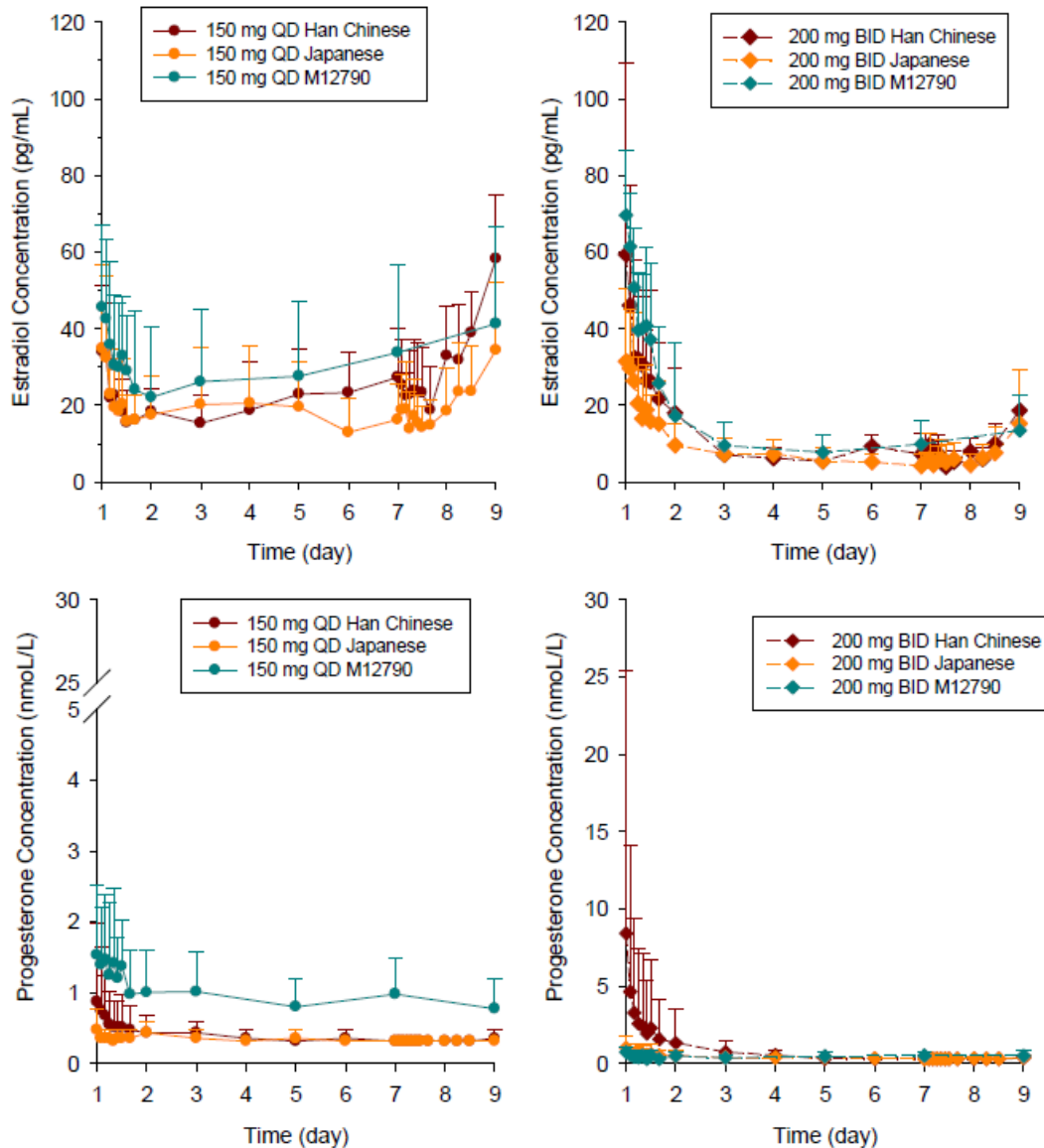


Figure 3.4-6. Mean + SD Estradiol and Progesterone Concentrations Following Multiple Doses of Elagolix and Placebo in Japanese, Han Chinese (Study M12-654) and Western Subjects (Study M12-790)

A cross-study comparison of the pharmacodynamic effects on the ovarian hormones between Study M12-654 and Study M12-790 was shown in **Figure 3.4-6**. Average estradiol concentrations were consistently lower than 40 pg/mL for the 7 days of dosing in the three populations treated with 150 mg QD regimen. Similar mean estradiol concentration-time profiles were observed in the three populations treated with 200 mg BID regimen.

Anovulatory concentrations of progesterone (< 5 nM) were observed in all three populations treated with 150 mg QD or 200 mg BID regimen.

Reviewer's Comments:

While Western subjects in Study M12-790 receiving elagolix 150 mg QD appeared to have slightly higher concentrations of estradiol and progesterone for 7 days of dosing than Japanese and Han Chinese

subjects, the higher baseline levels of estradiol and progesterone in Western subjects enrolled in the 150 mg QD group precluded a meaningful conclusion for the cross-study comparison.

The hormone profiles for LH and FSH appeared to be similar for Asian subjects (Japanese, Han Chinese) and Western subjects receiving elagolix 150 mg QD or 200 mg BID (Figure 3.4-7).

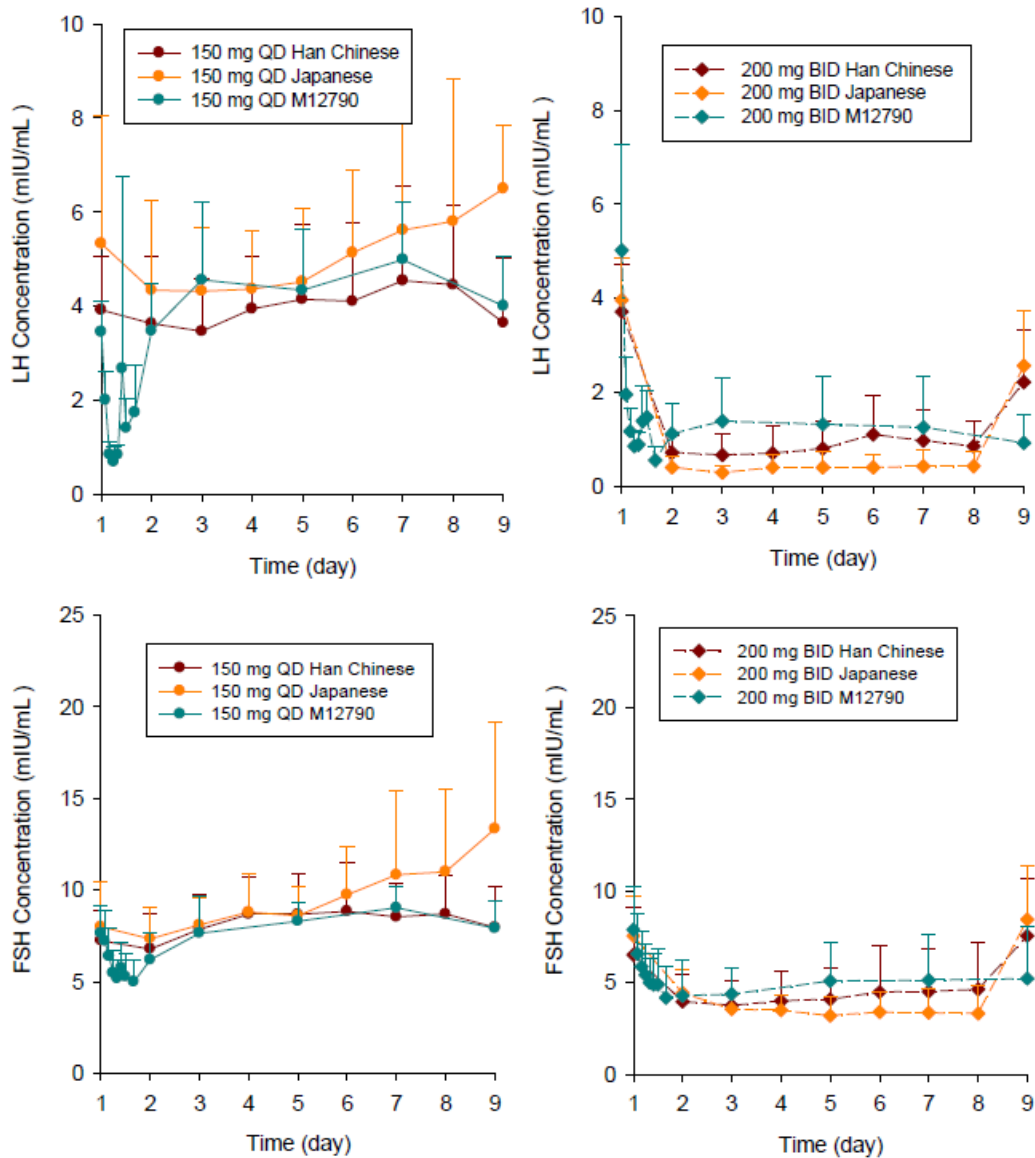


Figure 3.4-6. Mean + SD LH and FSH Concentrations Following Multiple Doses of Elagolix and Placebo in Japanese, Han Chinese (Study M12-654) and Western Subjects (Study M12-790)

Safety Results:

For the Japanese subjects, nine (9/16, 56%) subjects receiving elagolix and one (1/4, 25%) subject receiving placebo reported at least one treatment-emergent AE. For the Han Chinese subject, nine (9/16, 56%) subjects receiving elagolix and four (4/4, 100%) subjects receiving placebo reported at least one treatment-emergent AE. Three subjects prematurely discontinued from the study. Two subjects withdrew consent to participate in the study, and one subject discontinued with an adverse event of toothache that

was not related to study to study drug. No clinically significant abnormal ECG findings were reported for this study. No deaths, serious adverse events or pregnancies were reported during the study.

3.5 Study M12-673 (Ovulation study)

Title: *A Phase 1, Open-Label Study of the Effects of Elagolix on Ovarian Activity, Ovulation and Ovarian Reserve in Adult Premenopausal Females*

Objectives:

- To determine the effects of different doses and dosing regimens of elagolix (alone or with the hormonal add-back therapy Activella [standard (Std) dose: estradiol 1.0 mg/norethindrone acetate 0.5 mg]) on ovulation, ovarian activity and ovarian reserve when administered to healthy, adult premenopausal females and to assess the effect of elagolix alone or with the standard-dose Activella (Std Activella) on selected endocrine hormone parameters.
- To assess the safety and tolerability, pharmacokinetics and pharmacodynamics of each elagolix treatment regimen (alone or with the Std Activella).

Study Design:

This Phase 1 open-label, multi-center, multiple-dose study was conducted in premenopausal female subjects to evaluate the effects of different dosing regimens of elagolix (alone or with Std Activella) on ovulation, ovarian activity and ovarian reserve when administered to healthy, adult premenopausal females and to assess the effect of elagolix (alone or with Std Activella) on selected endocrine/hormone parameters. A total of 205 subjects (N = 205) were randomly assigned to seven treatment groups (**Table 3.5-1**). Women aged 18 to 40 years, inclusive, with a history of regular menstrual cycles (24 to 32 days long) were selected to participate in the study. Subjects self-administered the assigned doses of elagolix with approximately 8 ounces (240 mL) of water under fasting conditions. The study consisted of 3 periods: a Screening Period of up to 60 days prior to first dose, a Treatment Period of 3 cycles (Cycles 1 through 3), and a Follow-up Period up to 60 days (**Figure 3.5-1**). A cycle was defined as 28 days.

During the Treatment Period, blood samples were sparsely collected every other Friday or Saturday (Weeks 2 and 4, of Cycles 1, 2 and 3) during the clinic visit to measure the concentrations of elagolix and norethindrone in plasma. Blood samples for assay of concentrations of estradiol (E2), progesterone (P), LH, FSH, and hormones were obtained 3 times per week (M, W, F or T, Th, S schedule) throughout the entire study duration (Screening, Treatment, and Follow-up Periods). During the Screening and Treatment Periods, ovulation/inhibition of ovulation and ovarian activity were assessed via serial transvaginal ultrasound (TVU) evaluations of the leading follicle (development and size) and hormone levels (P and E2). Serial TVU were performed 3 times weekly.

Table 3.5-1. Treatment Groups in Study M12-673

Regimen	Number of Subjects Dosed
100 mg BID	38
150 mg QD	40
100 mg QD	9
200 mg QD	35
200 mg BID	41
300 mg BID	22
300 mg BID + Activella	20

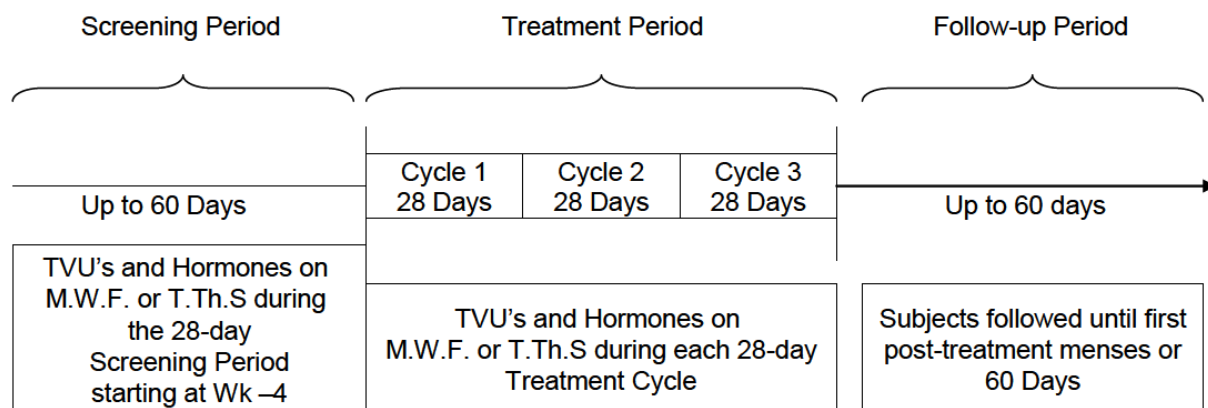


Figure 3.5-1. Study Design (Study M12-673)

Ovulation classification was defined based on mean follicular diameter, follicular rupture, and serum progesterone by using two approaches: protocol-defined ovulation and adjudicated ovulation.

Protocol-defined ovulation:

The protocol for this study defined ovulation as a follicular (mean) diameter of > 13 mm with rupture and 2 consecutive P concentrations above 5 nmol/L (1.57 ng/mL) within 10 days of this follicular measurement. A follicle greater than 2.5 cm would be considered an ovarian cyst.

Adjudicated ovulation:

An Adjudication Committee (AC) was established that conducted a review of hormonal and follicular data to determine the occurrence of ovulation. Members of the AC committee were blinded to study treatment and subject identifiers. Manual adjudication was conducted for cases that did not meet the protocol pre-specified definition of ovulation, where the hormonal data were inconsistent with ovulation, or the follicular rupture was not captured. The criteria for adjudicated ovulation include:

- Definition of ovulation with follicle rupture: the same as protocol-defined ovulation.
- Ovulation based on follicular activity at ultrasound and hormonal response without rupture: Presence of a follicle of at least 13 mm diameter without rupture, and a robust luteal phase (based on 2 consecutive P concentrations above 5 nmol/L within 10 days of this follicle measurement).
- Ovulation based on hormonal response: No evidence of follicular activity at ultrasound, but evidence of rising E2 levels followed by a robust luteal phase (based on 2 consecutive P concentrations above 5 nmol/L).
- No evidence of follicular or hormonal response consistent with ovulation.
- Insufficient information to determine due to missing data.

PK Results:

PK samples were sparsely collected for populations PK analysis. The PK data were not assessed in this individual study review.

PD Results:

Ovulation:

A summary of ovulation/anovulation rates based on protocol-defined ovulation classification are presented in **Table 3.5-2**. A dose-dependent inhibition of ovulation was observed. The ovulation rates by subject count for elagolix 150 mg QD and 200 mg BID were 47.5% and 26.8%, respectively.

Table 3.5-2. Protocol-Defined Ovulation Rates

	100 mg QD N = 9	150 mg QD N = 40	200 mg QD N = 35	100 mg BID N = 38	200 mg BID N = 41	300 mg BID N = 22	300 mg BID + Std Activella N = 20
Number (%) of Ovulations by Subject Count							
Number (%) of Subjects with ovulation(s) at any time point during Treatment	5 (55.6%)	19 (47.5%)	19 (54.3%)	15 (39.5%)	11 (26.8%)	6 (27.3%)	2 (10.0%)
Number (%) of Subjects without ovulation (i.e., anovulatory) at any time point during Treatment	4 (44.4%)	21 (52.5%)	16 (45.7%)	23 (60.5%)	30 (73.2%)	16 (72.7%)	18 (90.0%)

Std Activella = estradiol/norethindrone acetate 1/0.5 mg; QD = once daily; BID = twice daily

Adjudication-defined ovulation rates are shown in **Table 3.5-3**. A dose-dependent inhibition of ovulation was observed. The ovulation rates by subject count for elagolix 150 mg QD and 200 mg BID were 50.0% and 31.7%, respectively. The 300 mg BID regimen had an ovulation rate of 27.3%. When Std Activella was co-administered with elagolix 300 mg BID, the ovulation rate decreased to approximately 10%.

Table 3.5-3. Adjudication-Defined Ovulation Rates

	100 mg QD N = 9	150 mg QD N = 40	200 mg QD N = 35	100 mg BID N = 38	200 mg BID N = 41	300 mg BID N = 22	300 mg BID + Std Activella N = 20
Number (%) of Ovulations by Subject Count							
Number (%) of Subjects with ovulation(s) at any time point during Treatment	7 (77.8%)	20 (50.0%)	20 (57.1%)	18 (47.4%)	13 (31.7%)	6 (27.3%)	2 (10.0%)
Number (%) of Subjects without ovulation (i.e., anovulatory) at any time point during Treatment	2 (22.2%)	19 (47.5%)	13 (37.1%)	17 (44.7%)	28 (68.3%)	16 (72.7%)	18 (90.0%)
Number (%) of Subjects with Missing Hormone/TVU Data	0	1 (2.5%)	2 (5.7%)	3 (7.9%)	0	0	0

Estradiol Suppression:

During the Treatment Phase, suppression of E2 levels was observed in a dose-dependent manner (**Figure 3.5-2**). The mean E2 concentrations were the highest with the elagolix 100 mg QD regimen (60-70 pg/mL). The 150 mg QD, 200 mg QD and 100 mg BID regimens appeared to have similar mean E2 levels (~ 43 pg/mL and 54 pg/mL, 45 pg/mL and 58 pg/mL, and 30 pg/mL and 50 pg/mL at Cycle 1 and Cycle 3, respectively). The 200 mg BID and 300 mg BID regimens appeared to have the lowest mean E2 levels (~ 19 pg/mL and 41 pg/mL and 18 pg/mL and 32 pg/mL, at Cycle 1 and Cycle 3, respectively). When Std Activella was added to the 300 mg BID dose, the mean E2 concentrations were maintained in the 50 to 100 pg/mL range throughout each cycle and were above the mean E2 concentrations observed in the regimens of 150 mg QD.

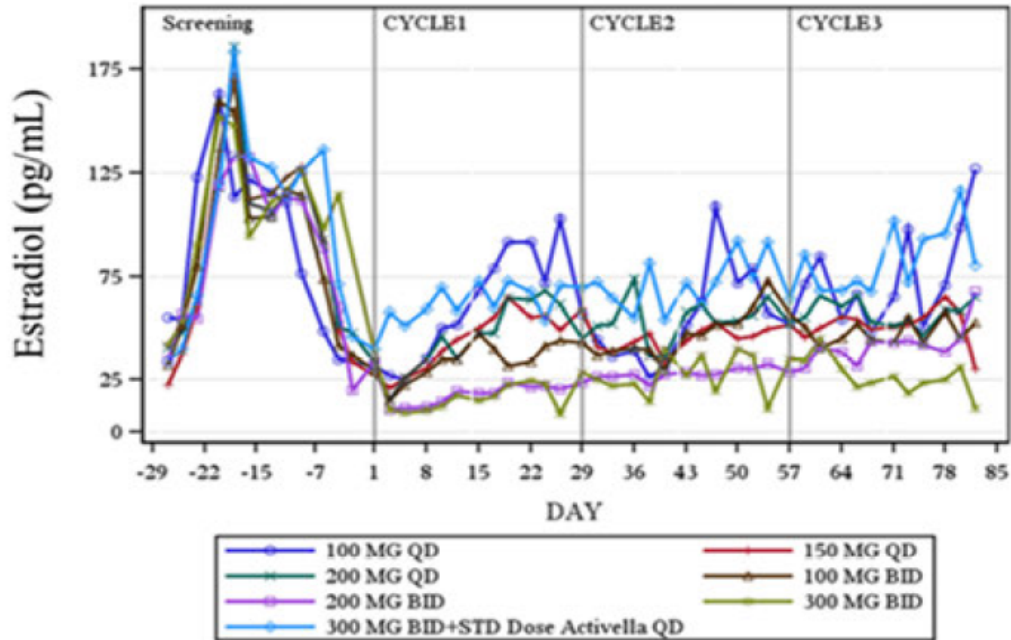


Figure 3.5-2. Mean Estradiol Concentration-Time Profiles for Elagolix Regimens 100 mg QD through 300 mg BID $\pm$ Std Activella

Progesterone Suppression:

During the Treatment Phase, A dose-dependent suppression of progesterone was observed (**Figure 3.5-3**). During the Treatment Phase, ovulatory P concentrations (> 5 nM) were observed more often at the lower elagolix doses than at the higher doses. The highest mean P concentrations were observed at 100 mg QD. Anovulatory mean P concentrations were observed at doses of 150 mg QD and 200 mg BID. The lowest mean P concentrations were observed with 300 mg BID/Std Activella.

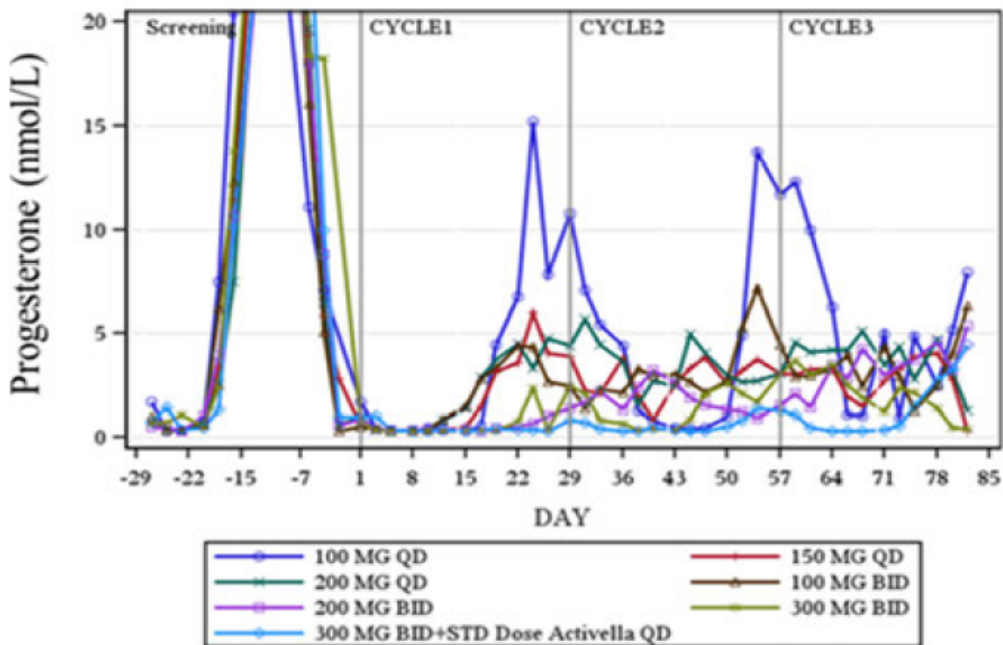


Figure 3.5-3. Mean Progesterone Concentration-Time Profiles for Elagolix Regimens 100 mg QD through 300 mg BID $\pm$ Std Activella

LH Suppression:

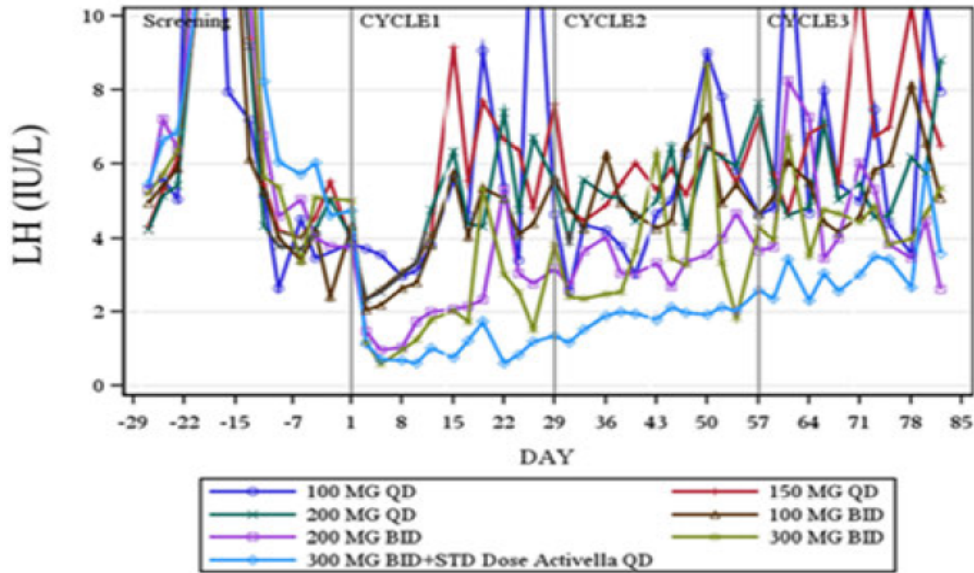


Figure 3.5-4. Mean LH Concentration-Time Profiles for Elagolix Regimens 100 mg QD through 300 mg BID ± Std Activella

During the Treatment Phase, LH concentrations were suppressed in a dose-dependent manner (**Figure 3.5-4**). The 100 mg QD, 150 mg QD, 200 mg QD and 100 mg BID doses appeared to have similar mean LH concentrations, with minimal suppression at the 100 to 200 mg QD regimens. The mean LH concentrations further decreased at the 200 mg BID and 300 mg BID doses. When Std Activella was added to the 300 mg BID regimen, the mean LH concentrations (~ 1.0 IU/L and 3.0 IU/L in Cycle 1 and Cycle 3, respectively) appeared to be the lowest among all regimens.

FSH Suppression:

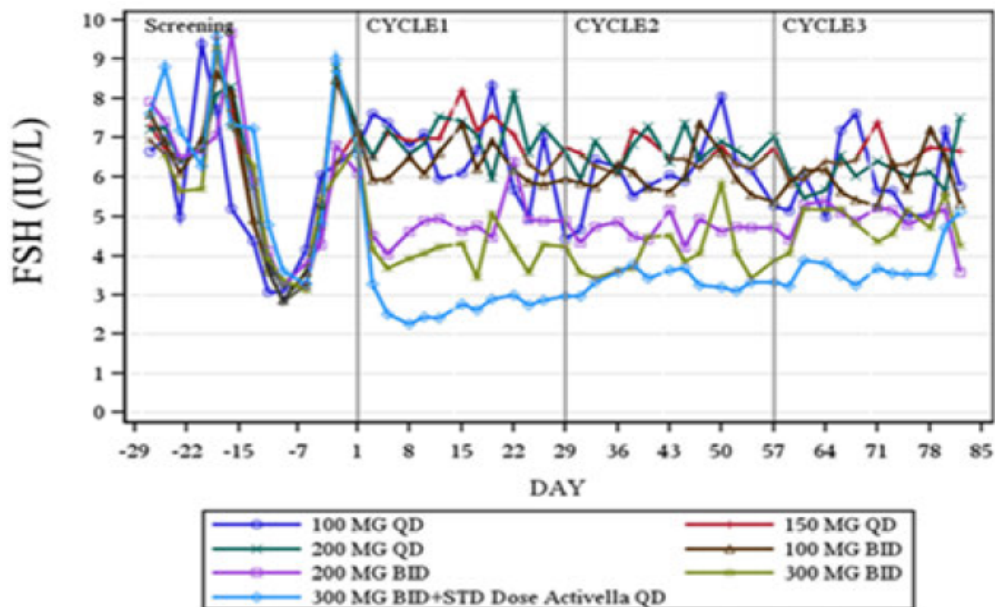


Figure 3.5-5. Mean FSH Concentration-Time Profiles for Elagolix Regimens 100 mg QD through 300 mg BID ± Std Activella

During the Treatment Phase, the 100 mg QD, 150 mg QD, 200 mg QD and 100 mg BID regimens appeared to have similar mean FSH concentrations of 6 to 7 IU/L. The 200 mg BID regimen appeared to have lower mean FSH concentrations of 4 to 5 IU/L. concentrations of 6 to 7 IU/L. The 200 mg BID regimen appeared to have lower mean FSH concentrations of 4 to 5 IU/L. The 300 mg BID doses had slightly lower mean FSH concentrations of approximately 4 IU/L compared to the 200 mg BID dose. When Std Activella was added to the 300 mg BID regimen, the mean FSH concentrations appeared to be the lowest among all the regimens with mean concentrations ranging from 3 to 4 IU/L.

Reviewer's Comments:

- *The hormone suppression observed in the MAD study (Study M12-790) was greater than that observed in this study. For example, the mean estradiol concentration in subjects treated with 200 mg BID regimen was approximately 10-15 pg/mL in Study M12-790 while the mean estradiol concentration observed in this study was approximately 25 pg/mL. The Applicant's explanation of the observed difference is the less than optimal adherence to dosing schedules in current study (Study M12-673). In Study M12-790, dosing was observed and hand/mouth compliance checks were performed for 21 day. In contrast, doses were self-administered in Study M12-673. The non-adherence to dosing schedules may cause the less hormone suppression.*
- *In women with endometriosis, ovulation can make the symptoms of endometriosis worse. Suppression of ovulation is one of the action mechanisms of elagolix to manage the pain associated with endometriosis. The dose-dependent suppression of ovulation by elagolix demonstrated in Study M12-673 provides additional evidence for the management of endometriosis associated pain.*
- *Based on the potency of hormone suppression and ovulation suppression, the dose regimens tested in this study are divided into four categories:*

Group 1 with limited suppression: 100 mg QD

Group 2 with moderate suppression: 150 mg QD, 200 mg QD and 100 mg BID

Group 3 with potent suppression: 200 mg BID and 300 mg BID

Group 4 with highest suppression: 300 mg BID + Std Activella

The different potency of 150 mg QD and 200 mg BID regimens in hormone suppression and ovulation suppression may provide options to patients with different severity of symptoms.

Safety Results:

Overall, for all regimens combined, 162 of 205 subjects (79.0%) experienced at least one treatment emergent adverse event. The incidence of adverse events for each treatment group is ranked in order of decreasing frequency below:

- 200 mg QD 91.4%, 32/35
- 300 mg BID/Std Activella 85.0%, 17/20
- 200 mg BID 82.9%, 34/41
- 100 mg QD 77.8%, 7/9
- 300 mg BID 72.7%, 16/22
- 150 mg QD 72.5%, 29/40
- 100 mg BID 71.1%, 27/38

The most frequently reported treatment-emergent adverse events ($\geq 5\%$ of subjects for all regimens combined), in order of decreasing frequency, were headache (24.9%), hot flush (22.9%), nausea (18.5%), upper respiratory tract infection (7.3%), back pain (7.3%), dizziness (6.8%), acne (6.8%), diarrhea (5.9%), abdominal pain (5.4%), and insomnia (5.4%). The majority of subjects, across all regimens,

experienced adverse events that were assessed by the investigator as either mild (80/205, 39.0%) or moderate (65/205, 31.7%) in intensity. Seventeen subjects (17/205, 8.3%) experienced adverse events assessed as severe.

There were no deaths during the study. Four subjects experienced adverse events during the Treatment Period, which led to discontinuation of study drug. Pregnancy (including 1 ectopic pregnancy) was reported in 5 subjects who received elagolix.

3.6 Study M12-655 (Renal impairment)

Title: *Evaluation of the Safety and Pharmacokinetics of a Single Dose of Elagolix in Female Subjects with Normal and Impaired Renal Function*

Objective: to assess the safety and PK of elagolix following oral administration of a single dose in female subjects with normal renal function to mild renal impairment, moderate to severe renal impairment, and end-stage renal disease (ESRD) without dialysis or requiring dialysis

Study Design:

This was a Phase 1, single-dose, fasting, open-label study designed to assess the safety and pharmacokinetics of elagolix in female subjects with normal or impaired renal function. A total of 15 pre- or post-menopausal female subjects were enrolled and assigned to three groups: 6 subjects with normal renal function to mild renal impairment (eGFR ≥ 60 mL/min/1.73m², Group I), 3 subjects with moderate to severe renal impairment (eGFR between 15 and < 60 mL/min/1.73m², Group II), and 6 subjects with end stage renal disease (ESRD) (eGFR < 15 mL/min/1.73m², Group III, 5 subjects required dialysis). Each subject received a single dose of 200 mg elagolix on Day 1 under fasting conditions. Blood samples for elagolix assay were collected by venipuncture approximately 15 minutes prior to dosing (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after elagolix dosing.

PK Results:

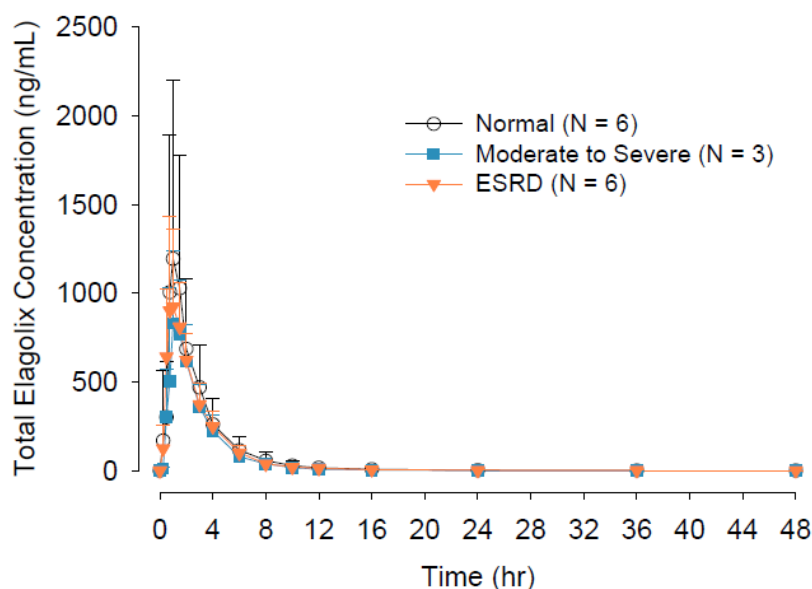
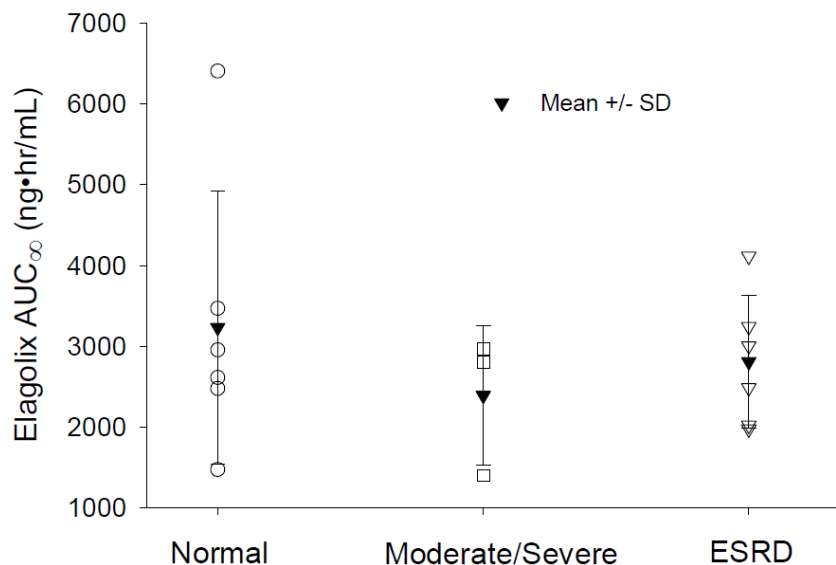


Figure 3.6-1. Mean + SD Total Elagolix Plasma Concentration-Time Profiles (Study M12-655)

Table 3.6-1. Mean $\pm$ SD Pharmacokinetic Parameters of Total Elagolix (Study M12-655)

Pharmacokinetic Parameters (units)		Treatment Group		
		Normal Function N = 6	Moderate to Severe N = 3	ESRD N = 6
		Total Elagolix		
C_{max}	(ng/mL)	1314 $\pm$ 878	857 $\pm$ 370	1063 $\pm$ 330
T_{max}	(hr)	1.4 $\pm$ 0.8	1.3 $\pm$ 0.4	1.1 $\pm$ 0.5
AUC_t	(ng•hr/mL)	3227 $\pm$ 1688	2387 $\pm$ 860	2800 $\pm$ 817
AUC_{∞}	(ng•hr/mL)	3231 $\pm$ 1688	2390 $\pm$ 861	2806 $\pm$ 819
$t_{1/2}^a$	(hr)	5.33 $\pm$ 0.97	6.10 $\pm$ 1.77	6.19 $\pm$ 1.51
CL/F	(L/hr)	75.0 $\pm$ 34.6	93.9 $\pm$ 42.5	76.3 $\pm$ 21.1
Vd_{β}/F	(L)	564 $\pm$ 182	897 $\pm$ 559	686 $\pm$ 132

The mean values of C_{max} and AUC in female subjects with normal renal function to mild renal impairment, moderate to severe renal impairment, or ESRD were comparable (**Table 3.6-1**). Elagolix mean C_{max} , AUC_t , and AUC_{∞} appeared to be slightly higher in subjects with normal renal function to mild renal impairment compared to subjects with moderate to severe renal impairment and subjects with ESRD. **Figure 3.6-2** showed the distribution of individual subject AUC values by groups.

**Figure 3.6-2.** The Exposure of Elagolix in Female Subjects with Normal Renal Function to Mild Renal Impairment, Moderate to Severe Renal Impairment, or ESRD

Plasma binding study showed that renal impairment status did not impact protein binding of elagolix. The mean plasma unbound fraction of elagolix in subjects with normal renal function to mild renal impairment, moderate to severe impairment, and ESRD was 0.097 ± 0.007 , 0.106 ± 0.014 , and 0.119 ± 0.008 , respectively. The mean C_{max} , AUC_t , and AUC_{∞} of unbound elagolix were approximately similar across the three groups.

Reviewer's Comment:

- Due to the difficulty in recruiting subjects with moderate to severe renal impairment, the Applicant enrolled 3 subjects only. The sample size is small.
- Since approximately 3% of elagolix in human body is cleared by renal excretion, it is unexpected that the AUC of elagolix in ESRD patients is lower than that in subjects with normal renal function to mild renal impairment. **Figure 3.6-2** showed one outlier (Subject (b) (6)) in the group with normal renal function to mild renal impairment. Subject (b) (6) had an AUC value of more than 6000 ng*h/mL. After Subject (b) (6) was removed, this reviewer recalculated the mean PK parameters of elagolix, which are summarized in **Table 3.6-2**. The exclusion of Subject (b) (6) does not affect the conclusion that renal impairment status does not impact elagolix exposure.

Table 3.6-2. Mean ± SD PK Parameters of Elagolix in Female Subjects with Normal Renal Function, Moderate to Severe Renal Impairment, or ESRD Excluding Subject (b) (6)

PK Parameters	Treatment Group		
	Normal Function to Mild Impairment N = 5	Moderate to Severe N = 3	ESRD N = 6
C_{max} (ng/mL)	987 ± 402	857 ± 370	1063 ± 330
AUC_{0-t} (ng*h/mL)	2593 ± 734	2387 ± 860	2800 ± 817
AUC_{0-inf} (ng*h/mL)	2596 ± 735	2390 ± 861	2806 ± 819
CL/F (L/h)	83.7 ± 30.4	93.9 ± 42.5	76.3 ± 21.1

- Renal impairment did not significantly alter the exposures of total elagolix or unbound elagolix. This reviewer agrees with the Applicant's proposal that no dose adjustment is recommended in women with any degree of renal impairment or end-stage renal disease (including women on dialysis).

Safety Results:

A total of 4 subjects experienced at least one treatment-emergent AE and a total of 11 mild or moderate AEs were reported: 2 subjects (2/6, 33.3%) with normal renal function, 1 subject (1/3, 33.3%) with moderate to severe renal impairment, and 1 subject (1/6, 16.7%) with ESRD. The most frequently reported treatment-emergent AEs were nausea (one in each treatment group) and headache (one in each treatment group). No deaths, other serious adverse events or other significant adverse events occurred during the study. No adverse events led to discontinuation during the study.

3.7 Study M12-662 (Hepatic impairment)

Title: Evaluation of the Safety and Pharmacokinetics of a Single Dose of Elagolix in Female Subjects with Mild, Moderate, or Severe Hepatic Insufficiency

Objective: to assess the safety and pharmacokinetics of elagolix following oral administration of a single dose in female subjects with normal hepatic function, mild stable chronic hepatic impairment, moderate stable chronic hepatic impairment or severe stable chronic hepatic impairment

Study Design:

This was a Phase 1, single-dose, fasting, open-label study designed to assess the safety and PK of elagolix in female subjects with mild, moderate or severe hepatic impairment relative to female subjects with normal hepatic function. A total of 22 adult female subjects were enrolled for study participation

according to the subject selection criteria: 6 subjects with normal hepatic function (Group I), 6 subjects with mild stable chronic hepatic impairment (Child-Pugh A, Group II), 6 subjects with moderate stable chronic hepatic impairment (Child-Pugh B, Group III), and 4 subjects with severe stable chronic hepatic impairment (Child-Pugh C, Group IV). Study drug was administered in the morning on Study Day 1, as a single 150 mg dose of elagolix in tablet form, for Groups I, II, III, and IV, after an overnight fast of at least 10 hours and 1 hour before breakfast. Blood samples for elagolix and metabolites were collected by venipuncture approximately 15 minutes prior to dosing (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours after dosing.

PK Results:

Elagolix:

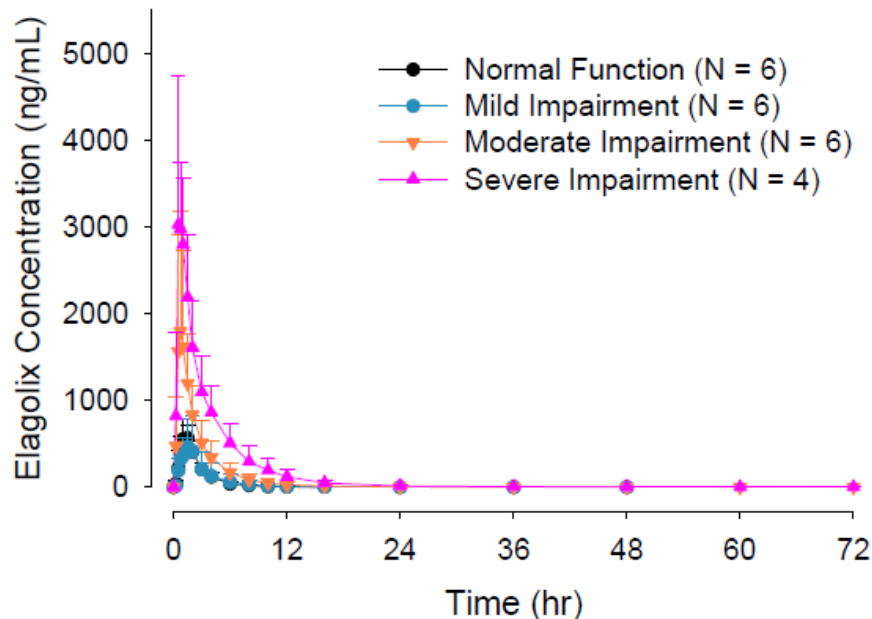


Figure 3.7-1. Mean + SD Elagolix Plasma Concentration-Time Profiles in Subjects with Normal or Impaired Hepatic Function (Study M12-662)

Table 3.7-1. Mean ± SD PK Parameters of Elagolix in Female Subjects with Normal Hepatic Function, Mild, Moderate or Severe Hepatic Impairment (Study M12-662)

PK Parameters	Treatment Group			
	Normal Function N = 6	Mild N = 6	Moderate N = 6	Severe N = 4
C_{max} (ng/mL)	617 ± 166	566 ± 362	1896 ± 1275	3713 ± 367
T_{max} (h)	1.1 ± 0.3	1.3 ± 0.5	1.0 ± 0.4	0.7 ± 0.2
AUC_{0-t} (ng*h/mL)	1517 ± 384	1491 ± 1401	4615 ± 2533	10363 ± 3979
AUC_{0-inf} (ng*h/mL)	1520 ± 384	1494 ± 1401	4624 ± 2533	10374 ± 3988
$T_{1/2}$ (h)	9.88 ± 1.69	8.54 ± 2.61	9.37 ± 3.03	7.45 ± 1.45
CL/F (L/h)	104.6 ± 29.0	145.6 ± 61.9	43.3 ± 24.7	15.7 ± 4.4

As shown in **Table 3.7-1**, the exposure of elagolix (C_{max} and AUCs) was comparable between subjects with normal hepatic function and subjects with mild hepatic impairment. The elagolix mean C_{max} and AUCs values were much higher for subjects with moderate or severe hepatic impairment compared to subjects with normal hepatic function. The relative bioavailability analysis showed that elagolix C_{max} and

AUCs for subjects with moderate and severe hepatic impairment were approximately 2.6- to 2.7-fold and 6.2- to 6.7-fold higher, respectively, than those for subjects with normal hepatic function (**Table 3.7-2**).

Table 3.7-2. Analyses of Relative Bioavailability of Elagolix (Study M12-662)

Treatment Group Test vs. Reference	Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Elagolix					
Mild vs. Normal	C _{max}	487	595	0.818	0.499 – 1.343
	AUC _t	1176	1475	0.797	0.477 – 1.332
	AUC _∞	1180	1478	0.798	0.478 – 1.332
Moderate vs. Normal	C _{max}	1573	595	2.643	1.611 – 4.338
	AUC _t	3999	1475	2.712	1.624 – 4.530
	AUC _∞	4008	1478	2.712	1.626 – 4.525
Severe vs. Normal	C _{max}	3698	595	6.215	3.572 – 10.814
	AUC _t	9893	1475	6.709	3.781 – 11.903
	AUC _∞	9903	1478	6.701	3.780 – 11.876

a. Antilogarithm of the least squares means for logarithms.

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

Metabolite A-1298847:

A-1298847 is a N-dealkyl metabolite of elagolix and its formation is mainly catalyzed by CYP3A enzymes. The exposure of A-1298847 in subjects with mild hepatic impairment and subjects with severe hepatic impairment was lower compared to subjects with normal hepatic function (**Table 3.7-3**). The mean AUC values were approximately 27% higher for subjects with moderate hepatic impairment compared to subjects with normal hepatic function. Hepatic impairment did not significantly increase the exposure of A-1298847.

Table 3.7-3. Mean ± SD Pharmacokinetic Parameters of A-1298847 (Study M12-662)

Pharmacokinetic Parameters (units)	Treatment Group			
	Normal Function N = 6	Mild N = 6	Moderate N = 6	Severe N = 4
A-1298847				
C _{max} (ng/mL)	4.7 ± 2.4	3.1 ± 1.0	4.1 ± 2.1	2.1 ± 0.6*
T _{max} (hr)	2.3 ± 0.6	2.1 ± 0.5	1.8 ± 1.0	1.3 ± 0.6
AUC _t (ng•hr/mL)	35.2 ± 11.0	23.8 ± 8.4	44.7 ± 20.9	25.9 ± 9.8
AUC _∞ (ng•hr/mL)	39.0 ± 11.4	26.6 ± 8.5	49.7 ± 19.7	30.5 ± 10.4
t _{1/2} ^a (hr)	11.0 ± 2.8	10.2 ± 1.6	14.9 ± 4.9*	16.7 ± 5.5*

a. Harmonic mean ± pseudo-SD; evaluations of t_{1/2} were based on statistical tests for β.

* Statistically significantly different from subjects with normal hepatic function (ANCOVA or ANOVA, p < 0.05).

Metabolite A-1323217

A-1323217 is an O-demethyl metabolite of elagolix and its formation is catalyzed by CYP 3A4 (43%), 2D6 (52%) and 2C8 (5%). A comparable exposure of A-1323217 was observed in subjects with mild hepatic impairment and subjects with normal hepatic function (**Table 3.7-4**). The mean C_{max} and AUCs values of A-1323217 were much higher for subjects with moderate or severe hepatic impairment compared to subjects with normal hepatic function. The relative bioavailability analysis showed that the C_{max} and AUCs of A-1323217 for subjects with moderate and severe hepatic impairment were approximately 3.8- to 5.4-fold and 8.8- to 17-fold higher, respectively, than those for subjects with normal hepatic function (**Table 3.7-5**).

Table 3.7-4. Mean $\pm$ SD Pharmacokinetic Parameters of A-1323217 (Study M12-662)

Pharmacokinetic Parameters (units)		Treatment Group			
		Normal Function N = 6	Mild N = 6	Moderate N = 6	Severe N = 4
A-1323217					
C_{max}	(ng/mL)	8.3 $\pm$ 3.3	9.3 $\pm$ 12.7	43.1 $\pm$ 34.2*	77.2 $\pm$ 44.1*
T_{max}	(hr)	1.9 $\pm$ 0.2	1.8 $\pm$ 0.3	1.9 $\pm$ 0.2	2.3 $\pm$ 1.5
AUC _t	(ng•hr/mL)	25.0 $\pm$ 8.5	31.7 $\pm$ 46.9	219.9 $\pm$ 190.7*	520.7 $\pm$ 416.0*
AUC _∞	(ng•hr/mL)	25.6 $\pm$ 8.4	32.4 $\pm$ 47.2	222.0 $\pm$ 191.4*	525.1 $\pm$ 417.1*
$t_{1/2}$ ^a	(hr)	1.88 $\pm$ 0.51	1.92 $\pm$ 0.44	5.07 $\pm$ 3.52*	5.52 $\pm$ 5.74*

a. Harmonic mean $\pm$ pseudo-SD; evaluations of $t_{1/2}$ were based on statistical tests for β .

* Statistically significantly different from subjects with normal hepatic function (ANOVA, $p < 0.05$).

Table 3.7-5. Analyses of Relative Bioavailability of A-1323217 (Study M12-662)

Treatment Group Test vs. Reference	Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
A-1323217					
Mild vs. Normal	C_{max}	5.8	7.8	0.743	0.331 – 1.670
	AUC _t	18.3	23.8	0.769	0.300 – 1.968
	AUC _∞	19.0	24.4	0.779	0.308 – 1.969
Moderate vs. Normal	C_{max}	29.3	7.8	3.773	1.679 – 8.478
	AUC _t	129.7	23.8	5.450	2.130 – 13.948
	AUC _∞	132.6	24.4	5.430	2.148 – 13.729
Severe vs. Normal	C_{max}	68.7	7.8	8.848	3.579 – 21.876
	AUC _t	400.0	23.8	16.807	5.878 – 48.058
	AUC _∞	404.1	24.4	16.556	5.870 – 46.700

a. Antilogarithm of the least squares means for logarithms.

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

Reviewer's Comments:

- Compared to subjects with normal hepatic function, the exposures of elagolix and its two metabolites (A-1298847 and A-1323217) did not increase in subjects with mild hepatic impairment. No dose adjustment in women with mild hepatic impairment is required.
- Compared to subjects with normal hepatic function, the AUC values of elagolix and A-1323217 in subjects with severe hepatic impairment increased by 6.7 fold and 17 fold, respectively. Elagolix should be contraindicated in women with severe hepatic impairment.
- Compared to elagolix, metabolite A-1298847 exhibited a slightly higher inhibition activity on GnRH receptor. Elagolix and A-1298847 produced inhibition of GnRH-stimulated inositol phosphate (IP) production in RBL-1 cells expressing the human GnRH receptor with IC_{50} of 1.5 nM and 0.8 nM, respectively. Compared to subjects with normal hepatic function, although averagely a 27% increase in A-1298847 exposure was observed in subjects with moderate hepatic impairment, its exposure in subjects with severe hepatic impairment decreased. Overall, the slightly increased exposure of A-1298847 is unlikely to have a clinically relevant impact on efficacy or safety.
- The AUC ratio of A-1323217 and elagolix observed in subjects with normal hepatic function was small (1.7%). Furthermore, the GnRH receptor inhibition activity of A-1323217 is lower compared to elagolix. Elagolix and A-1323217 produced inhibition of GnRH-stimulated inositol phosphate (IP) production in RBL-1 cells expressing the human GnRH receptor with IC_{50} of 1.5 nM and 14 nM, respectively. Thus, the 5.4 fold increase in the AUC of A-1323217 observed in subjects with moderate hepatic impairment is not likely to contribute significantly to the overall GnRH receptor inhibition.
- Compared to subjects with normal hepatic function, the AUC value of elagolix in subjects with moderate hepatic impairment increased by 2.7 fold. For women with moderate hepatic impairment, dose adjustment is required, considering the safety risk of bone loss, the use of elagolix 150 mg QD should be limited to 6 months and the 200 mg BID regimen is not recommended.

4. Clinical Drug Interaction Assessments

4.1 Study M12-660

Title: A Study to Evaluate the Effects of the Coadministration of Ketoconazole on the Pharmacokinetics and Safety of a Single Dose of Elagolix (ABT-620) in Healthy Premenopausal Females

Objectives:

To assess the pharmacokinetics and safety/tolerability of elagolix when administered alone and in combination with ketoconazole in healthy premenopausal females

Methodology:

This was a Phase 1, single-dose, two-period, open-label, fasting study conducted following a sequential design (**Table 4.1-1**). In Period 1, subjects received a single dose of elagolix 150 mg on Study Day 1. In Period 2, subjects received ketoconazole 400 mg once daily (QD) for 6 days on Study Days -3 through 3 and a single dose of elagolix 150 mg on Study Day 1 (elagolix and ketoconazole were co-administered on the fourth day of ketoconazole dosing). A washout interval of at least 5 days separated the dosing of elagolix in Period 1 and the first dose of ketoconazole given in Period 2.

Table 4.1-1 Study Schematic (Study M12-660)

Study Schematic (Study M12-660)

Period 1		Period 2		
Study Day 1	Minimum 5-day washout	Study Days -3 to -1	Study Day 1	Study Days 2 to 3
Elagolix 150 mg			Ketoconazole 400 mg QD	Ketoconazole 400 mg + Elagolix 150 mg

Note: All study drugs were administered under fasting conditions.

Results and conclusion:

Table 4.1-2 Relative Bioavailability of Elagolix and 90% Confidence Intervals (Study M12-660)

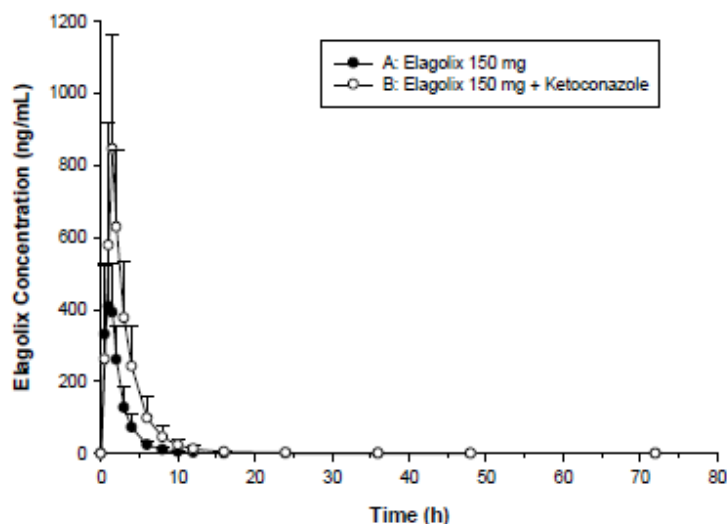
Regimens Test vs. Reference	Elagolix Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Elagolix + Ketoconazole	C _{max}	820	463	1.771	1.480 – 2.118
vs.	AUC _t	2325	1056	2.203	1.986 – 2.443
Elagolix Alone	AUC _∞	2330	1060	2.198	1.981 – 2.439

a. Antilogarithm of the least squares means for logarithms.

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

Note: Units presented for C_{max} and AUC central values are ng/mL and ng•hr/mL, respectively.

Mean Elagolix Plasma Concentration-Time Profiles, Linear Scale



Mean Elagolix Plasma Concentration-Time Profiles, Log-Linear Scale

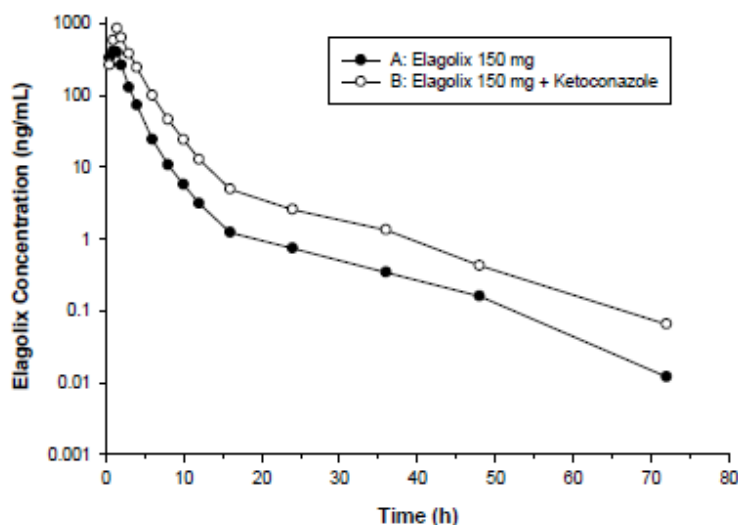


Figure 4.1-1. Mean Elagolix Plasma Concentration-Time Profiles, Linear Scale and Log-Linear Scale.

Out of 12 enrolled premenopausal female subjects, 11 subjects received both periods of study and were included in the statistical and pharmacokinetic analysis. After coadministration of elagolix with ketoconazole, elagolix C_{max} and AUC values increased 1.8- and 2.2-fold (**Table 4.1-2, Figure 4.1-1**), respectively, relative to administration of elagolix alone. Elagolix is considered a moderate sensitive substrate for CYP3A. Elagolix half-life was similar with or without ketoconazole coadministration. The regimens tested were generally well tolerated by the subjects. No clinically significant vital signs, ECG or laboratory measurements were observed during the study.

4.2 Study M12-659

Title: A Study to Evaluate the Effects of the Coadministration of Rifampin on the Pharmacokinetics and Safety of a Single Dose of Elagolix in Healthy Premenopausal Females

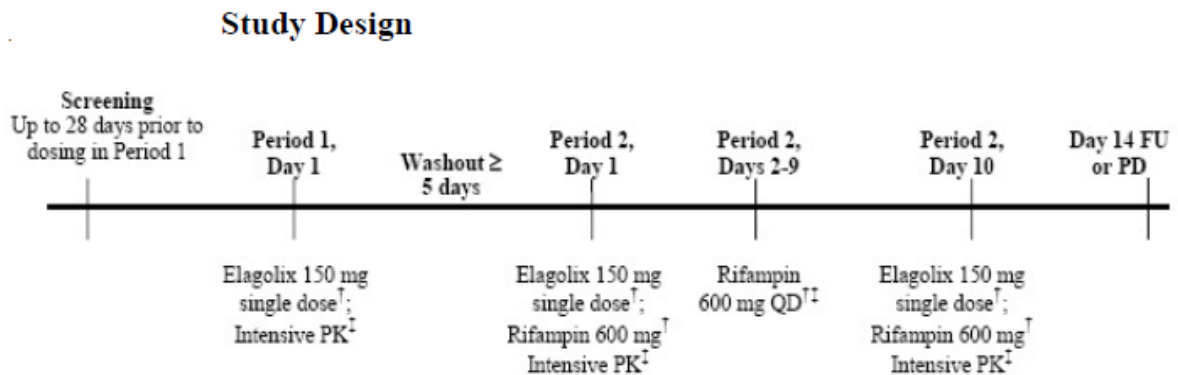
Objectives:

The objective of this study was to assess the pharmacokinetics, safety, and tolerability of elagolix when administered alone and in combination with rifampin in healthy premenopausal females.

Methodology:

This was a Phase 1, fasting, open-label study conducted according to a two-period sequential design (Table 4.2-1). Adult, healthy, premenopausal females (N = 12) were selected to participate in the study according to the inclusion/exclusion criteria. In Period 1, a single dose of elagolix 150 mg was administered on Study Day 1. In Period 2, a single dose of elagolix 150 mg was administered in the morning on Study Day 1 and Study Day 10 and rifampin 600 mg once daily (QD) was administered in the morning on Study Days 1 through 10. Study drugs were administered under fasting conditions in both periods. There was at least a 5-day washout period between dosing of elagolix in Period 1 and the first dose of elagolix given in Period 2.

Table 4.2-1 Study Schematic (Study M12-659)



FU = Follow-up; PD = Patient discontinuation

[†] Elagolix was dosed in the morning; rifampin was dosed in the morning beginning on Study Day 1 of Period 2 and ending on Study Day 10.

[‡] Intensive pharmacokinetic (PK) was performed for elagolix for 36 hours after elagolix dosing on Study Day 1 of Period 1, and on Study Day 1 and Study Day 10 of Period 2; blood samples for rifampin assay were collected 2 hours after rifampin dosing on Study Days 1, 6, 8, and 10 of Period 2.

Results and conclusion:

Table 4.2-2 Relative Bioavailability of Elagolix and 90% Confidence Intervals (Study M12-659)

The bioequivalence/bioavailability results are listed in the following table.

Regimens ^a Test vs. Reference	Pharmacokinetic Parameter	Central Value ^b		Relative Bioavailability	
		Test	Reference	Point Estimate ^c	90% Confidence Interval
Elagolix + Rifampin SD vs. Elagolix Alone	C _{max} (ng/mL)	2244	513	4.371	3.622 – 5.275
	AUC _t (ng•hr/mL)	7293	1307	5.580	4.881 – 6.379
	AUC _∞ (ng•hr/mL)	7294	1308	5.575	4.877 – 6.372
Elagolix + Rifampin QD vs. Elagolix Alone	C _{max} (ng/mL)	1027	513	2.000	1.657 – 2.414
	AUC _t (ng•hr/mL)	2162	1307	1.654	1.447 – 1.891
	AUC _∞ (ng•hr/mL)	2163	1308	1.653	1.446 – 1.889

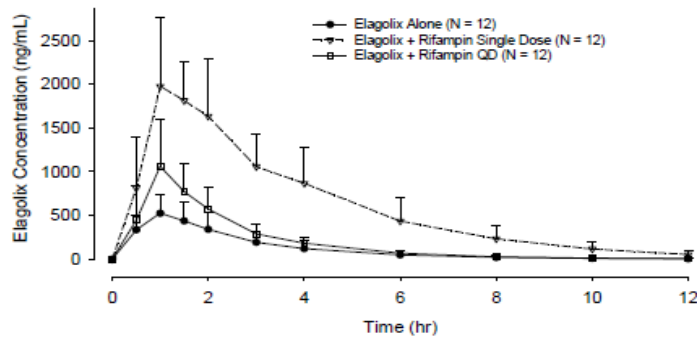
SD = single dose; QD = once daily

a. Elagolix 150 mg was administered as a single tablet on Study 1 in Period 1 and Study Days 1 and 10 in Period 2. Rifampin 600 mg was administered as two 300 mg tablets once daily (QD) on Study Days 1 through 10 in Period 2.

b. Antilogarithm of the least squares means for logarithms.

c. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Mean + SD Elagolix Plasma Concentration-Time Profiles for Elagolix Administered with Single and Multiple Doses of Rifampin Versus Elagolix Administered Alone, Linear Scale, Up to 12 hours



Mean + SD Elagolix Plasma Concentration-Time Profiles for Elagolix Administered with Single and Multiple Doses of Rifampin Versus Elagolix Administered Alone, Log-Linear Scale, Full Profile

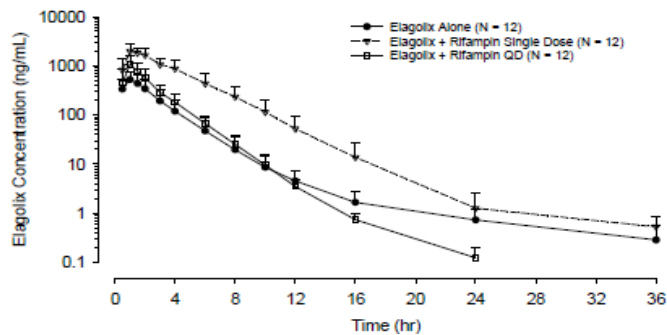


Figure 4.2-1. Mean + SD Elagolix Plasma Concentration-Time Profiles for Elagolix Administered with Single and Multiple Doses of Rifampin Versus Elagolix Administered Alone, Linear and Log-Linear Scale, Full Profile

A total of 12 adult premenopausal female subjects enrolled in the study, and 12 subjects completed both periods of the study and were included for statistical and pharmacokinetic analysis. Elagolix C_{max} and AUC increased by 4.4- and 5.6-fold, when co-administered with a single rifampin dose, and by 2.0 fold and 1.65 fold after multiple rifampin dosing, respectively (**Table 4.2-2, Figure 4.2-1**). Coadministration of elagolix with drugs that inhibit OATP1B1 may increase elagolix plasma concentrations and coadministration of elagolix with drugs that induce CYP3A and P-gp may decrease elagolix plasma concentrations.

The regimens tested in this study were generally well tolerated by the subjects. No clinically significant vital signs, ECG or laboratory measurements were observed during the study.

4.3 Study M13-756

Title: A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics, Safety and Tolerability of the Co-administration of Rosuvastatin Calcium and Elagolix in Healthy Premenopausal Females

Objectives:

The primary objective of this study was to:

- Evaluate the pharmacokinetics of rosuvastatin calcium (rosuvastatin) when administered alone and in combination with elagolix in healthy premenopausal females.

The secondary objectives were to:

- Evaluate the pharmacokinetics of elagolix when administered alone and in combination with rosuvastatin in healthy premenopausal females.
- Assess the safety and tolerability of the co-administration of elagolix and rosuvastatin.

Methodology:

This Phase 1, open-label study was conducted according to a two-period, sequential design.

Table 4.3-1 Study Schematic (Study M13-765)

Study Schematic (Study M13-756)

Period 1		Period 2	
Study Day 1	Minimum	Study Days 1 – 7	Study Days 8 – 14
Elagolix 300 mg	5-day washout	Rosuvastatin 20 mg QD	Rosuvastatin 20 mg QD Elagolix 300 mg BID

Note: Rosuvastatin doses and elagolix morning doses were administered under fasting conditions.

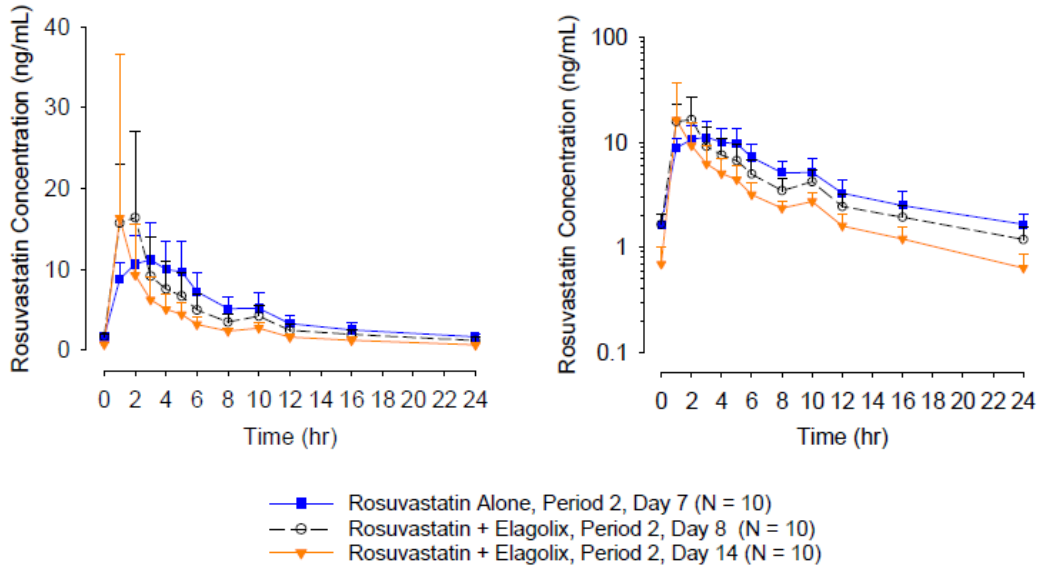
Each dose of study drug was taken orally with approximately 240 mL of water. A washout interval of at least 5 days separated the single dose of elagolix on Day 1 of Period 1 from the first dose of rosuvastatin on Day 1 of Period 2.

- Blood Samples for Rosuvastatin and Elagolix Assay
 - ✓ Rosuvastatin: Blood samples were obtained in Period 2 on Study Days 7, 8, and 14 prior to dosing (0-hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post dose (Note: the Day 7, 24-hour collection was the same as the Day 8, 0-hour collection) and on Study Days 10 and 12 immediately prior to administration of the morning dose of rosuvastatin.
 - ✓ Elagolix: Blood samples were obtained in Period 1 on Study Day 1 prior to its morning dosing (0-hour), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours post dose and in Period 2

on Study Day 8 prior to its dosing (0-hour), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours post dose. Blood samples for elagolix were also obtained in Period 2 on Study Days 10, 12 and 14 immediately prior to administration of the morning dose of elagolix.

Results and conclusion:

Mean + SD Rosuvastatin Plasma Concentration-Time Profiles for Rosuvastatin Administered with the First Dose or Multiple Doses of Elagolix versus Rosuvastatin Administered Alone, Linear Scale and Log-Linear Scales



Mean + SD Elagolix Plasma Concentration-Time Profiles for Elagolix Administered after Multiple Doses of Rosuvastatin Versus Elagolix Administered Alone, Linear Scale and Log-Linear Scales

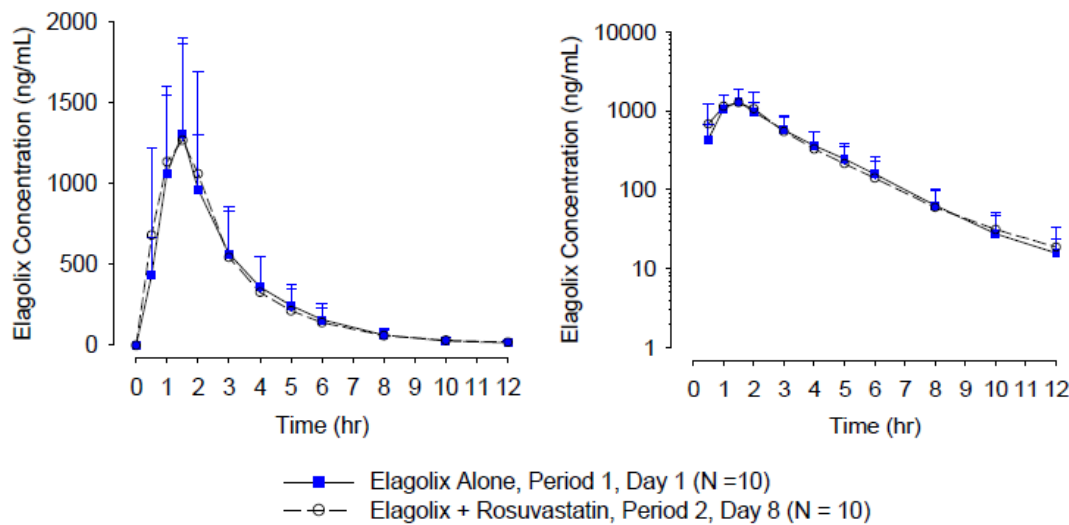


Figure 4.3-1. Mean + SD Rosuvastatin and Elagolix Plasma Concentration-Time Profiles, Linear Scale and Log-Linear Scales

Table 4.3-2 Relative Bioavailability of Rosuvastatin and Elagolix 90% Confidence Intervals (Study M13-756)

The relative bioavailability results for rosuvastatin are presented in the following table.

Regimens Test vs. Reference	Rosuvastatin Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Rosuvastatin + FD Elagolix	C _{max}	18.88	11.33	1.67	1.224 – 2.267
vs. Rosuvastatin Alone	AUC ₂₄	96.98	109.79	0.88	0.742 – 1.051
Rosuvastatin + MD Elagolix BID	C _{max}	11.25	11.33	0.99	0.729 – 1.351
vs. Rosuvastatin Alone	AUC ₂₄	65.37	109.79	0.60	0.500 – 0.709

FD = first dose of elagolix BID on Study Day 8; MD = multiple doses of elagolix BID

a. Antilogarithm of the least squares means for logarithms.

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

Note: Units presented for C_{max} and AUC are ng/mL and ng·hr/mL, respectively.

The relative bioavailability results for elagolix are presented in the following table.

Regimens Test vs. Reference	Elagolix PK Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Elagolix + Rosuvastatin QD	C _{max}	1348.7	1301.3	1.04	0.879 – 1.222
vs. Elagolix Alone	AUC ₁₂	3553.5	3508.6	1.01	0.900 – 1.139

PK = pharmacokinetic

a. Antilogarithm of the least squares means for logarithms.

a. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Note: Units presented for C_{max} and AUC are ng/mL and ng·hr/mL, respectively.

Out of 12 enrolled premenopausal female subjects, 10 subjects completed both periods of study and were included in the statistical and pharmacokinetic analysis. Co-administration of 20 mg QD multiple doses of rosuvastatin (steady-state) with the first 300 mg dose of elagolix resulted in increase in rosuvastatin C_{max} by 67% and comparable AUC₂₄ to rosuvastatin administered alone. Co-administration of 20 mg QD multiple doses of rosuvastatin (steady-state) with multiple dose 300 mg BID of elagolix resulted in comparable rosuvastatin C_{max} and, rosuvastatin AUC₂₄ decreased by approximately 40% (**Table 4.3-2, Figure 4.3-1**). The mechanism(s) for decrease in rosuvastatin AUC when co-administered with multiple-dose elagolix is unknown. Elagolix single dose pharmacokinetics was comparable in the absence or presence of rosuvastatin.

The regimens tested were generally well tolerated by the subjects. No clinically significant vital signs, ECG or changes in laboratory measurements were observed during the study.

4.4 Study M15-973

Title: A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics of the Co-Administration of Elagolix with Sertraline in Healthy Premenopausal Females

Objectives:

The study objective was to assess the pharmacokinetics of elagolix and sertraline when administered alone or in combination in healthy premenopausal females.

Methodology:

This Phase 1, open-label study was conducted using a three-period sequential design. Adult premenopausal female subjects (N = 20) in general good health were administered study drugs as follows (Table 4.4-1 and Figure 4.4-1):

Table 4.4-1 Study Schematic (Study M15-973)

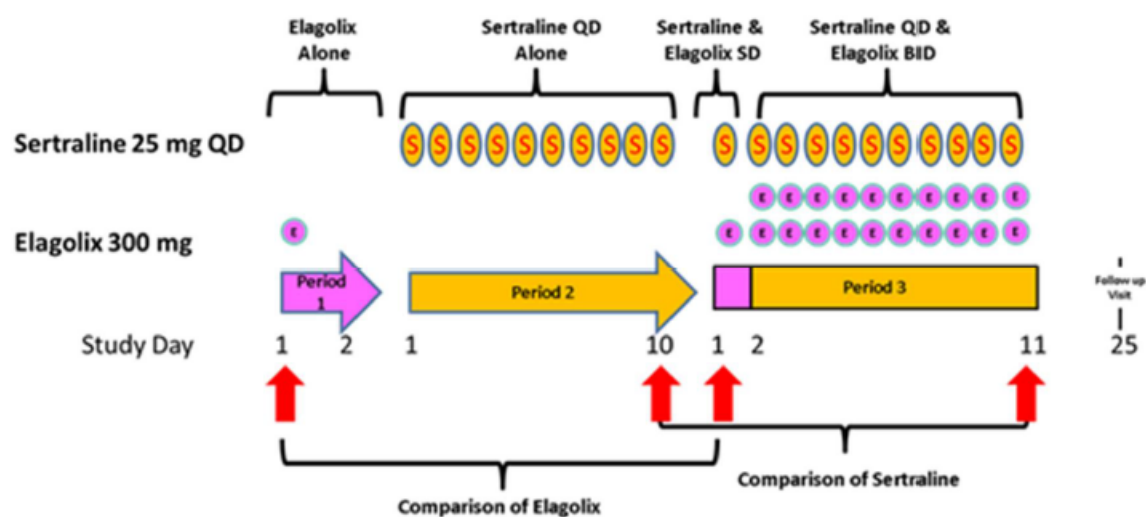
Study Schematic (Study M15-973)

Period 1	Period 2	Period 3	
Study Day 1	Study Days 1 – 10	Study Day 1	Study Day 2 – 11
Elagolix 300 mg	Sertraline 25 mg QD	Elagolix 300 mg Sertraline 25 mg	Elagolix 300 mg BID Sertraline 25 mg QD

Note: Sertraline doses and elagolix morning doses were administered under fasting conditions. Elagolix evening doses were administered approximately 2.5 hours after dinner.

Figure 4.4-1 Study Schematic (Study M15-973)

Study Design Schematic



Period 1 (Day 1) A single dose of elagolix 300 mg was administered in the morning on Study Day 1.

Period 2 (Days 1 – 10) Sertraline 25 mg once daily (QD) was administered in the morning on Study Days 1 through 10. Period 2 began 24 hours after the last pharmacokinetic sampling for elagolix on Period 1 Day 2.

Period 3 (Day 1) A single dose of elagolix 300 mg and a single dose of sertraline 25 mg were administered in the morning on Study Day 1. The elagolix and sertraline doses were administered at the same time.

Period 3 (Days 2 – 11) Elagolix 300 mg twice daily (BID) and sertraline 25 mg QD were co-administered on Study Days 2 through 11. Each elagolix BID dose was separated by approximately 12 hours. Sertraline QD dose was administered in the morning with elagolix. There was no washout interval between periods.

Elagolix pharmacokinetic sample collection:

Period 1: Blood samples were collected prior to study drug dosing (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing on Day 1 of Period 1.

Period 3: Blood samples were collected prior to morning dosing (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after morning dosing on Day 1 of Period 3. Blood samples were collected prior to morning dosing (0-hour), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after morning dosing on Day 11 of Period 3. Blood samples for assay of trough concentrations were collected on Days 8, 9 and 10 of Period 3.

Sertraline pharmacokinetic sample collection:

Period 2: Blood samples were collected prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours after dosing on Day 10 of Period 2. Blood samples for assay of trough concentrations of sertraline were collected on Days 6, 7, 8, and 9 of Period 2.

Period 3: Blood samples were collected prior to sertraline dosing and elagolix morning dosing (0-hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours after morning dosing on Day 11 of Period 3. Blood samples for assay of trough concentrations of sertraline were collected on Days 6, 7, 8, 9 and 10 of Period 3.

Results and conclusion:

Table 4.4-2 Relative Bioavailability of Sertraline and Elagolix 90% Confidence Intervals (Study M15-973)

Regimens Test vs. Reference	Sertraline Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Sertraline QD + Elagolix BID					
Sertraline + Elagolix	C _{max}	24.9	18.6	1.337	1.217 – 1.469
vs. Sertraline Alone	AUC ₂₄	413	292	1.417	1.276 – 1.572

a. Antilogarithm of the least squares means for logarithms.

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

Note: Units presented for C_{max} and AUC central values are ng/mL and ng•hr/mL, respectively.

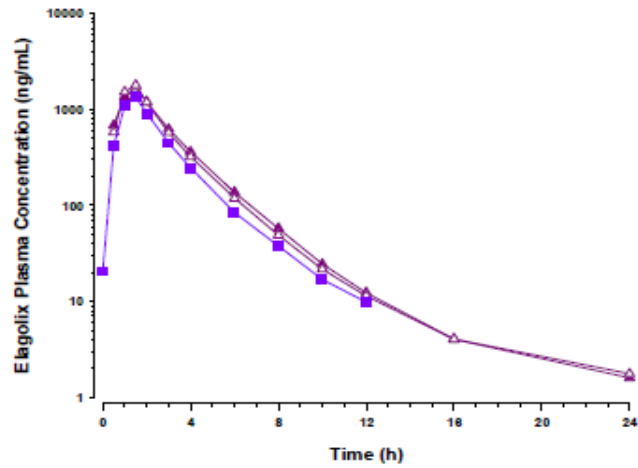
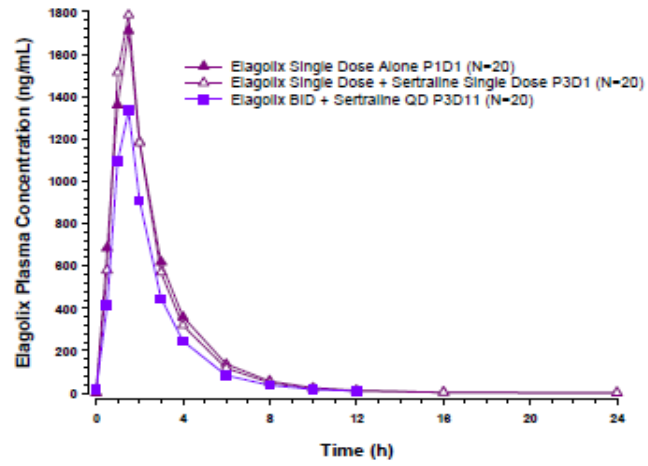
Regimens Test vs. Reference	Elagolix Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Sertraline Single Dose + Elagolix Single Dose					
Elagolix + Sertraline	C _{max}	1804	1727	1.045	0.918 – 1.189
vs. Elagolix Alone	AUC ₂₄	3997	4095	0.976	0.890 – 1.071

a. Antilogarithm of the least squares means for logarithms.

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

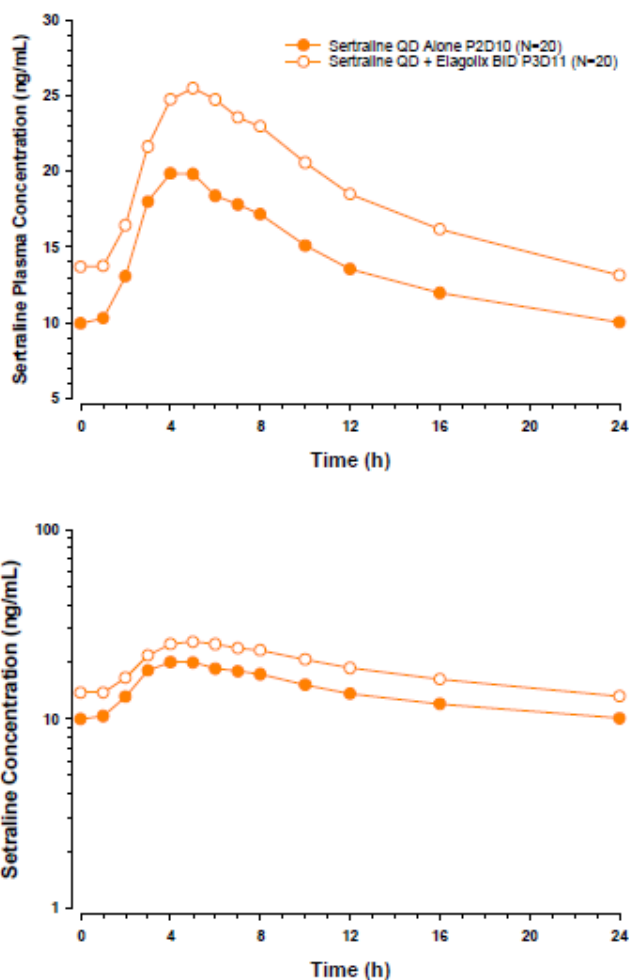
Note: Units presented for C_{max} and AUC central values are ng/mL and ng•hr/mL, respectively.

Mean Elagolix Plasma Concentration-Time Profiles



P1D1 = Period 1 Day 1; P3D1 = Period 3 Day 1; P3D11 = Period 3 Day 11

Mean Sertraline Plasma Concentration-Time Profiles for Sertraline



P2D10 = Period 2 Day 10; P3D11 = Period 3 Day 11

Figure 4.4-2 Mean Elagolix and Sertraline Plasma Concentration-Time Profiles, Linear Scale and Log-Linear Scales

All enrolled premenopausal female subjects (N = 20) completed the study and were included in the safety and pharmacokinetics analyses. Multiple-dose administration of sertraline did not affect single-dose exposures (C_{max} and AUC) of elagolix. However, multiple-dose administration of elagolix increased the sertraline steady-state C_{max} and AUC_{24} by 34% and 42%, respectively (**Table 4.4-2, Figure 4.4-2**).

4.5 Study M15-974

Title: A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics of the Co-Administration of Elagolix with Fluconazole in Healthy Premenopausal Females

Objectives:

The objective of this study was to assess the pharmacokinetics of elagolix and fluconazole when administered alone or in combination in healthy premenopausal females.

Methodology:

Open-label study conducted according to a two-period sequential design in healthy adult premenopausal females (Table 4.5-1).

Period 1 (Day 1): A single dose of fluconazole 200 mg was administered in the morning on Day 1.

Period 2 (Days 1 – 12): Elagolix 300 mg twice daily (BID) was administered on Days 1 through 12. Each elagolix dose was separated by approximately 12 hours. Fluconazole 200 mg was administered in the morning of Day 10 with elagolix.

Table 4.5-1 Study Schematic (Study M15-974)
Study Schematic (Study M15-974)

Period 1	Period 2	Period 2	Period 2
Study Day 1	Study Days 1 – 9	Study Day 10	Study Days 11 – 12
Fluconazole 200 mg	Elagolix 300 mg BID	Elagolix 300 mg BID Fluconazole 200 mg	Elagolix 300 mg BID

Note: Fluconazole doses and elagolix morning doses were administered under fasting conditions. Elagolix evening doses were administered approximately 2.5 hours after dinner.

Study drugs were orally administered on an empty stomach; no food was consumed for 2 hours prior to dosing continuing through 1 hour after study drug administration in each period. A washout interval of 4 days separated dosing on Day 1 of each period. Serial blood samples for intensive pharmacokinetic analysis were collected for 72 hours after dosing on Day 1 of Period 1 and Day 10 of Period 2 for fluconazole, and for 12 hours after dosing on Days 9 and 10 of Period 2 for elagolix.

Results and conclusion:

Table 4.5-2 Relative Bioavailability of Elagolix and Fluconazole 90% Confidence Intervals (Study M15-974)

The effect of fluconazole on elagolix exposure:

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Period 2 Day 10 vs. Period 2 Day 9	C_{max}	1440	1100	1.310	1.156 – 1.486
	AUC_{12}	3460	2680	1.290	1.196 – 1.392

Period 2 Day 9: Elagolix 300 mg BID

Period 2 Day 10: Elagolix 300 mg BID + Fluconazole 200 mg

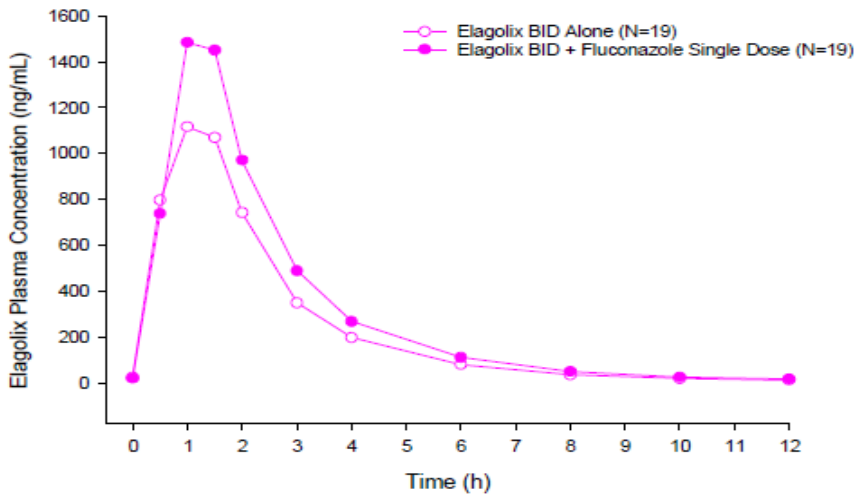
The effect of elagolix on fluconazole exposure:

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Period 2 Day 10 vs. Period 1 Day 1	C_{max}	5710	5640	1.013	0.962 – 1.068
	AUC_t	177000	175000	1.011	0.967 – 1.057
	AUC_{inf}	227000	222000	1.024	0.962 – 1.090

Period 1 Day 1: Fluconazole 200 mg

Period 2 Day 10: Elagolix 300 mg BID + Fluconazole 200 mg

Mean Elagolix Plasma Concentration-Time Profiles



Mean Fluconazole Plasma Concentration-Time Profiles

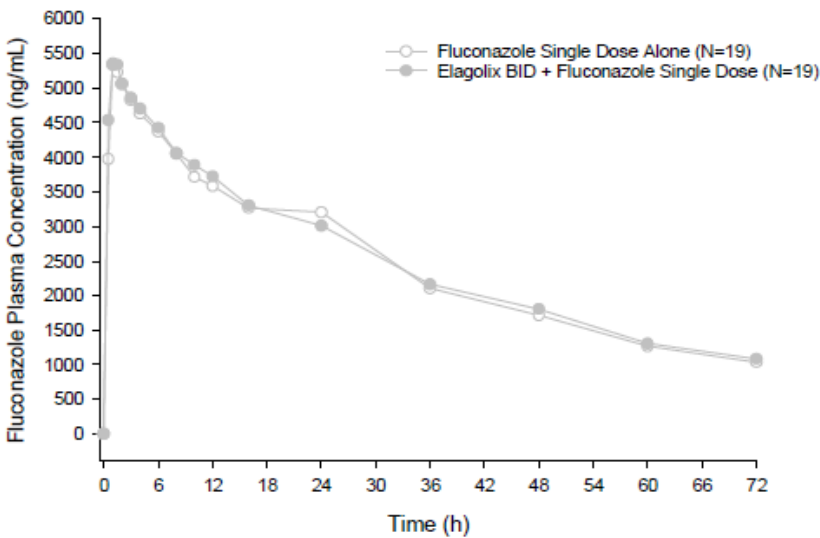


Figure 4.5-1. Mean Elagolix and Fluconazole Plasma Concentration-Time Profiles.

A total of 20 adult premenopausal female subjects enrolled in the study, and a total of 19 subjects completed the study and were included for statistical and pharmacokinetic analysis. The steady-state exposure of elagolix 300 mg BID (C_{max} and AUC_{12} after 10 days) was increased by approximately 30% following the co-administration with a single dose of fluconazole 200 mg. The mean C_{max} , AUC_t and AUC_{inf} values of fluconazole were comparable with and without co-administration of elagolix ($\leq 2\%$ change, and 90% confidence interval within 0.8 and 1.25) (Table 4.5-2, Figure 4.5-1). As a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor, fluconazole increased elagolix exposures by approximately 30%. In the meantime, elagolix did not affect fluconazole exposures.

Reviewer's note: The study evaluated the effect of a single dose of fluconazole on the PK of elagolix. The effect of multiple dose of fluconazole on the PK of elagolix is unknown.

4.6 Study NBI-56418-0502

Title: A Phase I, Open-Label, Single-Sequence, Interaction Study to Evaluate the Influence of NBI-56418 on the Pharmacokinetics of Midazolam in Healthy Male Subjects

Objectives:

To determine the effect of multiple-doses of 150 mg QD elagolix on the pharmacokinetics, safety and tolerability of single dose midazolam and to describe the pharmacodynamic effects and evaluate the safety and tolerability of multiple doses of elagolix.

Methodology:

Adult male subjects (N = 12) in general good health enrolled in the study. Intensive pharmacokinetic blood samples were collected on Study Days 1, 4, and 14 for assay of midazolam and 1-hydroxy-midazolam and for assay of elagolix on Study Days 2 and 13 (Table 4.6-1).

Table 4.6-1 Study Schematic (Study NBI-56418-0502)

Study Schematic (Study NBI-56418-0502)

Study Day 1	Study Day 2 – 3	Study Day 4	Study Day 5 – 13	Study Day 14
Midazolam 2 mg	Elagolix 150 mg QD	Midazolam 2 mg Elagolix 150 mg	Elagolix 150 mg QD	Midazolam 2 mg Elagolix 150 mg

Note: Subjects were required to fast overnight before dosing on Study Days 1, 2, 4, 13, and 14.

Results and conclusion:

Table 4.6-2 Midazolam and 1-OH-Midazolam Pharmacokinetic Parameters – Days 4 and 14 Versus Day 1 (Study NBI-56418-0502)

Pharmacokinetic Parameters for Midazolam on Days 1, 4, and 14

Parameter	Day 1 (N=12)		Day 4 (N=12)		Day 14 (N=11)	
	Geometric Mean	Geometric CV (%)	Geometric Mean	Geometric CV (%)	Geometric Mean	Geometric CV (%)
C _{max} (ng/mL)	10.15	32.86	9.71	30.51	8.65	36.18
AUC _{0-t} (ng-hr/mL)	31.89	53.73	25.19	43.57	22.05	55.59
AUC _{0-inf} (ng-hr/mL)	33.20	55.84	26.09	43.81	22.90	55.56
T _{max} (hr) ^a	0.76	0.50, 2.00	0.75	0.50, 1.00	1.00	0.50, 1.00
t _{1/2} (hr)	4.27	59.67	3.51	46.66	3.63	37.35

Pharmacokinetic Parameters for 1-Hydroxy-Midazolam on Days 1, 4, and 14

Parameter	Day 1 (N=12)		Day 4 (N=12)		Day 14 (N=11)	
	Geometric Mean	Geometric CV (%)	Geometric Mean	Geometric CV (%)	Geometric Mean	Geometric CV (%)
C _{max} (ng/mL)	46.56	34.27	57.66	23.22	58.24	24.49
AUC _{0-t} (ng-hr/mL)	134.21	10.61	142.18	9.67	141.84	13.50
AUC _{0-inf} (ng-hr/mL)	143.40	11.65	152.74	12.37	157.48	13.39
T _{max} (hr) ^a	1.00	0.50, 2.00	0.75	0.50, 1.00	0.51	0.50, 1.00
t _{1/2} (hr)	7.88	27.50	7.58	40.93	9.12	52.97

Table 4.6- 3 Comparison of Midazolam and 1-OH-Midazolam Pharmacokinetic Parameters – Days 4 and 14 Versus Day 1 (Study NBI-56418-0502)

Test vs. Reference	Pharmacokinetic Parameter	Geometric Means ^a		Ratio of Geometric Means	90% Confidence Interval
		Day 4	Day 1		
Midazolam					
Day 4					
Midazolam + Elagolix 150 mg QD Day 4 vs. Midazolam Alone, Day 1	C _{max}	9.71	10.1	0.957	0.871 – 1.051
	AUC _t	25.2	31.9	0.790	0.714 – 0.874
	AUC _∞	26.1	33.2	0.786	0.711 – 0.869
Day 14					
Midazolam + Elagolix 150 mg QD Day 14 vs. Midazolam Alone, Day 1	C _{max}	8.21	10.1	0.809	0.735 – 0.891
	AUC _t	20.7	31.9	0.649	0.585 – 0.720
	AUC _∞	21.5	33.2	0.647	0.583 – 0.718
1-OH-Midazolam					
Day 4					
Midazolam + Elagolix 150 mg QD Day 4 vs. Midazolam Alone, Day 1	C _{max}	57.7	46.6	1.238	1.110 – 1.381
	AUC _t	142	134	1.059	1.011 – 1.110
	AUC _∞	153	143	1.065	1.008 – 1.125
Day 14					
Midazolam + Elagolix 150 mg QD Day 14 vs. Midazolam Alone, Day 1	C _{max}	59.0	46.6	1.267	1.132 – 1.418
	AUC _t	143	134	1.067	1.017 – 1.120
	AUC _∞	160	143	1.113	1.052 – 1.178

a. Values for Days 14, 4 and 1 are the geometric means from the analysis of variance (ANOVA) with the effects for day (fixed). Parameters are natural log (ln)-transformed parameters.

Individual Subject Midazolam AUC₀₋₂₄ and C_{max} – Days 1, 4, and 14

(b) (6)



Figure 4.6-1. Individual Subject Midazolam AUC₀₋₂₄ and C_{max} – Days 1, 4, and 14

A total of 12 adult male subjects enrolled in the study, and a total of 11 subjects and 1 subject partially completed the study and were included for statistical and pharmacokinetic analysis. Midazolam AUC decreased by approximately 21% and 35%, respectively, when administered as a single dose on Study Day 4 and Study Day 14 along with 150 mg QD elagolix (Table 4.6-2, Table 4.6-3, Figure 4.6-1).

Reviewer’s note: This indicated only weak induction of CYP3A following elagolix 150 mg QD dosing regimen. The effect of the clinical dose of 200 mg BID was not evaluated in this study.

4.7 Study M15-629

Title: A Phase 1 Study to Evaluate the Effect of the Co-Administration of Elagolix on the Pharmacokinetics of Midazolam in Healthy Premenopausal Females

Objectives:

The objective of this study was to assess the pharmacokinetics of midazolam when administered in combination with elagolix compared to midazolam alone in healthy premenopausal females.

Methodology:

Table 4.7-1 Study Schematic (Study M15-629)

Study Schematic (Study M15-629)

Period 1		Period 2		
Study Day 1	Study Day 1	Study Day 2 – 9	Study Day 10	Study Day 11
Midazolam 2 mg	Midazolam 2 mg Elagolix 300 mg BID	Elagolix 300 mg BID	Midazolam 2 mg Elagolix 300 mg BID	Elagolix 300 mg BID

Note: Midazolam doses and elagolix morning doses were administered under fasting conditions. Elagolix evening doses were administered approximately 2.5 hours after dinner.

Open-label study conducted according to a two-period single-sequence design in healthy adult premenopausal females (**Table 4.7-1**).

Period 1 (Day 1): Single dose of midazolam 2 mg was administered in the morning on Day 1.

Period 2: (Days 1 – 11): Elagolix 300 mg twice daily (BID) was administered on Days 1 through 11. Each elagolix dose was separated by approximately 12 hours. Single dose of midazolam 2 mg was administered in the morning on Day 1 and Day 10. Each dose of midazolam was co-administered with the morning dose of elagolix.

The midazolam doses and elagolix morning doses were orally administered under fasting conditions in each period. The elagolix evening dose was administered approximately 2.5 hours after dinner. A washout period of 3 days separated the single dose of midazolam on Period 1 Day 1 and the administration of midazolam with elagolix on Period 2 Day 1.

Serial blood samples for intensive pharmacokinetic analysis were collected for 48 hours after dosing on Period 1 Day 1 and Period 2 Days 1 and 10 for assay of midazolam and its active metabolite, 1-hydroxy (OH)-midazolam, and for 12 hours after dosing on Period 2 Day 10 for assay of elagolix.

Results and conclusion:

Table 4.7-2 Relative Bioavailability of Midazolam and 1-OH-Midazolam and 90% Confidence Intervals (Study M15-629)

Effect of a single dose of elagolix on midazolam and 1-OH-midazolam exposures:

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Midazolam					
Period 2 Day 1 vs. Period 1 Day 1	C_{max}	14.9	12.6	1.181	1.072 – 1.300
	AUC_t	31.8	25.0	1.274	1.148 – 1.413
	AUC_{inf}	32.6	25.6	1.272	1.149 – 1.409
1-OH-Midazolam					
Period 2 Day 1 vs. Period 1 Day 1	C_{max}	9.05	6.79	1.332	1.176 – 1.509
	AUC_t	17.7	12.7	1.391	1.261 – 1.534
	AUC_{inf}	18.3	13.3	1.374	1.244 – 1.518

Period 1 Day 1: Midazolam 2 mg

Period 2 Day 1: Midazolam 2 mg + Elagolix 300 mg BID

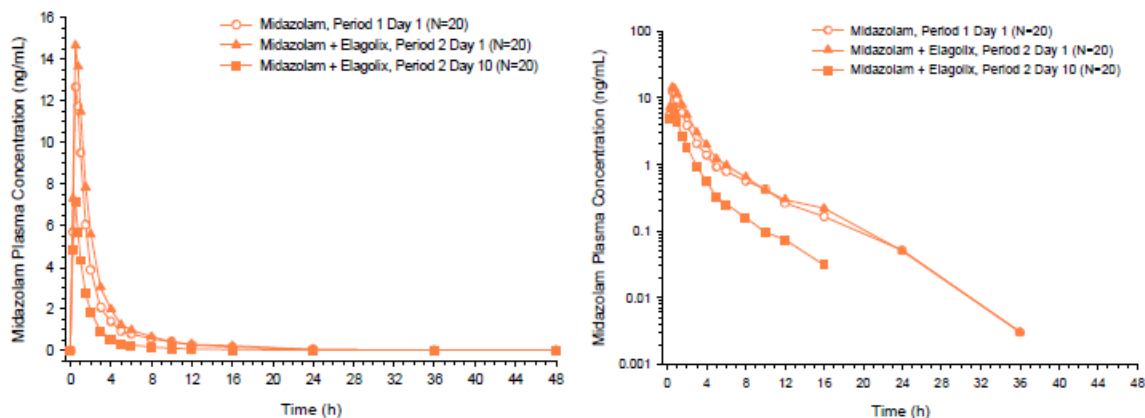
Effect of multiple doses of elagolix on midazolam and 1-OH-midazolam exposures:

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Midazolam					
Period 2 Day 10 vs. Period 1 Day 1	C_{max}	7.05	12.6	0.559	0.507 – 0.615
	AUC_t	11.2	25.0	0.447	0.403 – 0.496
	AUC_{inf}	11.6	25.6	0.455	0.411 – 0.504
1-OH-Midazolam					
Period 2 Day 10 vs. Period 1 Day 1	C_{max}	6.13	6.79	0.902	0.797 – 1.022
	AUC_t	10.3	12.7	0.811	0.735 – 0.895
	AUC_{inf}	10.8	13.3	0.809	0.732 – 0.893

Period 1 Day 1: Midazolam 2 mg

Period 2 Day 10: Midazolam 2 mg + Elagolix 300 mg BID

Mean Midazolam Plasma Concentration-Time Profiles, Linear and Log-Linear Scales



Mean 1-OH-Midazolam Plasma Concentration-Time Profiles, Linear and Log-Linear Scales

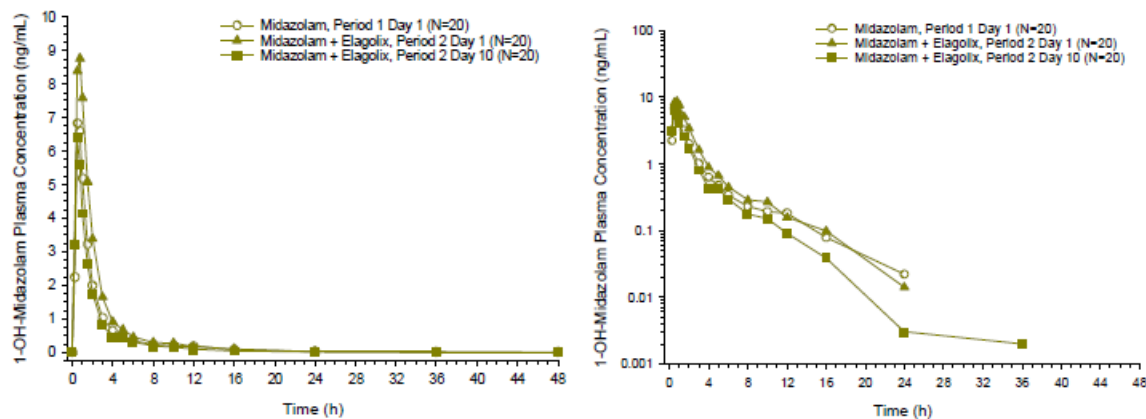


Figure 4.7-1. Mean Midazolam and 1-OH-Midazolam Plasma Concentration-Time Profiles, Linear and Log-Linear Scales

Data of all subjects ($N = 20$) were included in the safety and pharmacokinetic analyses. Following co-administration of single dose midazolam with a single dose of elagolix 300 mg, midazolam C_{max} and AUC increased by 18% and 27%, respectively, and the 1-OH-midazolam metabolite C_{max} and AUC increased by 33% and 39%, respectively.

Following co-administration of single dose midazolam with multiple doses of elagolix 300 mg BID, midazolam C_{max} and AUC decreased by 44% and 55%, respectively, and the 1-OH-midazolam metabolite C_{max} and AUC decreased by 10% and 19%, respectively (**Table 4.7-2, Figure 4.7-1**).

Reviewer's note: These results indicate that elagolix is an inducer of CYP3A, and the induction effect is weak with 150 mg QD (Study MNBI-56418-0502), and moderate with 200 mg BID or 300 mg BID. Thus, plasma concentrations of drugs that are CYP3A substrates may be decreased when co-administered with elagolix.

4.8 Study M12-652

Title: A Study to Evaluate the Effects of the Coadministration of Elagolix on the Pharmacokinetics and Safety of Digoxin in Healthy Premenopausal Females

Objectives:

The objective of this study was to assess the pharmacokinetics and safety of digoxin when co-administered with elagolix compared to digoxin alone in healthy premenopausal females.

Methodology:

Table 4.8-1 Study Schematic (Study M12-652)
Study Schematic (Study M12-652)

Period 1		Period 2		
Study Day 1	Minimum	Study Day 1	Study Day 2 – 9	Study Day 10
Digoxin 0.5 mg	14-day washout	Digoxin 0.5 mg Elagolix 200 mg BID	Elagolix 200 mg BID	Digoxin 0.5 mg Elagolix 200 mg BID

Note: Digoxin doses and elagolix morning doses were administered under fasting conditions. Elagolix evening doses were administered approximately 2.5 hours after dinner.

This was a Phase 1, open-label study that was conducted according to a two-period, sequential design. Adult, healthy, premenopausal female subjects (N = 12) were selected to participate in the study according to the selection criteria. Study drug was administered under fasting conditions in both periods as follows (**Table 4.8-1**):

Period 1: Two 0.25 mg tablets (0.5 mg dose) of digoxin administered in the morning on Day 1 after an approximate 10-hour fast.

Period 2: Two 0.25 mg tablets (0.5 mg dose) of digoxin administered in the morning on Day 1 and Day 10 after an approximate 10-hour fast. One 150 mg tablet and one 50 mg tablet (200 mg dose) of elagolix twice daily (BID) (morning dose at least 1 hour before breakfast and evening dose at least 2.5 hours after dinner separated by approximately 12 hours) were administered on Days 1 through 10.

Each dose of study drug was taken orally with approximately 8 ounces (240 mL) of water. A wash-out interval of 14 days separated the single dose of digoxin in Period 1 with the first dose of digoxin in Period 2.

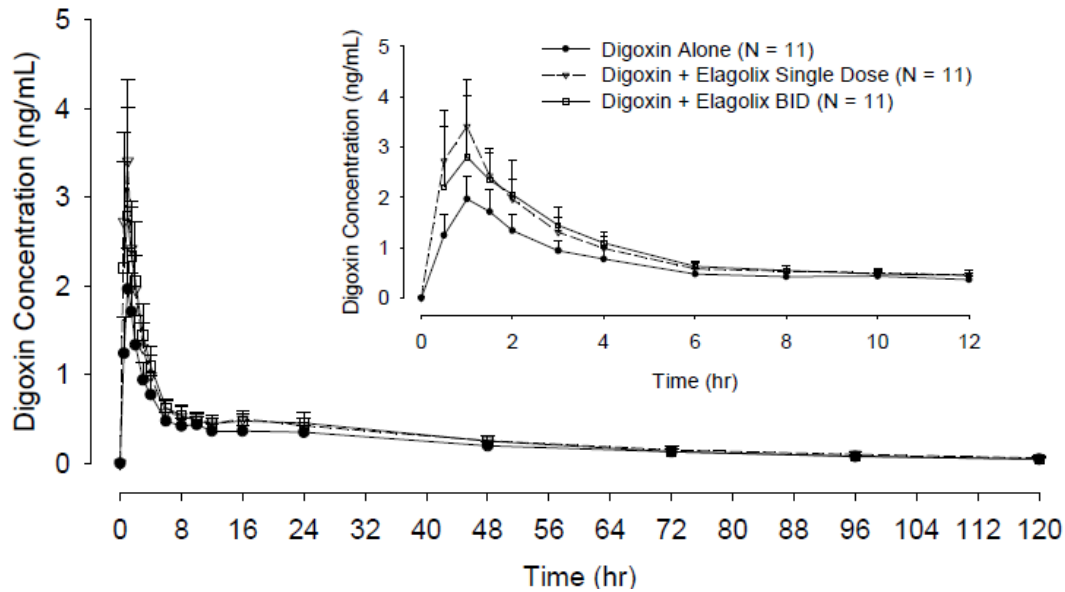
Results and conclusion:

Table 4.8-2 Relative Bioavailability of Digoxin and 90% Confidence Intervals (Study M12-652)

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Digoxin + Elagolix SD	C _{max}	3.329	1.924	1.730	1.551 – 1.929
vs.	AUC _t	35.155	26.867	1.308	1.221 – 1.402
Digoxin Alone	AUC _∞	38.116	28.969	1.316	1.225 – 1.413
Digoxin + Elagolix BID	C _{max}	3.290	1.924	1.710	1.533 – 1.907
vs.	AUC _t	34.268	26.867	1.275	1.191 – 1.366
Digoxin Alone	AUC _∞	36.467	28.969	1.259	1.172 – 1.352

SD = single dose; BID = twice daily

Mean + SD Digoxin Plasma Concentration-Time Profiles for Digoxin Administered with Single or Multiple Doses of Elagolix versus Digoxin Administered Alone, Linear Scale



Mean + SD Digoxin Plasma Concentration-Time Profiles for Digoxin Administered with Single or Multiple Doses of Elagolix versus Digoxin Administered Alone, Log-Linear Scale

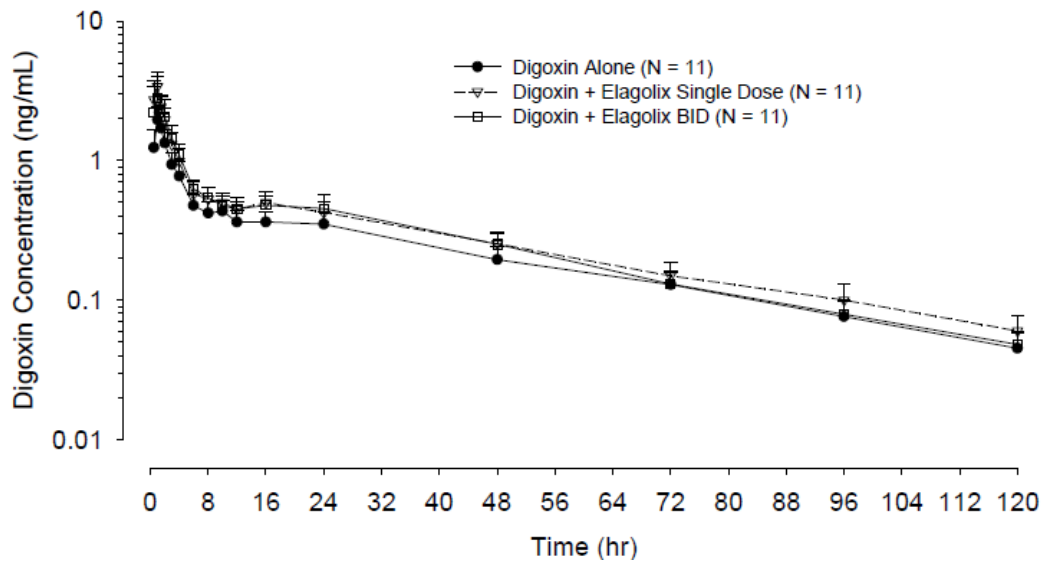


Figure 4.8-1. Mean + SD Digoxin Plasma Concentration-Time Profiles for Digoxin Administered with Single or Multiple Doses of Elagolix versus Digoxin Administered Alone, Linear and Log-Linear Scale

A total of 12 adult premenopausal female subjects enrolled in the study, and a total of 11 subjects completed both periods of the study and were included for statistical and pharmacokinetic analysis. Digoxin C_{max} and AUC increased by approximately 70% and 30%, respectively, after administration of elagolix as single or multiple doses (**Table 4.8-2, Figure 4.8-1**).

4.9 Study M12-765

Title: Assessment of the Effect of Elagolix on the Pharmacokinetics and Pharmacodynamics of Norethindrone in Healthy Premenopausal Female Volunteers Who Receive Progestin-Only Oral Contraceptive Therapy

Objectives:

To assess the potential effect of elagolix on the pharmacokinetics of norethindrone, the effect of elagolix administration on various hormone parameters, and the safety and tolerability of the co-administration of elagolix and progestin-only (norethindrone 0.35 mg) contraception in healthy premenopausal female subjects.

Methodology:

Table 4.9-1 Study Schematic (Study M12-765)

Study Schematic (Study M12-765)

Screening	Lead-in Cycle ^a 28 Days	Period 1		Period 2		Follow-Up
		Cycle 1 Days 1 – 28	Cycle 2 Days 29 – 56	Cycle 3 Days 57 – 84		
	norethindrone 0.35 mg QD	norethindrone 0.35 mg QD	norethindrone 0.35 mg QD Elagolix 150 mg QD			Up to 60 days

a. Norethindrone naïve subjects or subjects on norethindrone < 3 months only.

This was a Phase 1, multiple-dose, open-label study conducted using a 2-period, sequential design. Thirty-four adult female subjects who were currently receiving maintenance therapy with norethindrone (a progestin-only oral contraceptive) or who were willing to receive norethindrone were selected to participate in the study (**Table 4.9-1**).

The Treatment Phase consisted of 2 periods:

Period 1 (Cycle 1, Study Days 1 to 28): subjects were to receive norethindrone 0.35 QD alone

Period 2 (Cycles 2 and 3, Study Days 29 to 84), subjects were to concurrently receive norethindrone 0.35 mg QD and elagolix 150 mg QD throughout Cycles 2 and 3

Subjects were instructed to take norethindrone and elagolix at the same time in the morning, on an empty stomach (at least 1 hour before or 2 hours after a meal), with 8 ounces (240 mL) of water.

Blood Samples for Norethindrone and Elagolix Pharmacokinetic Assay:

Intensive pharmacokinetic blood samples were collected for norethindrone on Study Day 7, Period 1 and for norethindrone and elagolix on Study Day 63, Period 2. Blood samples for assay of E2, P, LH, and FSH were collected on Study Day 7, Period 1, Study Day 63, Period 2, and twice weekly on non-consecutive days during Periods 1 and 2.

Blood Samples for Hormone Pharmacodynamic Assay

Blood samples for assay of estradiol (E2), progesterone (P), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were collected at the following times: prior to dosing (0 hour) and at 24 hours after dosing on Study Day 7 of Period 1, prior to dosing (0 hour) and at 24 hours after dosing on Study Day 63 of Period 2, and twice weekly (on non-consecutive days) during the Treatment Phase.

Results and conclusion:

The pharmacokinetic parameters (mean $\pm$ SD) of norethindrone and elagolix after administration of norethindrone alone and norethindrone with elagolix are presented in the following table:

Table 4.9-2 Norethindrone Pharmacokinetic Parameters and Relative Bioavailability and 90% Confidence Intervals (Study M12-765)

Pharmacokinetic Parameters (units)		Regimens	
		Period 1	Period 2
		Norethindrone 0.35 mg QD Alone (N = 26)	Norethindrone 0.35 mg QD + Elagolix 150 mg QD (N = 26)
Norethindrone			
C_{max}	(ng/mL)	2.76 $\pm$ 0.88	2.59 $\pm$ 0.76
T_{max}	(hr)	1.67 $\pm$ 0.45	1.44 $\pm$ 0.32*
C_{trough}	(ng/mL)	0.137 $\pm$ 0.122	0.097 $\pm$ 0.082*
AUC ₂₄	(ng•hr/mL)	14.16 $\pm$ 5.89	12.30 $\pm$ 4.02
$t_{1/2}^a$	(hr)	7.85 $\pm$ 2.69	7.87 $\pm$ 3.51
CL/F ^b	(L/hr)	28.61 $\pm$ 11.99	32.34 $\pm$ 14.60
Vd _{β} /F ^b	(L)	332.7 $\pm$ 118.2	387.3 $\pm$ 152.4
Elagolix			
C_{max}^b	(ng/mL)	--	555.4 $\pm$ 254.6
T_{max}^b	(hr)	--	1.23 $\pm$ 0.38
C_{trough}^b	(ng/mL)	--	0.775 $\pm$ 0.449
AUC ₂₄ ^b	(ng•hr/mL)	--	1215.1 $\pm$ 540.6
$t_{1/2}^{a,b}$	(hr)	--	3.76 $\pm$ 1.42
CL/F ^b	(L/hr)	--	148.3 $\pm$ 64.0
Vd _{β} /F ^b	(L)	--	938.3 $\pm$ 565.3

The bioavailability results for comparison of administration of norethindrone administered with elagolix versus norethindrone administered alone are presented in the following table:

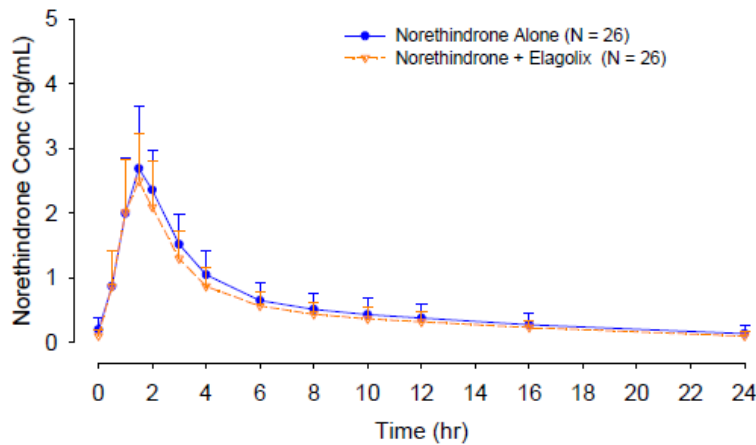
Regimens Test vs. Reference	Norethindrone Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Norethindrone + Elagolix vs. Norethindrone Alone	C_{max}	2.48	2.62	0.947	0.856 – 1.047
	AUC_{24}	11.6	13.2	0.882	0.788 – 0.987

a. Antilogarithm of the least squares means for logarithms.

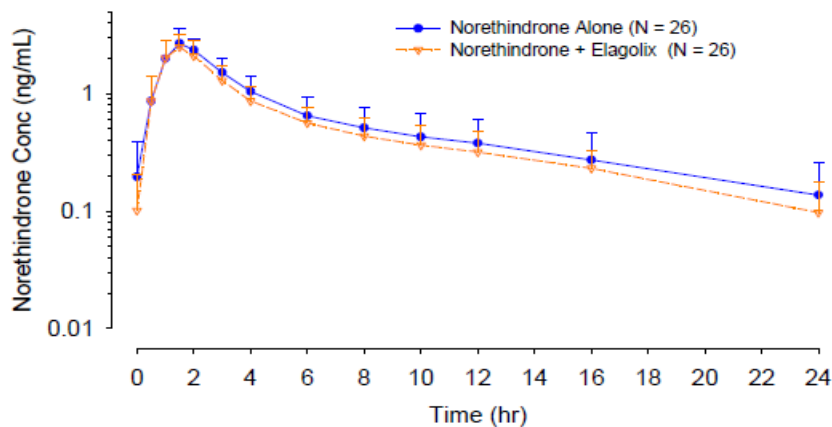
b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

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

Mean + SD Norethindrone Plasma Concentration-Time Profiles, Linear Scale



Mean + SD Norethindrone Plasma Concentration-Time Profiles, Log-Linear Scale



Mean + SD Elagolix Plasma Concentration-Time Profiles, Linear (Top) and Log-Linear (Bottom) Scales

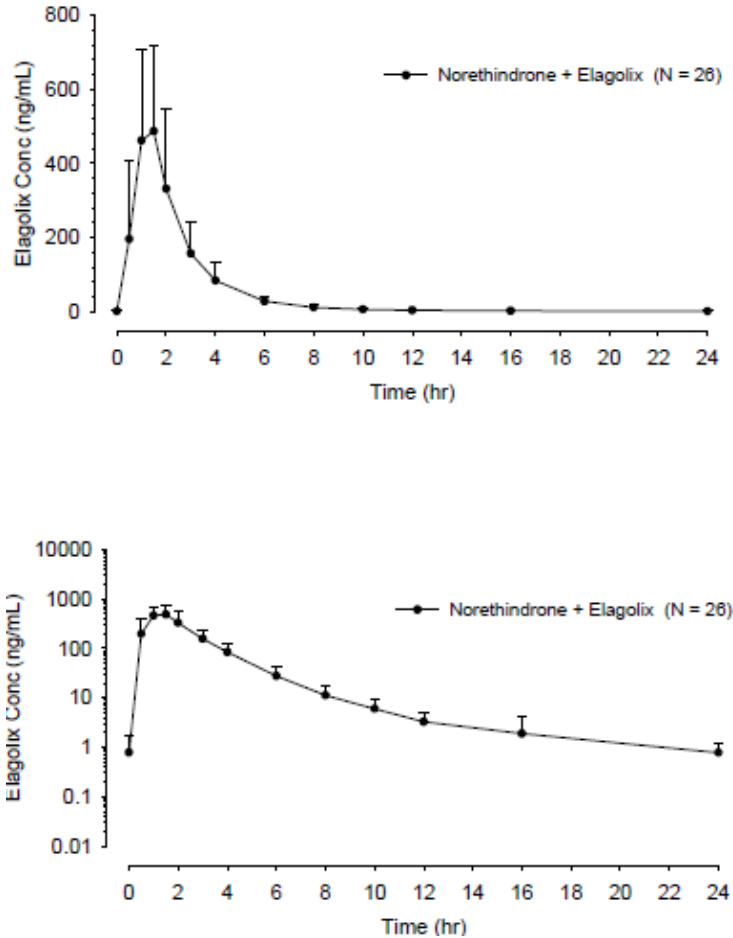


Figure 4.9-1. Mean + SD Norethindrone and Elagolix Plasma Concentration-Time Profiles, Linear Scale and Log-Linear Scales

A total of 34 adult premenopausal female subjects enrolled in the study, and a total of 26 subjects completed both periods of the study and were included for statistical and pharmacokinetic analysis. Elagolix had minimal effect on norethindrone concentrations, as norethindrone C_{max} and AUC were slightly decreased by approximately 5% and 12%, respectively, when co-administered with elagolix 150 mg QD (Table 4.9-2, Figure 4.9-1). When elagolix was co-administered with norethindrone, the hormone profiles for P, LH and FSH were similar to those observed when norethindrone was administered alone. The mean E2 concentrations were lower when elagolix was co-administered with norethindrone, compared to treatment with norethindrone alone. The regimens tested in this study were generally well tolerated.

4.10 Study M12-651

Title: Assessment of the Effect of Elagolix on the Pharmacokinetics and Pharmacodynamics of Estradiol/Norgestimate in Healthy Premenopausal Female Volunteers Who Are Receiving Combination Oral Contraceptive (Ethinyl Estradiol/Norgestimate) Therapy.

Objectives:

To assess the effect of elagolix on the pharmacokinetics of ethinyl estradiol and norgestimate, the effect of elagolix administration on endocrine hormone pharmacodynamics, and the safety and tolerability of the co-administration of elagolix and combination oral contraceptive containing ethinyl estradiol and norgestimate in healthy premenopausal female subjects.

Methodology:

Table 4.10-1 Study Schematic (Study M12-651)

Study Schematic (Study M12-651)

Screening	Period 1	Period 2		Follow-Up
	Cycle 1 Days 1 – 28	Cycle 2 Days 29 – 56	Cycle 3 Days 57 – 84	
	Triphasic OC QD	Triphasic OC QD elagolix 150 mg QD		

Triphasic OC = ethinyl estradiol 0.035 mg and triphasic norgestimate 0.18/0.215/0.25 mg and placebo tablets;
OC = oral contraceptive

This was a Phase 1, multiple-dose, open-label study conducted using a 2-period, sequential design. Thirty-two adult female subjects were to receive a triphasic oral contraceptive (OC) product, containing doses of ethinyl estradiol and norgestimate equivalent to ethinyl estradiol 0.035 mg and triphasic norgestimate 0.18/0.215/0.25 mg or placebo tablets, for ≥ 3 months prior to initial study drug administration.

Intensive pharmacokinetic blood samples were collected for ethinyl estradiol and norgestimate metabolites (norelgestromin [NGMN] and norgestrel [NG]) on Study Day 21, Period 1 and Study Day 77, Period 2 and for assay of elagolix on Study Day 77, Period 2. Blood samples for assay of E2, P, LH, and FSH were collected on Study Day 21, Period 1, Study Day 77, Period 2, and once a week approximately 7 days apart during Periods 1 and 2.

Results and conclusion:

Table 4.10-2 Relative Bioavailability Assessment of Triphasic OC and 90% Confidence Intervals (Study M12-651)

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value ^a		Relative Bioavailability	
		Test	Reference	Point Estimate ^b	90% Confidence Interval
Ethinyl Estradiol					
Triphasic OC + Elagolix vs. Triphasic OC Alone	C _{max}	0.181	0.157	1.15	1.066 – 1.248
	AUC ₂₄	1.50	1.16	1.30	1.186 – 1.416
NGMN					
Triphasic OC + Elagolix vs. Triphasic OC Alone	C _{max}	1.93	2.21	0.872	0.781 – 0.973
	AUC ₂₄	14.9	17.6	0.847	0.782 – 0.918
NG					
Triphasic OC + Elagolix vs. Triphasic OC Alone	C _{max}	2.16	2.44	0.886	0.784 – 1.002
	AUC ₂₄	36.1	39.1	0.923	0.840 – 1.013

Triphasic = ethinyl estradiol 0.035 mg and triphasic norgestimate 0.18/0.215/0.25 mg and placebo tablets;

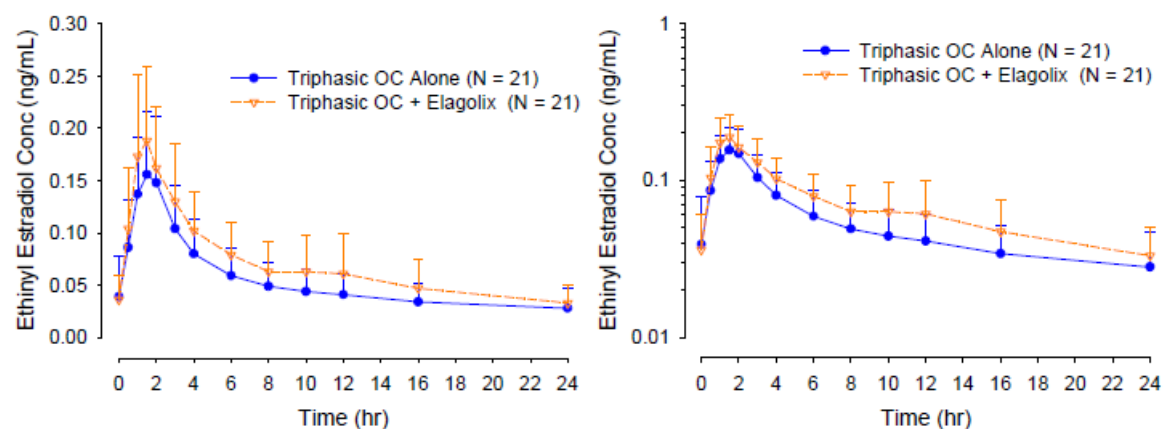
OC = oral contraceptive; NGMN = norelgestromin; NG = norgestrel

a. Antilogarithm of the least squares means for logarithms.

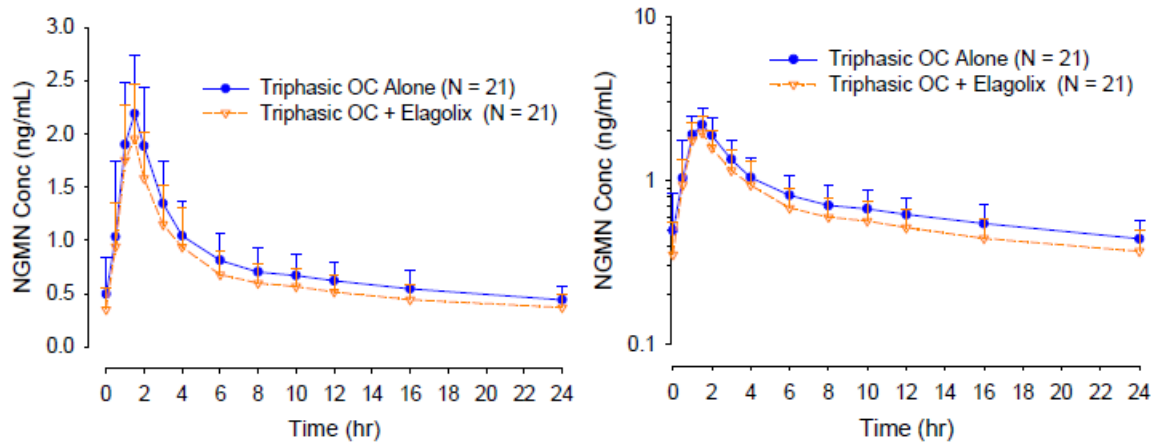
b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Note: Units presented for C_{max} and AUC central values are ng/mL and ng•hr/mL, respectively.

Mean + SD Ethinyl Estradiol Plasma Concentration-Time Profiles, Linear (Left) and Log-Linear (Right) Scales



**Mean + SD NGMN Plasma Concentration-Time Profiles,
Linear (Left) and Log-Linear (Right) Scales**



**Mean + SD NG Plasma Concentration-Time Profiles,
Linear (Left) and Log-Linear (Right) Scales**

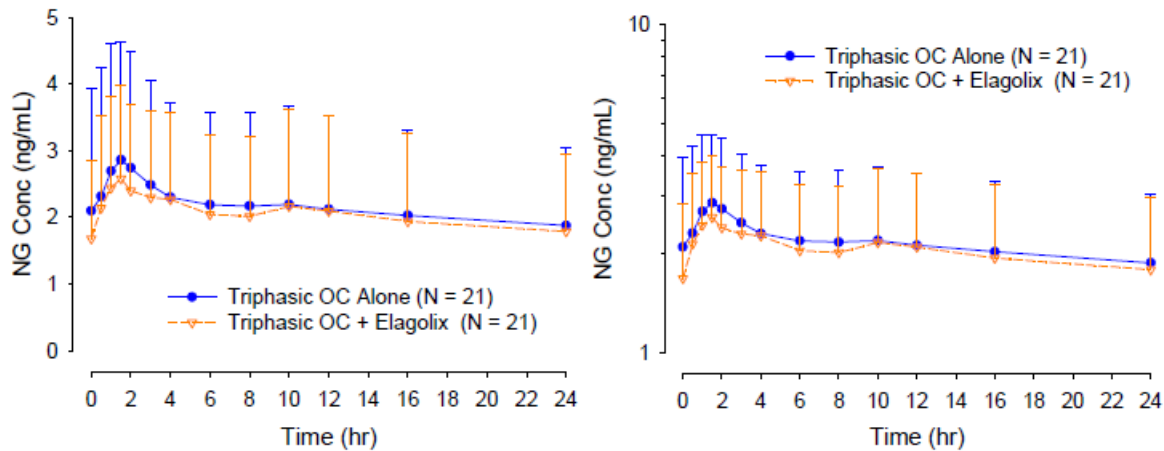


Figure 4.10-1. Mean + SD Ethinyl Estradiol, NGMN and NG Plasma Concentration-Time Profiles, Linear (Left) and Log-Linear (Right) Scales

A total of 32 adult premenopausal female subjects enrolled in the study, and a total of 21 subjects completed both periods of the study and were included for statistical and pharmacokinetic analysis. When elagolix 150 mg QD was administered with triphasic OC, ethinyl estradiol C_{max} and AUC₂₄ increased by approximately 15% and 30%, respectively (Table 4.10-2, Figure 4.10-1). There was minimal decrease in exposures for the norgestimate metabolites, NGMN and NG (decreased by up to 15%).

4.11 Study RD170098 (PBPK modeling)

Title: *Physiologically Based Pharmacokinetic Report Assessment of Elagolix Drug-Drug Interaction Potential Using Physiologically-Based Pharmacokinetic Modeling and Simulations*

Objectives: This review evaluates the adequacy of the Applicant's PBPK models to:

- Predict the DDI potential of elagolix as a CYP3A inducer at a dose of 200 mg BID
- Predict the DDI potential of elagolix as a P-gp inhibitor at a dose of 150 mg QD

Background:

Elagolix is primarily metabolized by the CYP3A enzyme and to a lesser extent by CYP2D6 and CYP2C8 enzymes. Elagolix is also a substrate of P-glycoprotein transporter (P-gp), and organic anion transporter protein 1B1 (OATP1B1). Clinical study M12-660 showed that the steady state C_{max} and AUC of elagolix increased by 1.8- and 2.2-fold, respectively, when elagolix 150 mg QD was co-administered with ketoconazole, a strong CYP3A inhibitor. When a single dose of 150 mg elagolix was co-administered with a single dose of rifampin, a strong CYP3A inducer and dual modulator for P-gp and OATP transporters, the C_{max} and AUC of elagolix increased by 4.4- and 5.6-fold, respectively (Study M12-659). When a single dose of 150 mg elagolix was given at day 10 of repeat dosing of rifampin, the C_{max} and AUC of elagolix increased by 2.0- and 1.7-fold, respectively (Study M12-659).

Elagolix is an inducer of CYP3A enzymes. Study NBI-56418-0502 showed that the C_{max} and AUC of midazolam (CYP3A4 substrate) decreased by 19% and 35%, respectively, when administered with multiple doses of elagolix at the dose of 150 mg QD. Study M15-629 showed that the C_{max} and AUC of midazolam decreased by 44% and 55%, respectively, when administered with multiple doses of elagolix at the dose of 300 mg BID. The DDI potential of elagolix as a CYP3A inducer at the dose of 200 mg BID was not clinically evaluated. The applicant used PBPK model to predict the DDI effect of elagolix at a dose of 200 mg BID on a single-dose of midazolam at 5 mg.

Elagolix is an inhibitor of P-gp transporter. After administration of elagolix as a single (200 mg) or multiple (200 mg BID) doses, the C_{max} and AUC of digoxin (substrate of P-gp transporter) increased by approximately 70% and 30%, respectively (Study M12-652). The applicant used PBPK model to predict the DDI effect of elagolix at a dose of 150 mg QD on a single-dose of digoxin at 0.5 mg.

This review evaluates the adequacy of applicant's elagolix PBPK models to predict the DDI potential of elagolix as a perpetrator, and provides dosing recommendations based on the predicted DDIs.

Method:

The models and simulation results described here were performed using Simcyp (V15.0.86.0, Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). The workflow of the DDI prediction model development, verification and application is described below:

Model Development and Optimization: A full PBPK model was developed and optimized using the human pharmacokinetic data of elagolix in healthy female subjects from Study M12-790. The relative contribution of various enzymes and transporters in the disposition of elagolix was initially based on in vitro transporters and metabolism data, optimized based on mass balance data from an ADME study in humans (Study NBI-56418-0601) and the rifampin DDI study (Study M12-659). Data from Study NBI-56418-0502 and Study M12-652 were used to optimize the elagolix perpetrator model.

Model Verification: Clinical data from the ketoconazole-elagolix DDI study (Study M12-660) was used to verify the contribution of CYP3A4/P-gp in overall disposition of elagolix.

Model Application: After model development and verification, the elagolix PBPK model was used to predict the effect of elagolix as a perpetrator on the pharmacokinetics of digoxin and midazolam at 150 QD and 200 mg BID doses of elagolix, respectively.

Model Parameters:

The physiological parameters for a healthy population were the same as reported by Simcyp (Version 15.0.86.0). The P-gp expression level in liver and the intestine was increased by 4-fold on Day 10 of the

rifampin-elagolix DDI study because rifampin has been reported to induce P-gp expression by 4-fold¹. The drug specific parameters for digoxin and midazolam PBPK models were the same as reported by Simcyp. The drug specific parameters for elagolix are provided below:

Parameter	Experimental/ Initial Parameter Value	Final Parameter Value used in SimCYP Model	Source
Physiochemical and Blood Binding			
Molecular Weight (g/mol)	631.600	631.600	[20]
log P	1.340	1.340	[20]
Compound Type	Ampholyte	Ampholyte	[20]
pK _a 1	4.000	4.000	[20]
pK _a 2	7.900	7.900	[20]
Blood Plasma	0.62	0.62	[5]
f _u	0.210	0.210	[21]
Absorption			
Absorption Model		ADAM	
Peff.man Type		Regional	
P Caco-2 (10 ⁻⁶ cm/s)	2.00	10.000	Optimized to predict elagolix PK Profile
Reference Compound		Propranolol	[22] (Table 3)
Reference Value (10E ⁻⁶ cm/s)		19.600	
Scalar		1.079	SimCYP Default
Peff.man (10 ⁻⁴ cm/s)		1.650	SimCYP Predicted
Peff.man Duodenum (10 ⁻⁴ cm/s)		1.650	SimCYP Predicted
Peff.man Jejunum I (10 ⁻⁴ cm/s)		4.000	Optimized to predict elagolix PK profile
Peff.man Jejunum II (10 ⁻⁴ cm/s)	NA	2.000	
Peff.man Ileum I (10 ⁻⁴ cm/s)		1.650	SimCYP Predicted
Peff.man Ileum II (10 ⁻⁴ cm/s)		1.650	SimCYP Predicted
Peff.man Ileum III (10 ⁻⁴ cm/s)		1.650	SimCYP Predicted
Peff.man Ileum IV (10 ⁻⁴ cm/s)		1.650	SimCYP Predicted
Peff.man Colon (10 ⁻⁴ cm/s)		1.650	SimCYP Predicted
Input Form	High solubility compound	Solution	[20]

¹ Westphal K, Weinbrenner A, Zschiesche M, et al. Induction of p-glycoprotein by rifampin increases intestinal secretion of talinolol in human beings: a new type of drug/drug interaction. Clin Pharmacol Ther. 2000;68(4):345-55.

Distribution			
Distribution Model		Full PBPK Model	
V _{ss} input type	NA	Predicted using Method 2	SimCYP Predicted
log Po:w	1.340	1.340	[20]
K _a , AP input type	NA	Predicted	NA
logP vo:w input type	NA	Predicted	NA
Elimination			
Clearance Type			
In vitro metabolic system			
Enzyme		CYP3A4	
CL _{int} (μL/min/pmol of isoform)	0.072	0.300	[23] optimized based on rifampin DDI Study (Study M12-659) [7]
f _{u mic}	0.581	0.581	[23]
System	NA	BD SUP	NA
ISEF	0.240	0.240	SimCYP Default
Enzyme		CYP2C8	
CL _{int} (μL/min/pmol of isoform)	0.029	0.029	[23]
f _{u mic}	0.633	0.633	[23]
System	NA	BD SUP	NA
ISEF	0.430	0.430	SimCYP Default
Enzyme		CYP2D6	
CL _{int} (μL/min/pmol of isoform)	0.49	0.700	[23]
f _{u mic}	0.596	0.596	[23]
System	NA	BD SUP	NA
ISEF	0.750	0.750	SimCYP Default
CL _{renal} (L/h)	NA	1.600	To account for non-CYP clearance pathways and
Additional Systemic CL/F (L/h)	NA	9.000	optimized to predict elagolix PK Profile (Study M12-790) [1]
Transport			
Transporter		ABCB1 (P-gp/MDR1)	
J _{max} (pmol/min)	Could not be estimated	6.000	rd101249 [24]/Optimized based on elagolix PK and rifampin DDI study (Studies M12-790 and M12-659) [1] [7]
K _m (μM)		1.500	
Transporter		SLCO1B1 (OATP1B1)	
J _{max} (pmol/min/million cells)	41.05	215.000	rd160741 [25] (* mean calculated from reported values)/Optimized based on rifampin DDI study (Study M12-659) [7]
K _m (μM)	0.660	0.660	rd160741 [25]
CYP3A4 Interaction			
Enzyme		CYP3A4	
MBI K _{app} (μM)	74.000	74.000	[23]
MBI K _{inact} (1/h)	0.019	0.019	[23]
Ind _{max}	20.000	20.000	[23]
Ind C ₅₀ (μM)	6.700	2.000	[23]/Optimized based on Midazolam DDI study (Study NBI-56148-0502) [8]
P-gp Interaction			
Transporter		ABCB1 (P-gp/MDR1)	
K _i (μM)	IC ₅₀ : 54 μM	0.500	[23]/Optimized based on digoxin DDI study (Study M12-652) [10]

Simulation Study Design:

The study design for each simulation is summarized in **Table 4.11-1**.

Table 4.11-1. Trial designs for PBPK simulations

Study	Drug	Route	Dose	Time of Administration	Fasting/Fed	Duration
Multiple Ascending Dose	Elagolix	PO	150 mg	QD for 21 days	Fasting	23 days
Multiple Ascending Dose	Elagolix	PO	200 mg	BID for 21 days	Fasting	23 days
Elagolix as Victim Drug						
Rifampin DDI Study	Elagolix (Victim)	PO	150 mg	SD on Day 1 and Day 10	Fasting	13 days
	Rifampin (Perpetrator)	PO	600 mg	QD 12 days	Fasting	13 days
Ketoconazole DDI Study	Elagolix (Victim)	PO	150 mg	SD on Day 4	Fasting	8 days
	Ketoconazole (Perpetrator)	PO	400 mg	QD for 6 days	Fasting	8 days
Elagolix as Perpetrator Drug						
Midazolam DDI Study	Midazolam (Victim)	PO	5 mg	SD Day 14	Fasting	17 days
	Elagolix (Perpetrator)	PO	150 mg	QD for 16 days	Fasting	17 days
Digoxin DDI Study	Digoxin (Victim)	PO	0.5 mg	QD Day 1 and Day 10	Fasting	13 days
	Elagolix (Perpetrator)	PO	200 mg	BID for 13 days	Fasting	13 days
Application – Elagolix as Perpetrator Drug						
Midazolam DDI Study	Midazolam (Victim)	PO	5 mg	SD Day 14	Fasting	17 days
	Elagolix (Perpetrator)	PO	200 mg	BID for 16 days	Fasting	17 days
Digoxin DDI Study	Digoxin (Victim)	PO	0.5 mg	QD Day 1 and Day 10	Fasting	13 days
	Elagolix (Perpetrator)	PO	150 mg	QD for 13 days	Fasting	13 days

Source: Table 1 in the Applicant's study report R&D/17/0098

Reviewer's Comment:

The simulation study designs were consistent with clinical DDI study designs except the dose of midazolam. In the clinical DDI study (Study NBI-56418-0502), midazolam was administered as a single dose of 2 mg on Day 14. This difference in trial setting does not impact model verification or application.

Study Results:

Elagolix Model Performance in Predicting Multi-dose PK:

As shown in **Table 4.11-2**, the PBPK model was able to capture the pharmacokinetic profile and pharmacokinetic parameters reasonably well following multiple doses of elagolix 150 QD or 200 mg BID. The %PE values for the predicted AUC, C_{max} and CL/F was less than 15%.

Table 4.11-2. Elagolix PBPK Model Development: Predicted vs. Observed Pharmacokinetic Parameters of Elagolix Following Multiple Doses in Healthy Subjects

Pharmacokinetic Parameter (units)		Study M12-790					
		150 mg QD (N = 6)			200 mg BID (N = 7)		
		Predicted	Observed	%PE	Predicted	Observed	%PE
Day 1							
C _{max}	(ng/mL)	552	507	8.9 (50%)	779	712	9.4 (50%)
T _{max}	(hr)	0.95	1.3	26.9 (50%)	0.95	1.1	13.6 (50%)
AUC _τ	(ng•hr/mL)	1321	1331	0.8 (50%)	1759	1813	3.0 (50%)
Day 21							
C _{max}	(ng/mL)	524	574	8.7 (50%)	680	774	12.1 (50%)
AUC _τ	(ng•hr/mL)	1213	1292	6.1 (50%)	1518	1725	12.0 (50%)
CL/F	(L/hr)	124	123	0.8 (50%)	132	144	8.3 (50%)
t _{1/2}	(hr)	4.57	6.42	28.8 (50%)	4.54	4.29	5.8 (50%)

%PE = percent prediction error

% in bracket indicates the acceptance criteria.

Note: AUC_τ where τ (tau) is the dosing interval (i.e., 12 hours for BID, 24 hours for QD).

Predicted T_{max} is mean value while the observed value is median T_{max}.

Source: Table 2 in the Applicant's study report R&D/17/0098

Model Performance in Predicting Elagolix As a Victim Drug:

The contribution of OATP1B1 in the uptake of elagolix was optimized using the DDI Study M12-659 (elagolix with a single 600 mg dose of rifampin). Following coadministration of a single dose of elagolix 150 mg and a single dose of rifampin 600 mg, the observed C_{max} and AUC ratios for elagolix on Day 1 were 4.37 and 5.58, respectively. The simulated ratios for the DDI, following model optimization, for C_{max} and AUC were 3.20- and 4.00-fold, respectively (**Table 4.11-3**). The CYP3A4 and P-gp contributions were also optimized using clinical data from Study M12-659. Following coadministration of multiple doses of rifampin 600 mg QD for 12 days and a single dose of elagolix 150 mg on Day 10, the model simulated elagolix C_{max} and AUC ratios on Day 10 were 2.28 and 2.29, respectively (**Table 4.11-3**). The predicted C_{max} and AUC ratios were within the predefined acceptance limit.

Contribution of the CYP3A4/P-gp pathway in the metabolism of elagolix was verified using the DDI study with ketoconazole. The model simulated C_{max} and AUC ratios of elagolix were 2.01 and 2.13, respectively, and the observed C_{max} and AUC ratios were 1.77 and 2.20, respectively (**Table 4.11-3**). The performance of the model prediction is acceptable.

Model Performance in Predicting Elagolix As a Perpetrator Drug:

For DDI between elagolix 150 mg QD and single-dose midazolam 5 mg, the model-based simulations (predicted AUC ratio of 0.69) closely matched with the observed AUC ratio of 0.65 (**Table 4.11-3**).

For the DDI between multi-dose elagolix 200 mg BID and single-dose digoxin 0.5 mg, the Day 1 and Day 10 predicted C_{max} ratios were 1.74 and 1.73, respectively, and the AUC ratios were 1.22 and 1.19, respectively. These model results were in agreement with the observed Day 1 and Day 10 C_{max} ratios (1.73 and 1.71) and the Day 1 and Day 10 AUC ratios (1.32 and 1.26) (**Table 4.11-3**).

Table 4.11-3. Elagolix PBPK Model Development: Predicted vs Observed DDI C_{max} and AUC Ratios Following Co-Administration of Elagolix with Prototypical Perpetrators or Substrates

Co-Administered Drug with Elagolix	Elagolix Dose	Mean C_{max} Ratio			Mean AUC Ratio		
		Predicted	Observed	%PE	Predicted	Observed	%PE
As Victim							
Rifampin Day 1	150 mg ^a	3.20	4.37	27 (77%)	4.00	5.58	28 (82%)
Rifampin Day 10	150 mg ^a	2.28	2.00	14 (50%)	2.29	1.65	39 (39%)
Ketoconazole	150 mg ^a	2.01	1.77	14 (44%)	2.13	2.20	3.2 (55%)
As Perpetrator							
Midazolam Day 14	150 mg QD	0.75	0.81	7.4 (77%)	0.69	0.65	6.2 (46%)
Digoxin Day 1	200 mg BID	1.74	1.73	0.6 (42%)	1.22	1.32	7.6 (24%)
Digoxin Day 10	200 mg BID	1.73	1.71	1.2 (42%)	1.19	1.26	5.6 (21%)

%PE = percent prediction error (acceptance criteria)

a. Single dose elagolix.

Source: Table 3 in the Applicant's study report R&D/17/0098

Reviewer's Comments:

1. The reviewer noted the underprediction of OATP1B1 inhibition by rifampin on Day 1. The predicted C_{max} and AUC ratios were still within the predefined acceptance limit. The objectives of current study were to assess elagolix as a perpetrator to inhibit P-gP and to induce CYP3A. As long as the model can accurately predict multi-dose PK of elagolix, the underprediction of OATP1B1 inhibition would not be a major concern as OAT1B1 is not involved in the transport of digoxin or midazolam.
2. The reviewer repeated the applicant's elagolix-midazolam DDI model in Simcyp Version 16. The predicted C_{max} and AUC ratios for 2 mg midazolam after 14 days of elagolix 150 mg QD were 0.67 and 0.62. The model performance in terms of C_{max} and AUC ratio was acceptable. The reviewer recommends that the model be further verified with the DDI data between elagolix 300 mg BID regimen and a single-dose of midazolam from Study M15-629.
3. The reviewer verified the applicant's elagolix-digoxin DDI model in Simcyp Version 16. The predicted C_{max} and AUC_{0-72hr} ratios for digoxin on Day 1 of elagolix 200 mg BID treatment were 1.73 and 1.26, respectively, and on Day 10 were 1.52 and 1.23, respectively. Possible sources for the differences between reviewer and applicant's exposure ratios are 1) Simulation trial setting: the applicant's verification trial for Day 10 was incorrectly simulated under elagolix 150 mg QD; and 2) Calculation method: the applicant calculated digoxin AUC up to 48 hours post dose while the reviewer calculated digoxin AUC up to 72 hours post dose. The performance of sponsor's model prediction is acceptable based on reviewer's analysis.

PBPK Model Applications:

The elagolix PBPK model was used to predict the DDI effect on a single dose of 5 mg midazolam at the proposed clinical dose of 200 mg BID. At the 200 mg BID dose, the AUC of midazolam is predicted to decrease by 56% while the C_{max} is predicted to decrease by 49% (Table 4.11-4). The model was also used to predict the change in C_{max} and AUC of digoxin, following multiple doses of elagolix 150 mg QD. On Day 1 the C_{max} and AUC of digoxin are predicted to increase by 68% and 19%; while on Day 10, C_{max} and AUC of digoxin are predicted to increase by 73% and 19%, respectively (Table 4.11-4).

Table 4.11-4. Elagolix PBPK Model Application: PBPK Model Predictions as Perpetrator

Co-Administered Drug with Elagolix	Elagolix Dose	Mean C_{max} Ratio		Mean AUC Ratio	
		Predicted	Observed	Predicted	Observed
Midazolam	200 BID	0.51	NA	0.44	NA
Digoxin Day 1	150 mg QD	1.68	NA	1.19	NA
Digoxin Day 10	150 mg QD	1.73	NA	1.19	NA

Source: Table 4 in the Applicant's study report R&D/17/0098

Reviewer's Comments:

DDI between elagolix 200 BID and midazolam:

Study M15-629 showed that the C_{max} and AUC of midazolam decreased by 44% and 55%, respectively, when administered with multiple doses of elagolix 300 mg BID. The Applicant's PBPK analysis predicted that C_{max} and AUC of midazolam would decrease by 49% and 56%, respectively, when administered with multiple doses of elagolix 200 mg BID. In reviewer's analysis using the Applicant's PBPK model, the predicted midazolam C_{max} and AUC ratios were 0.40 and 0.35 with multiple dose of elagolix at the 200 mg BID dose level, or 0.34 and 0.29 with multiple doses of elagolix at the 300 mg BID dose level. The CYP3A induction appeared to be over-predicted. The applicant is recommended to verify the PBPK model with elagolix 300 mg BID data. The applicant's proposal, "Consider increasing the dose of midazolam and individualize therapy based on patient's response" appears reasonable based on clinical DDI studies.

DDI between elagolix 150 mg QD and digoxin:

The reviewer verified the Applicant's analysis in Simcyp Version 16. The simulation results supported the Applicant's conclusion that "elagolix 150 mg QD is expected to increase digoxin AUC < 1.25-fold". Since elagolix is predicted to increase the C_{max} of digoxin by >50% following a single 150 mg dose, the Applicant's proposal to monitor patients receiving digoxin along with elagolix is acceptable.

5. Population PK and/or PD Analyses

5.1 Population PK Analyses

The Applicant submitted a population PK report entitled "Population Pharmacokinetics of Elagolix in Healthy Subjects and Subjects with Moderate to Severe Endometriosis-Associated Pain Based on Data from Five Phase 1 and Four Phase 3 Studies". The pharmacometrics reviewer has reviewed the submitted data and report and generally agreed with the conclusions of the population pharmacokinetics analysis by the Applicant.

Objectives: The objectives of the report were to describe elagolix population pharmacokinetics and factors affecting elagolix exposure in healthy women and women with moderate to severe endometriosis-associated pain.

Data: The population pharmacokinetic analysis included data from five Phase 1 studies (Studies M12-790, M12-653, M13-995, M14-731, and M12-673) and four Phase 3 studies (Studies M12-665, M12-667, M12-671, and M12-821). A total of 1624 subjects were included in the analysis from Studies M12-790 (n = 34), M12-653 (n = 23), M13-995 (n = 23), M14-731 (n = 54), M12-673 (n = 179), M12-665/M12-667 (n = 682), and M12-671/M12-821 (n = 629). The demographic data for subjects included in the final population PK dataset is summarized in **Table 5.1-1** and **Table 5.1-2**.

Table 5.1-1: Summary of Continuous Covariates at Baseline

All Subjects (N=1624)	Mean (SD)	Range
Age (year)	32.3(6.5)	18.0-49.0
Body Weight (kg)	73.7(17.3)	40.0-148.0
Body Mass Index (kg/m ²)	27.3(6.2)	16.2-55.6)
Albumin (g/DL)	4.5(0.3)	3.6-5.4
Total Bilirubin (mg/dL)	0.5(0.2)	0.1-1.9
Serum Creatinine(mg/dL)	0.7(0.1)	0.4-1.3)
Aspartate Amino Transferase (IU/L)	18.8(10.9)	9.0-275.0
Alanine Amino Transferase (IU/L)	15.9(15.3)	4.0-367.0
Creatinine Clearance (mL/min)	133.3 (36.4)	53.6-346.8

Table 5.1-2: Summary of Categorical Covariates

All Subjects (N=1624)	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	1283(79.0)
	User	341(21.0)
Alcohol Use	Never Used	658(40.5)
	User	966(59.5)
OATP Transporter Status	ET	858(52.8)
	IT	279(17.2)
	PT	30(1.9)
	Others	457(28.1)
Geographic Region	United States	1287(79.2)
	Others	337(20.8)

Population PK Model Development

Base Model: The selected base model was a two-compartment model with lag time, combined residual error model, and inter-individual variability on CL/F, V2/F (incorporating correlation using a block matrix). The estimated pharmacokinetic parameter values and their associated variability for the elagolix pharmacokinetic base model are summarized in **Table 5.1-3**.

Table 5.1-3: Summary of Fixed and Random Effects Parameter Estimates for Elagolix Population Pharmacokinetic Base Model (Run13)

Parameter	Population Estimate (SEE) ^a	%RSE ^b	95% Confidence Interval
Pharmacokinetic Parameters			
CL/F (L/h)	115 (1.48)	1.30	(112, 117)
V ₂ /F (L)	257 (4.53)	1.76	(248, 266)
K _A (1/h)	2.49 (0.078)	3.14	(2.34, 2.65)
Q/F (L/h)	5.83 (0.270)	4.63	(5.30, 6.36)
V ₃ /F (L)	59.7 (1.61)	2.70	(56.5, 62.9)
Lag-time (h)	0.202 (0.002)	0.919	(0.199, 0.206)
Inter-Individual and Residual Variability			
Inter-Individual Variability on CL/F (%CV) ^c	0.176 (43.9)	5.03	(0.159, 0.193)
Inter-Individual Variability on V ₂ /F (%CV) ^c	0.233 (51.2)	6.35	(0.204, 0.262)
Covariance of Inter-Individual Variability on CL/F and V ₂ /F	0.140 (38.8)	7.03	(0.121, 0.159)
Inter-Individual Variability on Residual Error (%CV) ^c	0.130 (37.3)	6.44	(0.114, 0.146)
Proportional Error	0.227 (0.006)	2.81	(0.215, 0.239)
Additive Error	0.149 (0.016)	10.6	(0.118, 0.180)

K_A = first-order absorption rate constant; Q/F = apparent inter-compartmental clearance; V₃/F = apparent volume of distribution in the peripheral compartment

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 = SQRT(exp(ETA)-1)*100.

Source: Table 6 on page 47 of Applicant's population PK report rd170088

Final Model: Covariates investigated for influence on each of the elagolix pharmacokinetic parameters such as apparent clearance (CL/F) and apparent volume of distribution (V₂/F) included age, body weight, body mass index, race, ethnicity, albumin, bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT), tobacco use, alcohol use, organic anion-transporting polypeptide (OATP) genotype status, and study region. Creatinine and creatinine clearance were also tested on apparent clearance (CL/F). The only covariate lowering the OFV significantly was the OATP genotype as a covariate on CL/F. None of the other covariates tested were significant. As the p-value for the addition of OATP genotype was < 0.001, the full model was also the final model. Addition of this covariates to the model resulted in a minor decrease in inter-individual variability on CL/F from 43.9% to 42.5%. The parameter estimates from the final model including covariate effects (run120) are summarized in **Table 5.1-4**.

Table 5.1-4: Parameter Estimates and Covariate Effects for Elagolix Population Pharmacokinetic Final Model (run120)

Parameter	Population Estimate (SEE) ^a	%RSE ^b	95% Confidence Interval
Pharmacokinetic Parameters			
CL/F (L/h)	118 (1.54)	1.30	(115, 121)
V ₂ /F (L)	257 (4.46)	1.74	(248, 266)
K _A (1/h)	2.49 (0.076)	3.04	(2.34, 2.64)
Q/F (L/h)	5.83 (0.247)	4.23	(5.35, 6.32)
V ₃ /F (L)	59.6 (1.56)	2.62	(56.5, 62.7)
Lag-time (h)	0.202 (0.002)	0.925	(0.198, 0.206)
OATP = IT/PT on CL/F	-0.142 (0.020)	-13.7	(-0.180, -0.104)
Inter-Individual and Residual Variability			
Inter-Individual Variability on CL/F (%CV) ^c	0.166 (42.5)	5.12	(0.149, 0.183)
Inter-Individual Variability on V ₂ /F (%CV) ^c	0.231 (51.0)	6.36	(0.202, 0.260)
Covariance of Inter-Individual Variability on CL/F and V ₂ /F	0.133 (37.7)	7.18	(0.114, 0.152)
Inter-Individual Variability on Residual Error (%CV) ^c	0.131 (37.4)	6.46	(0.114, 0.148)
Proportional Error	0.228 (0.006)	2.79	(0.216, 0.240)
Additive Error	0.149 (0.016)	10.6	(0.118, 0.180)

a SEE = Standard error of estimate.

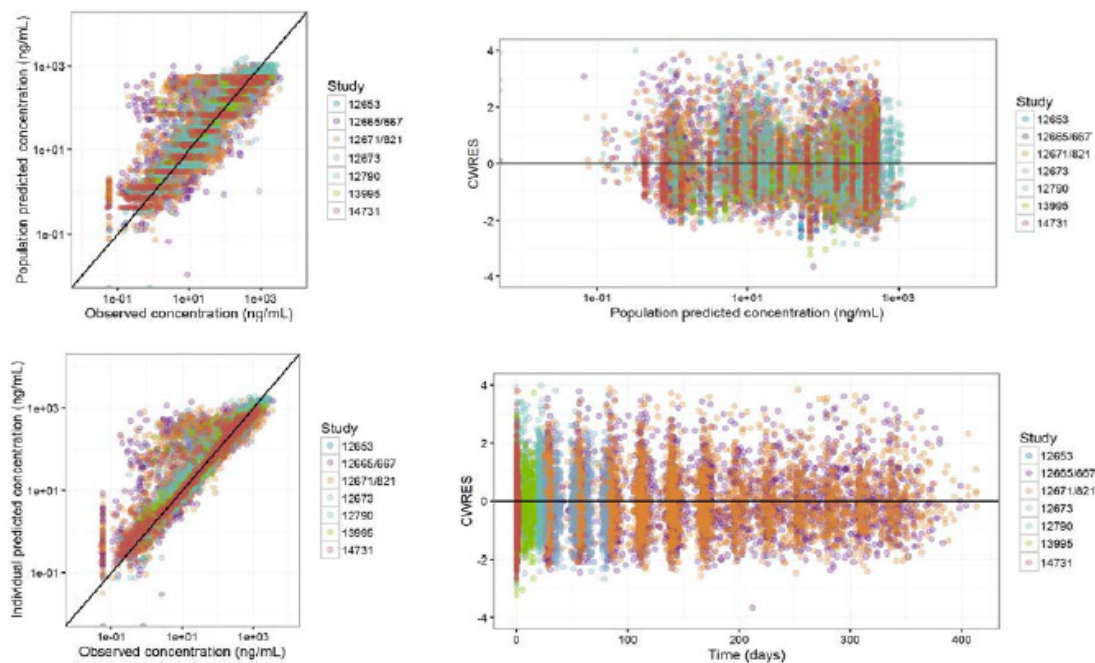
b %RSE was estimated as the SEE divided by the population estimate multiplied by 100.

c %CV = SQRT(exp(ETA)-1)*100.

Source: Table 7 on page 50 of Applicant's population PK report rd170088

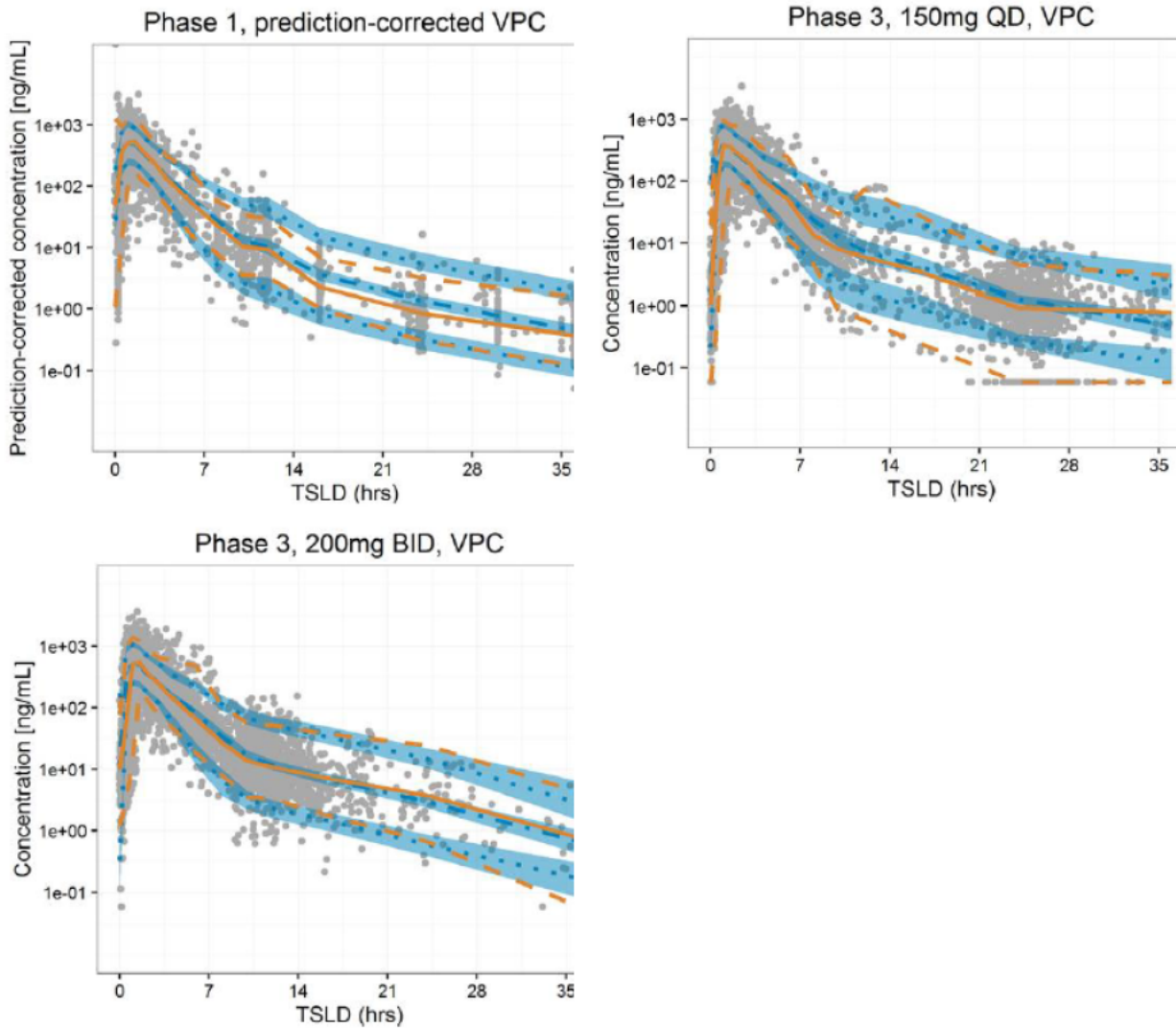
Model Evaluation: The final model was evaluated graphically by goodness-of-fit plots, visual predictive checks (VPCs) as well as bootstrap evaluation. The goodness-of-fit plots for the final model are displayed in **Figure 5.1-1** and the VPCs plots are demonstrated in **Figure 5.1-2**.

Figure 5.1-1: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figure 11 on page 52 of Applicant's population PK report rd170088

Figure 5.1-2: Prediction-Corrected Visual Predictive Checks for Phase 1 and Phase 3 Studies in the Final Population PK Model



The gray dots represent observed data, the orange lines represent observed median (solid) and observed 5%/95% quantiles (dashed), and the blue bands represent predicted median (dashed-dotted) and predicted 5%/95% quantiles (dotted) with 95% prediction bands.

Note: VPCs are cut-off at 36 hours after last dose, as data are too sparse beyond

Source: Adapted from Figure 12 to 14 on page 53-55 of Applicant's population PK report

Bootstrap evaluation was used to estimate confidence intervals of the model parameters. A total of 967 out of 1000 bootstrap replicates plus the original dataset converged successfully. The bootstrap results are summarized in **Table 5.1-5**.

Table 5.1-5: Summary of Elagolix Pharmacokinetic Parameters Estimated from Bootstrap Evaluation

Pharmacokinetic Parameter (units)	Model Result	Bootstrap Evaluation Results (N = 967)		
		Mean	Median	95% Confidence Interval
CL/F (L/h)	118	118	118	(114, 121)
V ₂ /F (L)	257	257	257	(246, 270)
K _A (1/h)	2.49	2.51	2.50	(2.21, 2.83)
Q/F (L/h)	5.83	5.78	5.83	(4.46, 7.00)
V ₃ /F (L)	59.6	60.0	59.8	(53.5, 68.5)
Lag-time (h)	0.202	0.202	0.203	(0.192, 0.215)
OATP on CL/F	-0.142	-0.142	-0.142	(-0.182, -0.102)
Residual Variability - Proportional Error	0.228	0.228	0.228	(0.215, 0.240)
Residual Variability - Additive Error	0.149	0.148	0.143	(0.072, 0.251)
Inter-Individual Variability on CL/F	0.166	0.167	0.167	(0.147, 0.191)
Inter-Individual Variability on V ₂ /F	0.231	0.235	0.233	(0.194, 0.279)
Inter-Individual Variability on Residual Error	0.131	0.128	0.128	(0.084, 0.166)

Source: Table 9 on page 56 of Applicant's population PK report

Posthoc PK Parameter Estimation: Predicted elagolix exposures using the final model are summarized in Table 5.1-6 for 150 mg QD and 200 mg BID dosing regimens.

Table 5.1-6: Predicted Elagolix Exposures Using the Final Model

Dose	Parameter	Mean	Median	5 th Percentile	95 th Percentile
150 mg QD	AUC ₀₋₂₄ (ng•h/mL)	1120	1050	340	2400
	C _{avg} (ng/mL)	46.5	43.6	14.2	99.9
	C _{trough} (ng/mL)	1.34	0.847	0.0634	5.58
	C _{max} (ng/mL)	302	282	96.7	633
200 mg BID	AUC ₀₋₂₄ (ng•h/mL)	3120	2890	916	6300
	C _{avg} (ng/mL)	130	120	38.2	262
	C _{trough} (ng/mL)	9.30	6.51	0.204	34.8
	C _{max} (ng/mL)	511	468	188	1080

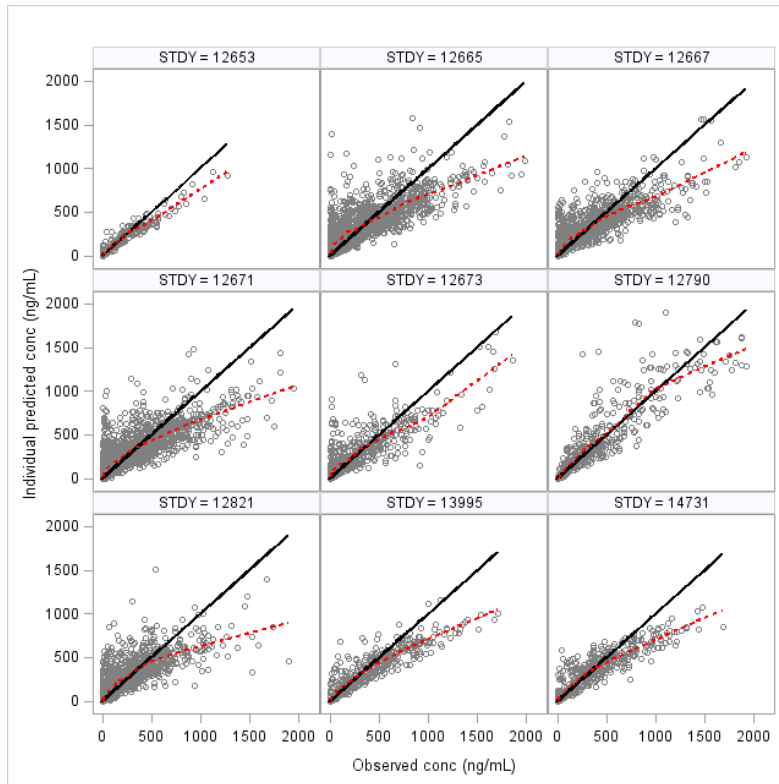
C_{avg} = average plasma concentration

Source: Table 8 on page 51 of Applicant's population PK report

Reviewer's comments: 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. However, a lot of observations were not well predicted in the plots which brought uncertainty to PK parameter estimation. However, the VPCs plots indicated that the prediction performance of the final model was good. The reviewer was able to verify the Applicant's analysis.

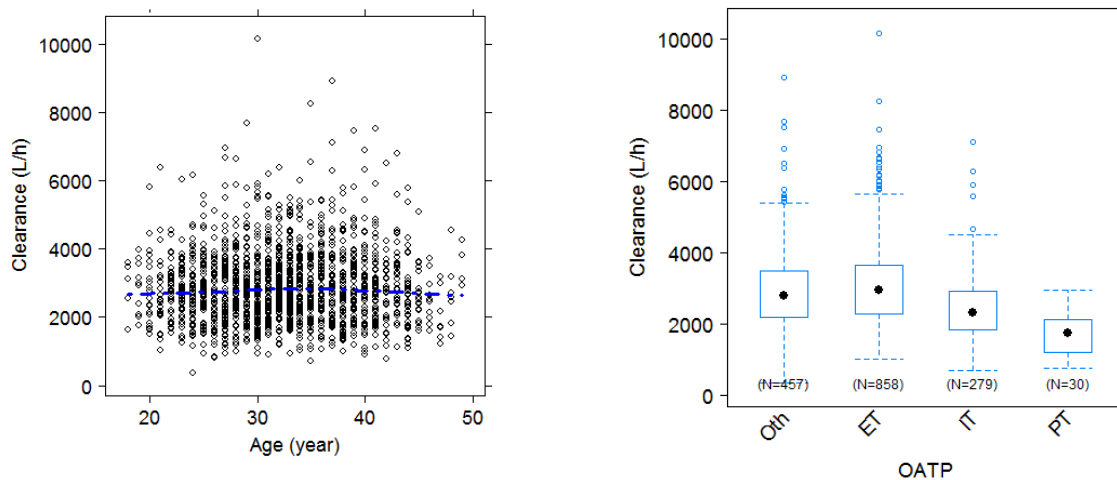
Additional analysis was conducted by the reviewer to further assess the appropriateness of the model and evaluate the effect of covariates. The reviewer's goodness-of-fit plots by study are presented in Figure 5.1-3. As indicated, a lot of elagolix concentrations, especially those on high values were underestimated.

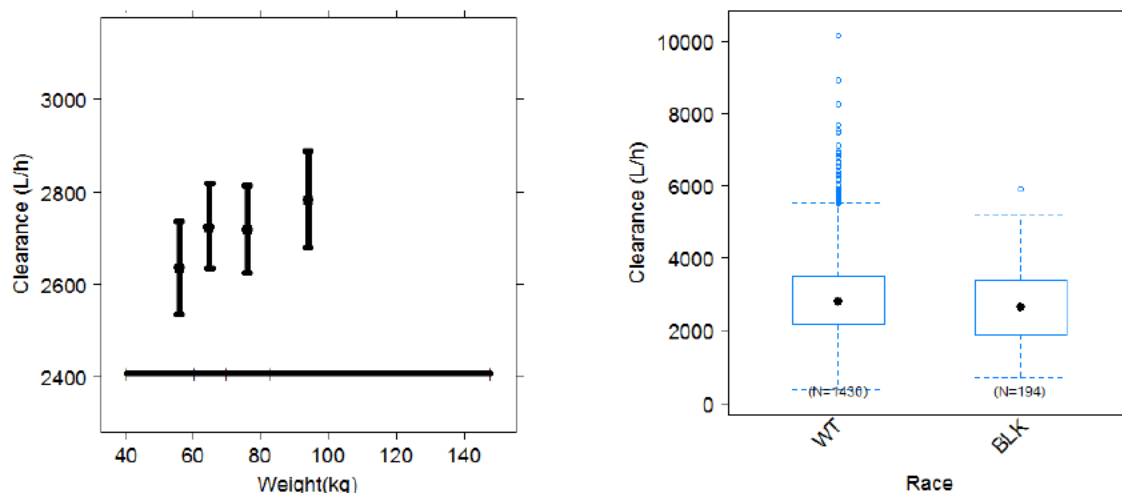
Figure 5.1-3: Goodness-of-fit plots for the Final model by Study



The relationships between covariates and elagolix apparent clearance are shown in **Figure 5.1-4**. Covariates of age, body weight, BMI, and creatinine clearance, AST, ALT at the observed range had no effect on elagolix clearance, but poor OATP transporter demonstrated much lower clearance than subjects extensive and immediate transporter.

Figure 5.1-4: Effect of Covariates on Elagolix Clearance





The effect of OATP1B1 Transporter on elagolix clearance and exposure: *Posthoc estimation of elagolix clearance and steady state AUC after 150 mg QD is summarized in Table 5.1-7. As shown in the table, OATP1B1 poor transporters have much lower clearance relative to other OATP1B1 phenotypes. Subjects with poor OATP1B1 transporter function had about 1.8-fold steady-state AUC relative to subjects with extensive OATP1B1 transporter function.*

Table 5.1-7: Predicted Steady-State AUC after 150 mg QD of Elagolix

AUC _{0-24, ss} (ng.hr/mL) after 150 mg QD					
OATP Type	N	Mean	Std Dev	Minimum	Maximum
Extensive	858	55.3	20.7	14.8	148.2
Intermediate	279	68.3	24.4	21.1	209.1
Poor	30	98.5	37.1	50.5	195.1
Others	457	59.1	29.1	16.8	407.2

6. Exposure-Response Analyses

6.1 Exposure-Response for Primary Efficacy Endpoints

The applicant submitted a separate exposure-response (ER) analysis report entitled Exposure-Efficacy Analyses for Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain Based on Data from Four Phase 3 Studies. The ER model was able to describe relationship between elagolix exposure and the transition probabilities between responder and nonresponder states.

Objective: The objective of this report was to describe the relationship between elagolix exposure and clinical efficacy response variables (primary endpoints: DYS and NMPP) using data from four Phase 3 clinical trials in women with moderate to severe endometriosis-associated pain and to identify the

influence of subject-specific characteristics on the model parameters associated with the clinical efficacy response

Data: Elagolix exposure (average plasma concentration [C_{avg}] or concentration at pre-dose in repeated dosing [C_{trough}]) and clinical response variables (primary endpoints: DYS and NMPP) was evaluated using data from four Phase 3 studies: Studies M12-665, M12-667, M12-671, and M12-821. A combined dataset for primary endpoints was generated. The dataset included subject identification number, demographic variables, covariates, drug exposure variables (C_{avg} and C_{trough}), and clinical response variables. Elagolix pharmacokinetic parameters were estimated from the population pharmacokinetic model and were used to provide elagolix exposure variables (C_{avg} or C_{trough}) for the exposure-response analyses. Demographics of the subjects at baseline in the ER analysis is summarized in **Table 6.1-1**.

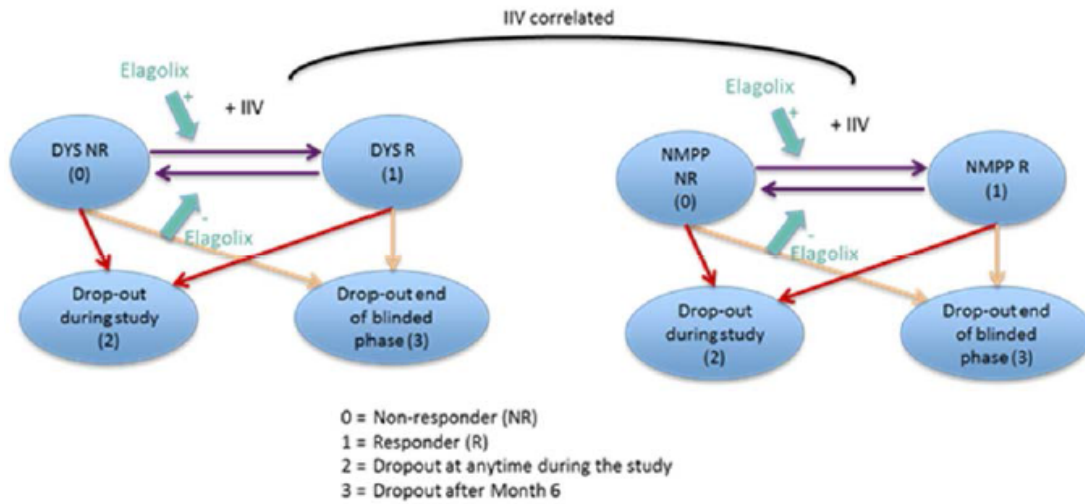
Table 6.1-1: Summary of Demographic Data for Exposure-Efficacy Analysis

		All subjects (N=1671)		
Treatment		N (%)	Mean(SD)	Range
	Placebo	731(43.8)		
	Elagolix 150 mg QD	469(28.1)		
	Elagolix 200 mg BID	471(28.2)		
Age (year)			32.4(6.5)	18-49
Weight (kg)			74.4(18.0)	40.0-148.0
Body Mass Index (kg/m ²)			27.6(6.4)	16.2-54.5
Race	White and Other	1524(91.4)		
	Black	11(8.6)		
Hispanic Ethnicity	No	1426(85.3)		
	Yes	245(14.7)		
Region	US	1260(75.4)		
	Outside of the US	411(24.6)		
Baseline DYS score			2.2(0.5)	0.0-3.0
Baseline NMPP Score			1.6(0.5)	0.1-3
Baseline Estradiol Level (pg/mL)			83.3(84.3)	3.2-839.0
Baseline FSH Level (IU/L)			8.4(7.7)	0.9-126.6
Baseline LH Level (IU/L)			8.0(9.6)	0.2-118.8
Baseline Progesterone Level (ng/mL)			0.7(2.3)	0.1-26.4
Time since endometriosis diagnosis	Less than 2 years	588(35.2)		
	2 to < 5 years	597(35.7)		
	5 to <10 years	450(26.9)		
	>=10 years	36(2.2)		
Previous GnRH Therapy	No	1234(73.8)		
	Yes	437(26.2)		

Source: Adapted from Table 1 on page 33 of applicant's PKPD report rd170089

Exposure-Response Modeling: The exposure-response models for the clinical endpoints were built using non-linear mixed-effects modeling based on NONMEM 7.3 compiled with the GNU Fortran compiler (Version 4.8.3). The relationship between elagolix exposure and clinical outcome (DYS or NMPP response) was described by a discrete-time Markov Chain model. A schematic of the model is shown in **Figure 6.1-1**. The model included a first-order Markovian feature which implies that the probabilities for subjects being in the responder or nonresponder states at each study visit are conditioned on their state at the previous visit.

Figure 6.1-1: Schematic of the Markov Chain Model



Source: Figure 3 on page 23 of applicant's PKPD report rd170089

Equations to describe the process were as followed:

$$P_{01} = \frac{\exp(\text{logit}(P_{01}))}{1 + \exp(\text{logit}(P_{01}))} \quad \text{Equation 1}$$

$$\text{logit}(P_{01}) = \text{Pla}_{01} + \text{eta}_1 \quad \text{Equation 2}$$

$$\text{logit}(P_{01}) = \text{Pla}_{01} + E_{\max 01} * \frac{C_{\text{avg}}}{EC50_{01} + C_{\text{avg}}} + \text{eta}_1 \quad \text{Equation 3}$$

Where

- P_{01} represents the probability of achieving responder state from the nonresponder state.
- Pla_{01} is the probability of achieving responder state from the nonresponder state when treated with placebo.
- eta_1 is the inter-individual variability (IIV) parameter on P_{01}

And

$E_{\max 01}$ is the maximum probability (in logit scale) of achieving the transition from nonresponder state to the responder state. $EC50_{01}$ is the elagolix monthly C_{avg} for half-maximal probability (in logit scale) of achieving the transition from nonresponder state to the responder state. C_{avg} is the elagolix monthly average of daily C_{avg} .

Exposure-Efficacy Analyses of Primary Endpoints (DYS and NMPP): A discrete-time first-order Markov Chain model was built to describe exposure-response between elagolix monthly average exposure (monthly C_{avg} values) and transition probabilities between responder and nonresponder states. The estimated parameters values, covariates effect values and the variabilities from the final model are summarized in **Table 6.1-2**.

Table 6.1-2: Exposure-Efficacy Parameter Estimates and Variability for the Final Model

Parameter	Population Estimate	% RSE	95% Confidence Interval
DYS			
Transition 01 (NR to R)			
Pl _{a01D}	0.0995 ^a	0.0515	(0.0863, 0.114)
E _{max01D}	2.42	14.5	(1.74, 3.11)
EC50 _{01D}	36.1 ^b	35.9	(18.2, 71.5)
BLDYS on logit Pl _{a01D}	-0.282	15.5	(-0.368, -0.196)
Transition 10 (R to NR)			
Pl _{a10D}	0.402 ^a	0.125	(0.358, 0.446)
E _{max10D}	-3.03	24.1	(-4.47, -1.60)
EC50 _{10D}	134 ^b	42.3	(60.4, 296)
BLDYS on logit Pl _{a10D}	0.826	42.0	(0.146, 1.51)
REGEFF on E _{max01D} and E _{max10D}	1.30	8.07	(1.09, 1.50)
IIV on P _{01D}	1.26	10.5	(1.00, 1.52)
NMPP			
Transition 01 (NR to R)			
Pl _{a01N}	0.168 ^a	0.0788	(0.146, 0.191)
E _{max01N}	1.23	19.2	(0.765, 1.69)
EC50 _{01N} = EC50 _{10N}	53.8 ^b	47.9	(22.0, 131)
AGE on EC50 _{01N} = EC50 _{10N}	-0.0234	39.4	(-0.0415, -0.00533)
BLNMPP on logit Pl _{a01N}	-0.422	16.3	(-0.556, -0.287)
Transition 10 (R to NR)			
Pl _{a10N}	0.195 ^a	0.0903	(0.170, 0.222)
E _{max10N}	-1.43	17.7	(-1.92, -0.931)
IIV on P _{01N}	2.17	9.31	(1.77, 2.57)
Covariance between IIV on P _{01D} and IIV on P _{01N}	1.64	7.89	(1.39, 1.89)
Dropout Transitions			
P _{02D} /P _{12D}	0.0459 ^a	0.00824	(0.0422, 0.0499)
P _{02N}	0.0522 ^a	0.0142	(0.0471, 0.0578)
P _{12N}	0.0375 ^a	0.0188	(0.0326, 0.0430)
P _{03D} = P _{13D} = P _{03N} = P _{13N}	0.242 ^a	0.104	(0.212, 0.274)

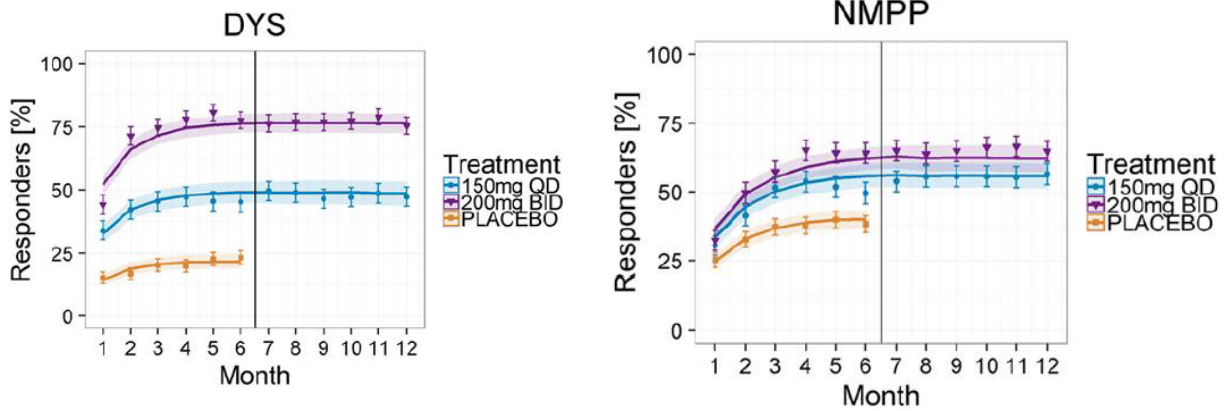
a. Estimated in logit transformation; transformed back for table.

b. Estimated in exponential transformation (base 10); transformed back for table.

Source: Table 5 on page 43 of applicant's PKPD report rd170089

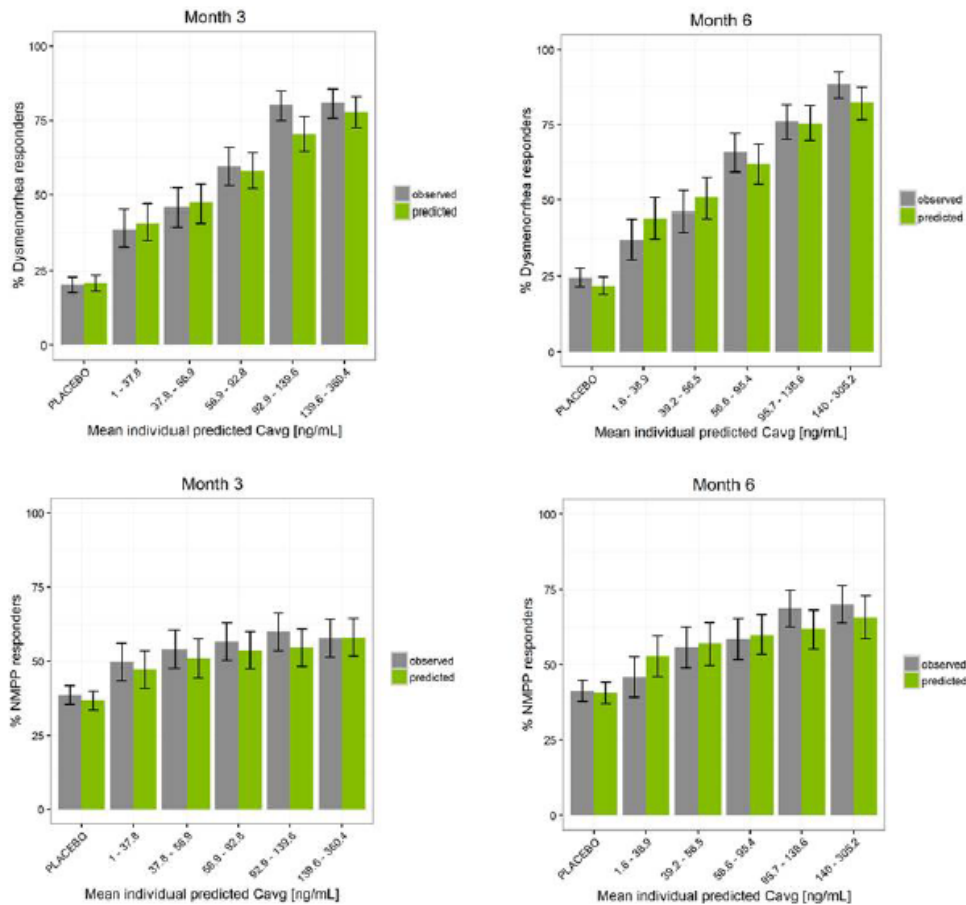
Model Evaluation: The final model was evaluated with goodness-of-fit plots, VPCs and bootstrap evaluation. The observed and predicted DYS and NMPP are shown in **Figure 6.1-3**, the VPC plot are shown in **Figure 6.1-2**, and the bootstrap results are shown in **Table 6.1-3**.

Figure 6.1-2: Exposure-Response Visual Predictive Checks



Symbols with the 90% confidence interval represent the data, solid lines and the shaded region around them represent the median of the simulated data and the region of the 90% confidence interval

Figure 6.1-3: Observed and Model Predicted Quintile Plots for DYS and NMPP Response at Month 3 and Month 6



Source: Source: Figure 10 on page 51 of applicant's PKPD report rd170089

Table 6.1-3: Median and 95% Confidence Intervals for Exposure-Response Model Parameters Estimated from Bootstrap Evaluation

Parameter	Bootstrap Evaluation Results (N = 734)		
	Model Result	Median	95% Confidence Interval
DYS			
Transition 01 (NR to R)			
Pl _{a01D}	0.0998 ^a	0.0998	(0.0863, 0.114)
E _{max01D}	2.42	2.43	(1.85, 3.28)
EC50 _{01D}	36.3 ^b	36.3	(15.1, 69.2)
BLDYS on logit Pl _{a01D}	-0.282	-0.279	(-0.373, -0.194)
Transition 10 (R to NR)			
Pl _{a10D}	0.402 ^a	0.402	(0.361, 0.448)
E _{max10D}	-3.03	-3.07	(-5.00, -2.00)
EC50 _{10D}	135 ^b	135	(61.7, 288)
BLDYS on logit Pl _{a10D}	0.826	0.848	(0.305, 2.03)
REGEFF on E _{max01D} = E _{max10D}	1.30	1.30	(1.10, 1.53)
IV on P _{01D}	1.26	1.27	(1.04, 1.54)
NMPP			
Transition 01 (NR to R)			
Pl _{a01N}	0.168 ^a	0.168	(0.146, 0.190)
E _{max01N}	1.23	1.25	(0.801, 1.90)
EC50 _{01N} = EC50 _{10N}	53.7 ^b	56.2	(8.13, 135)
AGE on EC50 _{01N} = EC50 _{10N}	-0.0234	-0.0230	(-0.171, -0.0088)
BLNMPP on logit Pl _{a01N}	-0.422	-0.421	(-0.567, -0.302)
Transition 10 (R to NR)			
Pl _{a10N}	0.195 ^a	0.195	(0.169, 0.223)
E _{max10N}	-1.43	-1.46	(-2.20, -0.969)
IV on P _{01N}	2.17	2.17	(1.83, 2.65)
Covariance between IV on P _{01D} and IV on P _{01N}	1.64	1.63	(1.40, 1.88)
Dropout Transitions			
P _{02D} = P _{12D}	0.0461 ^a	0.0461	(0.0423, 0.0497)
P _{02N}	0.0522 ^a	0.0522	(0.0479, 0.0573)
Bootstrap Evaluation Results (N = 734)			
Parameter	Model Result	Median	95% Confidence Interval
P _{12N}	0.0373 ^a	0.0377	(0.0323, 0.0435)
P _{03D} = P _{13D} = P _{03N} = P _{13N}	0.242 ^a	0.241	(0.211, 0.275)

*Reviewer's Comments: Dose frequency such as QD and BID for the same daily dose has an effect on treatment response, therefore using C_{avg} as exposure metric may confound the ER relationship for both DYS and NMPP. The model-predicted treatment effect does not match well with that observed in the studies. As shown in **Figure 6.1-3**, the proportions of responders for both DYS and NMPP at higher quantile of C_{avg} were underestimated. Therefore, the ER-for efficacy may not adequately describe with the model.*

Based on observations, the treatment response has reached a plateau after 4-6 months of treatment for both DYS and NMPP.

6.2 Exposure-Response Analyses for Safety

The applicant submitted an exposure-response analyses report for safety entitled *Exposure-Safety Analyses for Changes in Bone Mineral Density and Hot Flush with Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain Based on Data from Four Phase 3 Studies* to describe the effects of elagolix concentrations on BMD changes in women with moderate to severe endometriosis-associated pain.

Objectives:

The objectives of this report are:

- 1) To describe the relationship between elagolix exposure and changes in BMD and occurrence of hot flush
- 2) To identify patient covariates associated with changes in BMD, and occurrence of hot flush
- 3) Predict BMD changes following different elagolix treatment scenarios

Data: The relationship between elagolix exposure and safety outcomes was evaluated using data from four Phase 3 studies: Studies M12-665, M12-667, M12-671 and M12-821. Data from 1684 premenopausal female subjects were included in the exposure-safety analysis for BMD. Data from 1685 subjects in pivotal studies M12-665 and M12-671 were included in the exposure-safety analysis for hot flush.

Covariates investigated for influence on the BMD included:

- Demographics (age, weight, body mass index [BMI], race, tobacco use, alcohol use, region (outside of the United States [non-US] versus [US]))
- Hormone (E2, progesterone, luteinizing hormone [LH] and follicle stimulating hormone [FSH] concentration at baseline)
- Screening Z-score*
- Baseline bone biomarkers (osteocalcin, type I collagen C-telopeptide [CTX], and procollagen type I N-propeptide [PINP]) concentrations.
- Concomitant medication (calcium use and vitamin D use)
- Prior GnRH therapy

Covariates investigated for the influence of hot flush parameters included:

- Demographics (age, weight, BMI, race, tobacco use, and alcohol use)
- Hormone (E2, progesterone, LH and FSH concentration at baseline)
- Concomitant medication (anti-depressants)
- Prior GnRH therapy

Exposure-BMD Modeling: The exposure-BMD model was built using nonlinear mixed effects modeling in NONMEM 7.3 compiled with the GNU Fortran compiler (Version 4.8.3). The structure model is an indirect response model that describes the changes from baseline BMD (BLBMD) and assumes a baseline steady state between bone formation and resorption. Some equations used to describe the model is as followed:

$$\frac{dR(t)}{dt} = K_{in} - K_{out} * R(t) \quad \text{Equation 1}$$

$$BMD(t) = BLBMD * R(t) \quad \text{Equation 2}$$

$$R(0) = 1 \text{ and } K_{out} = K_{in}/1 \quad \text{Equation 3}$$

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 baseline (BLBMD) at time (t) . Baseline BMD was modelled as a typical value for the population with its associated interindividual variability, and a different baseline value was estimated for each type of DXA scan machine (Hologic and Lunar) used.

The effects of elagolix on BMD were modeled using a stimulatory E_{max} function on the bone resorption(K_{out}), as follows:

$$\frac{dR(t)}{dt} = k_{in} - k_{out} \cdot \left(1 + \frac{E_{max} \cdot C_{avg}^{HILL}}{EC_{50}^{HILL} + C_{avg}^{HILL}} \right) \cdot R(t) + PLAC\_EFF$$

Equation 7

where, E_{max} is the elagolix maximum stimulatory effect on K_{out} , EC_{50} is the elagolix monthly average concentration producing 50% of maximum stimulation, and $HILL$ is the stimulatory E_{max} curve shape factor.

Covariate Selection: Relationships between individual model parameter estimates and possible covariates were first explored using graphical methods, and then final covariate selection was performed using the forward inclusion and backward elimination procedures. The resulting model after backward elimination is referred to as the final NONMEM model.

Model Evaluation: The developed models were evaluated both during development and after the model development was completed. Methods used in model evaluation included goodness-of-fit plots, visual predictive checks (VPCs), and bootstrap evaluation

The parameter estimates from the final exposure-BMD model are summarized in **Table 6.2-1**. The goodness-of-fit plots for the final exposure-BMD model are shown in **Figure 6.2-1**. The Visual Predictive Check plots are demonstrated in **Figure 6.2-2**.

Table 6.2-1: Parameter Estimates for the Final Exposure-BMD Model

Parameter	Population Estimate	%RSE ^c	95% Confidence Interval
BLBMD; Hologic (g/cm ³)	1.06	0.36	1.05 – 1.07
BLBMD (Lunar) (g/cm ³)	1.24	0.30	1.23 – 1.25
PLAC_EFF (1/day)	0.00002 (fix)	-	-
K_{IN} (and K_{OUT}) (1/day)	0.0015	5.84	0.0013 – 0.0017
E_{MAX}	0.30	14.5	0.22 – 0.39
EC_{50} (ng/mL)	240	20.9	142 – 338
BMI_BLBMD	0.10	10.3	0.08 – 0.12
RACE_BLBMD	0.05	16.6	0.03 – 0.07
BLCTX_BLBMD	-0.67	-23.2	-0.97 – -0.36
BMI_KIN	-0.020	-23.6	-0.029 – -0.011
InterIndividual Variability on BLBMD (%CV ^a)	0.00816 (9.1)	3.75	-
InterIndividual Variability on PLAC_EFF (%CV ^b)	0.93 (fix)	-	-
InterIndividual Variability on EC_{50} (%CV ^b)	0.77 (107)	20.7	-
Proportional Residual Error (%CV ^b)	0.00032 (1.789)	1.84	-

RSE = relative standard error; CV = coefficient of variation; SEE = standard error of the estimate

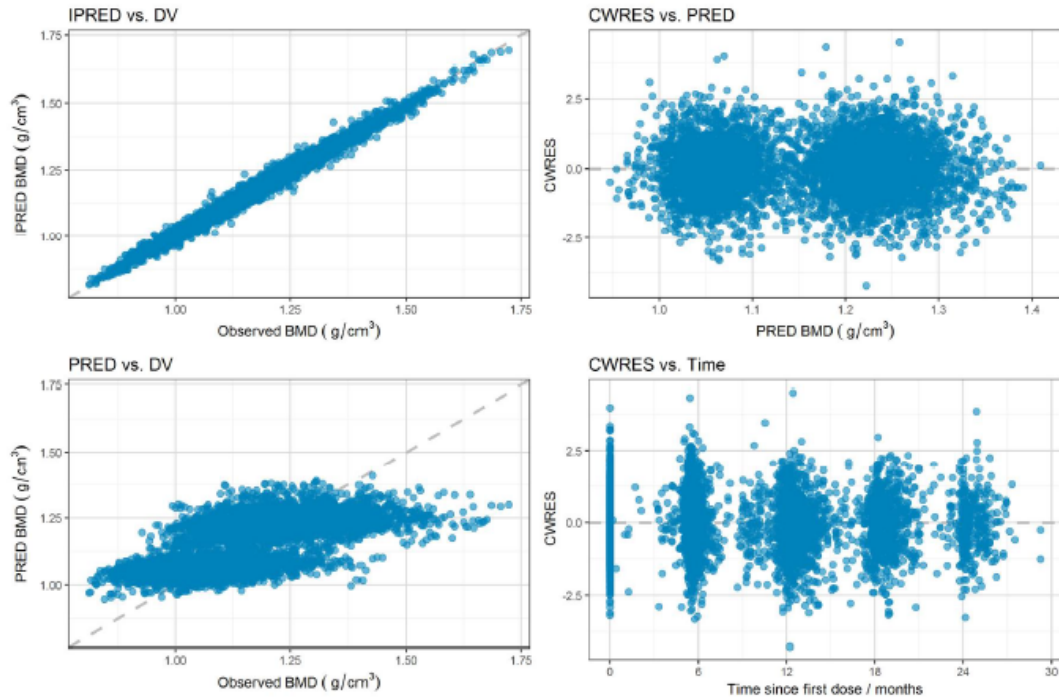
a. $\%CV = 100 \cdot (\sqrt{e^{\omega^2}} - 1)$.

b. $\%CV = 100 \cdot (\sqrt{\sigma^2})$.

c. %RSE was estimated as the SEE divided by the population estimate and multiplied by 100.

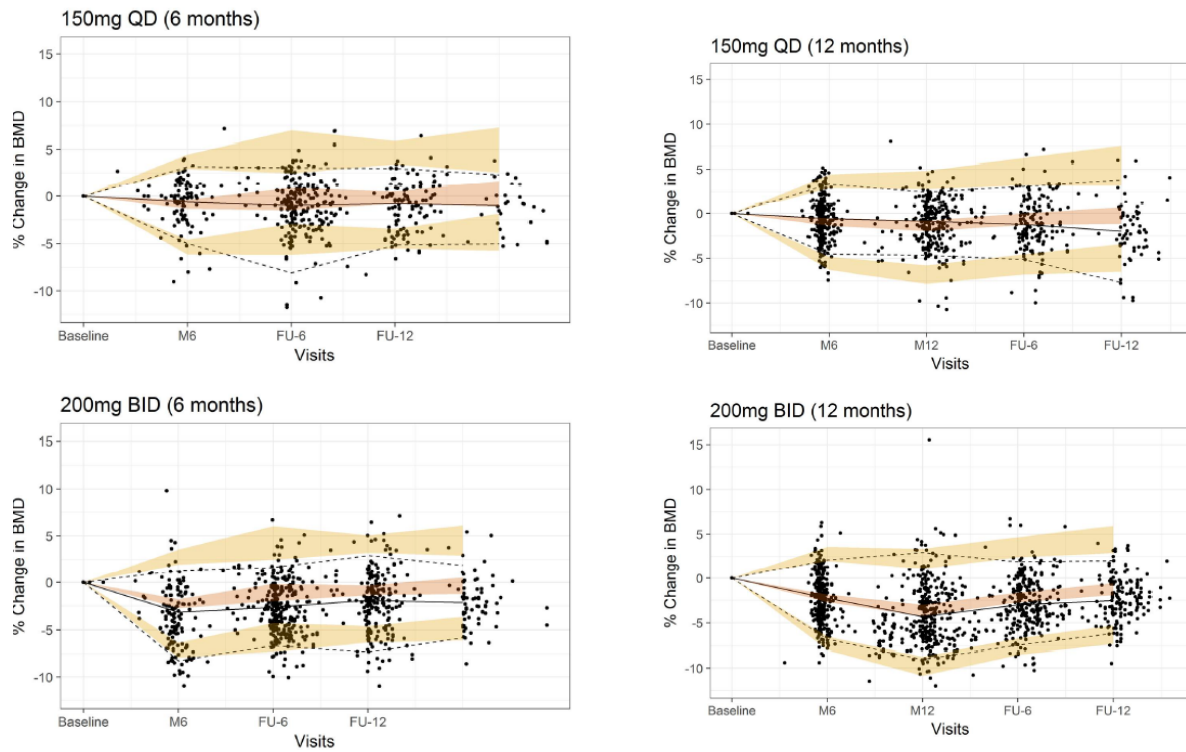
Source: Table 4 on page 52 of applicant's PKPD report rd170090

Figure 6.2-1: Goodness-of-Fit Plots for the Final Exposure-BMD Model



Source: Figure 7 on page 54 of applicant's PKPD report rd170090

Figure 6.2-2: Visual Predictive Check Plots for the Final Exposure-BMD Model



Source: Adapted from Figure 9 and 10 on page 59 to 60 of applicant's PKPD report rd170090

Bootstrap Evaluation for the Final Exposure-BMD Model: A total of 996 of the 1000 bootstrap replicates plus the original dataset converged successfully. Median and 95% Confidence Intervals for the model parameters are presented in **Table 6.2-2**. The estimated parameter values based on the original dataset were in good agreement with the medians of the parameter estimates from the bootstrap replicates.

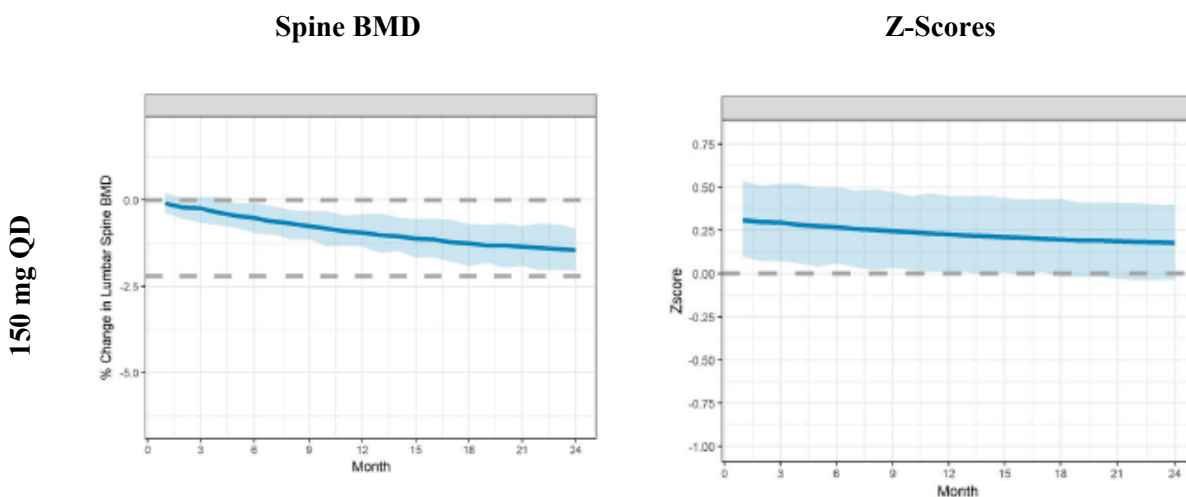
Table 6.2-2: Median and 95% Confidence Intervals for Elagolix Exposure-BMD Model Parameters Estimated from Bootstrap Evaluation

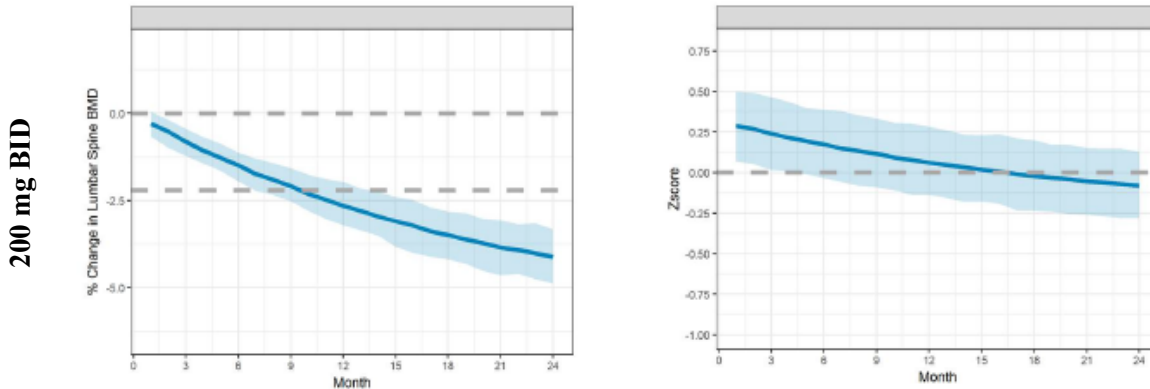
Pharmacodynamic Parameter	Model Result	Bootstrap Evaluation Results (N = 996)		
		Mean	Median	95% Confidence Interval
BLBMD (Hologic)	1.060	1.061	1.060	1.050 – 1.070
BLBMD (Lunar)	1.240	1.238	1.240	1.230 – 1.240
K _{IN} & K _{OUT}	0.001	0.001	0.001	0.001 – 0.002
E _{MAX}	0.302	0.306	0.300	0.232 – 0.401
EC ₅₀	240.0	241.8	239.0	176.5 – 323.5
BMI_BLBMD	0.100	0.101	0.101	0.081 – 0.119
RACE_BLBMD	0.049	0.049	0.049	0.033 – 0.066
BMI_K _{IN}	-0.665	-0.669	-0.664	-1.010 – -0.343
BLCTX_BLBMD	-0.020	-0.020	-0.020	-0.029 – -0.011
IIV on BLBMD	0.008	0.008	0.008	0.008 – 0.009
IIV on EC ₅₀	0.765	0.780	0.771	0.476 – 1.140

Source: Table 5 on page 60 of applicant's PKPD report rd170090

BMD Simulations: Simulations were conducted with the final model using demographics and baseline characteristics from the screen population from studies M12-665 and M12-671. Simulated Mean % change in BMD and Z-Score over time for elagolix 150 mg QD and 200 mg BID are summarized in **Table 6.2-3** and shown in **Figure 6.2-3**.

Figure 6.2-3: Simulated Mean % BMD Changes and Z-Scores Over Time for Treatment with Elagolix for 24 Months





Note: solid line represents mean and shaded area represents 95% confidence interval of the mean. Dashed lines represent 0% and -2.2% change or Z-score of 0

Table 6.2-3: Summary Statistics of Predicted Mean % BMD Changes and Z-Scores for Treatment with Elagolix 150 mg QD for 24 Months

Month	Mean % Change in BMD	95% Confidence Interval	Mean Z-Score	95% Confidence Interval	% Subjects with Z-Score < -1.5	% Subjects with Z-Score < -2.0
6	-0.519	-0.955 – -0.0885	0.269	0.0594 – 0.502	4.56	1.44
12	-0.942	-1.34 – -0.408	0.228	0.0120 – 0.448	5.09	1.57
24	-1.45	-2.04 – -0.814	0.179	-0.0352 – 0.401	5.75	1.96

BMD = bone mineral density

Source: Table 8 on page 65 of Applicant's PKPD report rd170090

Exposure-Hot Flush Modeling: The exposure-hot flush model was a logistic regression model that was built using nonlinear mixed effects modeling within NONMEM 7.3. An Emax relationship on the logit scale was used to describe the relationship between the probability of hot flush (any grade or moderate/severe) and elagolix exposure or E2 concentrations using the following equations:

$$f(\text{predictor}) = BL \pm \frac{E_{\text{max, hot flush}} * \text{predictor}}{EC_{50, \text{hot flush}} + \text{predictor}} \quad \text{Equation 12}$$

$$P(Y_i = \text{Event}) = \frac{e^{f(\text{predictor})}}{1 + e^{f(\text{predictor})}} \quad \text{Equation 13}$$

$$P(Y_i = \text{No Event}) = 1 - \frac{e^{f(\text{predictor})}}{1 + e^{f(\text{predictor})}} \quad \text{Equation 14}$$

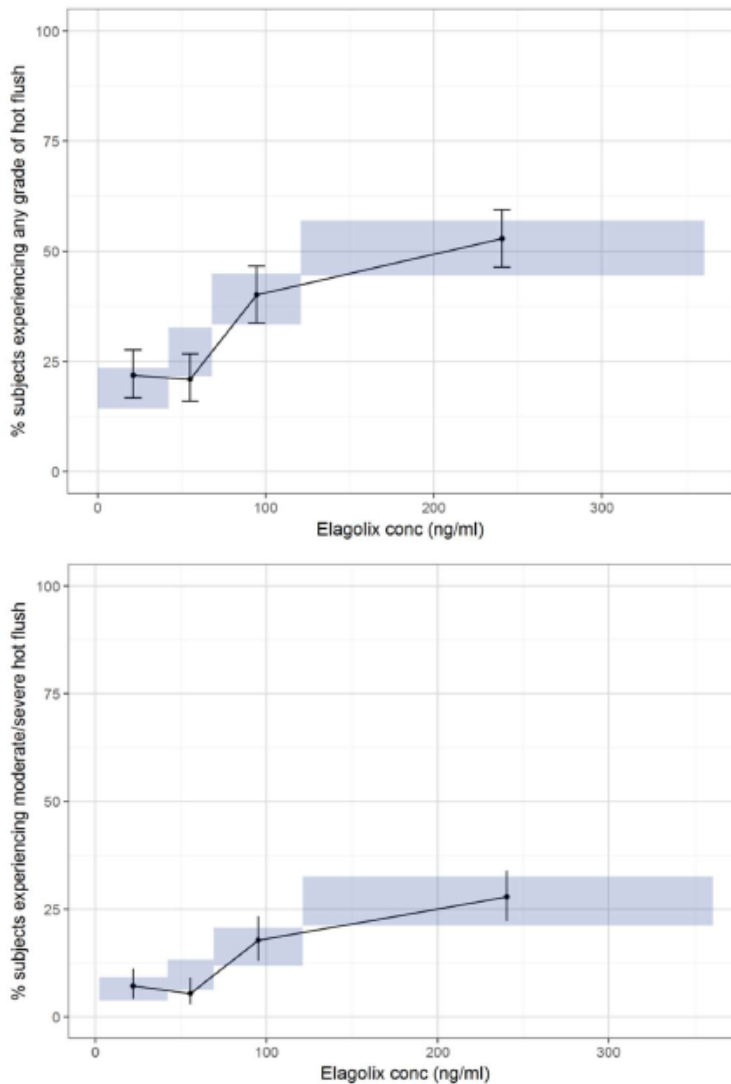
Where BL is the intercept for the logistic regression model, E_{max} is the maximal probability of occurrence of hot flush under elagolix treatment. EC50 is the predictor exposure or concentration resulting in half the maximum response. The parameter estimates for the final elagolix exposure-hot flush model are summarized in **Table 6.2-4**. The Visual Predictive Check plots for the final model by hot-flush grade are shown in **Figure 6.2-4**. The model predicted hot-flush response is line with those observed in clinical studies.

Table 6.2-4: Parameter Estimates for the Final Elagolix Exposure-Hot Flush Model

Parameter ^a	Population Estimate	%RSE ^b	95% Confidence Interval
Any Grade vs None (ANYHF_run002_1)			
BL_ANYHF	-2.37	-5	-2.62 – -2.12
EMAX_ANYHF	3.00	15	2.11 – 3.89
EC50_ANYHF (ng/mL)	91.4	32	33.6 – 149
Alcohol intake on Emax	0.356	39	0.08 – 0.63
Moderate/Severe vs None/Mild (MODSEV_run002)			
BL_MODSEVHF	-3.48	-6	-3.87 – -3.09
EMAX_MODSEVHF	4.55	17	2.99 – 6.11
EC50_MODSEVHF (ng/mL)	143	38	36.0 – 250

Source: Table 14 on page 74 of Applicant’s PKPD report rd170090

Figure 6.2-4: Visual Predictive Checks for the Final Exposure-Hot Flush Model



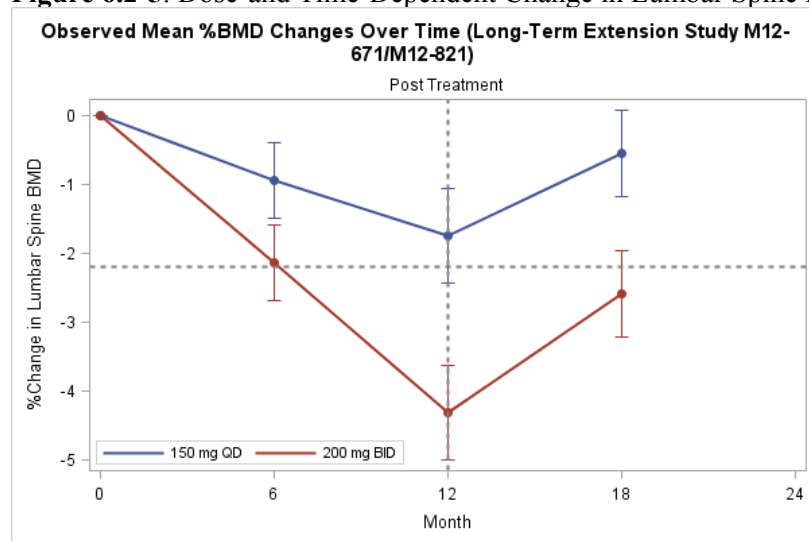
Source: Figure 14 on page 75 of Applicant’s PKPD report rd170090

Reviewer's Comments:

Overall, the applicant's exposure-BMD and exposure-Hot flush analyses are acceptable. The exposure-BMD was able to describe the observed BMD changes following treatment with elagolix 150 mg QD and 200 mg BID. The prediction performance of the final model as shown in the VPC plots is acceptable.

As shown in the reviewer's **Figure 6.2-5**, elagolix demonstrated both dose- and time-dependent decrease in BMD, and model prediction suggests that treatment with 200 mg BID for more than 12 months would result in a significant bone loss. Please also note that bone loss can be partially recovered once treatment stops. As such, the reviewer supports the use of 150 mg QD in all subjects but does not recommend the use of 200 mg BID for more than six months.

Figure 6.2-5: Dose- and Time-Dependent Change in Lumbar Spine Bone Mineral Density (BMD).



A logistic Emax model was able to describe the relationship between Elagolix and rate of hot flushes well. Higher elagolix was associated with increased incidence of hot-flushes. This is expected as elagolix suppress E2. Alcohol intake may increase the probability of hot flushes.

7. Enrichment, Stratification, and/or Biomarker-based Assessment

Study R&D/16/1306 (Pharmacogenomics Report)

Title: Pharmacogenetic Analysis of Sample for Elagolix Phase 1 and Phase 3 Studies

Objectives

To assess whether the presence of variants in OATP1B1/SLCO1B1 gene that have been previously associated with functional impact affects a subject's exposure to elagolix.

Background

Elagolix is metabolized via multiple cytochrome P450 (CYP) enzymes, with the applicant reporting CYP3A4 as the major contributor and CYP2D6 and CYP2C8 to a lesser extent. Elagolix is a substrate of the efflux transporter, p-glycoprotein (P-gp) and the uptake transporter, organic anion-transporting polypeptide (OATP)1B1. The applicant evaluated the influence of OATP1B1 genotype status on the exposure to elagolix by conducting *SLCO1B1* (the gene encoding the OATP1B1 transporter protein) genotyping in subjects from 19 Phase 1 clinical studies (17 in healthy women and 2 in female subjects with renal or hepatic impairment) and 4 Phase 3 studies in female subjects with moderate to severe

endometriosis-associated pain (2 pivotal studies and their extension studies). The applicant has submitted a pharmacogenetics report providing descriptive statistics of the population genotyped, the number of samples analyzed, phenotypic classifications of alleles and distribution of phenotypes.

Method

Per protocols of the clinical trials in the submission, one 4 mL whole blood sample was collected for DNA isolation prior to study drug dosing on Day 1 from each subject who consented to provide a sample for pharmacogenetic analysis. The applicant performed DNA extraction from whole blood using Qiagen reagent kits (Qiagen Inc., Valencia, CA) applied to an automated DNA extraction instrument, AutoGeneprep 3000. According to the applicant's report, genotypes were determined via pyrosequencing using an in-house assay. The applicant determined genotype for a single nucleotide polymorphism (b) (4) in *SLCO1B1*.

Table 7-1. Number of PG Samples Analyzed/Genotyped from the Elagolix Phase 1 and Phase 3 Studies

Study ID	Sample Available and Analyzed
Phase 1	
M12-652	12
M12-653	24
M12-654	25
M12-655	12
M12-659	12
M12-660	12
M12-661	42
M12-662	15
M12-673	45
M12-765	22
M12-790	44
M13-756	10
M13-784	18
M13-995	23
M14-731	33
M15-629	20
M15-817	54
M15-973	20
M15-974	20
Phase 3	
M12-665/667	706
M12-671/821	608

Studies highlighted in yellow are included in the population pharmacokinetics (popPK) analysis

SLCO1B1 allele 521T > C (*5) genotype was assayed to classify subjects into transporter categories defined as:

Homozygous variant 521T > C (s5) → Poor transporters (PT)

Heterozygous for 521T > C (s5) → Intermediate transporters (IT)

Homozygous wild-type 521T > C (s5) → Extensive transporter (ET)

Missing data for 521T > C(s5) → Unable to analyze/genotype sample

Study Results

Summarized Table of OATP1B1 Transporter Status for Phase 1 and Phase 3 Studies

	ET (T/T)	IT (T/C)	PT (C/C)	Missing Data
Phase 1 (463) [#]	371 (80.3%)	86 (18.6%)	5 (1.1%)	0 (0%)
Phase 3 (1314) *	945 (71.9%)	333 (25.3%)	33 (2.5%)	3 (0.2%)

one subject excluded from analysis, *Missing data in 3 subjects

Summarized from Table 3 and Table 4 of RD161306 report

Reviewer's Comments

Published literature

More than 45 nonsynonymous SNPs have been identified in *SLCO1B1*, few of which have been associated with impaired hepatic uptake, clearance and toxicity of statins. A notable common variant, 521T>C (rs4149056), results in reduced membrane expression and transport activity and occurs with an allele frequency of 8-20% in Caucasians, 1-8% in African Americans and 8-16% in Asians. Additionally, the 388A>G variant (rs23062830) has been associated with potentially reduced transport activity and is observed with an allele frequency of 30-45% in Caucasians, 72-83% in African Americans and 59-89% in Asians². These two variants exist in partial linkage disequilibrium and form distinct haplotypes *1A (388A/521T), *1B (388G/521T), *5 (388A/521C) and *15(388G/521C)³. The low transport activity haplotypes, *5 and *15, have a combined frequency of approximately 15-20% in Europeans, 10-15% in Asians and 2% in sub-Saharan Africans⁴.

Reviewer's analysis

*While there are other variants in SLCO1B1 with functional implications on the OATP1B1 transporter, the applicant genotyped for the rs4149056 SNP to determine the transporter phenotype. Given the single SNP genotyping, it is plausible that the designation of subjects will also include definite *15 haplotypes; however, this does not impact the phenotypic assignment derived from the genotype. The determination of rs4149056 genotype is consistent with conventional assignment of the *5 haplotype⁴. The assignment of transporter phenotype by homozygous variant, heterozygous, and homozygous wild type for poor, intermediate and extensive transporters, respectively, is consistent with diplotype-phenotype assignments in the literature where 1) extensive transport is defined by homozygous wild-type for the extensive transport haplotypes, 2) intermediate transport is defined by heterozygous for the low activity haplotype, and 3) poor transport is defined by homozygous or compound heterozygous for the low transport haplotypes^{5,6}.*

Re-analysis of the assigned phenotype is consistent with the analysis performed by the applicant.

	<i>Applicant designation (CPIC-consensus term⁷)</i>				
	<i>ET (Normal transporter function)</i>	<i>IT (Decreased transporter function)</i>	<i>PT (Poor transporter function)</i>	<i>MISSING</i>	
<i>PHASE 1</i>	<i>372 (Applicant notes 1 subject excluded)</i>	<i>86</i>	<i>5</i>	<i>0</i>	<i>463</i>
<i>PHASE 3</i>	<i>945</i>	<i>333</i>	<i>33</i>	<i>3</i>	<i>1314</i>
<i>Total</i>	<i>1317</i>	<i>419</i>	<i>38</i>	<i>3</i>	<i>1777</i>

² Lee HH and Ho RH. Br J Clin Pharmacol. 2017 Jun;83(6):1176-1184

³ Pasanen MK, Neuvonen PJ, Niemi M. Pharmacogenomics. 2008 Jan;9(1):19-33.

⁴ Oshiro C et. al. Pharmacogenet Genomics. 2010 Mar;20(3):211-6.

⁵ Niemi M et. al. Pharmacol Rev. 2011 Mar;63(1):157-81

⁶ Emami Riedmaier A et. al. J Clin Pharmacol. 2016 Jul;56 Suppl 7:S132-42

⁷ Caudle KE et. al. Genet Med. 2017 Feb;19(2):215-223

The applicant did not assess genetic variation in elagolix-metabolizing enzymes, CYP3A4, and the highly polymorphic CYP2D6, and the impact of such variation on the exposure, safety and efficacy of elagolix.

The applicant did not include all genotyped samples in the popPK study. Data from 294 subjects across 14 studies were not included in the popPK study. See pharmacometrics assessment in Appendix 5 for the impact of subject transporter phenotype on elagolix exposure.

8. Mechanistic Safety Assessment

8.1 Study M12-661 (QT)

Title: Placebo- and Active-Controlled Crossover Study of the Potential for Cardiac Repolarization Effects After Single Doses of Elagolix in Healthy Premenopausal Adult Female Volunteers

The report for Study M12-661 was submitted to DBRUP under IND 64802 on July 8th, 2015 (SDN 339 in DARRTS under IND 64802). The Interdisciplinary Review Team for QT Studies (QT IRT) reviewed this report and concluded that no significant QTc prolongation effect of elagolix (300 mg and 1200 mg) was detected in this TQT study (**Table 8.1-1**)⁸.

Table 8.1-1. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Elagolix (300 mg and 1200 mg) and the Largest Lower Bound for Moxifloxacin 400 mg (QT IRT Analysis)

Treatment Group	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Elagolix of 300 mg	1.5	2.4	(0.4, 4.4)
Elagolix of 1200 mg	1	5.9	(4.0, 7.9)
Moxifloxacin 400 mg*	1	13.0	(11.0, 15.1)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 10.3 ms.

The PK and safety data were also reviewed by QT IRT and found acceptable. Thus, this study report is not assessed in current review. The PK data collected from Study M12-661 showed that $C_{\max}$ of elagolix increased ~10-fold and the AUC (AUC_t and AUC_{∞}) increased ~14-fold, on average, from the 300 to 1200 mg dose (**Figure 8.1-1** and **Table 8.1-2**). In the dose range of 300 – 1200 mg, single-dose PK showed a greater than dose proportional increase in $C_{\max}$ and AUCs. Combined with the single-dose PK results from Study M13-784 (600 mg and 900 mg) and the PK data collected on Day 1 in Study 12-790 (100 - 400 mg) (**Table 8.1-3**), this reviewer concluded that single-dose elagolix showed a more than dose-proportional PK from 200 mg to 1200 mg. The suprathreshold dose (1200 mg) produces a mean $C_{\max}$ value (13229 ng/mL) of ~17-fold the mean steady-state $C_{\max}$ at the therapeutic dose of 200 mg BID (774 ng/mL) and ~23-fold the mean steady-state $C_{\max}$ at the dose of 150 mg QD (574 ng/mL).

⁸ Interdisciplinary Review Team for QT Studies Consultation Report for IND 64802 by Dr. Moh Jee NG et. al. dated 09/23/2015

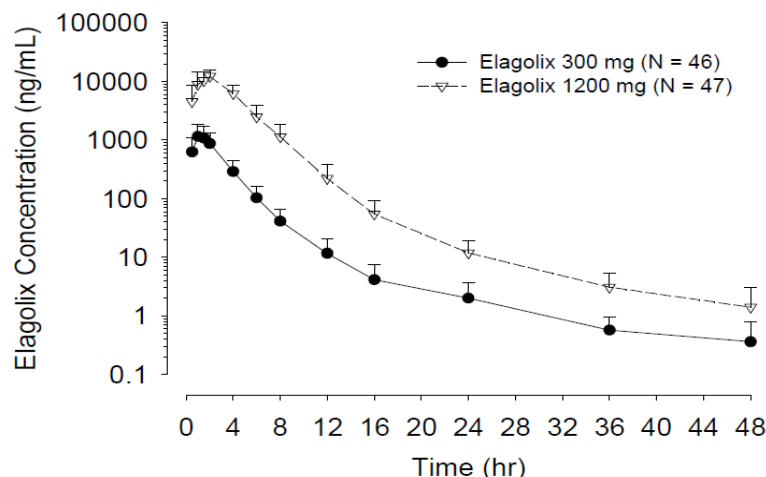


Figure 8.1-1. Mean + SD Elagolix Plasma Concentration-Time Profiles (Study M12-661)

Table 8.1-2. Mean ± SD Pharmacokinetic Parameters of Elagolix Following Administration of a Single Dose of 300 or 1200 mg Elagolix

Pharmacokinetic Parameters (units)		Regimens	
		C: Elagolix 300 mg (N = 46)	D: Elagolix 1200 mg (N = 47)
C_{max}	(ng/mL)	1356 ± 751	13229 ± 4218
T_{max}	(hr)	1.3 ± 0.4	1.7 ± 0.4
AUC_t	(ng•hr/mL)	3507 ± 1650	49055 ± 18409
AUC_{∞}	(ng•hr/mL)	3514 ± 1652	49070 ± 18414
$t_{1/2}^a$	(hr)	7.13 ± 3.65	6.06 ± 2.28
CL/F	(L/hr)	103 ± 43	29 ± 14
Vd_{β}/F	(L)	1267 ± 713	287 ± 170
$C_{max}/Dose$	(ng/mL)/mg	4.52 ± 2.50	11.02 ± 3.52
$AUC_t/Dose$	(ng•hr/mL)/mg	11.69 ± 5.50	40.88 ± 15.34
$AUC_{\infty}/Dose$	(ng•hr/mL)/mg	11.71 ± 5.51	40.89 ± 15.35

a. Harmonic mean ± pseudo-standard deviation.

Table 8.1-3. Pharmacokinetic Parameters of Elagolix Across Studies M12-790, M13-784, and M12-661

Pharmacokinetic Parameters (units)	Study M12-790 ^a		Study M13-784 ^b		Study M12-661 ^b		
	Elagolix 150 mg (N = 6)	Elagolix 300 mg (N = 8)	Elagolix 600 mg (N = 6)	Elagolix 900 mg (N = 6)	Elagolix 300 mg (N = 46)	Elagolix 1200 mg (N = 47)	
T_{max}	(hr)	1.3 ± 0.3	1.2 ± 0.4	1.4 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	1.7 ± 0.4
C_{max}	(ng/mL)	507 ± 207	1479 ± 740	5022 ± 3860	8992 ± 4901	1356 ± 751	13229 ± 4218
AUC_t^c	(ng•hr/mL)	1331 ± 487	3509 ± 1556	11590 ± 7786	28934 ± 20695	3507 ± 1650	49055 ± 18409
$C_{max}/Dose$	(ng/mL)/mg	3.38 ± 1.38	4.93 ± 2.47	8.37 ± 6.43	9.99 ± 5.45	4.52 ± 2.50	11.02 ± 3.52
$AUC_t/Dose$	(ng•hr/mL)/mg	8.87 ± 3.25	11.70 ± 5.19	19.32 ± 12.98	32.15 ± 22.99	11.69 ± 5.50	40.88 ± 15.34

a. Study M12-790 conducted in healthy adult premenopausal females: 150 mg QD and 300 mg BID, parameters from Study Day 1.

b. Studies M13-784 and M12-661 were single dose studies conducted in healthy adult premenopausal females.

c. AUC_t for Study M12-790; exposure over a 24-hour dosing interval for 150 mg QD and over a 12-hour dosing interval for 300 mg BID; AUC_t for Studies M13-784 and M12-661; exposure from time zero to the last measurable concentration.

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DA ZHANG
07/19/2018

FANG LI
07/19/2018

OLUSEYI A ADENIYI
07/19/2018

NAN ZHENG
07/19/2018

JINGYU YU
07/19/2018

CHRISTIAN GRIMSTEIN
07/19/2018

DOANH C TRAN
07/19/2018

GILBERT J BURCKART
07/19/2018

**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:	210450
Supporting document/s:	1 and 43
Applicant's letter date:	8-23-2017, 6-15-2018
CDER stamp date:	8-23-2017, 6-15-2018
Product:	Elagolix
Indication:	Endometriosis
Applicant:	Abbvie, Inc
Review Division:	Division of Bone, Reproductive, and Urologic Drugs
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Maria Wasilik, RPh

1 Executive Summary

1.1 Recommendations

The text for the PharmTox sections of the label as submitted by the sponsor in SDN43 (6-15-18) below is acceptable.

1.1.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited human data with the use of ORILISSA in pregnant women are insufficient to (b) (4) a drug-associated risk for major birth defects or miscarriage. Although (b) (4) cases of congenital malformations were reported in clinical trials with ORILISSA (b) (4) no pattern identified and miscarriages were reported similar (b) (4) the treatment group (b) (4) (*see Data*), use of ORILISSA is contraindicated in pregnant women. Discontinue ORILISSA 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 20 times the maximum recommended human dose (MRHD). Spontaneous abortion and total litter loss was observed in rabbits at doses 7 and 12 times the MRHD. There were no structural abnormalities in the fetuses at exposures up to 40 and 12 times the MRHD for the rat and rabbit, respectively (*see Data*).

The background risk for major birth defects and miscarriage in the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

In clinical studies of more than 3,500 women (of whom more than 2,000 had endometriosis) treated with ORILISSA for up to 12 months, 49 pregnancies (b) (4) while receiving ORILISSA (b) (4) or within 30 days after stopping ORILISSA (b) (4). Among these 49 pregnancies, 2

major congenital malformations were reported. In one case of infant cleft palate, the mother was treated with ORILISSA 150 mg daily and the estimated fetal exposure to ORILISSA was the first 30 days of pregnancy. In one case of infant tracheoesophageal fistula, the mother was treated with ORILISSA 150 mg daily and the estimated fetal exposure to ORILISSA was the first 15 days of pregnancy.

In addition, among these 49 pregnancies, there were 5 cases of spontaneous abortion (miscarriage) compared to 5 cases among the 20 pregnancies that occurred in more than 1100 women treated with placebo. Although the duration of fetal exposure was limited in ORILISSA clinical trials, there were no apparent decreases in birth weights associated with ORILISSA (b) (4) in comparison to placebo.

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 6 deaths and decreases in body weight gain and food consumption. Increased post implantation losses were present in the mid dose group, which was 20 times the MRHD based on AUC. In rabbits, three abortions and a single total litter loss were observed at the highest, maternally toxic dose, which was 12 times the MRHD based on AUC. A single total litter loss occurred at a lower non-maternally toxic dose of 150 mg/kg/day, which was 7 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 40 and 12 times the MRHD for the rat and rabbit, respectively. However, because elagolix binds (b) (4) poorly to the rat GnRH receptor (~1000 fold less than to the human GnRH receptor), the rat study is (b) (4) pharmacologically mediated effects of elagolix on embryofetal development. The rat study (b) (4) provide information for potential non-target-related effects of elagolix (b) (4)

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 only 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 end-points were unaffected.

Maternal plasma concentrations on lactation day 21 at 100 and 300 mg/kg/day (47^(b)₍₄₎ and 125 ng/mL), which were 0.06-fold and 0.16-fold the human C_{max} at the MRHD. Because the exposures were much lower than the human MRHD, this study ^(b)₍₄₎ humans.

8.2 Lactation

Risk Summary

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. There are no adequate animal data on the excretion of ORILISSA in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORILISSA and any potential adverse effects on the breastfed child from ORILISSA.

Data

There are no adequate animal data on excretion of ORILISSA in milk.

8.3 Females and Males of Reproductive Potential

Based on mechanism of action, there is a ^(b)₍₄₎ risk of early pregnancy loss if ORILISSA 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 ORILISSA. Pregnancy testing ^(b)₍₄₎ if pregnancy is suspected during treatment with ORILISSA [see *Warnings and Precautions (5.3)*].

Contraception

Advise women to use effective non-hormonal ^(b)₍₄₎ during treatment with ORILISSA and for one week after discontinuing ORILISSA. [see *Warnings and Precautions (5.2) and Drug Interactions (7.3)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ORILISSA is (b) (4) GnRH receptor antagonist that (b) (4) endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of ORILISSA results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, leading to decreased blood (b) (4) of the ovarian sex hormones, estradiol and progesterone. (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) by the dietary route (b) (4) revealed no increase in tumors in mice at up to 19-fold the maximum recommended human dose (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 (12 to 13-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). (b) (4) AUC at the MRHD, the exposure multiple for women (b) (4) the highest dose of 300 mg/kg/day in female rats is approximately 5-fold. However, because elagolix has low affinity for the GnRH receptor in the rat [*see Section 8.1*], and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

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LESLIE C MCKINNEY
07/02/2018

KIMBERLY P HATFIELD
07/03/2018

I concur with Dr. McKinney's review, and sign on behalf of Dr. Mukesh Summan.

Post Marketing Commitment Protocol Memo

NDA#	NDA 210450
Protocol #	M18-969
Applicant	AbbVie
Drug	Elagolix
To be Approved Indication	Treatment of endometriosis with moderate to severe pain
Date Protocol Submitted	April 10, 2018
Subject:	PMC Safety and Efficacy of Elagolix in combination with COCs

Background:

Elagolix is a non-peptide gonadotropin-releasing hormone (GnRH). If approved, elagolix will have the indication for treatment of endometriosis with moderate to severe pain based on pivotal trials showing reduction in dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP). The mechanism of action is presumed to be a decrease in estradiol levels. However, suppression of estradiol is incomplete and reduction in the estradiol level does not appear to fully prevent pregnancy. As observed in the clinical data submitted to the NDA, 49 pregnancies have occurred with elagolix use.

During the pivotal trials, hormonal contraception was not allowed. Because women with endometriosis are women of reproductive age and elagolix does not fully prevent pregnancy, the use of a highly effective contraceptive method with elagolix would provide both contraception and treatment of endometriosis-associated pain (EAP).

Use of combination oral contraceptives (COC) may increase the estradiol level, thus decreasing the efficacy of elagolix on treatment of EAP. Conversely, elagolix may affect the efficacy of COCs to prevent pregnancy. Given the target population in whom elagolix is indicated, additional information on how the co-administration of elagolix and COC impacts efficacy of both regimens is needed for providers and patients to make informed treatment decision. The proposed PMC is designed to address both issues of efficacy.

Protocol Review:



(b) (4)

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05/21/2018

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210450
Supporting document/s:	1
Applicant's letter date:	8-23-2017
CDER stamp date:	8-23-2017
Product:	Elagolix
Indication:	Endometriosis
Applicant:	Abbvie, Inc
Review Division:	Bone, Reproductive, and Urologic Products
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Maria Wasilik, RPh

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 210450 are owned by Abbvie, Inc. or are data for which Abbvie has obtained a written right of reference. Any information or data necessary for approval of 210450 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, Inc. 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 210450.

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a PharmTox perspective, the application is approvable.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

Labeling will be addressed in a separate review.

1.2 Brief Discussion of Nonclinical Findings

Proposed clinical use:

The proposed dosing for elagolix is 150 mg QD or 200 mg BID in women with endometriosis. As of this writing, the proposed maximum duration of use for the high dose is (b) (4), but may be further restricted by the clinical team to 6 months. For purposes of calculating multiples of exposure (MOEs) compared to the maximum recommended human dose (MRHD), the human C_{max} value used is for a single 200 mg dose: 774 ng/mL (1.2 uM). The human AUC for a single 200 mg dose is 1725 ng.hr/mL. This value is doubled to reflect the BID dosing and to give the approximate exposure over 24 hrs: 3450 ng.hr/mL (5.5 uM.hr), which is the value used for comparison to daily animal dosing.

Characterization of the drug substance: Impurities

The elagolix drug substance has a very large number of impurities that have structural alerts for genotoxicity, which led to an extensive program of impurity testing (reviewed under IND 64802; see reviews dated 11/22/2017 and 12/19/2017 by this reviewer). Some compounds were tested using a non-standard 6-well Ames format that was deemed acceptable. During review, particular attention was paid by this reviewer to verifying that testing was sufficient to rule out false negatives. Consultation with the CMC reviewer verified that (b) (4) impurities are controlled to appropriate levels. Qualification of specified impurities was achieved in repeat-dose tox studies, and in a special 6-week dietary study in the rat using spiked feed.

Adequacy of the nonclinical development program:

The pharmacology and toxicology of elagolix was characterized in a standard full nonclinical development program. The pivotal safety pharmacology and repeat dose tox studies were conducted in rat and dog. Reprotox studies were conducted in rat and rabbit, and standard 2 year carcinogenicity studies were conducted in mouse and rat.

Pharmacology:

The mechanism of action of elagolix is antagonism at the GnRH receptor. Elagolix binds reversibly with very high affinity to the human GnRH receptor (K_d = 54 pM) and inhibited GnRH action in vitro in functional assays with K_i values in the low nM range (1.5, 2.8 nM). The rank order of binding across species is: human > monkey ~ rabbit >>> rat. There were no binding studies conducted against the dog GnRH receptor. Functional assays demonstrated activity at the rabbit, monkey, and human GnRH receptors.

Binding of elagolix to the GnRH receptor suppresses LH and FSH secretion and subsequently reduces production of sex steroid production by the ovaries or testes. Pain associated with endometriosis is ameliorated in women by reduced proliferation of endometrial tissue subsequent to lowering circulating estrogens.

Efficacy of elagolix was not assessed in nonclinical species for several reasons:

- (1) there are no animal models of endometriosis
- (2) binding of elagolix to the GnRH receptor in nonclinical species was weak (rat, rabbit) or not characterized (dog, mouse)
- (3) sufficient exposure could not be achieved with repeat dosing (monkey)

Receptor-mediated pharmacological effects were largely absent in nonclinical species. These included (when they were measured) reductions in LH, FSH, estrogen or testosterone, or changes in reproductive organs that would be expected from prolonged reductions in sex steroids. The clinical endpoint of bone mineral density was not measured in any nonclinical species. It should be kept in mind that toxicity that might result from prolonged reduction of sex steroids could not be reliably assessed in nonclinical studies for this drug due to low affinity of elagolix at the GnRH receptor in the nonclinical species and thus a lack of receptor-mediated pharmacological effects. However, the pivotal nonclinical studies are deemed sufficient to evaluate non-receptor-mediated or off-target effects of elagolix treatment.

There were no findings in a screen of 100 receptors for off-target binding of elagolix.

Safety pharmacology studies were conducted in rat and monkey at adequate multiples of exposure (>20) and were negative. In agreement with nonclinical findings, a clinical thorough QT study was negative for arrhythmia risk.

ADME:

The pharmacokinetics of elagolix were determined in CD-1 mice, SD rats, Beagle dogs and cynomolgus monkeys. In vivo absorption, distribution, metabolism and excretion (ADME) studies were conducted in rat and dog with radiolabeled compound and compared to absorption, metabolism and excretion studies conducted with [¹⁴C]elagolix in humans.

The pharmacokinetic profile of elagolix was generally characterized by rapid absorption, high plasma clearance, moderate volumes of distribution and a short elimination half-life in mouse, dog and monkey. Bioavailability ranged from ~10% (mouse and monkey) to 100% (dog). Human and rat had similar bioavailability (~50%). Protein binding ranged from 78-90% across species.

Distribution after oral dosing was primarily to the GI tract. Elagolix did not cross the blood brain barrier, did not accumulate in pigmented tissue, and did not partition into red blood cells. It did, however, freely cross the placenta (assessed in the rat).

Elagolix is not extensively metabolized, circulating primarily as unchanged drug in plasma and remaining largely intact through clearance. Metabolic pathways were similar across species (including humans). There were no major metabolites in any species (although M14 and M15 were borderline major in the rat), and no unique human metabolites. Importantly, there were six active metabolites. The two most significant were NBI-61962 (M3), the O-desmethyl metabolite, and NBI-54058 (M6x), the N-dealkylated metabolite. M3 has a binding affinity comparable to elagolix, and M6X has a 6-fold *higher* affinity. These

metabolites were monitored throughout the nonclinical development program and were verified to remain below 10% of parent across species.

Clearance of elagolix was primarily via the fecal route. Excretion into milk was not determined.

In vitro and in vivo studies demonstrated the following potentially clinically relevant interactions of elagolix with metabolizing enzymes and drug transporters: elagolix is a substrate for CYP3A, Pgp and OATP1B1, a weak to moderate inducer of CYP3A and 2B6, and an inhibitor of Pgp and OATP1B1 and 1B3.

In vitro metabolism studies were conducted with the two active metabolites, M3 (NBI-61692) and M6x (NBI-54048). The most significant potential effect was inhibition of CYP3A4/5, 2C9, and 2C19 by M6x. However, concentrations of this metabolite would have to reach micromolar levels for inhibition to become significant, which is not clinically relevant.

Toxicokinetics of elagolix were similar in mouse, rat, dog, and human. Exposure was proportional or somewhat greater than proportional to dose, there were no strong gender differences, and there was no evidence of accumulation. Toxicokinetics were strikingly different in rabbit and monkey. In the rabbit, repeat dosing in the dose range of <300 mg/kg led to dramatic increases in exposure that were not associated with accumulation. In the monkey, repeat dosing led to a dramatic reduction in exposure that was unexplained.

Toxicology:

Single and repeat-dose toxicology studies were conducted in mouse, rat, rabbit, dog, and monkey. The SD rat and Beagle dog were chosen for the pivotal repeat-dose toxicology studies based on the ability to achieve higher systemic exposures when compared to mouse and monkey. However, as was previously discussed, affinity of elagolix for the rat GnRH receptor was poor (~1000-fold less compared to human), and receptor affinity in the dog was not measured.

In the rat, elagolix would have to reach free concentrations in the range of 12 uM (C_{max} = 7740 ng/mL) to fully inhibit the GnRH receptor. The highest plasma concentration (C_{max}) seen in the rat was at a single dose of 2000 mg/kg (~60 uM or ~6 uM free). For that reason, the toxicities revealed in the rat pivotal studies should generally be interpreted as being non-receptor-mediated. The toxicities revealed in the dog pivotal studies, given the absence and/or lack of characterization of expected pharmacodynamic effects, should also be interpreted as possibly being non-receptor mediated.

Single dose studies:

Single dose toxicity studies were conducted in rat and monkey at the same doses: 300, 600, 1200, or 2000 mg/kg, with ~4-fold higher exposures achieved in the monkey than the rat per unit dose. NOAELs were 300 mg/kg for both species, but MTDs diverged, being set at the low dose for the monkey and the high dose for the rat.

Repeat-dose studies:

A significant feature of the repeat-dose studies that complicated interpretation of the results was mortality that was apparently related to the drug formulation and not the toxicity of elagolix itself. In the rat 2-week study, there was ~50% mortality at the high dose (1200 mg/kg/d) that was attributed to gavage error or aspiration of the dose that resulted in ulcerative tracheitis/ bronchitis. The subsequent repeat-dose studies (6, 13, and 26-week) reduced the high dose to 600 mg/kg/d but still had significant dose-related mortality

(sometimes >50% at the high dose). The main clinical sign was respiratory distress with confirmatory histological findings in the trachea and bronchii.

In the dog, mortality associated with dosing error/aspiration of test article was observed in both the 6-week (high dose 300 mg/kg/d) and 26-week (high dose 150 mg/kg/d) studies, and led the sponsor to reformulate the drug as a capsule for 9-month study. In that study, a high dose of 150 mg/kg/d was administered without mortality.

If it is accepted that mortality in the repeat-dose studies was likely due to aspiration leading to respiratory toxicity, the overall toxicity profile of elagolix is fairly benign and is summarized below by species.

RAT:

In the rat, the highest dose administered in the 6, 13, and 26-week studies was 600 mg/kg/d. The NOAEL decreased with increasing duration in each study, from 600 to 300 to 100 mg/kg/d; exposures corresponded to 19, 11, and 2-fold the MRHD, respectively. There were no new toxicities in the 26-week studies that had not appeared in the shorter duration studies. In fact, liver toxicity, which manifested in the 13-week study as increased liver weight (up to 45%), mild hepatocellular hypertrophy, and elevated enzymes (<3-fold) at the high dose, were not reported in the 26-week study. Inconsistent changes in adrenal weights in the shorter duration studies were not repeated in the 26-week studies. Elevations in platelets and reticulocytes observed in shorter duration studies were also not observed in the 26-week study.

Estradiol and testosterone levels were assessed in the 6-week study and, unsurprisingly, were found to be highly variable. For that reason, the sponsor did not attempt to draw any conclusions about the effect of elagolix on sex hormone levels in the rat.

Studies by the dietary route were conducted at 6, 15, and 28 week durations. These studies were conducted to qualify impurities, determine dose-ranging for carcinogenicity studies, and bridge from the liquid formulation. The highest dose administered in these studies was 800 mg/kg/d. As expected, exposures by the dietary route were less than by oral gavage for a given dose. However, maximum exposures still reached ~9-fold the human MRHD.

A unique adverse finding in the 28-week dietary study was reported: focal degeneration / necrosis localized to the limiting ridge of the glandular stomach at both of the test doses (600 and 800 mg/kg/d). Erosion, inflammation, ulceration, and hyperplasia were noted, and it was suggested that this finding might explain hematology findings of minimally lower Hb and Hct, and mildly elevated white blood cell counts. In the 2-year carcinogenicity study (top dose 800 mg/kg/d), dose-dependent erosion and hyperkeratosis were noted in the stomach. The limiting ridge is a structure unique to the rat, and microscopic findings in the stomach were not noted in other species. Relevance to human is therefore low.

DOG:

In the dog, the highest dose administered in the 6 and 26 week studies by gavage was 300 mg/kg/d, and the NOAELs were similar: 50, and 75 mg/kg/d, respectively. Exposures were higher than in the rat per unit dose, and reached an MOE of 23 based on AUC at the higher NOAEL. However, continuing problems with aspiration of the liquid formulation led to the sponsor to reformulate elagolix as a capsule for the pivotal 9-month study. The NOAEL in the longer duration study was 30 mg/kg/d (MOE = 8).

The pattern of toxicity in the dog was similar to the rat. Body weights were reduced ~20% for both males and females at the high dose. There were reactive changes in the liver that

were reflected in elevated ALP (7.5-fold max) and increased organ weight. There were mild reductions in Hb and Hct and slight elevations in white blood cells. Relative spleen weight was reduced, but there were no corresponding histological findings. There was gall bladder irritation at the high dose that recovered.

The only pharmacodynamic signal in the dog was reduced prostate weight in the 9-month study (up to 56% at the high dose that did not recover). Estradiol and testosterone levels were assessed in the 6 and 26-week studies, and no treatment-related effects were noted. Testosterone values were highly variable.

MONKEY:

Use of the monkey as a nonclinical model for the action of elagolix was limited due to unusual toxicokinetics in this species. Repeat-dosing in the monkey led to a very rapid reduction in exposure, the cause of which was not explained by the sponsor. Two, 6, and 13-week studies were conducted in the monkey using the liquid formulation by oral gavage. The NOAEL for all three studies was the same: 300 mg/kg/d. MOEs were calculated based on exposure at day 1, since exposure fell off by ~50% within 2 weeks of dosing and continued to fall. At the NOAEL, the highest MOE based on AUC was 49.

Findings included modestly increased liver and kidney weights that did not have corresponding histology, were reversible, and so were considered reactive and not adverse. At the highest dose tested (600 mg/kg/d), the thymus showed involution and atrophy. An ECG study was conducted in the 13-week study that was negative, but this finding is not useful since it was conducted at the end of the study when exposures were low.

There was a pharmacodynamic signal of atrophy in the uterus, cervix, and vagina in the 6-week study. No effects were noted in sex organs of the males, but the sponsor considered the male animals to be sexually immature. Estradiol and testosterone levels were assessed and found to be highly variable. For that reason, the sponsor did not attempt to draw any conclusions about the effect of elagolix on sex hormone levels in the monkey.

Genotoxicity / Carcinogenicity:

Elagolix was found not genotoxic by the standard battery of in vitro and in vivo genotoxicity tests. Carcinogenicity was evaluated in 2-year studies in the mouse and rat by the dietary route. Elagolix was found not carcinogenic in the mouse. In the rat, liver and thyroid neoplasms were observed that were deemed species specific. The potential for carcinogenic risk in humans is thus deemed to be negligible.

Reproductive toxicity:

Fertility and early embryonic development was evaluated in the rat at doses of 30, 150, and 300 mg/kg/d. There was mortality in this study that followed the pattern of the repeat dose toxicity studies, that is, with signs of aspiration and respiratory distress. Treatment with elagolix had no effect on reproductive parameters (estrous cycle, reproductive performance, sperm count, sperm motility, pregnancy rate, mating behavior) or observations at Cesarean section related to implantation or embryo-fetal viability. However, as discussed above, these negative findings are likely due to the low affinity of elagolix for the rat GnRH receptor.

The NOAEL for maternal and paternal effects was 50 mg/kg/day and the NOEL for reproductive performance, fertility, and embryo/fetal viability was $\geq$ 300 mg/kg/d. With respect to the AUC at the MRHD, the exposure multiple for women based on the AUC at the NOEL of 300 mg/kg/day for the fertility effects in the female rat is ~4.6-fold. However, the

sponsor calculated that, when adjusted for the difference in affinity of elagolix for the rat and human GnRH receptor, this exposure multiple translates to 0.007-fold. Thus, this fertility study is not informative for human risk arising from intended or exaggerated pharmacology.

Teratogenicity of elagolix was evaluated in the rat and the rabbit. There was a striking difference between the rat and the rabbit in the ability to tolerate dosing, possibly due to the large difference in affinity of elagolix for the rat vs the rabbit GnRH receptor (low vs. moderate), and/or possibly due to a striking increase in exposure that occurred in the rabbit with repeat dosing. In both rat and rabbit, dose range finding studies were conducted using the liquid formulation by oral gavage to establish the doses for the definitive study. Rats were dosed from GD6-GD17 up to 1200 mg/kg/d and rabbits were dosed from GD7-GD20 up to 600 mg/kg/d. Pregnant rat dams tolerated dosing well but pregnant rabbit dams did not; there was a high rate of mortality and abortion which led to a low and very limited dose range being set for the definitive study.

In the rat, an embryofetal development (EFD) study was successfully completed using doses of 300, 600, and 1200 mg/kg/d. The NOEL for both maternal toxicity and fetal viability and growth was set at the low dose, based on unscheduled deaths in the dams (likely due to aspiration of the test article) and decreased fetal weight and increased post-implantation loss (likely due to reduced feed consumption and body weight loss in the dams). There were no treatment-related external, visceral, or skeletal findings, so the NOAEL for fetal teratogenicity was set at the high dose. Elagolix was shown in distribution studies to freely cross the placental barrier, so it can be assumed that fetuses were fully exposed to the drug. This study was useful for evaluating teratogenicity of elagolix to the developing fetus that was independent of changes in estrogen or progesterone. Using rat AUC values obtained on GD17 compared to the AUC at the MRHD of 3.5 ug.hr/mL, at 300 mg/kg/day, the MOE is 6.5 and at 1200 mg/kg/day, the MOE is 39.4.

In the rabbit, the definitive EFD study was conducted at lower doses than in the rat, and was conducted over a very limited dose range (100, 150, and 200 mg/kg/d). Exposures at the high dose in this study were roughly comparable to exposures at the low dose in the rat EFD study. There was significant maternal and fetal toxicity at the high dose, as reflected in mortality, abortion, and reduced fetal weight. The NOAEL for maternal toxicity was thus set at the mid dose (MOE = 6.6). One mid-dose and one high-dose dam had litters with no viable fetuses, which resulted in an increase in post-implantation loss at those two doses. Based on these findings plus reduced fetal weight, the NOEL for embryofetal toxicity was considered by the reviewer to be the low dose (MOE = 2.7). Fetal external, visceral, and skeletal examinations were negative, indicating no teratogenic effects of elagolix. The NOEL for teratogenicity was set at the high dose (MOE = 11.6).

Taken together, the results from the rat and rabbit EFD studies are informative for human teratogenic risk. Exposures were achieved that were greater than the exposures expected at the MRHD and because elagolix crosses the placental barrier, fetuses can assume to have been exposed. Elagolix was found negative for teratogenicity in both species.

However, the EFD studies are less informative for risk of early pregnancy loss in humans. In the rat, hormones necessary for maintenance of pregnancy were likely not affected, so the lack of effect of elagolix on litter viability does not translate to the human. In the rabbit, the species that is more sensitive to the pharmacological action of elagolix, it was concerning that there were single instances of total litter loss at both the mid and high doses. The sponsor has recognized that an effect of elagolix on pregnancy maintenance in the human cannot be ruled out, and appropriately contraindicates its use during pregnancy.

Lastly, a pre- and post-natal development study was conducted in the rat, using the dietary route of administration. Only two, relatively low doses were assessed: 100 and 300 mg/kg/d. Dams were dosed from gestation day 2 (GD2) through lactation day 20 (LD20). Steady state plasma concentrations measured in dams on LD21 were roughly 10-fold lower than Cmax concentrations via oral gavage at the same doses. There were minimal findings. The NOAEL for F1 neonatal/early postnatal toxicity/developmental toxicity was 100 mg/kg/d and the NOAEL for toxicity for F1 post-weaning/reproductive toxicity and F2 neonatal/early postnatal toxicity was 300 mg/kg/d. Because AUC data were not generated, calculation of the safety margins could not be made.

Conclusion:

Elagolix has been thoroughly evaluated in a full set of nonclinical toxicity studies. Based on in vitro and in vivo animal data, the safety profile of elagolix does not raise concerns for administration to women at the proposed doses and durations. Appropriate labeling to inform pregnancy risk will be included in labeling. From a PharmTox perspective, elagolix is approvable.

2 Drug Information

2.1 Drug

- 2.1.1 CAS Registry Number** 832720-36-2
- 2.1.2 Generic Name** Elagolix Sodium
- 2.1.3 Code Name** NBI-56418 Sodium; ABT-620; A-1278823.5
- 2.1.4 Chemical Name**

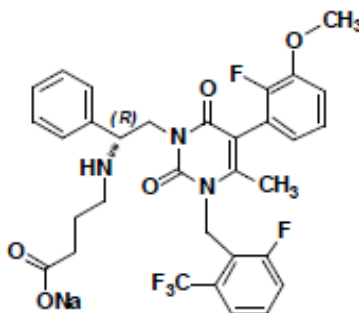
Sodium R-(+)-4-{2-[5-(2-Fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino}-butyrate

2.1.5 Molecular Formula/Molecular Weight

C₃₂H₂₉F₅N₃O₅ • Na / 653.57 (salt); 631.59 (acid)

(b) (4)

2.1.6 Structure



Elagolix contains one chiral center (b) (4). It is an amphoteric molecule, with low to moderate lipophilicity (LogP 1.34, LogD_{pH7.3} 1.23). Apparent permeability across cultured cell monolayers ranged from 0.5 – 2.8 10⁻⁶ cm/sec, indicating low to moderate in vitro permeability.

The acid association constants are pKa(1) 4.0 (carboxylic acid) and pKa(2) 7.9 (secondary amine); the molecule is zwitterionic between pH 4.0 and 7.9.

The aqueous solubility is high at pH values below pKa(1) and above pKa(2), with lower values between the two pKa values. At 37°C, the aqueous solubility of the amorphous zwitterion was 33.4 mg/mL (51 mM) at pH 1.8 and ~1 mg/mL (~1.5 mM) at pH values from 3.9-6.8. The solubility of the amorphous sodium salt was >170 mg/mL (> 260 mM) in water.

2.1.7 Pharmacologic class

GnRH antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s

INDs 64802, (b) (4) (All from Abbvie, Inc)

Other approved GnRH antagonists: abarelix (NDA 21320), cetrorelix (NDA 21197), degarelix (NDA 22201), ganirelix (NDA 21057).
Not all are marketed in the US.

In development: relugolix (TAK-385), KLH-2109, ASP-1707.

2.3 Clinical Formulation

2.3.1 Drug Formulation

Elagolix tablets are immediate release tablets containing 150 or 200 mg elagolix (b) (4) per tablet.

			Dosage Strength	
			150 mg	200 mg
Component	Quality Standard	Function	Amount (mg)/Tablet	
(b) (4)				
Elagolix Sodium	In-house standard	Drug Substance	155.2	207.0
Mannitol	USP/Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Pregelatinized Starch	NF			
Povidone (b) (4)	USP/Ph. Eur.			
Sodium Carbonate Monohydrate	NF/Ph. Eur.			
Magnesium Stearate	NF/Ph. Eur.			
(b) (4)				
Film-Coating (b) (4)	In house standard	Film Coat	(b) (4)	-
Film-Coating (b) (4)	In house standard	Film Coat	-	(b) (4)
(b) (4)				
Coated Tablet Weight			468.0	624.0

(b) (4)

Component	Quality Standard	Amount per Tablet (mg) in:	
		150 mg Tablet	
Polyvinyl Alcohol	USP/Ph. Eur./EC	(b) (4)	
Titanium Dioxide	USP/Ph. Eur./CFR/EC		
Polyethylene glycol (b) (4)	NF/Ph. Eur./CFR/EC		
Talc	USP/Ph. Eur./CFR/EC		
Carmin High Tint	CFR/EC		

Component	Quality Standard	(b) (4)	
		Amount per Tablet (mg) in:	
		200 mg Tablet	
Polyvinyl Alcohol	USP/Ph. Eur./EC	(b) (4)	(b) (4)
Titanium Dioxide	USP/Ph. Eur./CFR/EC	(b) (4)	(b) (4)
Polyethylene glycol (b) (4)	NF/Ph. Eur./CFR/EC	(b) (4)	(b) (4)
Talc	USP/Ph. Eur./CFR/EC	(b) (4)	(b) (4)
Iron Oxide Red	NF/CFR/EC	(b) (4)	(b) (4)

2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants of Concern

Elagolix has 95 named impurities: 15 are specified and 11 are unspecified in the final drug product (see tables below and Appendix 1). A large number of these impurities had structural alerts for genotoxicity and underwent further testing. After Ames testing, most were identified as (b) (4) impurities (see table below). A detailed review of the Ames tests for the various impurities was submitted to IND 64802 on 11-22-2017.



(b) (4)

2.4 Proposed Clinical Population and Dosing Regimen

Clinical population: (b) (4) women with endometriosis

Dosing regimen: 150 mg QD or 200 mg BID. The 150 mg QD dose was selected to partially suppress estradiol to elicit a response on pain measures with minimal generation of hypoestrogenic sequelae. Because some patients with more established and intractable pain could require a higher dose, elagolix 200 mg BID was selected as it provides nearly full estradiol suppression. Pending a final decision by the clinical team for review of the NDA, maximum duration of use will be set at (b) (4) months for the 150 mg dose, and 6 months for the 200 mg dose.

2.5 Regulatory Background

IND 64802 was opened by Neurocrine Biosciences Inc. (NBI) in July 2003.

IND 64802 was transferred from NBI to AbbVie (formerly Abbott Laboratories) in June 2010.

The nonclinical reviewer for this IND was Krishan Raheja from 2003 until 3-28-2016 when it was transferred to this reviewer.

3 Studies Submitted

Nearly all of the studies submitted to IND 64802 were also submitted to NDA 210450. In a few cases, studies were redone with improved methodologies.

3.1 Studies Reviewed

The following studies were reviewed by this reviewer: Pharmacology (primary, secondary, and safety), pharmacokinetics (ADME), single-dose toxicity (rat and monkey), repeat-dose toxicity (rat - 2, 6, and 26 week oral; rat - 6, 15, and 28 week dietary; dog - 6, 26, and 9 month oral; monkey - 2, 6, and 13 week oral), genotoxicity (including genotoxicity testing for impurities), carcinogenicity, and reproductive toxicity.

3.2 Studies Not Reviewed

Analytical methods and validation (4.2.2.1), and environmental studies (4.2.3.7.7).

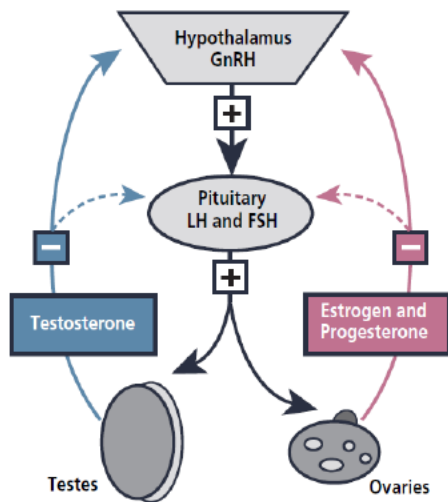
3.3 Previous Reviews Referenced

Approximately two dozen reviews and memos were filed by Dr. Krishan Raheja between 2004 and 2014 for IND 64802. In some cases, relevant text from Dr. Raheja's reviews has been included in this review without attribution.

4 Pharmacology

4.1 Primary Pharmacology

Gonadotropin-releasing hormone (GnRH) is a decapeptide that controls the synthesis and release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior lobe of the pituitary gland. GnRH receptor antagonists cause an immediate suppression of LH and FSH secretion. Elagolix is an orally administered non-peptide small molecule GnRH antagonist.

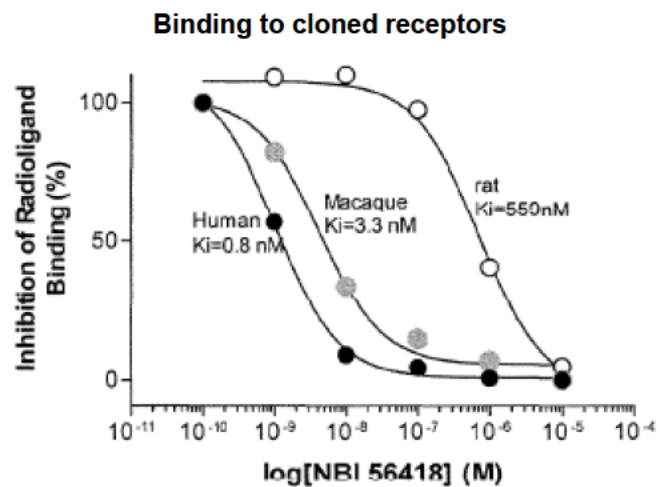


The expected pharmacodynamic effects of using a GnRH antagonist result from reduced levels of the sex hormones estrogen, progesterone, and testosterone, and are well understood for this class of drug. The sponsor did not conduct pharmacology studies to specifically characterize the effect of elagolix on levels of sex hormones in animal studies, but did characterize some of these parameters in the repeat-dose toxicology studies.

Figure credit: Colameco and Coren, 2009

4.1.1 Mechanism of action

Elagolix binds reversibly with high affinity to the human GnRH receptor. It is a potent antagonist of the mammalian GnRH receptor with a rank order of affinity as follows: human > monkey ~ rabbit >>> rat. The structural basis of the differences in affinity between human, rat, and monkey have been characterized (Reinhart et al., 2004). There were no binding studies conducted against the dog GnRH receptor. Functional assays demonstrated activity at the rabbit, monkey, and human GnRH receptors.



Species	Kd (nM) Equilibrium binding	Ki (nM) Pituitary membrane binding	Ki (nM) Cloned receptor membrane binding	IC ₅₀ (nM) Cloned receptor function IP production	IC ₅₀ (nM) Cloned receptor function Ca ⁺⁺ flux
Rat	-	566	1046 / 4400	-	-
Rabbit	-	3.3	44.5	342	-
Monkey	0.39	-	3.0 / 3.5	50	-
Human	0.054	-	0.87 / 0.9	1.5	2.8

Active metabolites – binding to the GnRH receptor and functional activity:

Study #s RD101256, 101259, and 11229

The pharmacological activity of a number of elagolix metabolites was characterized in *in vitro* binding assays (cloned receptor membrane binding). Metabolites NBI-61962 (O-demethyl) (M3) and (b) (4) had less affinity for the GnRH receptor compared to elagolix while the N-dealkyl metabolite NBI-54048 (M6x) showed *higher* affinity for the human GnRH receptor than elagolix. However, these metabolites are not expected to affect the pharmacodynamics of elagolix since they are produced at low levels in humans. Mean human C_{max} and AUC values for the M3 and M6x metabolites were approximately 1.7% and 2.4% and 0.6% and 3.3%, respectively (see sponsor's section 2.7.2.2.1 Table 3 p 15).

NBI 61962 primary metabolite M3 present in human, dog, rat
(b) (4) degradation product and possible metabolite

NBI 54048 minor metabolite: N-dealkylated metabolite M6x present in human, dog and rat
equilibrium binding K_d 0.009 nM is 6-fold higher affinity than elagolix (RD101259)

NBI 56408 possible metabolite not detected *in vivo*
(b) (4) degradation product (b) (4) present in human, dog, rat
(b) (4) enantiomer of parent

Cloned receptor membrane binding - metabolites

Species	61962 M3 Ki (nM)	(b) (4) 54048 M6x Ki (nM)	56408 Ki (nM)	(b) (4)
Rat	2441.7 / 5000	1400	3000	
Rabbit	--	--	--	
Monkey	82.1 / 41	0.06	1.1	
Human	5.4 / 3.5	<0.013	1.3	

Reviewer's table constructed from data in Study #s RD101256, 101259, and 11229

The functional efficacy of the compounds was determined by ability to inhibit GnRH stimulated accumulation of IP₃ (inositol phosphate) in RBL-1 cells stably expressing human, monkey or rat GnRH receptors.

The compounds were functional antagonists against each of the receptors with potencies generally corresponding to their *in vitro* binding affinities.

Functional activity - metabolites

Species	61962 M3 IC ₅₀ (nM)	(b) (4) 54048 M6x IC ₅₀ (nM)	5640 IC ₅₀ (nM)	(b) (4)
Rat	2500	270	2800	
Rabbit	--	--	--	
Monkey	690	2.0	83	
Human	14	0.8	3.3	

Reviewer's table constructed from data in Study #s RD101256, 101259, and 11229

Effect of metabolites on safety pharmacology: NBI 61962 (M3)

Functional activity analysis of the rat sodium channel and human potassium channel (hERG) shows that NBI 61962 did not significantly inhibit at up to 10 μM.

4.1.2 Drug mechanism related to indication

Because endometriosis is predominantly estrogen-dependent, with estrogen driving proliferation of endometrial tissue growth outside of the uterus, suppression of estrogen production by GnRH antagonists such as elagolix leads to suppression of the symptoms of endometriosis.

Because there are no animal models of endometriosis, there were no mechanistic studies conducted that could be extrapolated to humans. Pharmacodynamic effects of elagolix on plasma hormone levels were assessed in some of the repeat-dose toxicology studies. Importantly, bone parameters were not monitored in any of the long duration repeat-dose studies.

4.2 Secondary Pharmacology

Of the 100 receptor sites examined no activity was found with greater than 50% inhibition of binding of the cognate ligand or enzymatic activity at concentrations of 10 μ M.

Functional activity analysis of the rat sodium channel and human potassium channel (hERG) shows that elagolix does not inhibit at any concentration tested up to a maximum of 10 μ M.

Suppression of estrogen leads to bone loss in humans. Bone loss was not evaluated in any of the nonclinical studies.

4.3 Safety Pharmacology

CNS

Neurobehavioral testing: RD101073. GLP + QA. 2004. Lot #1675644.

The neurobehavioral responses to orally administered elagolix were evaluated in a rat modified Irwin assay (functional observational battery) that was conducted doses of 30, 300 or 1200 mg/kg (n = 10/sex/dose). Satellite groups of 6/sex/dose were used for TK.

There were no treatment-related effects. NOAEL = 1200 mg/kg. Systemic exposure at this dose level in the rat as measured by C_{max} and AUC₍₀₋₂₄₎ was 10.5 μ g/mL and 133 μ g $\cdot$ h/mL, respectively in the male, and 31.9 μ g/mL and 202 μ g $\cdot$ h/mL in the female. We note that the Pharmacology written summary gives C_{max} at the NOAEL as 21.2 μ g/mL, which is the average of the male and female exposures. **MOE based on human AUC of 3.5 μ g $\cdot$ hr/mL = 48.** The sponsor's table below gives exposure data for the parent compound NBI-56418 and primary metabolite NBI-61962 (M3).

Parameters of NBI-56418	Male dose groups (mg/kg)			Female dose groups (mg/kg)		
	30	300	1200	30	300	1200
C _{max} (ng/ml)	1050	4150	10500	979	5090	31900
Median T _{max} (h)	1.00	6.00	8.00	0.25	4.50	2.00
AUC (0-24 h), ng $\cdot$ h/ml	1590	32800	133000	1240	31400	202000
AUC (0-48 h), ng $\cdot$ h/ml	1620	33300	188000	1360	32000	274000
Parameters of NBI-61962						
C _{max} (ng/ml)	23.3	102	198	20.9	129	1740
Median T _{max} (h)	0.25	3.00	1.00	0.25	1.00	2.00
AUC (0-24 h), ng $\cdot$ h/ml	40.0	789	1960	27.7	730	4200
AUC (0-48 h), ng $\cdot$ h/ml	40.0	807	2460	27.7	755	5000

Cardiovascular

In vitro assays:

hERG and Na channel assays:

Elagolix and its primary metabolite, NBI-61692 (M3), were tested for their effects on potassium (hERG channel) and sodium currents. hERG channels were expressed in HEK cells, and native Na channels were assessed in rat primary neuronal cell cultures. There were no effects in the therapeutically relevant concentration range. Human C_{max} for a 200 mg dose is 774 ng/mL or 1.3 μM.

Two hERG channel assays were conducted: a non-GLP assay (4.2.1.2 RD101255, Neurocrine Biosciences, 2003) and a GLP assay (4.2.1.3. RD101347, (b) (4) 2007, Lot NU1-001). The first evaluated concentrations of 0.1 nM – 10 μM (n=4) and the second evaluated 6.29 and 83.8 μM (N=6). Low doses showed no effect but 16.2% inhibition was observed at the high dose.

The effect of elagolix on Na current was assessed as part of the non-GLP assay and found negative at up to 10 μM.

The primary metabolite NBI-61692 (M3) was tested in a non-GLP hERG assay at 0.1, 1, and 10 μM (n = 3) (4.2.1.1. RD101259, Neurocrine Biosciences, 2007). NBI-61962 had no effect at the two lower doses but significantly reduced hERG tail current by 21.3% at 10 μM. The extrapolated IC₅₀ was estimated to be 34 μM, which is not in the therapeutically relevant concentration range.

In the same study, the effect of NBI-61962 on sodium current was investigated. At the single concentration tested (10 μM), sodium current was not affected.

Cardiac action potential assay:

Effect of Elagolix on Canine Purkinje Fiber Repolarization In Vitro.

RD101070. GLP. 2003. (b) (4). Lot No. 1675644

Isolated canine (N=4) Purkinje fibers were exposed to NBI-56418 Na: 1, 5, 10 and 50 μM. Action potential parameters were assessed at stimulation frequencies of 0.5, 1, and 3 Hz.

Results:

At 1 Hz, there was a dose-dependent reduction in the maximum rate of depolarization (13, 24, and 33% at 5, 10, and 50 μM respectively). There were similar dose-dependent decreases at 0.5 and 3 Hz that did not reach statistical significance.

At the low dose, there was a small inverse frequency-dependent increase in action potential duration (APD) that was even less pronounced at 5 and 10 μM. At 50 μM APD was reduced.

The two findings of a slower rate of depolarization and reduced APD at the high dose were indicative of possible Na channel blockade, which can result in in vivo prolongation of the QRS complex and a secondary effect of shortening of the QT interval.

However, it should be noted that the in vivo cardiovascular monkey study showed no effect of elagolix on the QRS interval or QTc through the highest dose of 300 mg/kg (C_{max} estimated to be 18.5 μg/mL).

In vivo cardiovascular assays:

Effects of Elagolix on Cardiovascular Parameters in Conscious **Rats**. RD101087.

An evaluation of the effects of NBI-56418 (lot 1595201), (b) (4), administered by oral gavage, on cardiovascular function in the rat. (u) (4). 2002. Non-GLP. (b) (4)

Elagolix was orally administered by gavage to conscious male rats (n = 5/dose and 3/dose for TK) at 600 mg/kg or 1200 mg/kg. Elagolix produced no effects on mean arterial pressure, heart rate or the QRS and PR intervals. At 600 and 1200 mg/kg, elagolix produced a slight non-dose-dependent increase in QTc. **MOE** based on human AUC of 3.5 ug.hr/mL = **26 and 68** for the low and high doses, respectively.

Toxicokinetics RAT

Compound	NBI-56418			
	600 mg/kg		1200 mg/kg	
	Mean	SD	Mean	SD
Tmax (hr)	5.8	3.8	13.3	9.2
Cmax (ng/mL)	6910	2512	13600	1040
AUC(0-24) (ng*hr/mL)	90700	26500	238000	55100

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Effects of Elagolix on Cardiovascular Parameters in Conscious **Monkeys**. RD101067. GLP. (b) (4). 2003. NBI-56418. Lot 1675644.

The cardiovascular effects of orally administered elagolix were evaluated in telemetry instrumented male (n = 4) and female (n = 4) monkeys. Doses were 30, 150 or 300 mg/kg (n = 8 per group) and the cardiovascular parameters were monitored continuously for 48 hours. Elagolix had no effect on mean arterial pressure, heart rate, core body temperature, QTc or QRS and PR intervals through 300 mg/kg. Drug administration was associated with emesis, which led to plasma concentrations being highly variable. Blood samples were taken ~4 and 24 hrs post dose. In order to calculate a MOE, TK data were used from the following respiratory safety study in monkeys, which had more extensive sampling.

Mean plasma concentration (ng/mL) for male/female monkeys, and combined

Dose	Time (hr)	Male		Female		Combined	
		Mean	SD	Mean	SD	Mean	SD
30 mg/kg	0	0	0	0	0	0	0
	4	37.8	9.67	44.5	14.5	41.1	12
	24	0	0	0	0	0	0
150 mg/kg	0	0	0	0	0	0	0
	4	1710	1790	387	327	1050	1380
	24	20.8	10.7	18.5	15.4	19.7	11.9
300 mg/kg	0	0	0	0	0	0	0
	4	1520	935	1260	1710	1390	1280
	24	64.1	58.8	62.8	97.2	63.4	71.8

Sponsor's Table Appendix N p 1164

Respiratory (monkey)

Effects of Elagolix on Respiratory Function in Conscious Monkeys RD101063. GLP
 (b) (4) 2003. NBI-56418. Lot 1675644.

The respiratory effects of elagolix were evaluated in the conscious monkey using whole body plethysmography. Male (n = 4) and female (n = 4) cynomolgus monkeys were orally administered elagolix at doses of 30, 150 and 300 mg/kg (n = 8 per group). The vehicle and test drug were administered on 4 separate occasions, with 7 days between each treatment. Tidal volume, minute volume, and respiratory rate were collected and recorded one hour pre-dose and for up to 3.5 hours post-dose and for approximately 1 hour at 24 hours post-dose. Femoral artery blood samples were collected from each animal for TK at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hrs post dose. Parent and active metabolite were measured.

Results: Emesis was reported immediately following dosing in all groups. It occurred in 1, 3, 2, and 2 males in control and 3 treated groups, respectively. In females the corresponding incidence was 0, 1, 0, and 1, respectively. For this reason, exposure may have been underestimated.

Elagolix had no effect on respiratory rate, tidal volume or minute volume through 300 mg/kg.

TK: Mean of male and female for the parent compound at 300 mg/kg: C_{max} = 18.5 ug/mL; AUC₀₋₄₈ = 151.5 ug.hr/mL. We note that T_{max} at the highest dose occurred after the 3.5 hr sampling time. Exposure to the primary metabolite was ~7.4% of parent.

MOE for the high dose based on human AUC of 3.5 ug/hr/mL = 43.

MOE for the high dose based on human C_{max} of 774 ng/mL = 24.

Parent TK: monkey Sponsor's table Appendix H Table 7 p 145

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Mean T/K parameters of NBI-56418 following oral administration of NBI-56418

Parameter	Male dose groups			Female dose groups		
	30 mg/kg	150 mg/kg	300 mg/kg	30 mg/kg	150 mg/kg	300 mg/kg
C _{max} , ng/ml	704	8820	20400	987	5490	16500
T _{max} , h	0.75	2.00	6.00	1.5	4.00	8.00
AUC(0-24), ng h/ml	1150	43000	183000	2390	30300	116000
AUC(0-48), ng h/ml	1150	43000	184000	2390	30400	119000

Primary metabolite TK: monkey Sponsor's table Appendix H Table 8 p 146

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Mean T/K parameters of NBI-61962 following oral administration of NBI-56418

Parameter	Male dose groups			Female dose groups		
	30 mg/kg	150 mg/kg	300 mg/kg	30 mg/kg	150 mg/kg	300 mg/kg
C _{max} , ng/ml	50.1	544	1750	133	563	2570
T _{max} , h	1.00	2.00	2.00	2.00	4.00	2.25
AUC(0-24), ng h/ml	67.8	1940	9290	251	2460	13100
AUC(0-48), ng h/ml	67.8	1940	9310	251	2470	13200

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The pharmacokinetics of elagolix were determined in CD-1 mice, SD rats, Beagle dogs and cynomolgus monkeys. Radiolabeled in vivo absorption, distribution, metabolism and excretion (ADME) studies were conducted in rat and dog and compared to absorption, metabolism and excretion studies conducted with [¹⁴C]elagolix in humans.

The pharmacokinetic profile of elagolix was generally characterized by high plasma clearance, moderate volumes of distribution and a short elimination half-life in mouse, dog and monkey.

Absorption

In vitro permeability

Apparent permeability (Papp) values of elagolix across MDCK-MDR1 and Caco-2 cell monolayers ranged from 0.5 to 2.8 x10⁻⁶ cm/s, indicating low to moderate in vitro permeability (source data in sponsor's PK Tabulated Summary Table 2.6.5.3a).

In vivo pharmacokinetics and bioavailability

PK parameters and oral bioavailability were determined in mouse, dog, and monkey by comparing plasma values after iv and oral administration. In rat, dog, and human, bioavailability was determined from mass balance using radiolabeled elagolix.

Bioavailability (%):

Mouse	Rat	Dog	Monkey	Human
9.6	47-55	100	10.7	~52

2.6.5.3b Pharmacokinetics: Absorption after a Single Dose

Species	CD-1 Mouse	Beagle Dog †	Cynomolgus Monkey†	Human
Gender (M/F)	M	M/F	M	F
Number of Animals	22; 2/timepoint	3/3	4	23
Feeding Condition	fasted	fasted	nonfasted, fasted	fasted
Vehicle/Formulation	(1)/solution	(2)/solution	(3)/solution	(4)/tablet
Dosing Route	intravenous, oral	intravenous, oral	intravenous, oral	oral
Dose (mg active/kg)	8.47, 8.47	9.66, 46.6	9.66, 9.66	150 mg
Sample	plasma	plasma	plasma	plasma
Analyte	A-1278823	A-1278823	A-1278823	A-1278823
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
PK Parameters				
IV:				
t _{1/2} (hr)	0.3	2.2*	1.2	
V _d (L/kg)	1.2	0.83 (0.18)	1.4 (0.2)	
CL _n (L/hr·kg)	2.5	0.74 (0.14)	1.5 (0.2)	
AUC _{0-inf} (µg·hr/mL)	3.35	13.6 (2.91)	6.65 (0.77)	
PO:				
t _{1/2} (hr)	0.7	2.6*	0.79	2.21* (0.60)
C _{max} (µg/mL)	0.742	25.8 (13.1)	0.526 (0.217)	0.51 (0.23)
T _{max} (hr)	0.2	0.5 (0.4)	0.69 (0.38)	1.12 (0.42)
AUC _{0-inf} (µg·hr/mL)	0.321	65.3 (14.2)	0.708 (0.066)	1.28 (0.52)
F (%)	9.6	105 (35)	10.7 (1.1)	
Study No.	R&D/10/1242	R&D/10/1223	R&D/10/1221	M12-653 (Regimen B)

(1) aqueous solution of the TFA salt;

(2) solution of the sodium salt in dextrose 5% in water (D5W) for IV dosing; solution of the sodium salt in water for oral administration

(3) solution of the sodium salt in saline for IV dosing; solution of the sodium salt in water for oral administration

(4) 150 mg IR tablet from M12-653 (Regimen B)

Mouse: Elagolix pharmacokinetics in mice were characterized by high plasma clearance (2.5 L/hr•kg), with high volumes of distribution (V_{ss} 1.2 L/kg) and a short half-life of 0.3 hours following an 8.47 mg/kg intravenous dose. Peak plasma concentrations averaged 0.74 $\mu\text{g/mL}$ following an equivalent oral dose (aqueous formulation), with 9.6% bioavailability. In the mouse, elagolix plasma concentrations in samples collected from the hepatic portal vein were ~10-fold higher than circulating levels, suggesting that high first pass metabolism was a major contributing factor to the low oral bioavailability (data in study report #RD101242).

Dog: Peak plasma concentrations following a single 46.6 mg/kg oral dose averaged 25.8 $\mu\text{g/mL}$, declining with an apparent half-life of 2.6 hr. Plasma clearance values in dog were moderate (0.74 L/hr•kg), with moderate volumes of distribution (V_{ss} 0.83 L/kg) and an apparent elimination half-life of 2.2 hr. The oral bioavailability in the dog was substantially higher than in monkey and mouse, with values averaging ~100%.

Monkey: Elagolix plasma clearance was also high in monkey (CL_p 1.5 L/hr•kg), with high volumes of distribution (V_{ss} 1.4 L/kg) and an apparent elimination half-life of 1.2 hours. Peak plasma concentrations averaged 0.53 $\mu\text{g/mL}$ (0.84 μM) following a 9.66 mg/kg oral dose, with 10.7% bioavailability in monkey.

Bioavailability based on mass balance:

- In the rat, the extent of absorption, based on urinary and biliary recovery of [^{14}C]elagolix-derived radioactivity, was approximately 47% to 55% of the administered dose (source data in sponsor's PK Tabulated Summary Table 2.6.5.13).
- In dog, the radioactivity was well absorbed, with an apparent bioavailability of 100%.
- In human, the extent of absorption was estimated to be ~52%, which was based on the percentage of [^{14}C]elagolix-derived radioactivity excreted as metabolites, assuming little or no metabolism occurred in the gut.

Distribution

Protein binding: Elagolix protein binding was measured across the concentration range encompassing the average clinical plasma concentrations using equilibrium dialysis. Binding of elagolix to mouse, rat, dog, and monkey, plasma proteins was measured in study RD101243 (non-validated equilibrium dialysis method) and RD101245 (validated method). Results from the two studies were generally comparable. Binding to human plasma proteins was reported in RD13245 using subjects in study M12-655. Plasma protein binding was moderate across species and was independent of concentration.

% bound				
Mouse	Rat	Dog	Monkey	Human
78.5	90.4	82	77.6*	79.5

Values from low and high concentrations were averaged and rounded to the nearest 0.1% by the reviewer

*Value obtained using the nonvalidated method

Whole Blood: Ex vivo blood to plasma ratios were independent of concentration and averaged ~0.6-0.7 in rat (RD101239), dog (RD101240) and human (NBI-56418-0601), indicating low distribution into red blood cells.

Tissue distribution: Tissue distribution was measured following administration of a single 300 mg/kg oral dose of [^{14}C]elagolix to male and female Sprague Dawley and Long Evans rats. RD101209. (Source data in sponsor's PK Tabulated Summary Table 2.6.5.5.)

- [¹⁴C] Elagolix distributed to limited tissues in the rat after oral dosing, with the highest concentrations observed in the gastrointestinal tract and liver. The highest concentrations in tissues were observed in cecum, esophagus, large intestine, liver, small intestine and stomach with a lower distribution into other tissues including kidney, pancreas, spleen, renal cortex and renal medulla.
- [¹⁴C] Elagolix did not distribute into brain (cerebellum, cerebrum, medulla) or spinal cord tissue in rats, suggesting that elagolix does not cross the blood brain barrier
- [¹⁴C] Elagolix did not accumulate in the eyes or skin of the pigmented Long-Evans rat, suggesting that radioactivity does not bind to melanin.

Placental Transfer: Elagolix freely crosses the blood/placental barrier in the rat.

Evaluation of the Ability of Elagolix to Distribute to Fetal Tissue after Oral Administration to Pregnant Rats. RD11261. 2011. Non-GLP. Review by Raheja filed 2-16-2012. See also sponsor's Table 2.6.5.7.

In this study rats were given a single oral dose of 1200 mg/kg of elagolix on GD12, and maternal blood and fetal tissue (fetus plus chorion) samples were collected at 1 and 4 hours post-dose (N=4 per time point).

The mean maternal plasma concentration at 1 hr was 6260 ± 2054 ng/mL (~10 uM) and at 4 hrs was 2317 ± 531 ng/mL. The corresponding values for fetal tissue concentration at 1 and 4 hours were 2253 ± 924 and 2174 ± 810 ng/g, respectively. The LLOQ for elagolix in maternal blood was 5 ng/mL and was linear over the range of 5-12500 ng/mL. The LLOQ for elagolix in fetal tissue homogenate was 0.5 ng/mL and was linear over the range of 0.5-1250 ng/mL.

Conclusion: Elagolix can cross the rat blood-placental barrier, with a fetal tissue to maternal plasma ratio of ~36% (at 1 hr) and 94% (at 4 hr). We note that in the rat developmental toxicity study, no fetal test article-related malformations and no evidence for teratogenicity were observed at doses up to 1200 mg/kg/day.

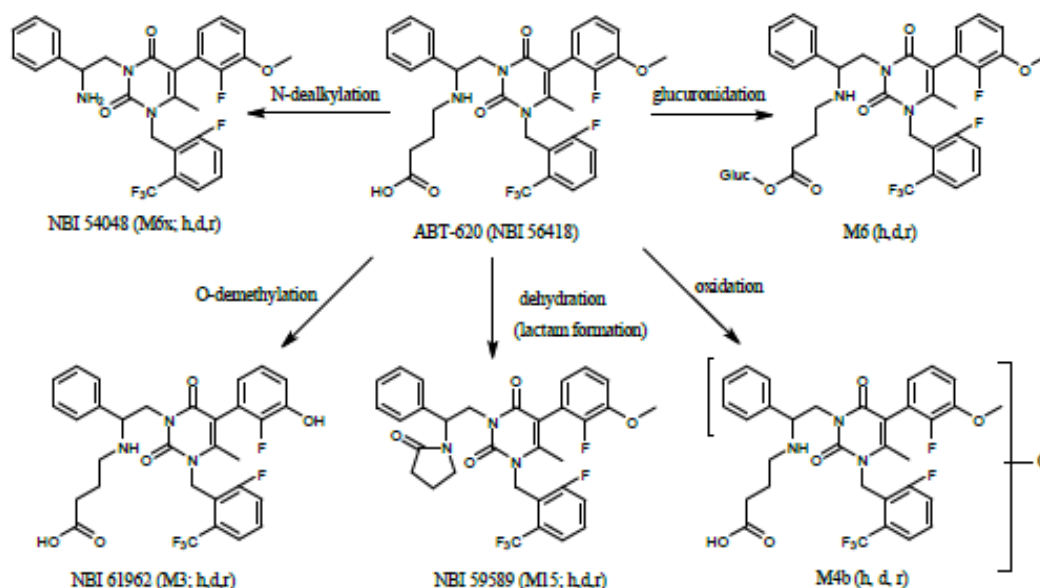
Metabolism Text from sponsor's section 2.4.3.3 and 2.6.4.1, respectively

Elagolix is primarily metabolized by O-demethylation, with minor metabolites formed via N-dealkylation, dehydration (lactam formation), glucuronidation, and oxidation. There were no unique human metabolites.

Sponsor's Table 2.6.5.9b

Metabolite Abbreviation	Metabolite ID	Metabolite Abbreviation	Metabolite ID
O-Demethylation:		Mono-oxidation:	
M3	O-desmethyl elagolix	M2a,b,c,d	elagolix mono-oxy glucuronide
M1	O-desmethyl elagolix glucuronide	M4	elagolix mono-oxy
M2x	O-desmethyl elagolix acyl glucuronide	M4a,b,c,d,e	elagolix mono-oxy
M10	O-desmethyl N-desalkyl elagolix ketone glucuronide	M7a,b	elagolix mono-oxy
M12	O-desmethyl elagolix glucuronide lactam	M13a,b	elagolix mono-oxy glucuronide lactam
M14	O-desmethyl elagolix lactam	M14x	elagolix mono-oxy
M19	O-desmethyl elagolix mono-oxy lactam	M23	elagolix sulfate mono-oxy hydration
M20	O-desmethyl N-desalkyl elagolix	M24	elagolix di-oxy
M21	O-desmethyl N-desalkyl elagolix ketone	N-dealkylation:	
M22	O-desmethyl elagolix mono-oxy	M6x	N-desalkyl elagolix
Glucuronidation:		M8	N-desalkyl elagolix N-oxide
M6	elagolix acyl glucuronide	M9a,b	N-desalkyl elagolix ketone mono-oxy
Dehydration (Lactam formation):		M9x	N-desalkyl elagolix ketone mono-oxy glucuronide
M15	elagolix lactam	M11	N-desalkyl elagolix ketone mono-oxy glucuronide
M14y,z	elagolix mono-oxy lactam	M14w	N-desalkyl elagolix ketone
M17	elagolix di-oxy lactam	M16	N-desalkyl elagolix ketone mono-oxy
M19	O-desmethyl elagolix mono-oxy lactam		

Metabolites of Elagolix in Rat, Dog and Human Formed by Representative Pathways



In vitro metabolism:

The liver microsomal and hepatocyte metabolite profiles of elagolix among various animal species including CD-1 mouse, Sprague- Dawley rat, rabbit, beagle dog, cynomolgus monkey and human were qualitatively similar; there were no sex differences. In human liver microsomes, there was no metabolic chiral inversion of elagolix (b) (4)

These results are consistent with the in vivo metabolism findings in mouse, rat, dog, and human.

In vitro studies showed that O-demethylation was primarily mediated by CYP3A4 and CYP2D6, with minor contributions from CYP2C8. N-dealkylation was catalyzed primarily by CYP3A4/5 and dehydration (lactam formation) was the result of non-enzymatic cyclization of the butyric acid. In addition to CYPs, UDP-glucuronosyl transferase enzymes and biliary excretion contribute to the clearance of elagolix.

In vivo metabolism: (See study #s RD101210, RD101246, and RD101247)

Study RD101210 "Metabolic profiling in SD rats following single 300 mg/kg dose of [¹⁴C]NBI-56418" was reviewed by Dr. Raheja and submitted to DARRTS on 4-30-08.

In vivo metabolite profiling was conducted in mouse, rat and dog, and humans using radiolabeled elagolix. There were no unique human metabolites; all circulating human metabolites were also observed in plasma or excreta of rats and dogs. (Mouse study did not include metabolite quantitation).

2.4.3.7. Sponsor's Table 5. Data from sponsor's table 2.6.5.9a

Metabolite	Mouse	Rat	Dog	Human
Elagolix	✓	major	major	major
M1: O-demethyl elagolix glucuronide	✓	minor	minor	minor
M2 series: mono-oxy elagolix glucuronide	✓	ND	minor	minor
M3: O-demethyl elagolix	✓	minor	minor	minor
M4b: mono-oxy elagolix	✓	ND	minor	minor
M6: elagolix glucuronide	✓	ND	minor	minor
M6x: N-dealkyl elagolix		minor	ND	minor
M9a: N-dealkyl elagolix, ketone mono-oxy	✓	minor	ND	minor
M10: O-demethyl, N-dealkyl elagolix ketone glucuronide		ND	ND	minor
M14: O-demethyl elagolix lactam	✓	minor	minor	minor
M15: elagolix lactam	✓	minor	minor	minor
M17: elagolix di-oxy lactam		ND	ND	minor

Metabolites in plasma:

Unchanged elagolix was the major drug-derived material in plasma in mouse (percent not given), rat (57% or greater), dog (94%) and human (93%). Reviewer notes that M14 and M15 are borderline major metabolites in the rat. The previous table lists them as minor.

Sponsor's Table 2.6.5.9a

Study: Comparison of elagolix plasma metabolites in mouse, rat and dog to those observed in human plasma															
Species (Dose)	Mean Percent of Radioactivity in Plasma§													U	Study No.
	Elagolix	M1	M2*	M3	M4b	M6	M6x	M9a/9x	M10	M14	M15	M17			
Mouse (300)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			R&D/10/1246
Rat (m, 300)	77	<1	u, b	1.8		u, b	<1	bile	bile	9.8	11	ND			R&D/10/1210
Rat (f, 300)	84	<1	u, b	<1		u, b	<1	bile	bile	12.1	4	ND			R&D/10/1210
Rat (100)	57	<1	urine	<1	u, f	u, f	8	<1	ND	6	14	u, f	5		R&D/10/1247
Dog (50)	94	1	<1	<1	<1	3	u, f	ND	urine	1	1	feces			R&D/10/1247
Human (150 mg)	93	<1	<1	0.4	0.7	1.8	0.3	<1	0.8	<1	<1	3.0	0.3		R&D/10/1247

Additional Information: Dose in mg/kg;

✓ - present in mouse plasma (study did not include quantitation); metabolites reported as <1% of radioactivity in plasma were detected by MS, but were below the limits of quantitation.

* Mono-oxy glucuronide metabolites 2a, b, c, & d; ND - not detected

u, f - metabolite present in urine and feces

u, b - metabolite present in urine and bile.

§ Metabolites M7, M11 and M12 were also detected in mouse plasma

M4c, M4d, M14y/z and M19 were detected in rat plasma

M4c, M14y/z and M18 were detected in dog plasma

M17 detected in dog feces after IV dosing only

Empty cells were not discussed; U - unknown

None of the metabolites in human plasma were classified as major (>10% of parent). The metabolites detected in human plasma (all <5% of plasma radioactivity) were identified as M3 (O-desmethyl elagolix), M4b (mono-oxy elagolix), M6 (elagolix glucuronide), M6x (N-desalkyl elagolix), M10 (O-desmethyl, N-desalkylated elagolix ketone glucuronide) and M17 (elagolix di-oxy lactam). M1 (O-desmethyl elagolix glucuronide), M2 (monooxy elagolix glucuronide), M9a (N-desalkyl elagolix ketone mono-oxy), M14 (O-desmethyl elagolix lactam) and M15 (elagolix lactam) were also present at trace levels in plasma (<1%).

Metabolites in excreta (urine, bile, feces): See sponsor's Table 2.6.5.9b (not shown).

Elagolix was primarily excreted in unchanged form in urine, bile, and feces. In urine, unchanged elagolix comprised the majority (>65%) of the drug-derived material across species. In feces, unchanged elagolix represented 43.7-59.0% of the dose in male-female rats (bile + feces), 25.8% of the dose in dogs and 26.3% of the dose in humans. The percentage of dose excreted as metabolites was 39%, 28%, and 52% in rats (male/female combined), dogs and humans, respectively.

The metabolic pathways involved in the clearance of elagolix were similar across species (including humans) with the exception of rats, where a greater proportion of the dose was excreted as unchanged elagolix.

A majority of the metabolites eliminated in feces were from the O-demethylation pathway, comprising 14.6-16.9% of the dose in male-female rats (bile + feces), 21.2% of the dose in dogs and 38.8% of the dose in humans. The primary metabolite in this subgroup was M3 (O-desmethyl elagolix) representing 7.9-10.7% of the dose in male-female rats (bile + feces), 10.8% of the dose in dogs and 37.6% of the dose in humans. All remaining human metabolites

accounted for <10% of the dose in excreta. The most abundant of the minor metabolites were from the oxidation pathway, with M4b and M4c (both mono-oxidation metabolites of elagolix) accounting for 6.7 and 2.5% of the dose in human feces.

While the *O*-desmethyl (M3; NBI-61062) and the *N*-dealkyl (M6x; NBI-54048) metabolites of elagolix have the ability to bind to the GnRH receptor, their low systemic exposure suggests that they are not likely to contribute to the pharmacological effects of elagolix (Section 2.6.2).

Excretion

Study #s RD101209 (rat – intact and bile-duct cannulated, oral administration), RD101239 (mass balance rat, oral administration), RD101240 (mass balance dog, oral and iv administration) and sponsor's Table 2.6.5.13.

Excretion of elagolix was determined in rat (intact and bile-duct cannulated; M/F), dog (M/F), and human (M), using radiolabeled compound. Orally administered elagolix (parent and metabolites) was mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance, in both nonclinical species and humans. No notable sex differences were noted. The reason for lower total recovery in the dog is not known.

% administered dose recovered (parent + metabolites)				
	Urine	Feces	Bile	Total
Rat (M/F)	2.3	41.4	49.0	96.6
Rat (M/F)	4.1	90.0		95.9
Dog (M/F)	4.9	53.8		63.4
Human (M)	2.9	90.1		93.0

Reviewer's table using data in sponsor's table 2.6.5.13.

Time point 168 h post-dose rat and dog, 216 h human. Male and female values averaged.

Excretion in Milk: A radiolabeled excretion study in lactating rats has not been conducted. Two pre- and post-natal studies have been conducted (dose-range finding RD121000 and definitive RD13581) in which elagolix was measured in the plasma of lactating pups. In the dose range finding study, pup exposure was much less than maternal exposure, and in the definitive study, pup exposure was approximately equal to maternal exposure. Methodological differences between the two studies led the sponsor to weight the dose range finding study more heavily

(b) (4)

Pharmacokinetic Drug Interactions

CYP inhibition Study #s RD101207, RD101215, RD13535

The potential for elagolix to inhibit the major CYP enzymes in pooled human liver microsomes was evaluated. Elagolix was a weak inhibitor of CYP450 enzymes in human liver microsomes with IC₅₀ values of 30 uM or greater for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Elagolix showed weak time-dependent inhibition of CYP3A4/5, CYP2C8 and CYP2C19 with Ki values all >10 uM.

Consistent with the mechanistic DDI predictions, in a clinical DDI study, midazolam (sensitive CYP3A4 substrate) exposure (AUC) decreased with multiple doses of elagolix (300 mg BID).

While elagolix is a time dependent inhibitor of CYP2C19, the inability to quantify the elagolix induction of CYP2C19 precludes a calculation of AUCR (ratio of AUC w/ or w/out inhibitor).

Sponsor's Table 2.6.5.12a Pharmacokinetics: Inhibition of drug-metabolizing enzymes

Type of Study: in vitro human liver microsomal incubations				
Method: Human cytochrome (CYP) activities				
CYP Enzyme	Enzymatic Reaction	IC₅₀ (μM)		Percent Metabolism-Dependent Inhibition^a
		No Pre-Incubation	15 min Pre-Incubation	
CYP1A2	Phenacetin O-deethylation ^b	>29	>29	<10
CYP2A6	Coumarin 7-hydroxylation	>30	>30	<10
CYP2B6	Bupropion hydroxylation ^b	>29	>29	NA ^c
CYP2C8	Paclitaxel 6α-hydroxylation	>30	24 ± 2	NA ^c
CYP2C9	Diclofenac 4'-hydroxylation	>30	>30	<10
CYP2C19	S-Mephenytoin 4'-hydroxylation	>30	>30	43
CYP2D6	Dextromethorphan O-demethylation	>30	29 ± 3	<10
CYP2E1	Chlorzoxazone 6-hydroxylation	>30	>30	12
CYP3A4/5	Testosterone 6β-hydroxylation	>30	>30	33
CYP3A4/5	Midazolam 1'-hydroxylation	>30	27 ± 9	52
CYP3A4/5	Nifedipine oxidation	>30	>30	45

Additional Information:

a Percent metabolism-dependent inhibition observed at ~30 μM, the highest concentration tested.

b The highest concentration of elagolix examined for these assays was 29 μM, due to an error in the preparation of the stock solution;

c Values not calculated because the 15-min pre-incubation no solvent controls were higher than zero-min pre-incubation no solvent controls.

Type of Study: in vitro metabolism-dependent inhibition of CYP2C8, CYP3C19, CYP3A4/5**Method:** Human liver microsomes or recombinant enzymes

Enzyme	k_{inact} (min⁻¹)	K_i (μM)	Study No.
CYP3A4/5 (in HLM)	0.019	74	R&D/10/1215
rCYP3A4	0.16	16	R&D/10/1215
rCYP3A5	0.022	11	R&D/10/1215
CYP2C8 (in HLM)	0.029	82	R&D/13/535
CYP2C19 (in HLM)	0.029	34	R&D/10/1215

Additional Information:

Elagolix (0-200 μM) was pre-incubated in human liver microsomes (HLM; final protein concentration 1-2 mg/mL) and NADPH-generating system. Elagolix was also tested using recombinant enzymes rCYP3A4 or rCYP3A5 (200 pmol/mL). Troleandomycin (10 μM) served as a positive control for metabolism-dependent inhibition of CYP3A4/5.

Tranlycypromine (300 μM) served as a positive control for inhibition of CYP2C19.

Phenelzine (50, 250 μM) served as the positive control for inhibition of CYP2C8.

The effect of two primary *metabolites* of elagolix NBI-61962 (M3) and NBI-54048 (M6x) on CYP enzyme activity was also measured in human liver microsomes (RD101215, review by Dr. Raheja filed on 6-22-2009).

In vitro CYP inhibition studies in human liver microsomes showed that NBI-61962 had little or no inhibitory effect on the major CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) at the highest tested concentration of 50 μM. Pre-incubation showed a weak metabolism-dependent inhibition of CYP3A4/5 with the IC₅₀ value shifting from 50 μM to 29 μM.

In humans given a dose of 150 mg of elagolix, the C_{max} values detected for NBI-61962 were ~6 ng/ml or 10 nM, which means that metabolite concentrations will not be high enough to affect CYP activity.

NBI-54048 showed weak to moderate inhibition of CYP2C9, CYP2C19 and CYP2D6 with IC₅₀ values of 22 μM, 16 μM and 8 μM, respectively, but was a relatively potent inhibitor of

CYP3A4/5, with an IC_{50} value of 1.6 μM . Pre-incubation of NBI-54048 in human liver microsomes showed evidence of metabolism-dependent inhibition of CYP2C9, CYP2C19 and CYP3A4/5 such that the IC_{50} values shifted from 22 μM to 9.6 μM , from 16 μM to 0.26 μM and from 1.6 to 0.43 μM , respectively.

Since this effect was the largest in CYP2C19 and CYP3A4/5, the sponsor carried out additional metabolism-dependent kinetic inhibition studies with NBI-54048 to determine its inactivation potential. The calculated K_i and K_{inact} values for NBI-54048 were ~ 4.6 μM and 0.056 min^{-1} respectively for CYP2C19, and ~ 5.9 μM and 0.079 min^{-1} for CYP3A4/5, respectively. These data indicated that NBI-54048 had a relatively high potential for inactivation of CYP2C19 and CYP3A4/5 enzymes through metabolism-dependent inhibition.

However, circulating levels of the NBI-54048 do not reach levels high enough to produce inactivation. In clinical studies where subjects were administered a 150 mg dose of elagolix the maximum concentration metabolite NBI-54048 was ~ 2.9 ng/mL or 6 nM, representing less than 1% of the of the parent compound.

CYP induction Study #s RD13135 and RD161459

The potential for elagolix to cause CYP induction was evaluated using a reporter gene construct screening assay in human hepatocytes. Elagolix was a measurable inducer of CYP3A4, CYP2B6 and CYP2C8 mRNA; elagolix should be considered a potential inducer of CYP2C9 and CYP2C19, but the response was too low to quantify accurately, giving a variable, dose-dependent response between 1.1 and 2.4-fold over control for both enzymes (RD13135). Elagolix was not an inducer of CYP1A2.

RD161157 Table 5. In vitro CYP mRNA Induction in Human Hepatocytes (EC_{50}/E_{max})

Enzyme	EC_{50}/E_{max}			Geometric Mean
	Donor (b) (6)	Donor (b) (6)	Donor (b) (6)	
CYP3A4	17 $\mu\text{M}/24$ -fold	5.1 $\mu\text{M}/29$ -fold	3.4 $\mu\text{M}/11$ -fold	6.7 $\mu\text{M}/20$ -fold
CYP2B6	17 $\mu\text{M}/37$ -fold	6.4 $\mu\text{M}/18$ -fold	15 $\mu\text{M}/18$ -fold	12 $\mu\text{M}/23$ -fold
CYP2C8	12 $\mu\text{M}/11$ -fold	7.5 $\mu\text{M}/4.2$ -fold	10 $\mu\text{M}/13$ -fold	9.7 $\mu\text{M}/8.4$ -fold

Since elagolix showed both time-dependent inhibition as well as evidence of induction of some CYP enzymes, the sponsor conducted modeling for DDI, which yielded the following AUCR values for relevant substrates:

RD161157 Table 6. Elagolix Calculated Model Parameters and Predicted AUCR Values for CYPs

Enzyme	Elagolix Predicted AUCR Values								AUCR ^a
	$[I]_g$ (μM)	A_g	B_g	C_g	$[I]_h$ (μM)	A_h	B_h	C_h	
CYP3A4	16	1.0	0.126	15.2	1.3	1.0	0.49	4.26	0.35 [*]
CYP2B6	-	-	-	-	1.3	1.0	1.0	3.26	0.47
CYP2C8	-	-	-	-	1.3	1.0	0.52	2.00	0.98

(a) The following fraction metabolized (fm) of CYP probe substrates were taken from Simcyp Version 15 (15.0.86.0), Release 1 for use in the AUCR calculations: CYP3A4, midazolam (fm 0.96); CYP2B6, bupropion (fm 0.50); CYP2C8, repaglinide (fm 0.64); and CYP2C19, S-mephenytoin (fm 0.98).

* The fraction of midazolam evading first-pass intestinal metabolism (F_g) was set as 0.60 (Simcyp Version 15 (15.0.86.0)).

The sponsor concluded that "Mechanistic DDI predictions based on the clinical dose and exposure indicate that elagolix has the potential to decrease the exposure of CYP3A4 and

CYP2B6 sensitive substrates as a net effect of time dependent inhibition and induction, and have minimal impact on CYP2C8 sensitive substrates. While elagolix is a time dependent inhibitor of CYP2C19, the AUCR value for CYP2C19 could not be determined, as the induction of CYP2C19 by elagolix could not be accurately quantified in vitro. Consistent with the mechanistic static DDI predictions, in a clinical DDI study, midazolam (sensitive CYP3A4 substrate) exposure (AUC) decreased with multiple doses of elagolix (300 mg BID).” Clinical data are shown on the following page at the end of this section.

Drug transporters: Study #s RD160741 and RD161157

Review note: In vitro studies investigating the effect of elagolix on hepatic and renal transporters were conducted between 2010 and 2016. Some of these studies were submitted to IND 64802 SDN180 on 10/27/11 and reviewed by Dr. Raheja (review filed 2-16-2012). For the NDA, data from these studies were included with additional newer studies under one study report - RD160741. Additional summaries and an assessment of the likelihood of DDI in humans are presented in RD161157. Because some of the experiments were done more than once using different methodologies (for a complete list see Appendix A p 35 of RD 160741) results are summarized below primarily in tabular form.

Drug efflux transporters: P-gp, BCRP, MRP2, BSEP

Elagolix is a substrate for P-gp but not for BCRP. It is an inhibitor of BCRP, MRP2, and BSEP.

RD161157 Table 8 In vitro inhibition parameters

Transporter	IC ₅₀ (μM)
P-gp (MDCK)	54
BCRP (MDCK)	150
BCRP (vesicle)	54
MRP2 (vesicle)	280
BSEP (vesicle)	36

Inhibition of P-gp and BCRP in the gut may be possible based on the theoretical concentrations (dose/250 mL) for elagolix in the GI tract; [I]₂/IC₅₀ values >10. Inhibition of P-gp or BCRP at other tissue sites is not predicted; [I]₁/IC₅₀ values <0.1.

For comparison, a similar study carried out under IND 64802 (4.2.2.6 Memo-03) obtained similar values for the IC₅₀ values for Pgp of 46 and 49 μM.

Hepatic uptake transporters: OATP1B1, OATP1B3, OCT1

Elagolix is a substrate for OATP1B1 but not for OATP1B3 or OCT1. Elagolix is an inhibitor of OATP1B1 and OATP1B3 but not OCT1 (IC₅₀ value >300 μM).

RD161157 Table 11 In vitro inhibition parameters

Transporter	IC ₅₀ (μM)
OATP1B1	1.7
OATP1B3	4.7
OCT1	>300

At an elagolix clinical dose of 200 mg, free drug exposure in the portal vein is estimated to be at a level where inhibition of OATP1B1 may be observed; R-value is >1.25. No inhibition of the hepatic uptake transporters, OATP1B3 and OCT1 by elagolix is predicted; R-value <1.25.

Renal transporters: OAT1, OAT3, OCT2, MATE1, MATE2K

Because elagolix is primarily eliminated by biliary-fecal routes, no specific in vitro renal transporter substrate studies were conducted. Elagolix is an inhibitor of OAT1, OAT3, MATE1 and MATE2K.

RD161157 Table 13 In vitro inhibition parameters

Transporter	IC₅₀ (μM)
OAT1	161
OAT3	45
OCT2	>100
MATE1	19
MATE2K	145

Elagolix free drug plasma exposures from a 200 mg dose are not predicted to inhibit OAT1, OAT3 or OCT2; C_{max,ss,u}/IC₅₀ values are less than 0.1. Elagolix is also not predicted to inhibit MATE1 or MATE2K; C_{max,ss,u}/IC₅₀ values <0.1.

For comparison, a similar study carried out under IND 64802 in 2010 (4.2.2.6 Memo-02) obtained similar values for the IC₅₀ values for OAT1, OAT3, and OCT2 (Dr. Raheja's review filed 2-16-2012).

IC₅₀ values of A-1278823, probenecid and cimetidine for the uptake of reference substrates of OAT1, OAT3 and OAT2

	OAT1-mediated PAH uptake (IC ₅₀ uM)	OAT3-mediated ES uptake (IC ₅₀ , uM)	OCT2-mediated MPP+ uptake (IC ₅₀ ,uM)
A-1278823	176	42.5	>1000
Probenecid	13.4	5.28	NA
Cimetidine	NA	NA	264

Reference substrates: PAH for OAT1, ES for OAT3 and MMP+ for OCT2

Clinical studies assessed the predictions of the in vitro data for the following drugs:

RD161157 Table 15. Clinical Drug Interaction Studies, Elagolix as a Victim of DDI

Enzyme or Transporter	Mechanism	Evaluated Inducer/Inhibitor (Study Number[s])
CYP3A	Inhibition	Ketoconazole (M12-660)
CYP3A	Inhibition	Fluconazole (M15-974)
P-gp ^a	Induction	Rifampin (M12-659)
P-gp ^a	Inhibition	Rifampin (M12-659)
OATP1B1/3	Inhibition	Rifampin (M12-659)

RD161157 Table 16. Clinical Drug Interaction Studies, Elagolix as a Perpetrator of DDI

Enzyme or Transporter	Evaluated Sensitive Substrates (Study Number[s])
CYP3A	Midazolam (NBI-56418-0502; M15-629)
P-gp	Digoxin (M12-652)
OATP1B1/3	Rosuvastatin (M13-756)
BCRP	Rosuvastatin (M13-756)

See Clinical Pharmacology reviews and labeling for final conclusions regarding clinical relevance.

Analytical methods

Sponsor's text section 2.6.4.2.

Specific and sensitive bioanalytical assays have been developed and validated for the quantitative determination of elagolix, NBI-61962 (O-desmethyl metabolite M3) and NBI-54048 (N-dealkyl metabolite M6x) in mouse, rat, rabbit, dog, and monkey plasma. Elagolix, NBI-61962 and NBI-54048 were stable for at least 6 months in rabbit, dog and monkey plasma, and for at least 341 days in mouse plasma when stored at -70°C or below. Stability of elagolix, NBI-61962 and NBI-54048 was demonstrated for at least 355 days in rat plasma when stored at -70°C.

Across all species, the method for quantitation of elagolix in plasma was generally validated over the 5-2000 ng/mL concentration range, with a 5 ng/mL (8 nM) limit of quantitation. The methods for the quantitation of NBI-61962 were generally validated over a 2-800 ng/mL concentration range, with a 2 ng/mL limit of quantitation. The methods for quantitation of NBI-54048 were generally validated over a 1-250 ng/mL concentration range, with a 1 ng/mL limit of quantitation.

Species	Compound	Validation Range	Stability (-70°C)	Study Report
Mouse	Elagolix	5-2000 ng/mL	at least 341 days	R&D/12/766 R&D/13/036
	NBI-61962	2-800 ng/mL		
	NBI-54048	1-250 ng/mL		
Rat	Elagolix	5-2000 ng/mL	at least 355 days	R&D/12/764 R&D/13/035
	NBI-61962	2-800 ng/mL		
	NBI-54048	1-250 ng/mL		
Rabbit	Elagolix	5-2000 ng/mL	at least 186 days	R&D/12/761 R&D/17/0139
Monkey	Elagolix	5-2000 ng/mL	at least 6 months	R&D/12/760 R&D/17/0141
	NBI-61962	2-800 ng/mL		
Dog	Elagolix	5-2000 ng/mL	at least 178 days	R&D/12/765 R&D/17/0140
	NBI-61962	2-800 ng/mL		
	NBI-54048	1-250 ng/mL		

NBI-61962: N-desalkyl metabolite; NBI-54048: O-desmethyl metabolite

An additional note from the review by Dr. Raheja 4-30-08 on homogeneity: Homogeneity determination of NBI-56418 (Lot No. DV050016, PN336 and PN336B) in water formulation using HPLC with UV detection. Report No. MC05249 and MC05251. This study was conducted by the (b) (4) in 2005. Analytical method was acceptable and homogeneity was demonstrated.

5.2 Toxicokinetics

Over the long course of development of elagolix, a large number of TK studies were done across the various nonclinical species. For ease of review, the sponsor collated the major results from each species and presented most of them graphically (See RD150352). Briefly, this section summarizes studies that addressed the following aspects of dosing on TK parameters: formulation, gender, dose proportionality, and accumulation with repeat dosing. Human TK is given at the end of this section for comparison.

Formulation

Studies were conducted to evaluate the contribution of salt form and formulation (various aqueous vehicles, diet, or tablet) on the TK profile. Because the aqueous formulation was associated with mortality in the rodent – presumably due to aspiration and subsequent respiratory toxicity – the sponsor had to develop different formulations in order to successfully complete the long-duration tox studies. Selected results from these studies are summarized below.

Salts

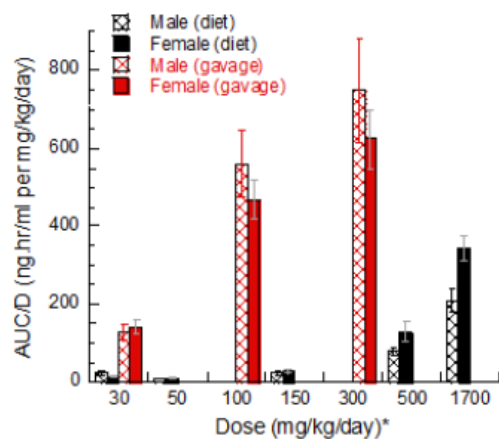
Various salt forms of elagolix (b) (4) were assessed for TK in mouse, rat, and dog. There were minimal differences in exposure between the salt forms. Given the similarities in exposures between salts, the sodium salt was utilized for most of the long term definitive toxicology studies.

Formulation

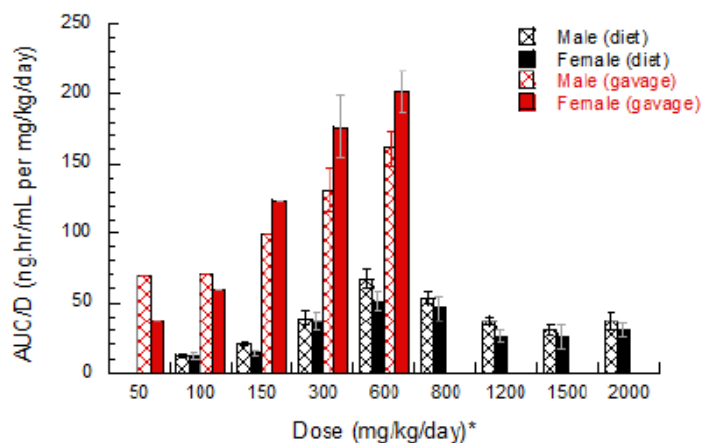
Various aqueous vehicles tested in mouse and rat will not be detailed here other than to note that exposures were comparable to each other and equal to or greater than exposures when corn oil was used as vehicle. More important were the studies characterizing dietary administration in the rat and mouse, and tablet formulation in the dog, since those are the formulations used in the long duration studies.

Gavage vs diet: AUCs from gavage dosing were ~2-3-fold higher than from administration in the diet in the rat and mouse. No gender differences were noted.

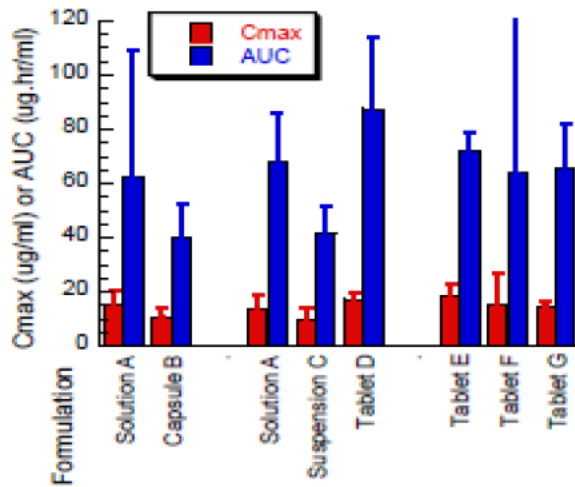
Effect of Gender, Dose and Route of Administration on Mean AUC following Multiple Oral Dosing in CD-1 Mice RD150352 Figure 3 p 9



Effect of Sex, Dose and Formulation on Mean AUC following Multiple Oral Dosing in SD Rats RD150352 Figure 7 p 12



In the dog, various aqueous and tablet or capsule formulations yielded similar exposures. Increased variability of exposure was generally associated with emesis following administration.



Effect of Formulation on the Elagolix Cmax or AUC following Single Oral Doses in Dog

Dogs [mean (SD); n=3-6]: sodium salt administered as a solution (A) or in a capsule (B); ^{(b) (4)} salt administered as a suspension (C) or as a ^{(b) (4)} based tablet (D); tablets of the sodium salt (E), the ^{(b) (4)} salt (F) or the ^{(b) (4)} salt (G)

2.6.4.3. Figure 2 p 9

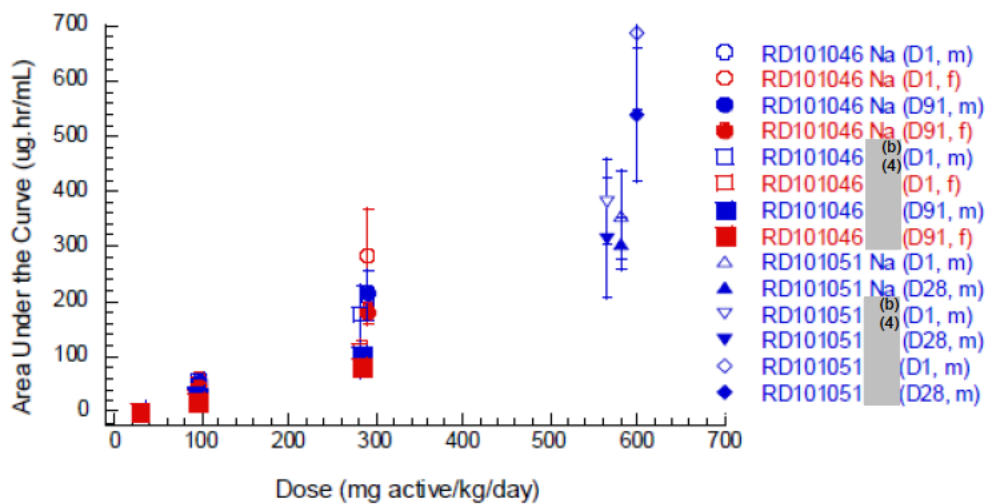
Gender

There were no consistent sex differences in AUCs from dogs or monkeys. AUCs in female rats were higher than in male rats when elagolix was dosed by gavage, but not when administered in the diet. AUCs in female mice were higher than in male mice only at high doses (>500 mg/kg/d) when administered via diet.

Dose proportionality

Elagolix exposures were generally slightly greater than proportional to the administered doses in all species. A representative graph is presented below from mouse study #RD150352. The graph depicts dosing using various salt forms of elagolix.

Mean A-1278823 Area Under the Curve following Oral Dosing in CD-1 Mice (Oral Gavage). RD



Accumulation with repeat dosing

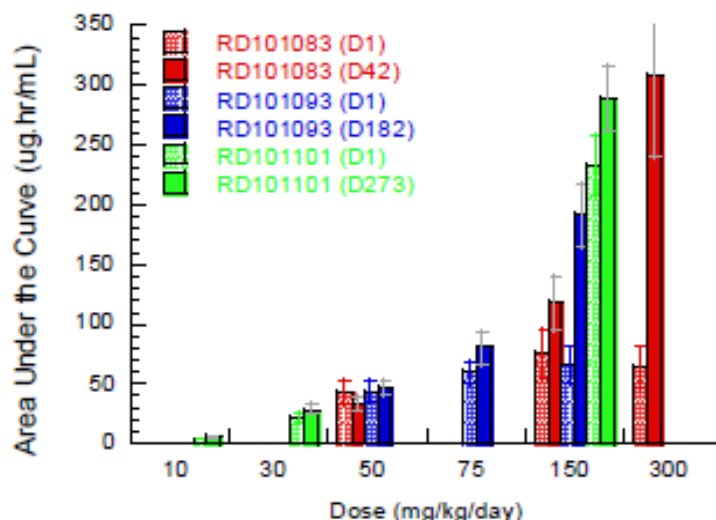
Mouse: Exposures after repeated daily dosing were comparable to those obtained at the beginning of the study in CD-1 mice.

Rat: In SD rats, the AUC after repeat dosing tended to remain unchanged at low doses (< 300 mg/kg), increased up to 3.5-fold after high doses (300 to 600 mg/kg) and decreased up to 68% after very high doses (1,200 mg/kg or above).

Rabbit: Exposures were 3-11-fold *higher* after multiple dosing in NZ white rabbits.

Dog: In the dog, the AUCs were comparable following up to 39 weeks of daily dosing up to 150 mg/kg; however, some exceptions were noted, particularly at high doses (≥ 150 mg/kg), where as much as a 5.4-fold increase in AUC was observed in the 6-week and 26-week studies.

Comparison of Elagolix Area Under the Curve (AUC) following Multiple Oral Dosing in Beagle Dog (Day 1 vs. end of study)
2.6.4. Figure 3 p 10.



Mean ($\pm$ SEM; males and females combined)

AUCs at the end of the study represented in closed bars; AUC on Day 1 graphed in cross-hatch bars
RD101083 (6w) and RD101093 (26w) administered solutions of the sodium salt in water (5 mL/kg);
RD101101 (9m) administered capsules ^{(b) (4)} of the sodium salt.

Monkey: In contrast, AUCs were nearly 10-fold *lower* after multiple dosing in cynomolgus monkeys. This decline occurred early in the study, with AUCs on Day 42 comparable to those measured on Day 91 in the 13-week study. The sponsor stated that the observed decrease in AUCs in monkey with multiple dosing did not appear to be caused by liver CYP enzyme induction, but did not provide data for an explanation. Because of the marked decline in AUC following multiple dosing in the monkey, it was not selected as the non-rodent species for toxicology studies.

HUMAN PK

Sponsor's text from section 2.5.1.4.: "Elagolix is rapidly absorbed from the gastrointestinal tract, with C_{max} occurring at approximately 1 hour. Elagolix affects the ovarian sex hormone cascade within hours of the first dose and has an elimination half-life of 4-6 hours. The shorter half-life as compared to other GnRH agonists is relevant, especially for patients experiencing adverse events, since the drug is eliminated within a week. The pharmacodynamic effect of elagolix on LH and FSH persists longer than the pharmacokinetic half-life, enabling efficacy with either QD or BID dosing.

Mean $\pm$ SD Pharmacokinetic Parameters of Elagolix (Study M12-790)

2.7.2 p 23 Clinical Pharmacology Summary Sponsor's Table 7

Pharmacokinetic Parameter (units)	150 mg QD N = 6	100 mg BID N = 7	200 mg BID N = 7	300 mg BID N = 8	400 mg BID N = 6
Study Day 1					
T_{max} (hr) ^a	1.3 (1.0 – 1.5)	1.5 (0.5 – 1.5)	1.0 (0.5 – 1.5)	1.3 (0.5 – 1.5)	1.3 (0.5 – 2.0)
C_{max} (ng/mL)	507 $\pm$ 207	285 $\pm$ 89	712 $\pm$ 362	1479 $\pm$ 740	1928 $\pm$ 783
AUC_{τ} (ng•hr/mL)	1331 $\pm$ 487	787 $\pm$ 288	1813 $\pm$ 876	3509 $\pm$ 1556	4918 $\pm$ 2070
Study Day 21^b					
T_{max} (hr) ^a	1.0 (0.5 – 1.0)	1.0 (0.5 – 1.5)	1.0 (0.5 – 1.5)	1.3 (0.5 – 1.5)	1.3 (0.5 – 1.5)
C_{max} (ng/mL)	574 $\pm$ 164	278 $\pm$ 131	774 $\pm$ 530	1200 $\pm$ 544	1758 $\pm$ 308
AUC_{τ} (ng•hr/mL)	1292 $\pm$ 403	779 $\pm$ 373	1725 $\pm$ 990	2826 $\pm$ 1231	3716 $\pm$ 592
$t_{1/2}$ (hr) ^c	6.42 $\pm$ 3.20	4.65 $\pm$ 2.54	4.29 $\pm$ 0.47	5.32 $\pm$ 1.52	5.62 $\pm$ 1.82
C_{trough} (ng/mL) ^d	0.84 $\pm$ 0.58	5.06 $\pm$ 4.25	5.92 $\pm$ 4.05	9.78 $\pm$ 4.68	11.9 $\pm$ 5.5
CL/F (L/hr)	123 $\pm$ 26	163 $\pm$ 91	144 $\pm$ 62	126 $\pm$ 58	110 $\pm$ 17
$V_{d\beta}$ /F (L)	1674 $\pm$ 1570	1499 $\pm$ 1709	881 $\pm$ 335	977 $\pm$ 327	1026 $\pm$ 512
R_{ac} ^e	0.98 $\pm$ 0.07	0.98 $\pm$ 0.15	0.89 $\pm$ 0.17	0.78 $\pm$ 0.09	0.84 $\pm$ 0.29
C_{max} /Dose	3.83 $\pm$ 1.09	2.78 $\pm$ 1.32	3.87 $\pm$ 2.65	4.00 $\pm$ 1.81	4.40 $\pm$ 0.77
AUC_{τ} /Dose	8.61 $\pm$ 2.68	7.79 $\pm$ 3.73	8.62 $\pm$ 4.95	9.42 $\pm$ 4.10	9.29 $\pm$ 1.48

a. T_{max} reported as median (range).

b. N = 6 on Study Day 21 for each of the dose groups.

c. Presented as the harmonic mean, pseudo-standard deviation.

d. C_{trough} is C_{12} for BID dose groups and C_{24} for the QD dose group.

e. Accumulation ratio calculated as the ratio of Study Day 21 AUC_{τ} to Study Day 1 AUC_{τ} .

Note: AUC_{τ} where τ is the dosing interval (i.e., 12 hours for BID and 24 hours for QD).

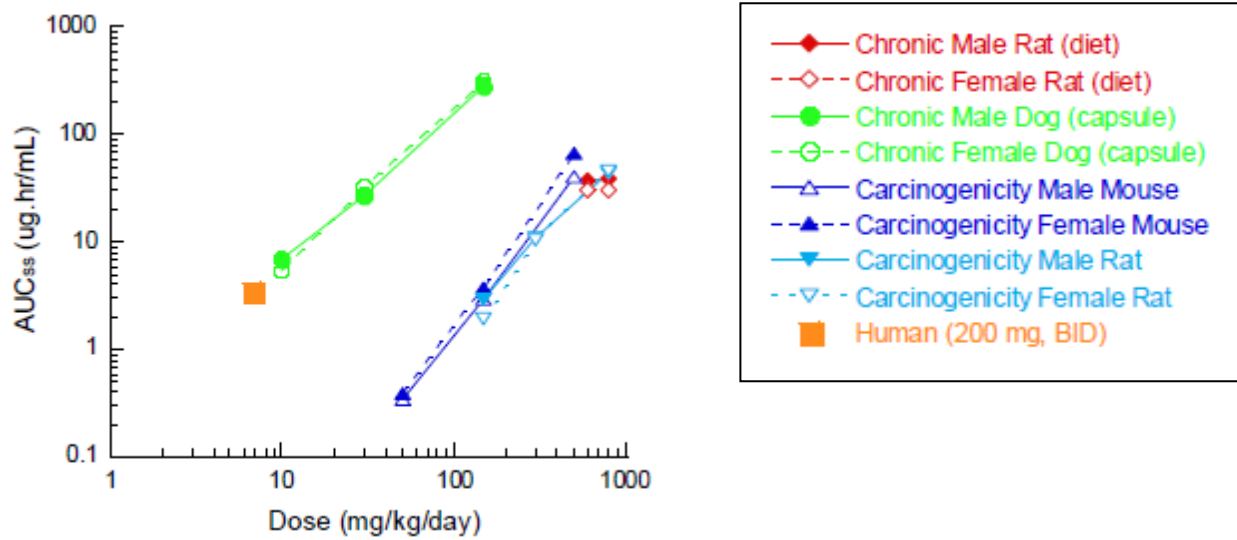
On the basis of steady-state pharmacokinetic data obtained on Study Day 21, elagolix is dose proportional from 100 mg BID to 400 mg BID, with mean T_{max} of 1 to 1.3 hours.

After reaching C_{max} , elagolix concentrations decline in a biphasic fashion, with a $t_{1/2}$ of ~4 to 6 hours. Through 400 mg BID, multiple doses of elagolix result in minimal accumulation as the mean accumulation ratio (R_{ac}) values based on AUC (Day 21/Day1) were close to 1 in all dose groups.

For calculation of MOEs relative to nonclinical dosing, the C_{max} and AUC for the 200 mg BID dose on d21 will be used. C_{max} = 774 ng/mL. The AUC value is doubled from 1725 ng.hr/mL to 3450 ng.hr/mL to account for exposure over 24 hrs.

Species comparison

**2.6.7.3 Toxicokinetics – Overview of Toxicokinetics Data
Steady state AUC**



Note: dosing in the carcinogenicity studies was via diet.

In general, exposure to primary metabolites was ~5% of parent across species.

6 General Toxicology

6.1 Single-Dose Toxicity

Non-GLP single-dose toxicity studies were conducted in rat and monkey and were not reviewed in detail. Methods and conclusions are briefly summarized below. Monkey was found to be the more sensitive species for single-dose exposure, likely due to much higher exposures for a given dose. Roughly 10-fold higher exposures were achieved in monkeys vs rats for a given dose.

Rat: Study #RD101041

Dosing: 300, 600, 1200, or 2000 mg/kg elagolix Na salt in water, oral gavage, 10 mL/kg
N = 3/sex/group SD rats

MTD was based on mortality, body weight, food consumption, clinical observations, and clinical pathology observed on Day 2. Gross pathology and organ weights were collected at necropsy on Day 4. Histopathology was not done.

3 animals were found dead (1 F at each of the 3 highest doses). Mortality was attributed to hypovolemia due to blood re-draws. At the two highest doses, there was an increase in bilirubin (~130% of control) in females. At the high dose, there were elevated liver enzymes (less than 2X) that were within the normal range for that facility. There was no other effect on clinical and gross pathology or organ weights. Males showed 50% decreased food consumption at the high dose.

MTD was set at 2000 mg/kg. NOAEL = 300 mg/kg. At this dose, the C_{max} and AUC₀₋₂₄ values were 2.5 µg/mL and 22.8 µg·hr/mL, respectively. Metabolite NBI-61962 was measured.

Monkey: RD101072

Dosing: 300, 600, 1200, or 2000 mg/kg elagolix Na salt in water, oral gavage, 10 mL/kg
N = 2/sex/group cynomolgus monkey

Due to error in body weight calculations, the actual doses ranged from 1380-1452 mg/kg for the 1200 mg/kg dose group and from 2320-2400 mg/kg for the 2000 mg/kg dose group. MTD was based on mortality, body weight, food consumption, clinical observations, and clinical pathology recorded on Day 2. Gross pathology and organ weights were recorded on Day 4 at necropsy. Liver was examined microscopically.

There was no mortality. Decreased food consumption was noted at the higher doses. Elevation in liver enzymes (ALT, AST) and total bilirubin was observed at all doses. ALT ↑ 1.2X - 2.2X. AST (males only) ↑5.8X at 1200 mg/kg and 11.9X at 2000 mg/kg. Increase in total bilirubin was maximal (7.6-fold) at 1200 mg/kg. Kidney-associated clinical chemistry changes included increases in creatinine level of up to 2.8-fold (maximal) and BUN level of up to 1.9-fold (maximal) at 1200 mg/kg only.

No changes were observed in gross pathology or organ weights. Hepatocellular centrilobular vacuolation consistent with microvesicular fatty changes was noted only in females at doses ≥ 600 mg/kg.

The 300 mg/kg dose was considered the MTD and the NOAEL, since changes in clinical chemistry parameters including ALT, AST, total bilirubin, blood urea nitrogen, creatinine, and glucose were ≤ 2.5-fold.

C_{max} and AUC₀₋₂₄ at the NOAEL (using the sex with the lower mean values) was 10.2 µg/mL and 75.8 µg·hr/mL, respectively. Metabolite NBI-61962 was measured.

6.2 Repeat-Dose Toxicity

RAT 2-week oral Reviewed by Dr. Raheja 1/12/07

A 14-day oral toxicity study of NBI-56418 in rats with a 7-day recovery. Study # RD101086 (b) (4) 882-013). GLP. N = 10 SD rats/sex/group in the main study and 3/sex/group in the control and high dose recovery groups. The dose levels were 0, 300, 600 and 1200 mg/kg/day by gavage.

Results:

Mortality: One female at 600 mg/kg/day and 5 males and 6 females in the 1200 mg/kg/day group. Gross necropsy findings consisted of discoloration of the lungs. Histopathological findings consisted of ulcerative tracheitis and/or bronchitis considered due to aspiration of test material. Cause of death in most of the animals was deemed due to gavage errors or test article in the chest cavity.

Clinical observations: In the surviving rats at the high dose there was red material around the mouth and/or nose, salivation, discolored hair, skin cold to touch, audible difficult and slow breathing, hunched posture and/or hypoactivity. Salivation at 600 and 1200 mg/kg. No clinical observations in the high dose recovery group.

Body weight: Body weight was decreased in the high dose group by 16% in males and 11% in females on day 14 and was correlated with decreased food consumption. Food consumption recovered but body weight did not fully recover at the end of the recovery period.

Clinical pathology: At the high dose: decreased hematocrit (7 – 11%); decreased Hb (11% in females only); increased reticulocytes (absolute and percent, 100- 169%); increased platelets (35 – 47%). Reticulocytes and platelets still elevated at 7-day recovery.

Gross pathology: red discoloration of lungs

Organ weights: 600 mg/kg females and 1200 mg/kg males and females had increased liver weight, increased adrenal weight, and one female with adrenal hyperplasia; decreased thymus weight, one female with thymic atrophy.

Histopathology: At the high dose, lymphoid necrosis in thymus, mandibular and mesenteric lymph nodes, and splenic atrophy in animals that died and in ¼ females at terminal sacrifice.

The sponsor considered 300 mg/kg/day as the **NOAEL** based on pulmonary microscopic changes, trace alveolar histiocytosis and hemorrhage at **300 mg/kg**. However, these findings were not due to toxicity of the drug, but were related to the formulation.

Systemic exposure at 300 mg/kg on day 1 was as follows:

C_{max}= 4.3 ug/ml and AUC₀₋₂₄= 35.3 ug.h/ml in males (minimum exposure value)

C_{max}= 3.3 ug/ml and AUC₀₋₂₄ = 21.4 ug.h/ml in females (minimum exposure value)

RAT - 6 week oral Reviewed by Dr. Raheja 1/12/07

Toxicity study by gavage administration to SD rats for 6 weeks followed by a 4-week recovery period. NBI-56418. Study # RD101089. (b) (4) /014. GLP. Dose levels were 0, 150, 300 and 600 mg/kg/day given by gavage. There were 10/sex/group in the main study, 12/sex/group in the TK dose groups and 5/sex/group in the control and high dose recovery groups.

Results:

Mortality: One female in the low dose TK group was sacrificed in extremis. Cause of death was not described and was considered unrelated to treatment.

Clinical observations: Rales in 1/10 males and 1/12 TK females. Salivation post-dose in all treated groups.

Body weight: A slight decrease in body weight gain in males given 600 mg/day (8%) and increase in females (5%) was reported.

Clinical pathology: Increased platelet count in 300 and 600 mg/kg females (up to 17.5%) and 600 mg/kg males (18.8%). Not considered adverse / within normal range. Platelet counts returned to normal in the recovery period. Immunotox: No effect on NK cell function or numbers of T and B cells. Decreased AST and ALT and decreased triglycerides in mid and high dose males and females.

Increased urinary pH in males and females and was reversible.

Organ weight: Increased relative liver weight in high dose males and females (up to 17%); reversible.

Gross pathology and histopathology: No treatment-related findings. Lymphoid system examined according to Kuper et al., Tox Path 28(3);454. (2000).

NOAEL = 600 mg/kg/day. At this dose C_{max} = 6.71 ug/ml and AUC_{0-24h} = 82.4 ug.h/ml in males and C_{max} = 3.05 ug/ml and AUC_{0-24h} = 48.4 ug.h/ml in females

RAT 13-week oral Reviewed by Dr. Raheja 5-2-2005.

A 13-week oral toxicity study of NBI-56418 in rats. Study #RD 101077. (b) (4) 882-033. GLP. 2004. Dose levels were 0, 100, 300 and 600 mg/kg/day.

(Note: a second 13-wk oral gavage study (RD101045) comparing (b) (4) salts of elagolix and a 15 week dietary range-finding study (RD101047) were conducted in the rat but were not reviewed).

Study design:

Group #	Dose level (mg/kg)	Number of animals	
		male	female
1 ^a	0 (control, sterile H ₂ O)	15	15
2	100	10	10
3	300	10	10
4 ^a	600	15	15
5 ^b	100	12	12
6 ^b	300	12	12
7 ^b	600	12	12

^a following 91 days of administration, 5 animals/sex were maintained for a 4-week recovery period.

^b TK groups

The animals were dosed via oral gavage at a volume of 10 mL/kg for 7 days and 5 mL/kg thereafter.

Observations: Mortality, morbidity, and availability of food and water were observed twice daily. Clinical observations and body weight measurements were conducted weekly. Food consumption for the main study animals was recorded weekly. Ophthalmoscopic examination was conducted prior to dosing and then at prior to scheduled necropsy. Blood and urine samples for clinical pathology evaluation were collected from main study animals prior to scheduled necropsies. Additional blood samples for determination of testosterone and estradiol were collected pretest and from main study animals prior to scheduled necropsies. Blood samples were collected from TK animals for the determination of plasma drug concentrations on Days 1, 42 and 91.

Results:

Mortality: Five main study animals were found dead: one male treated with 300 mg/kg/day (day 18 – dosing error), two males treated with 600 mg/kg/day (days 71-dosing error and 73 - undetermined) and two females treated with 600 mg/kg/day (days 11 and 62 – both undetermined).

There were four deaths in the TK groups. One male at 300 mg/kg/day (d1 after blood collection – due to anesthesia); one male at 600 mg/kg/day (d 51 dosing error); one female at 300 mg/kg/day (d 15 dosing error); and one female at 600 mg/kg/day (d 36, undetermined).

Clinical findings: Observations included incidences of decreased activity, salivation, soft or reduced number of feces and changes in respiration (audible and difficult breathing). Since salivation was not observed after week 2 of treatment, it suggests that salivation is treatment-related, physiological mechanism of which is not explained. The difficult breathing, audible breath sounds and subsequent death of these animals was considered to be related to dosing errors and could be related to macroscopic and microscopic findings in these animals i.e. presence of edema and foreign material in the lungs.

Body weight and food consumption: No treatment related effects.

Ophthalmoscopic examination: No treatment related effects.

Urine volume increased (up to 2.2 x). Urine pH was increased in both males and females at 600 mg/kg/day. It was unclear whether these changes were test article related or incidental.

Clinical pathology: Decreased Hb and Hct in 600 mg/kg females, increased platelet counts (up to 34%) and lymphocytes (up to 29%) in both genders. Sponsor considered changes small and not treatment related. Increased phosphorus, decreased ALT and cholesterol (29%) in high dose males; increased GGT (70%), total protein, globulin and cholesterol (30%) in high dose females. These changes considered not treatment-related due to lack of correlated histopathology.

As shown in the table below a significant increase was observed GGT, AST and ALT in high dose females, although none exceeded 3-fold. The mean ALT value in the high dose male group was significantly lower ($p < 0.05$) compared to control.

Parameter	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	600 mg/kg/day
GGT (U/L)	1.0 +/- 0.00	1.0 +/- 0.00	1.1 +/- 0.32	1.7 +/- 0.50 ^b
AST (U/L)	65.9 +/- 8.75	70.1 +/- 16.37	62.8 +/- 8.42	85.1 +/- 57.57
ALT (U/L)	30.8 +/- 6.76	30.2 +/- 9.85	30.4 +/- 7.21	73.8 +/- 91.02

^b significantly different from control $p < 0.01$.

2 females in the 600 mg/kg/day group had AST values of 202 and 165 U/L and this female had ALT values of 267 and 195 U/L.

Testosterone and estradiol analysis: Testosterone levels in males prior to test article administration were between 0 and 3 ng/ml with a mean of 1.67 ng/ml. Following terminal necropsies, males treated with 0, 100, 300 and 600 mg/kg/day had mean testosterone levels of 1.2 ng/ml (range of 0- 4), 1.8 (range 0 to 4), 1.7 (range 1 to 5), and 2.2 (range 0 to 40 ng/ml, respectively. Following the recovery period, mean testosterone level in both treated and control animals were the same, 1.2 ng/ml. In females, estradiol levels prior to drug administration ranged from 0 to 12 pg/ml. Estradiol levels were very variable and overall decreased in all treated groups. Due to these variations, the sponsor stated that evaluation of the effects of NBI-56418 on estradiol levels could not be determined.

Organ weights: Significant drug-related changes were present in male and female liver and adrenal weights. Adrenal weight was increased 140% in the 600 mg/kg/day female group but was decreased 75% in the 600 mg/kg/day male group. Liver weight changes are shown below. Maximum change was 45% (liver wt relative to body wt, high dose females).

Liver weight values for male rat				
Parameter	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	600 mg/kg/day
Liver (g)	14.95	13.95	15.41	17.62
Liver/B.Wt %	2.943	2.874	3.083	3.410 ^b
Liver/BrWt ratio	7.284	6.841	7.580	8.847 ^b
Liver weight values for female rat				
Liver (g)	7.81	8.13	9.52 ^b	11.24 ^b
Liver/BWt %	2.900	2.983	3.380	4.242 ^b
Liver/BrWt ratio	4.157	4.371	5.187 ^b	6.140 ^b

^b significantly different from control p<0.01
Values are mean for 10 rats.

Microscopic findings: Minimal to mild panlobular hepatocellular hypertrophy was present in 8 of 9 high dose females.

Taken together, the increased liver weights, increased liver enzymes, and microscopic findings of hepatocellular hypertrophy indicate a treatment-related adaptive response in the liver.

Plasma concentration of NBI-56418 for dosed groups is shown below:

Day	Dose	Gender	Tmax (hr)	Cmax (ng/ml)	AUC (ng.hr/ml)	Dose-adjusted Cmax (ng/ml)/mg/kg)	Dose adjusted AUC (ng.hr/ml)/(mg/kg)
1	100	F	0.25	1020	2890	10.2	28.9
1	300	F	0.25	1650	16100	5.5	53.7
1	600	F	8	3040	39000	5.07	65
1	100	M	0.25	1270	2850	12.7	28.5
1	300	M	0.5	1800	19500	6	65
1	600	M	8	3790	47100	6.32	78.5
42	100	F	0.5	2430	5460	24.3	54.6
42	300	F	1	3940	35300	13.1	118
42	600	F	1	5860	64600	9.77	108
42	100	M	2	1360	6030	13.6	60.3
42	300	M	4	2820	38400	9.4	128
42	600	M	4	6780	75100	11.3	125
91	100	F	0.5	1810	5420	18.1	54.2
91	300	F	1	5370	39500	17.9	132
91	600	F	2	13500	135000	22.5	225
91	100	M	1	1260	6250	12.6	62.5
91	300	M	0.5	3400	38300	11.3	128
91	600	M	2	9830	90300	16.4	151

Exposure increased with increasing dose and duration of administration suggesting drug accumulation.

The **NOAEL was 300 mg/kg** and the NOEL was 100 mg/kg. TK parameters at the NOAEL on day 91 was as follows (average of male and female):

Cmax = 4.4 ug/ml; AUC (0-24 h) = 38.9 ug.h/ml. MOE = 11.

RAT 26 week oral Reviewed by Dr. Raheja 1-12-07

Study title: A 26-week oral toxicity study in Sprague Dawley rats followed by a 4-week recovery period.	
Study no.:	RD101044
Study report location:	Application 210450 - Sequence 0000 - RD101044 26-Week Oral Toxicity Rat Recovery
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10-26-2005
GLP compliance and QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418, DV050016, 98.7%

Key Study Findings

There was significant dose-related mortality ascribed to respiratory distress secondary to aspiration of the test article. Treatment-related clinical observations included decreased activity and respiratory distress which included rales, gasping, wheezing, salivation and shallow respiration. Histopathology findings (inflammation) in the bronchii and trachea supported the inference of aspiration of drug as a cause of respiratory distress.

Based on mortality, histopathologic changes and clinical signs of respiratory distress observed at 300 mg/kg/day, the **NOAEL was set at 100 mg/kg/day**. On Day 182, exposure at this dose level was C_{max} and AUC_{last} equal to 1,730 ng/ml and 7,720 ng*hr/ml, respectively in the males, and C_{max} and AUC_{last} equal to 2,050 ng/ml and 6,540 ng*hr/ml, respectively for females.

Methods	
Doses:	0, 50, 100, 300, 600 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	Water; Formulation analysis acceptable
Species/Strain:	Rat / SD
Number/Sex/Group:	20/sex/group; 5/sex in the control and high dose groups for recovery
Age:	8-10 wks
Weight:	294-528 (M) 215-311 (F)
Satellite groups:	TK 12/sex/group Sampled on days 1, 42, 91 and 182
Deviation from study protocol:	During weeks 23 to 24, due to mortality and animal welfare issues, dosing activities were halted in high dose animals, which were then sacrificed during weeks 24 to 25 as scheduled sacrifices. Surviving high dose TK animals were reassigned to main and recovery study phases. The newly formed group 5 recovery study was allowed to recover for 29-day period. Also during week 26, 5 main study males and 4 main study females from the 300 mg/kg dose group were transferred to recovery study to provide the intermediate high dose of 300 mg/kg/day with recovery phase to assess reversibility following completion of 26-week treatment period.

Final study design

Treatment Groups	Dose Level (mg/kg)	Dose Conc. (mg/mL)**	Number of Animals					
			Main##		Toxicokinetics#		Recovery##	
			M	F	M	F	M	F
1. Control*	0	0	20	20	0	0	5	5
2. Low	50	10	20	20	12	12	0	0
3. Mid-Low	100	20	20	20	12	12	0	0
4. Mid-High	300	60	15	16	12	12	5	4
5. High	600	120	20	20	12	12	5	5

Observations and Results

Mortality

There were a total of 42 deaths during the study (38 main and 4 recovery) showing dose-related trend. There were also 17 TK deaths. Mortality in different groups is shown in table below:

Group	Dose mg/kg/day	Main		TK		Recovery	
		Male	Female	Male	Female	Male	Female
Control	0	0	1	0	0	0	1
Low	50	0	2	0	0	-	-
Mid-low	100	1	0	0	0	-	-
Mid-high	300	5	7	3	1	-	-
High	600	9	13	8	5	2	1
Total/Total #		15 / 95	23 / 96	11 / 48	6 / 48	2 / 15	2 / 15
% mortality		16	24	23	13	13	13

Clinical signs:

The major clinical signs were respiratory distress and salivation. Respiratory distress was reported in 0, 1, 0, 11 and 23 animals and salivation in 0, 0, 0, 6 and 12 animals, respectively in the 5 treatment groups. Respiratory distress included rales, gasping, wheezing, and increased/decreased/shallow respiration and was greater in severity in the 300 and 600 mg/kg dose groups. The sponsor attributed this to possible aspiration of stomach contents with dose formulation, resulting in irritation of the respiratory tract. Decreased activity was observed in 0, 1, 0, 7 and 6 animals, respectively.

There were no treatment-related clinical signs during the recovery period. The cause of death of 1/10 control and 1/10 group 5 recovery animals during the treatment phase was not determined.

Body Weights: Body weight was decreased in males given 600 mg/kg/day dose from week 5 onward. Only mild reductions were noted in high dose females.

Feed Consumption: Reduced in the high dose group during the first two weeks of treatment. Otherwise no significant changes

Ophthalmoscopy: No treatment related findings

ECG: not conducted

Hematology: No treatment-related effects

Clinical Chemistry: No treatment-related effects

Urinalysis: No treatment-related effects

Gross Pathology: Dilatation of the cecum, small intestine (duodenum, jejunum, ileum) was reported in 0, 1, 0, 3 and 17 rats, respectively, in the 5 treatment groups. Other treatment-related gross findings involved thymus (dark focus) in 1, 1, 1, 6 and 12 animals, respectively.

Lungs had dark discoloration and were mottled in 0, 1, 0, 5 and 6 rats, respectively. Foamy pale material or foamy or watery clear fluid in the tracheal lumen of a few preterminal animals at 300 mg/kg/day (Group 4) and 600 mg/kg/day (Group 5) were correlated with the tracheal inflammation/fibrin accumulation in the tracheal lumen.

Organ Weights: No treatment-related effects

Histopathology: Adequate Battery: yes Peer Review: no

Histopathology was centered on respiratory system. Tracheal changes in the found-dead animals (2 main females at 300 mg/kg/day, 2 main male and 5 main females at 600 mg/kg/day) were characterized by acute inflammation of the tracheal mucosa and/or necrosis of the tracheal epithelium and /or fibrin accumulation in the tracheal lumen, with or without hemorrhage of the tracheal mucosa, atrophy of the tracheal epithelium and hyperplasia/hypertrophy of the tracheal epithelium.

In animals that were pre-terminally sacrificed (1 main female at 300 mg/kg/day and 5 males at 600 mg/kg/day), findings were characterized by inflammation of the tracheal mucosa and/or necrosis (or atrophy/necrosis) of the tracheal epithelium and/or fibrin accumulation in the tracheal lumen, with or without atrophy of tracheal epithelium and hyperplasia/hypertrophy of the tracheal epithelium. The sponsor suggested that tracheal changes were initiated by regurgitated / refluxed stomach contents, which may be partially supported by the gaseous dilatation of the stomach in some rats.

Bronchial changes, including acute necrotizing inflammation of the bronchiolar lining and fibrin accumulation in the larger bronchial lumens, with or without atrophy/necrosis and hyperplasia/hypertrophy of bronchiolar epithelium, were noted in pre-terminally sacrificed rats (1 F at 50 mg/kg/day, 1 F at 300 mg/kg/day, 1 M and 3 F at 600 mg/kg/day) and in found-dead animals (1 M and 1 F at 300 mg/kg/day, 1 M and 4 F at 600 mg/kg/day). These findings were considered an extension of the tracheal changes in the preterminal rats.

The sponsor considered tracheobronchial inflammation or bronchial inflammation as the probable cause of death for most found-dead animals and tracheobronchial inflammation with fibrin accumulation as the main change responsible for the deteriorating condition of the pre-terminally sacrificed animals.

Pulmonary changes (intra-alveolar homogenous eosinophilic material, intra-alveolar histiocytosis, congestion, septal/interstitial edema, intra-alveolar hemorrhage) occurred at variable intensity and severity in preterminal animals from various NBI-56418-treated groups and were considered secondary to the tracheal and bronchial changes.

Treatment-related changes involving lymphoid tissue consisted of thymic cortical lymphoid atrophy, increased thymic cortical lymphoid single cell necrosis and splenic lymphoid atrophy of white pulp, noted at variable incidence and severity in preterminal rats from various NBI-56418-treated groups were considered most likely reactions to the stress of experimentation.

Toxicokinetics:

The C_{max} (ng/ml) and AUC_{last} (ng.h/ml) for treatment days 1, 42, 91 and 182 are given in the table below. Values at the NOAEL are highlighted.

Dose/Day mg/kg/day	T _{max} (h)		C _{max} (ng/ml)		AUC _{last} (ng.h/ml)	
	Male	female	male	female	male	female
50				963		
Day 1	1.0	0.5	776	974	2330	2800
42	0.5	0.5	984	1180	2410	2440
91	0.5	1.0	1230	840	2720	3020
182	0.5	1.0	877		3470	1990
100						
Day 1	4.0	4.0	1430	1360	8480	9220
42	0.5	0.5	1640	1640	5050	6670
91	1.0	1.0	2040	2360	6000	10400
182	0.5	0.5	1730	2050	7720	6540
300						
Day 1	8.0	8.0	2530	2610	22200	21700
42	1.0	8.0	4590	3590	24200	32700
91	1.0	1.0	2920	11500	25400	52000
182	8.0	8.0	3690	9140	31600	60900
600						
Day 1	2.0	1.0	3570	3200	41300	37100
42	12	2.0	10200	8250	143000	62500
91	2.0	2.0	14700	13000	88500	120000
182	NA	NA	NA	NA		NA

The 600 mg/kg/day group was terminated prior to day 182; hence no TK plasma samples were collected.

TK shows that there were no consistent gender differences. NBI-56418 exposure appears similar between day 1 and 182 for 50 and 100 mg/kg/day dose groups. However, with 300 and 600 mg/kg doses, exposure increased with duration of treatment suggesting drug accumulation.

Stability and Homogeneity: Adequate

Rat 28-week oral diet

Study title: 28-Week Bridging Chronic Toxicity and Toxicokinetic Study with A-1278823 Sodium in Rats Using the Dietary Route of Dosing	
Study no.:	RD11756
Study report location:	Application 210450 - Sequence 0000 - RD11756 28-Week Bridging Diet Rat
Conducting laboratory and location:	(b) (4)
Date of study initiation:	25 July 2011
GLP compliance and QA statement:	Yes / yes
Drug, lot #, and % purity:	A-1278823, 03805YS00 also assigned lot#30005277, 95.4%

Key Study Findings

There was no treatment related mortality.

Given the presence of adverse microscopic findings in the limiting ridge of the nonglandular stomach at both 600 and 800 mg/kg/day, a NOAEL could not be established in this study. However, since the gastric limiting ridge is unique to rats (and mice) and is not an anatomical structure present in humans, this finding is not considered clinically relevant.

The Day 193 AUC (lower of male or female mean value) at the 800 mg/kg/day dose was 29.9 $\mu\text{g}\cdot\text{hr}/\text{mL}$. This AUC provides a safety margin of **8.5-fold** with respect to the AUC of 3.5 $\mu\text{g}\cdot\text{hr}/\text{mL}$ at the MRHD.

Methods	
Doses:	0, 600, 800 mg/kg/d Both treatment groups were dosed at 150 mg/kg/d during week 1 and 300 mg/kg/d during week 2. Final doses were given starting at week 3 through termination.
Frequency of dosing:	Daily
Route of administration:	Oral diet
Dose volume:	N/A
Formulation/Vehicle:	(b) (4)
Species/Strain:	Rat / SD
Number/Sex/Group:	20/sex/group; 5/sex in the control and high dose groups for recovery
Age:	6.4-7.3 wks
Weight:	217-295 (M) 146-195 (F)
Satellite groups:	TK 5/sex/group Sampled on days 15, 39, 102, and 193
Deviation from study protocol:	None that affected study outcome

Observations and Results

Mortality: One high dose male was sacrificed on Day 134 because of a skin mass on the nose. Two toxicokinetic males, one control and one low dose were sacrificed in moribund condition on Days 194 and 22, respectively. None of these were deemed treatment-related.

Clinical signs: none-treatment related

Body Weights: At the end of the dosing period on Day 197, difference in body weight gain between the control and high dose animals (both male and female) was about 5%. The body weight decline in animals with histopathology findings in the limiting ridge of stomach was, overall, comparable to other animals in the respective dose levels.

Feed Consumption: Overall (between Days 1 and 194), food consumption showed a 2.8 or 6.6% decrease in males given up to 600 or 800 mg/kg/day, respectively, and a 6% decrease in both groups of females given up to >600 mg/kg/day, when compared to their respective controls. The food consumption decline in animals with histopathology findings in the limiting ridge of stomach was, overall, comparable to other animals in the respective dose levels.

Ophthalmoscopy: No treatment related findings

ECG: not conducted

Hematology:

- Minimally to mildly lower hemoglobin (5.5 to 11% lower), hematocrit (3.4 to 10% lower), mean corpuscular volume (3.3 to 5.3% lower), and mean corpuscular hemoglobin (3.8 to 6.0% lower) in males and females given 800 mg/kg/day and females given 600 mg/kg/day
- Minimally higher red cell distribution width (3.4 to 7.8% higher) in low dose females
- Minimally higher white blood cell (22% higher) and absolute neutrophil (46% higher) counts in high dose females

Sponsor's note: "Increases in white blood cell and neutrophil counts were consistent with inflammation that correlated with microscopic findings observed in the nonglandular stomach (erosion, inflammation, hyperplasia, and/or ulceration). Minimally higher platelet count in females given > 600 mg/kg/day may also have been associated with gastric inflammation. Changes in red cell parameters were minor and may have been due to reduced food consumption or secondary to inflammation."

Clinical Chemistry:

- Mildly higher globulin (20 to 32% higher) resulting in higher total protein (6.3 to 7.6% higher) and lower albumin-to-globulin ratio (9.5 to 24% lower) in low dose females
- Minimally to mildly higher cholesterol (29 to 49% higher) in low dose females
- Minimally higher ALP (1.3x) and GGT (1.7x) activities in high dose males

Sponsor's note: "High globulin in females, in combination with higher neutrophils seen at 800 mg/kg/day, was consistent with an inflammatory response observed microscopically in the nonglandular stomach (erosion, inflammation, and/or ulceration). Higher cholesterol may have been associated with follicular cell hypertrophy in the thyroid gland, and minor elevations in ALP and GGT correlated with hepatocellular hypertrophy and/or vacuolation observed microscopically in the liver. One high dose male had the most pronounced increase in ALP (2.3X) and GGT (>6X). Findings in the liver and thyroid were consistent with adaptive changes secondary to microsomal enzyme induction."

Urinalysis: No treatment-related effects

Gross Pathology:

Organ Weights:

Organ weight changes associated with microscopic findings were noted at both doses in the liver of males and females and thyroid/parathyroid glands (weighed together) of males, and at the high dose in the thyroid/parathyroid glands and ovary of females.

Daily Dose (mg/kg)	0 (Control)		600		800	
Number of Animals	M:20	F:20	M:20	F:20	M:20	F:20
Organ Weights (Absolute wt. (g) included for all groups for Thyroid/Parathyroid and Ovary because the absolute weights for these organs were too small)						
Liver (in 'g' for control and % change for others)	14.65	8.0	+15.7	+25	+31.9	+46.3
Thyroid/Parathyroid	0.030	0.023	0.040*	0.025	0.036	0.03*
Ovary	NA	0.15	NA	0.14	NA	0.12*

Histopathology: Adequate Battery: yes Peer Review: no

The following findings were considered non-adverse exaggerated pharmacology:

Liver: minimal to slight hepatocellular hypertrophy and/or vacuolation in males and females given ≥ 600 mg/kg/day and minimal to moderate increases in multinucleated hepatocytes in females given 800 mg/kg/day.

Thyroid: Follicular cell hypertrophy (minimal to slight) and/or hyperplasia (minimal) in males and females. A thyroid follicular cell adenoma was observed in one female.

Pituitary: The pituitary gland change in males was notable at 800 mg/kg/day and was characterized by minimally enlarged pituitary cells containing a single vacuole.

Ovaries: The ovaries at ≥ 600 mg/kg/day were characterized by a dose-responsive exacerbation of involution/decreased corpora lutea. The effect on ovaries was described in the study report as characteristic of an age-related involution, but a pharmacology-mediated effect cannot be ruled out given the high elagolix dose and the relatively long duration of exposure.

Findings in the stomach were considered adverse:

Minimal to moderate focal degeneration/necrosis in the nonglandular stomach at both doses. This focal change was localized to the limiting ridge of the nonglandular stomach and was characterized by edema, erosion, inflammation, hyperplasia of the epithelium, and/or ulceration. Similar changes were noted in control animals, but with a lower incidence and lower severity. The limiting ridge degeneration/necrosis was considered adverse for the rat, but is a rodent specific observation.

Daily Dose (mg/kg)	0 (Control)		600		800	
Number of Animals	M:20	F:20	M:20	F:20	M:20	F:20
Microscopic Observations (changes in liver and thyroid glands were considered adaptive to high doses of elagolix and not included) these included hepatocellular hypertrophy and /or vacuolation in liver and follicular cell hypertrophy and hyperplasia (minimal) for thyroid gland						
Stomach, non-glandular						
Degeneration/necrosis, limiting ridge, focal	1	3	7	4	5	8
- Minimal	0	3	5	3	1	4
- Slight	1	0	1	1	1	2
- Moderate	0	0	1	0	3	2

Toxicokinetics:

The C_{max} (ug/ml) and AUC_{last}(ug.h/ml) for treatment days 15, 39, and 193 are given in the table below (from Tabulated summary 2.6.7.7.7 p 62)

Daily Dose (mg/kg)	0 (Control)		600		800	
Number of Animals (Toxicokinetics - Satellite)	M:5	F:5	M:5	F:5	M:5	F:5
Toxicokinetics:						
C _{max} (ug/mL)						
Day 15:	BLQ	BLQ	3.33	2.54	3.21	1.79
Day 39:	BLQ	BLQ	2.18	1.86	2.15	1.48
Day 193:	BLQ*	BLQ*	2.62	2.61	3.19	4.76
AUC (ug•hr/mL)						
Day 15:	NA	NA	34.2	24.7	37.5	18.5
Day 39:	NA	NA	26.8	22.0	31.4	20.0
Day 193:	NA	NA	37.1	30.3	38.9	29.9

Stability and Homogeneity: Adequate

DOG

(b) (4)

DOG 6-week oral Reviewed by Dr. Raheja 1-12-07

A 6-week oral toxicity study of NBI-56418 in dogs with 4-week recovery. RD101083. GLP.

Doses were 0, 50, 150 and 300 mg/kg/day by gavage for 6 weeks. There were 6 dogs/sex in the control and 150 mg/kg dose groups, and 4 dogs/sex in the 50 and 300 mg/kg dose groups. 2 dogs/sex from the vehicle and high-dose groups were maintained for recovery.

Results:

Mortality: One high dose female was euthanized on day 7. The sponsor attributed it to possible gavage error and test article aspiration.

Clinical observations: Doses of 50 mg/kg and greater caused salivation, emesis and changes in feces which increased in incidence with increased dose.

Body weight: Decreased in high dose males by 33%. Feed consumption was also decreased by 41%.

Clinical pathology: At the high dose, erythrocyte count decrease was mild to moderate (% not given) while albumin was decreased up to 40%. Liver enzymes (ALT, ALP, AST) were elevated up to 299%.

ECG: No change

Gross pathology: At the high dose there was mild depletion of adipose tissue and thymic atrophy.

Organ weights: At the high dose thymus weight was decreased (absolute and relative to brain, approx. 80% of control); in the mid dose males and high dose males and females, liver weight was increased relative to body weight.

Histopathology: At 150 and 300 mg/kg, changes were noted in arteries, mild bone marrow depletion, spleen, liver, and gallbladder consistent with idiopathic canine polyarteritis (changes in these organs not detailed). Thymus was atrophied. There was mild extramedullary hematopoiesis noted in one mid-dose male after recovery.

Hormone analysis: There were no distinct test article-related effects on hormones. Testosterone was significantly decreased at termination at 300 mg/kg/day, and at recovery at 150 mg/kg/day, relative to controls, but in both cases the testosterone values were higher than pretest values. Estradiol was also decreased in the females at 300 mg/kg/day at termination, but was mostly due to one animal.

Samples for TK were taken on d1, d21, and d42. Exposures were higher on d21 than on d1 but comparable between d21 and d42. There were no gender differences.

NOAEL = 50 mg/kg. Exposure at the NOAEL on d42 was as follows:

C_{max} = 13.2 ug/ml; AUC = 36.3 ug.h/ml in males.

C_{max} = 10.0 ug/ml; AUC = 32.3 ug.h/ml in females

Metabolite NBI-61962 was <2% (C_{max}) or <1% (AUC) of parent.

DOG 26-week oral

Study title: A 26 Week Oral Toxicity of NBI-56418 in dogs	
Study no.:	101093
Study report location:	Application 210450 - Sequence 0000 - RD101093 26 Week Oral Toxicity Dog
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 2005
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418, DV050016, 95%

Key Study Findings

There was unscheduled mortality: 2 males at the low dose and 3 males at the high dose. Four were found dead and one was euthanized. Cause of death was attributed to dosing error/ aspiration of test article based on macroscopic and microscopic observation in the trachea and lungs. Treatment was associated with decreased activity, salivation, emesis and difficulty breathing.

There were minimal findings of toxicological significance. At the high dose, ALT was elevated 2.5-fold levels in males and ALP was elevated 39% in females. Testosterone in males and estradiol in females was not affected by treatment.

Based on elevated liver enzymes at the high dose, **NOAEL was set at 75 mg/kg/d.**

Cmax and AUC at the NOAEL on d182 (See Tox tabulated summary 2.6.7.7.8. p 64):
 Males: 22.7 ug/mL and 82.9 ug.hr/mL Females: 22.2 ug/mL and 77.3 ug.hr/mL.
 AUC was increased 22% (M) or 49% (F) at d182 compared to d1 (F).

The Cmax and AUC of metabolite NBI-61962 were both <5.0% of parent at all doses.

Methods	
Doses:	0, 50, 75, 150 mg/kg
Frequency of dosing:	daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	Water; pH adjusted to pH 8.56 – 9.00 Concentration was verified to be 87.7-108%
Species/Strain:	Beagle dog
Number/Sex/Group:	6/sex/dose at the control and high dose 4/sex/dose for the low and mid-dose 2/sex/dose at the control and high dose were used as recovery animals
Age:	7-8 months
Weight:	8.6-11.44 kg (M) 5.85-8.08 kg (F)
Satellite groups:	None. TK samples were taken from all animals on d1, d42, d91, and d182.
Deviation from study protocol:	None significant

Observations and Results

Mortality:

Dose mg/kg	Day of death	Clinical observations
50	1	Found dead following dosing; decreased activity, emesis and salivation and difficulty breathing.
50	144	Found dead
150	33	Found dead following dosing; decreased activity, emesis and salivation and difficulty breathing.
150	144	Found dead
150	158	Euthanized in extremis

Clinical Signs: pretest and weekly

Clinical signs included decreased activity, salivation, emesis, difficulty breathing and changes in feces. The incidence of these observations in both sexes was described as dose-related.

Body Weights: weekly

There were no significant effects on mean body weight or body weight gain.

Feed Consumption: weekly

Food consumption was not affected at the low and mid-dose. Food consumption in males at the high dose was significantly increased during several weeks of the study

Ophthalmoscopy: pretest and prior to the terminal and recovery necropsies

No treatment-related findings.

ECG: During week 26 (predose and 1 hour postdose) and at recovery

There were no treatment-related qualitative or quantitative ECG abnormalities.

Hematology and coagulation: pretest, during week 13, and prior to terminal and recovery necropsies. Significant treatment-related hematological changes are given in the table below:

Endpoint	Time Point	Males				Females			
		0 mg/kg/d	50 mg/kg/d	75 mg/kg/dy	100 mg/kg/d	0 mg/kg/d	50 mg/kg/d	75 mg/kg/d	100 mg/kg/d
Platelet s 10 ³ /ul	Pretest	380	394	390	370	403	380	413	354
	Wk 13	333	315	360	460^b	338	334	348	392
	terminal	313	307	356	515^b	321	374	443^b	431^b
Absolute reticulocytes 10 ³ /ul	Pretest	36	23	36	33				
	Wk 13	31	26	35	23				
	terminal	30	28	28	76 ^b				
% reticulocytes	Pretest	0.48	0.35	0.48	0.43				
	Wk13	0.43	0.38	0.48	0.34				
	terminal	0.40	0.40	0.35	1.03^b				
APTT sec	Pretest					9.35	9.93	8.98	9.08
	Wk13					9.08	9.45	8.38	8.37^a
	terminal					10.47	10.43	9.73	9.65^b

There were 6, 4, 4, and 6 dogs in the 0, 50, 75 and 100 mg/kg/day dose groups. b=p < 0.01 a= p <0.05

Unscheduled samples were collected from two male animals (one low dose and high dose) that were found in poor condition on days 98 and 158, respectively. Both of these animals had markedly increased RBC, Hb and Hct and moderately increased total protein, representative of dehydration. The high dose animal had increased leukocytes, reticulocytes, neutrophils, lymphocytes, monocytes and markedly prolonged APTT and PT. The low dose animal had mildly increased reticulocytes, APTT and PT. Biochemically, both of these animals had moderate to markedly increased bilirubin, AST and creatine kinase. In addition, the low dose animal had increased ALT and sorbitol dehydrogenase with moderate increased urea nitrogen while the high dose animal had mildly increased ALT and urea nitrogen.

Clinical Chemistry: pretest, during week 13, and prior to terminal and recovery necropsies. Significant treatment-related changes are given in the table below

Endpoint	Time point	Males				Females			
		0 mg/kg/d	50 mg/kg/d	75 mg/kg/d	100 mg/kg/d	0 mg/kg/d	50 mg/kg/d	75 mg/kg/d	100 mg/kg/d
GGT U/L	Pretest	2.8	3.0	2.8	3.0				
	Wk 13	2.3	2.8	2.8	1.8				
	terminal	3.8	4.0	3.8	6.5^a				
ALT U/L	Pretest	31.0	32.5	30.3	34.2				
	Wk 13	36.0	38.8	40.5	38.0				
	terminal	36.3	36.3	38.0	89.5^a				
ALP U/L	Pretest					107.8	84.3	84.8	82.7
	Wk 13					72.7	71.0	64.5	95.7
	terminal					68.8	74.5	84.3	115.2^a
Total protein g/dl	Pretest					6.13	6.03	5.88	5.95
	Wk 13					5.62	5.28	4.90^a	4.98^a
	terminal					6.23	5.63	5.65	5.55^a
Albumin g/dl	Pretest					3.22	3.20	3.03	3.23
	Wk 13					3.08	2.88	2.53	2.60^b
	terminal					3.48	3.13	2.88	2.58^b

A = p < 0.05 b = p < 0.01

Other significant treatment-related changes constituted increase in chloride in at week 13 and terminal determinations in the high dose female group. Also albumin/globulin ratio was significantly decreased in high dose females at termination.

Hormone changes:

Blood samples for serum hormone analysis (testosterone in males and estradiol in females) were collected from all animals on the day prior to randomization, during week 13, and on day prior to terminal and recovery necropsies.

Testosterone and estradiol levels were not affected by treatment, but testosterone levels were highly variable. Testosterone levels on week 13 and on terminal determination were higher compared to pretest, which could be possible if dogs were not mature at the start of the study.

Males: Testosterone

Endpoint	Interval of Study	0 mg/kg/day (Vehicle)			50 mg/kg/day			75 mg/kg/day			150 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Testosterone ng/dL	Pretest	183.3	178.17	6	82.5	44.31	4	118.5	53.98	4	191.0	113.91	6
	Week 13	292.7	189.64	6	212.5	138.13	4	198.3	217.24	4	65.0	53.61	5
	Terminal	264.5	155.36	6	217.0	115.47	3	367.8	198.35	4	312.8	41.87	4
	Recovery	186.0	63.64	2	NA	NA	0	NA	NA	0	341.5#	17.68	2

Females: Estradiol

Endpoint	Interval of Study	0 mg/kg/day (Vehicle)			50 mg/kg/day			75 mg/kg/day			150 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Estradiol pg/mL	Pretest	2.0	0.00	6	3.3	2.50	4	2.0	0.00	4	2.0	0.00	6
	Week 13	4.2	3.49	6	2.0	0.00	4	2.0	0.00	4	2.0	0.00	6
	Terminal	2.2	0.41	6	2.0	0.00	4	2.0	0.00	4	2.0	0.00	6
	Recovery	2.0	0.00	2	NA	NA	0	NA	NA	0	2.0#	0.00	2

Urinalysis: collected for the last 16 hours

There was an increase in urine volume in the high dose males at the terminal determination.

Gross Pathology

No treatment-related gross pathological changes were reported. It was noted that lung discoloration and /or fluid in the trachea were present in two high dose DOS male dogs and one mid dose terminal male. These were attributed to introduction of test article in to the respiratory tract.

Organ Weights: No treatment-related effect was reported on organ weights.

Histopathology Adequate Battery yes Peer Review no

Microscopic lesions were reported present in the lungs (hemorrhage and/or edema) of two high-dose male dogs were attributed to dosing error. There were minimal to moderate findings of reduced spermatogenesis in the mid and high dose male dogs.

Toxicokinetics:

The sponsor did not provide a summary table for TK but rather TK for each animal for days 1, 42, 91 and 182. Mean values for C_{max} and AUC at each dose on d1 and d182 are given in the nonclinical tabulated summary 2.6.7.7.8. The sponsor stated that marked between-animal variability was observed in this study, with the CV% for both C_{max} and AUC ranging from 28.5% - 95.8% and 29.3% - 84.9%, respectively. The variability was suggested at least in part to emesis after dosing. T_{max} was observed within 1.9 hours post-dose for all dose levels.

C_{max} and AUC for parent drug and its metabolite was independent of dose on Day 1, increased less than proportional to dose on Day 42 and increased approximately proportional to dose on Days 91 and 182.

Drug exposure was generally comparable between Days 182 vs Day 1 for both the 50 and 75 mg/kg/day dose levels, but was 2 to 4 fold higher on Day 182 vs Day 1 for the 150 mg/kg/day dose level. T_{1/2} values ranged 1.7 – 3.6 hours.

Stability and Homogeneity: Acceptable

DOG 9-month oral capsule

Study title: A 9-Month Toxicity and Toxicokinetic Study of NBI-56418 Administered by Oral Capsule to Beagle Dogs with a 1-Month Recovery Period	
Study no.:	RD101101
Study report location:	Application 210450 - Sequence 0000 - RD101101 9-Month Oral Toxicity Dog Recovery
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 2007
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418, Lot #NU1-002, 98.7%

Key Study Findings

Clinical observations included soft/mucoid stools, diarrhea and decreased mean body weights and food consumption. There were test article-related effects on hematology, coagulation, and clinical chemistry parameters for males and females at the high dose. Decreased spleen weights were noted in males and females, which were persistent in recovery for males, but did not have histological correlates. There were decreased prostate weights in males, without histological correlates, that did not recover. Histopathological effects were noted in the gallbladders of males in the high dose group that were absent in recovery.

The **NOAEL was 30 mg/kg/day**. Exposure at this dose was 8.4 ug/mL and 10.5 ug/mL for C_{max} and 26.0 ug•hr/mL and 31.4 ug•hr/mL for AUC on Day 273 for males and females, respectively.

Methods	
Doses:	0, 10, 30, 150 mg/kg/d
Frequency of dosing:	Daily
Route of administration:	Oral capsule
Dose volume:	N/A
Formulation/Vehicle:	(b) (4)
Species/Strain:	Beagle dog
Number/Sex/Group:	6/sex/group; 2/sex/group for recovery (except the low dose had no recovery group)
Age:	6 months
Weight:	M: 6.4-8.8 kg F: 5.4-7.8 kg
Satellite groups:	None
Deviation from study protocol:	None significant

Background for this study and dose justification (sponsor's text):

6 week study: The dose levels were selected to produce graded responses to the test article. NBI-56148 was administered to the Beagle dog at doses as high as 300 mg/kg for 6 weeks (oral gavage). The 300 mg/kg dose produced salivation, emesis, changes in feces, and decreased body weights (33% in males) and food consumption (up to 41%). Furthermore, the 300 mg/kg dose produced roughly a 3-fold increase in serum liver enzymes (ALT, AST and ALP). In addition, there was one mortality (female).

In a 6-month repeat dose study using oral gavage, the highest dose tested was 150 mg/kg. At this dose, roughly a 2-fold increase in ALT in the males was observed. Additionally, mortality was observed (3/7 males) that was attributed to dosing error/aspiration. The 150 mg/kg dose was associated with salivation, emesis, and changes in feces.

Both of the above-mentioned studies used oral gavage solution, which led to dose aspiration; therefore, solid formulation was tested to assess if it provides a safer method to administer this compound. In a preliminary 28-day repeat administration of NBI-56418 tablets in capsules, dogs were administered up to 150 mg/kg/day. There were no mortalities reported in this study; however, body weights were decreased up to 17%.

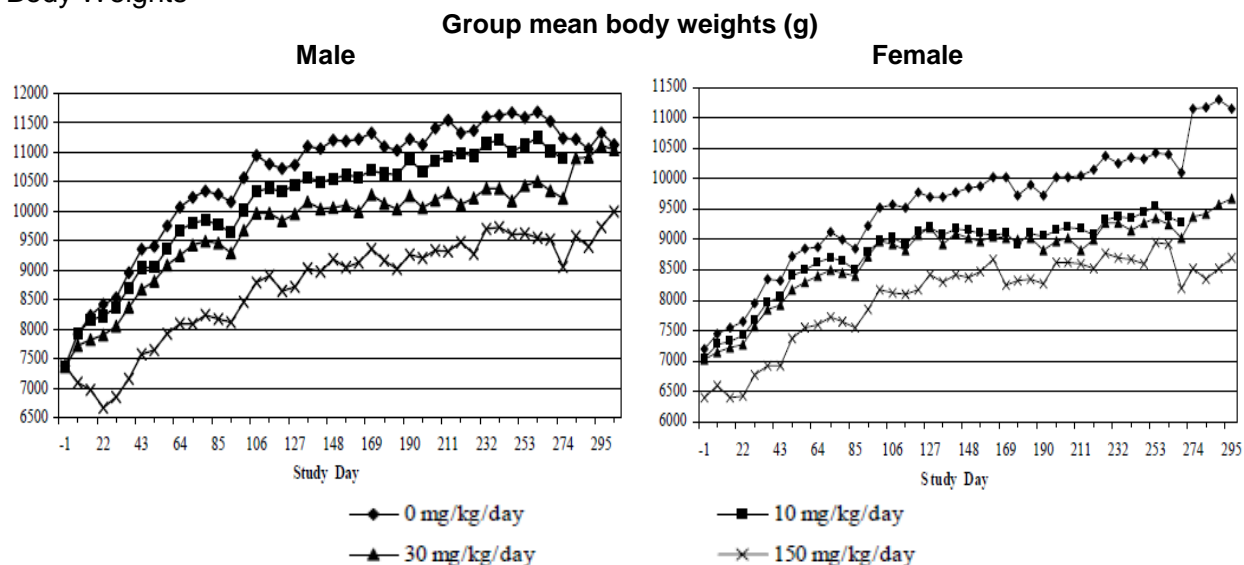
The 150 mg/kg dose was chosen to represent the high dose where some toxic effects, but not excessive lethality was anticipated to allow meaningful interpretation of the data. The mid and low doses (30 and 10 mg/kg, respectively) were expected to provide multiples of the human exposure at an efficacious dose. The low-dose level was anticipated to produce a NOEL. Test materials were administered after the dogs had been offered food, since in a preliminary study this reduced the incidence of emesis.

Observations and Results

Mortality: There was no mortality.

Clinical Signs: Soft/mucoid stools, vomitus, diarrhea that increased in a dose-dependent way throughout the dosing period. Because control groups had a significant incidence of vomiting, the sponsor attributed this to palatability.

Body Weights



Mean body weight was decreased throughout the dosing period for both males (19.4%) and females (18.7%) in the high dose group. Decreased mean body weight for the high dose males and females reached toxicological significance (i.e., more than 10% less than controls) by Day 8 and remained decreased throughout the remainder of the dosing phase (ending at day 274). No other toxicologically meaningful differences in mean body weight were noted in the remaining dose groups. Body weight gains rebounded in the recovery animals.

Feed Consumption

Statistically significant decreases in mean food consumption (21.4% - 68.0%) were noted for Weeks 1-4 and Week 10 for high dose males and (26.7% - 30.7%) for Weeks 1 and 2 for the females administered 150 mg/kg/day. No other significant test article-related differences in mean food consumption were noted during the dosing or recovery periods.

Ophthalmoscopy: No findings

ECG: No findings

Hematology

Test article-related effects on hematology and coagulation parameters included:

- ↓ decreased erythrocytes (15.1% to 19.7%)
- ↓ hemoglobin (12.7% to 16.6%)
- ↓ hematocrit (11.6% to 15.7%) for males in the high dose group,
- ↑ lymphocytes (19.9%) and monocytes (29.7%) for males in the high dose group
- ↑ platelets (29.1% to 54.8%) for females in the 150 mg/kg/day group

All of the changes returned to normal following the recovery period.

Clinical Chemistry

Test article-related differences in clinical chemistry parameters included statistically increased:

- ↑ ALP (82.1% to 356.7% for males and 211.5% to 754.7% for females),
- ↑ phosphorus (14.5% to 18.5% for males and 18.8% to 27.9% for females), and
- ↑ chloride (3.7% to 4.9% for males and 2.8% to 4.2% for females)
- ↓ albumin (21.4% to 25.4% for males and 13.0% to 20.5% for females),
- ↓ total protein (8.9% to 14.8% for males and 8.3% to 13.4% for females),

↓ A/G ratio (20.3% to 30.5% for males and 10.6% to 27.8% for females) for males and females in the 150 mg/kg/day group during the treatment period.

All of the changes returned to normal following the recovery period.

Urinalysis: No findings

Gross Pathology: No treatment-related findings

Organ Weights

Relative spleen weight was decreased in males at the mid and high doses (max 43%) and in females at the high dose (max 50%). At recovery, relative spleen weight was still reduced in males but not females. Relative prostate weight was decreased at the high dose, up to 56% and did not recover. There were no histological correlates of decreased organ weight in the spleen or prostate. Decreased prostate weight was likely due to the exaggerated pharmacology of elagolix.

Sex	Day	Organ	Absolute Weight	Relative to Body Weight	Relative to Brain Weight
Males	Day 274/275	Spleen	Group 2, 3, 4 ↓	Group 3, 4, ↓	Group 3, 4 ↓
		Prostate	Group 4 ↓	Group 4 ↓	Group 4 ↓
		Liver	--	Group 4 ↑	--
		Adrenals	--	Group 4 ↑	Group 4 ↑
		Pituitary	--	Group 4 ↑	--
		Lungs	--	Group 4 ↑	--
		Salivary glands	--	Group 4 ↑	--
Females	Day 274/275	Spleen	Group 4 ↓	Group 4 ↓	Group 4 ↓
		Liver	--	Group 4 ↑	--
		Adrenals	--	Group 4 ↑	--
		Thyroid	--	Group 4 ↑	--
		Lungs	--	Group 4 ↑	--
		Salivary glands	--	Group 4 ↑	--
Group 2 (10 mg/kg/day) Group 3 (30 mg/kg/day) Group 4 (150 mg/kg/day)					

Histopathology Adequate Battery yes Peer Review no

In two high dose males, there were findings in the gall bladder: granulomatous inflammation occurred in the lamina propria of the mucosa, and was characterized by mononuclear cell infiltrates as well as the formation of multinucleated giant cells which contained variably sized clear intracytoplasmic spicules. There were no findings at the end of the recovery period.

Incidence of Test Article-Related Histopathology Findings in the Gall Bladder

Group Dose (mg/kg/day) No. animals examined	Males				Females			
	1	2	3	4	1	2	3	4
	0	10	30	150	0	10	30	150
Gall Bladder								
Granulomatous Inflammation	(0) ^c	(0)	(0)	(2)	(0)	(0)	(0)	(0)
Mild	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	0

^c Numbers in parentheses represent the total incidence for the dose group.

Special Evaluation

Estradiol and testosterone measurements were not done in this study.

Stability and Homogeneity: Adequate

Formulation analysis confirmed content with 15%. Stability of the capsule formulation was tested and was acceptable.

Toxicokinetics

The plasma samples were analyzed using a GLP validated LC-MS/MS method (validation report #06-56418-025-BA) after liquid:liquid extraction; the lower limit of quantification (LLOQ) was 5.00 ng/mL.

Daily Dose (mg/kg)	0 (Control)		10		30		150	
Number of Animals	M:8	F:8	M:6	F:6	M:8	F:8	M:8	F:8
Toxicokinetics:								
<i>C_{max}</i> (µg/mL)								
Day 1:	BLQ	BLQ	0.86	1.20	8.09	4.69	26.1	17.9
Day 91	BLQ	BLQ	2.44	2.33	6.89	4.00	25.3	24.3
Day 273:	BLQ	BLQ	3.43	2.87	8.41	10.5	38.3	38.8
<i>AUC</i> (µg·hr/mL)								
Day 1:	NA	NA	2.97	3.79	26.6	17.0	277	189
Day 91	NA	NA	4.96	4.8	24.4	16.3	193	234
Day 273:	NA	NA	6.63	5.18	26.0	31.4	280	299

MONKEY

MONKEY 2-week oral study

Title: A 14-Day Oral Toxicity Study of NBI-56418 in Cynomolgus Monkeys with a 7-Day Recovery. Study #RD101085.

Doses: 0, 50, 150, 300 mg/kg/d.

In monkeys, NBI-56418 (Na salt) was well-tolerated following repeated administration for 14 days. There was no mortality.

Toxicokinetics

The systemic exposure to NBI-56418 increased in a more than dose-proportional manner in both male and female monkeys from 50 to 150 mg/kg, while the increase was approximately dose proportional from 150 to 300 mg/kg. There were no marked gender related differences. However, the systemic exposure to NBI-56418 decreased in both male and female monkeys from treatment day 1 to day 14.

The NOAEL was 300 mg/kg/day.

At this dose $C_{max} = 4.59$ µg/mL and $AUC_{0-24\text{ hr}} = 14.4$ µg·hr/mL (the minimum exposure values for gender and day at 300 mg/kg; females on Day 14). These values were significantly reduced from exposures on day 1: 6.72 µg/mL and 26.3 µg·hr/mL, respectively.

Metabolite NBI-61962 was <10% of parent (d1 Females).

MONKEY 6-week oral study

NBI-56418 Toxicity Study by Oral Gavage Administration to Cynomolgus Monkeys for 6 Weeks Followed by a 4 Week Recovery Period. Study #RD101088.

Doses: 0, 75, 150, 300, 600 mg/kg/d. N = 3/sex. An additional 2 /sex were allocated to control, 300 and 600 mg dosage groups for a 4-week recovery period.

Treatment was associated with dose-related incidence of vomiting, which was frequent enough to be classified to be toxicologically significant. Loose feces were observed at 300 and 600 mg/kg/d. Slight dehydration was diagnosed in 2 high dose monkeys, one of these showed hunched posture. Body weight losses and reduced food intake was reported at the two highest doses. During the recovery period, high dose animals showed increased feed consumption and weight gain.

In the high dose groups, findings that were apparently fully reversible included faster prothrombin time, prolonged APTT, and lower GGT, bilirubin, AST, urea and albumin.

Relative thymus weights were lower in high dose group, with evident of involution and histologically correlated with atrophy. This finding resolved in recovery. Relative liver weights were significantly greater in 150, 300 and 600 mg dose males and in 300 and 600 mg dose females (maximum increase of 1.4 fold was observed in males, dose dependent). Relative kidney weights were significantly higher in all treated female groups (maximum increase 1.2 fold, not dose dependent). Relative liver and kidney weights were not different from control following recovery. There were no histological correlates noted for liver or kidney.

Relative weights of lungs and bronchi and that of the salivary glands were greater in high dose females. (Note that mean organ weights are in Tables 6-8 and do not include recovery groups. Data for recovery groups are given in Appendices 8-10 as individual values.)

There was atrophy in the uterus of females at the three highest doses and in the cervix and vagina at all doses, with evidence of dose-relationship. In the recovery phase animals, minimal atrophy was seen in the uterine cervix and vagina of females at the high dose, indicating recovery. Evaluation of the male reproductive system was precluded due to sexual immaturity of the animals.

Conclusions

Oral administration of NBI-56418 to cynomolgus monkeys for 6 weeks was generally well tolerated up to 300 mg/kg/day. The high dose of 600 mg/kg/day was associated with poor clinical condition, marked bodyweight loss, reduced food intake and atrophy of the uterine cervix and vagina. All other changes were slight or attributed to the pharmacological action of elagolix and shown to be reversible.

The NOAEL was 300 mg/kg/day. Exposures at that dose are shown below and dramatically decreased between d1 and d42.

Exposure	Females		Males	
	Cmax (ug/mL)	AUC (ug.hr/mL)	Cmax (ug/mL)	AUC (ug.hr/mL)
Day 1	21.0	190	16.8	83.5
Day 42	5.18	24.8	5.1	27.4

MONKEY 13-week oral study

Study title: A 13 week oral toxicity study of NBI-56418 in cynomolgus monkeys	
Study no.:	RD101076
Study report location:	Application 210450 - Sequence 0000 - RD101076 13-Week Oral Toxicity Monkey
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 2004
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418, 01 NBI04-03-B2, 99.2%

Key Study Findings

There were essentially no findings other than occasional emesis after dosing. This study is of limited usefulness due to the rapid falloff in exposure with time (from previous studies ~ half at 2 weeks and more than two thirds at 6 weeks). In this study, plasma levels of NBI-56418 dropped a maximum of 59, 91, and 88% in animals treated at 75, 150, and 300 mg/kg/day, respectively. The sponsor did not put forward an explanation for the drop off.

The NOEL was set at 300 mg/kg/d, with a Cmax of 3.8 ug/mL and an AUC of 17.6 ug.hr/mL. These exposure values are the lowest of either male or female values taken on the last day of the study. The MOE calculated from these values is 5.1. Thus, at the high dose, even with the falloff in exposure, exposure exceeded the MRHD.

Methods	
Doses:	0, 75, 150, 300 mg/kg/d
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg on day 1 and 5 mL/kg thereafter
Formulation/Vehicle:	Water
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	6/sex/dose (control and high dose) 4/sex/dose (low and mid-dose) 2/sex (control and high dose) for the 4 week recovery period
Age:	~2-3 yrs; sourced from Vietman Males were deemed immature based on low testosterone
Weight:	1.98-2.39 kg (M) 1.95-2.63 kg (F)
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None that affected outcome.

Observations and Results

Blood and urine samples for clinical pathology evaluation were collected from animals pretest and at week 4, termination and recovery. Additional blood samples for determination of testosterone and estradiol was collected pretest and prior to the scheduled necropsy. Blood samples for drug determination were collected pretest and at designated time points on Days 1, 42 and 91.

Mortality

There was no mortality.

Clinical Signs: weekly

No treatment-related findings. Emesis after gavage was attributed to the procedure.

Body Weights: weekly

There were no treatment-related effects on body weight or body weight gain. No information was provided about feed consumption.

Ophthalmoscopy: conducted pre-test and during the last week of dosing. No findings.

ECG: conducted pre-test and during the last week of dosing

RR interval, PR interval, QRS duration, QT interval, and QTc interval were measured. All of the ECGs were stated to be qualitatively and quantitatively within normal limits.

Hematology: no dose-related findings

Clinical Chemistry: no dose-related findings

Urinalysis: No findings

Gross Pathology: No findings

Organ Weights

Relative liver and kidney weights were significantly increased (16 and 23% respectively) in high dose females. There were no corresponding microscopic findings.

Histopathology: Adequate Battery: yes

Peer Review: no

Histological Findings: No findings

Special Evaluation: testosterone and estradiol

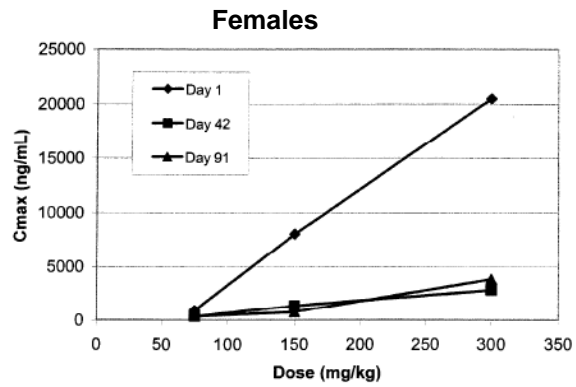
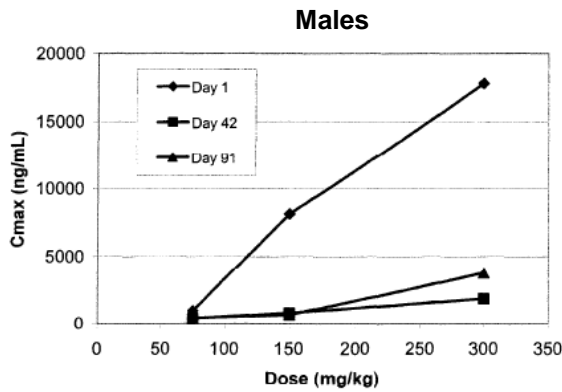
Testosterone levels in males prior to drug administration, and prior to termination and recovery necropsies were below values expected for mature male monkeys (2 - 8 ng/dl). Due to this, animals were considered not mature and evaluation of the effect of NBI-56418 on testosterone levels could not be determined. Estradiol levels prior to drug administration ranged between 41.8 and 67.9 pg/ml, with a high level of variability in each group. Individual values stayed very variable and the effect of NBI-56418 on estradiol levels could not be determined.

Stability and Homogeneity: Dosing formulations were acceptable.

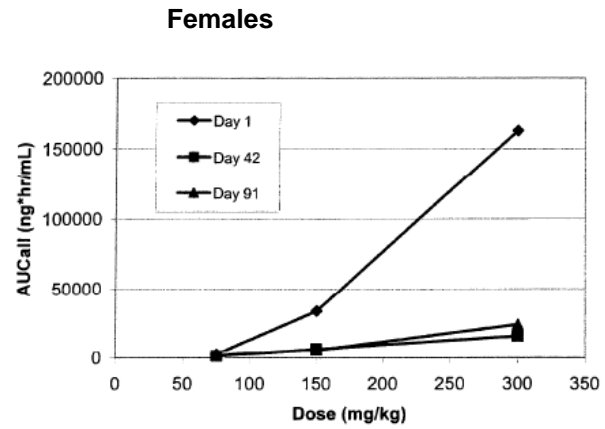
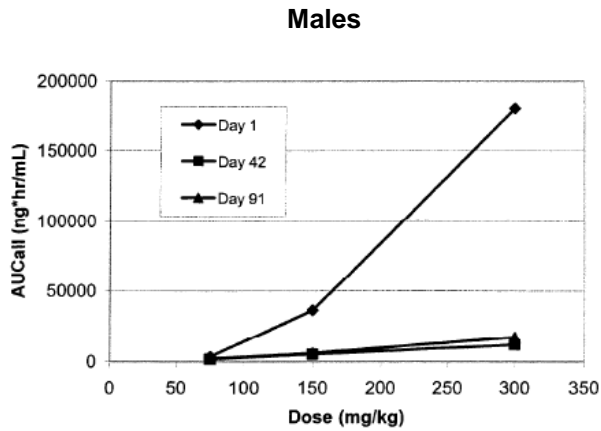
Toxicokinetics (see Appendix T of the study report)

C_{max} on Day 1 was 0.935, 8.04, and 19.2 ug/ml for animals treated at 75, 150 and 300 mg/kg/day, respectively. Plasma concentration dropped significantly between Days 1 and 42 of the study with C_{max} dropping 30% to 0.657 ug/ml, 87% to 1.07 ug/ml, and 88% to 2.34 ug/ml in animals treated at 75, 150 and 300 mg/kg/day, respectively. Plasma concentrations continued to drop between Days 42 and 91 in animals treated at 75 and 150 mg/kg/day with levels reaching 0.387 and 0.704 ug/ml. Plasma concentration increased slightly between Days 42 and 91 in animals treated at 300 mg/kg/day (3.79 ug/ml).

Cmax vs dose



AUC vs dose



Day	Dose	Gender	Tmax (hr)	Cmax (ng/mL)	AUC(all) (ng*hr/mL)
1	75	F	2.0	951	3760
1	150	F	3.0	8130	36600
1	300	F	4.3	17800	180000
1	75	M	1.0	919	3110
1	150	M	3.0	8040	34100
1	300	M	3.7	20500	163000
42	75	F	2.2	541	1990
42	150	F	4.0	792	5330
42	300	F	3.2	1860	12100
42	75	M	0.8	342	1620
42	150	M	1.5	1340	6640
42	300	M	3.2	2810	16000
91	75	F	2.6	428	2130
91	150	F	2.0	646	6180
91	300	F	1.1	3760	17600
91	75	M	0.8	352	1500
91	150	M	2.8	761	5770
91	300	M	2.0	3820	24400

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: <i>Salmonella-Escherichia coli</i>/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with NBI-56418	
Study no.:	RD101068
Study report location:	Application 210450 - Sequence 0000 - RD101068 Ames
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 2003
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418,1675644, 97.08%

Key Study Findings

Study was found negative for mutagenicity.

Methods	
Strains:	<i>Salmonella typhimurium</i> (TA98, TA100, TA1535 and TA1537), and <i>Escherichia coli</i> strain WP2uvrA
Concentrations in definitive study:	33.3, 100, 333, 1000, 3330 and 5000 ug/plate ± S9
Basis of concentration selection:	(b) (4) study 24223-0-401SC5
Negative control:	DMSO
Positive control:	Benzo[a]pyrene, 2-nitrofluorene, sodium azide, 2-aminoanthracene, ICR-191, 4-nitroquinoline-N-oxide
Formulation/Vehicle:	DMSO
Incubation & sampling time:	52 hrs

Study Validity

Dose formulations were found acceptable. Study was deemed valid.

Results

Study was found negative for mutagenicity. Cytotoxicity was observed with tester strain TA100 at 5000 µg/plate in the absence of S9 mix, as evidenced by a decrease in the background lawn and decrease in the number of revertants. No cytotoxicity was observed with the other strains and conditions tested.

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Study title: L5178Y TK +/- Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay with NBI-56418	
Study no.:	101065
Study report location:	Application 210450 - Sequence 0000 - RD101065 Mouse Lymphoma
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 2003
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418,1675644, 97.08%

Key Study Findings

NBI-56418 Na was found negative for mutagenicity.

Methods	
Cell line:	mouse lymphoma L5178Y cell line, heterozygous at the TK locus
Concentrations in definitive study:	10.0, 15.0, 25.0, 50.0, 75.0, 100, 125, 150, 175, 200, 225 and 250 ug/mL without S9 10.0, 25.0, 50.0, 75.0, 100, 125, 150, 175, 200, 250, 300 and 400 ug/mL with S9
Basis of concentration selection:	Range finding studies indicated that NBI-56418 induced a wide range of cytotoxicity, demonstrating weak cytotoxicity at 15.7 and 31.3 µg/mL, moderate cytotoxicity at 62.5 µg/mL, and high cytotoxicity at 125 µg/mL. Higher concentrations were 100% lethal.
Negative control:	DMSO
Positive control:	Methyl methanesulfonate, methylcholanthrene
Formulation/Vehicle:	DMSO
Incubation & sampling time:	4 hrs ± S9 24 hrs without S9

Study Validity

Study was deemed valid

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Mammalian Erythrocyte Micronucleus Test	
Study no.:	RD101091
Study report location:	Application 210450 - Sequence 0000 - RD101091 Mammalian Micronucleus
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 2004
GLP compliance /QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418, 01NBI04-05-82, 98.9%

Key Study Findings

NBI-56418 up to a dose of 2000 mg/kg was negative in the mouse micronucleus assay. The systemic exposure to the metabolite NBI-61962 was less than 10% of the parent drug exposure.

Methods	
Doses in definitive study:	500, 1000, 2000 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	water
Species/Strain:	ICR mice
Number/Sex/Group:	6/sex/group
Satellite groups:	TK; 3/sex/group
Basis of dose selection:	Range-finding study
Negative control:	water
Positive control:	cyclophosphamide

Study Validity

Study was deemed valid.

Results

There was no mortality.

Bone marrow examination: Bone marrow cells (PCEs and NCEs) collected 24 and 48 hours after treatment were examined microscopically for presence of micronuclei (MPCEs or MNCEs). The incidence of MPCEs per 10000 PCEs scored (2000 PCEs/animal) and proportion of PCEs/total erythrocytes are given in the table below:

Treatment	Sex	Time (hr)	N	PCE/total erythrocytes	Change from control (%)	Micronucleated polychromatic Erythrocytes	
						#/1000 PCEs	#/10000PCEs scored
Water	M	24	5	0.484	-	0.5	5
	F	24	5	0.495	-	0.7	7
NBI-56418 500 mg/kg	M	24	5	0.483	0	0.5	5
	F	24	5	0.452	-9	0.8	8
1000 mg/kg	M	24	5	0.497	3	0.6	6
	F	24	5	0.442	-11	0.7	7
2000 mg/kg	M	24	5	0.468	-3	0.7	7
	F	24	5	0.494	0	0.5	5
Cyclophosphamide 50 mg/kg	M	24	5	0.349	-28	10.9	109*
	F	24	5	0.359	-27	11.3	113
Distilled water	M	48	5	0.496	-	0.8	8
	F	48	5	0.491	-	0.4	4
NBI-56418 2000 mg/kg	M	48	5	0.443	-11	0.5	5
	F	48	5	0.494	1	0.2	2

*Statistically significant $p < 0.05$

TK for NBI-56418 and its metabolite NBI-61962 is given in table below:

Gender	Male	Female	Male	Female	Male	Female
Dose mg/kg/day	500	500	1000	1000	2000	2000
TK for NBI-56418 (parent)						
Tmax (hr)	2.0	0.25	0.5	1.0	2.0	1.0
Cmax (ng/ml)	34600	28500	41800	55900	96300	52500
AUC0-24 (ng.hr/ml)	428000	272000	427000	382000	817000	560000
AUC 0-t	428000	272000	427000	382000	1390000	1210000
TK for NBI-61962 (metabolite)						
Tmax (hr)	1.0	0.5	0.5	1.0	2.0	1.0
Cmax (ng/ml)	2640	1680	2850	4170	9830	3930
AUC0-24 (ng.hr/ml)	19400	6550	18800	12400	62000	16100
AUC0-t (ng.hr/ml)	19400	6550	18800	12400	83400	27300

7.4 Other Genetic Toxicity Studies

Study title: 6-Week Dietary Impurity Qualification Study Including Bone Marrow Micronucleus Evaluation using A-1278823 Sodium (ABT-620) Spiked and Unspiked with Impurities in Rats	
Study no.:	RD12556
Study report location:	Application 210450 - Sequence 0000 - RD12556 6-Week Dietary Rat Impurity Micronucleus
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11 June 2012
GLP compliance /QA statement:	Yes / yes
Drug, lot #, and % purity:	A-1278823, 13617PP01, 95.2% free acid, unspiked A1278823, 18635PP00, 93.0% free acid, spiked with impurities
COA from unspiked batch	COA from batch spiked with specified impurities
 (b) (4)	 (b) (4)

Key Study Findings

There was no mortality, and no novel or exacerbated toxicities after dietary administration of A-1278823 sodium at dose levels up to 650 mg/kg/day for 6 weeks with or without specified impurities. Group mean liver weight parameters (absolute and relative) were greater in females given unspiked A-1278823 sodium compared with the vehicle control group; however, no statistically significant difference occurred between the group given spiked A-1278823 sodium and the group given unspiked A-1278823 sodium.

The NOAEL was 650 mg/kg/day with or without the spiked impurities.

At the NOAEL on day 42, mean C_{max} = 2.33 µg/mL and AUC = 30.1 µg*hr/mL for the unspiked batch, and mean C_{max} = 2.73 µg/mL and AUC = 32.4 µg*hr/mL for the spiked batch.

Methods	
Doses in definitive study:	650 mg/kg/d Doses were titrated as follows: 100 mg/kg/d (d1-4), 200 mg/kg/d (d-5-8), 400 mg/kg/d (d9-12), 650 mg/kg/d (d13-42) Exposures to the specified impurities at 650 mg/kg/d: 1.1-1.3 mg/kg/d; actual amount: 0.3 mg (M) 0.2 mg (F)
Frequency of dosing:	Daily
Route of administration:	Dietary
Dose volume:	N/A
Formulation/Vehicle:	(b) (4)
Species/Strain:	SD rat
Number/Sex/Group:	10/sex/group
Satellite groups:	6/sex/group for TK
Basis of dose selection:	Range finding studies for carcinogenicity
Age:	6.7-7.6 weeks
Weight:	221-295g (M) 156-203g (F)
Formulation:	Homogeneity and concentration were verified. The test article consumption data indicate that the overall dose given to both males and females approximated the intended target concentration of 650 mg/kg/day (from 73.9 to 113.5% and 74.8 to 129.3% for impurity unspiked and spiked formulations, respectively)
Unique study design:	Bone marrow was taken from femurs at terminal sacrifice for evaluation of micronuclei
Deviations:	None that affected outcome

Study Validity

Study was deemed valid.

Results

There was no mortality. There were no consistent treatment-related findings for clinical observations, body weight, or food consumption. There were no ophthalmic findings.

Clinical chemistry:

There were minor treatment-related findings that were similar between the groups given elagolix with or without impurities. These included:

Females: lower red cell mass (i.e., red blood cell count, hemoglobin, and hematocrit; ↓2.8 to 5.0%) and higher absolute reticulocyte count (↑2.9 to 17%) and red cell distribution width (RDW; ↑4.5 to 5.4%)

Males: higher globulin (↑15%) resulting in lower albumin-to-globulin ratio (↓14%) and prolonged APTT (11% longer)

Although hematology changes were of small magnitude, high reticulocyte count and RDW indicated a regenerative response to lower red cell mass. Prolongation of APTT was of small magnitude, not indicative of coagulopathy, and not associated with prolongation in prothrombin time in males.

Urine: no treatment related findings.

Gross pathology: No treatment related findings

Organ weights:

Liver: There were no significant differences in liver weights between animals treated with spiked versus unspiked drug batches. There were increases in liver weight in both groups relative to controls: a 17% increase in absolute and relative liver weight in females receiving unspiked elagolix and in males, increased relative liver weight (11-2%) in both unspiked and spiked batches, possibly related to a statistically nonsignificant decrease in the terminal body weights of males given spiked or unspiked elagolix. There were no macroscopic or microscopic correlates for the liver weight variations.

Histology Adequate: yes Peer review: yes
No treatment related findings

Bone marrow examination:

A-1278823 sodium, whether spiked or unspiked with impurities, did not induce statistically significant increases in micronucleated PCEs. In addition, A-1278823 sodium, spiked or unspiked with impurities, was not cytotoxic to the bone marrow (i.e., no statistically significant decreases PCE:NCE ratio). The vehicle control group had 0.06% micronucleated PCEs for the males and females and the group means were within the historical control range.

Treatment	Group	% Micronucleated PCEs Mean $\pm$ SD		Ratio PCE:NCE Mean $\pm$ SD	
		Male	Female	Male	Female
Vehicle Control	1	0.06 $\pm$ 0.03	0.06 $\pm$ 0.05	0.75 $\pm$ 0.13	0.77 $\pm$ 0.10
Test Article	2 (Unspiked)	0.07 $\pm$ 0.04	0.06 $\pm$ 0.06	0.79 $\pm$ 0.09	0.78 $\pm$ 0.09
	3 (Spiked)	0.07 $\pm$ 0.07	0.07 $\pm$ 0.05	0.77 $\pm$ 0.13	0.82 $\pm$ 0.12

Toxicokinetics

Group	Dose (mg/kg/day)		Sex	C _{max} (μ g/mL)	T _{max} (hr)	AUC (μ g*hr/mL)
	Designated	Actual ^a				
Day 14						
2 (unspiked)	650	631.37	Female	3.66 $\pm$ 1.06	8.0 $\pm$ 12.4	37.8 $\pm$ 16.2
		608.07	Male	2.83 $\pm$ 0.384	18.7 $\pm$ 9.7	30.4 $\pm$ 7.97
3 (spiked)	650	553.02	Female	1.62 $\pm$ 0.527	18.7 $\pm$ 9.7	15.5 $\pm$ 5.36
		543.64	Male	1.87 $\pm$ 0.823	8.0 $\pm$ 12.4	17.2 $\pm$ 4.23
Day 42						
2 (unspiked)	650	556.53	Female	2.40 $\pm$ 0.692	10.7 $\pm$ 12.0	30.6 $\pm$ 8.51
		641.88	Male	2.27 $\pm$ 0.543	9.3 $\pm$ 10.6	29.7 $\pm$ 4.75
3 (spiked)	650	684.23	Female	2.93 $\pm$ 0.597	12.7 $\pm$ 8.9	33.9 $\pm$ 12.8
		620.17	Male	2.53 $\pm$ 0.814	13.3 $\pm$ 10.9	30.9 $\pm$ 5.83

8 Carcinogenicity

Study title: 2-Year Dietary Carcinogenicity and Toxicokinetic Study with NBI-56418 (Elagolix) in Mice	
Study no.:	RD101102
Study report location:	Application 210450 - Sequence 0000 - RD101102 2-Year Dietary Carcinogenicity Mouse
Conducting laboratory and location:	(b) (4)
Date of study initiation:	17 July 2009
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	Elagolix Na salt, lots 29001262 and 29001263, 99.7%
CAC concurrence:	Yes

Key Study Findings

No statistically or biologically significant neoplastic findings related to NBI-56418 were found. A slightly higher, but not significant, incidence of hepatocellular carcinoma in males at the high dose of 500 mg/kg/day was observed. In females, a dose-dependent trend of leiomyosarcoma in the cervix was noted. There was no pairwise significance. There were no significant findings of leiomyosarcoma in other tissues of the lower reproductive tract.

NBI-56418 did not alter the trend in mortality rates. The study achieved an MTD as the percent difference in body weight change (g) for the 500 mg/kg/day group (males and females) from controls was greater than 10% at Week 13 and at terminal necropsy.

The Week 26 AUC_{0-t} for NBI-56418 at the 500 mg/kg/day dose was 40.5 ug.hr/mL for males and 66.5 ug.hr/mL for females. This corresponds to an MOE of 12 and 19, respectively, as compared to the human AUC of 3.5 ug.hr/mL at the highest proposed therapeutic dose of 200 mg BID. Relatively minor exposure to metabolites NBI-61962 (M3) and NBI-54048 (M6x) was also evidenced.

Adequacy of Carcinogenicity Study

NBI-56418 administered via diet to Crl:CD1(ICR) mice for at least 102 weeks allowed acceptable numbers of surviving animals in all dose groups to provide a valid study for statistical analysis. There was sufficient histopathological data from the designated organs and tissues to evaluate both the non-neoplastic and neoplastic effects of NBI-56418 at all dose levels (and changes in control animals) for valid carcinogenicity evaluation.

Appropriateness of Test Models

Binding of elagolix to the GnRH receptor in the mouse was not characterized. It is known that elagolix binding to the GnRH receptor in two other rodent species (rat and rabbit) is significantly less potent (orders of magnitude) than in monkey or human. In addition, there were no obvious pharmacodynamic signs of drug activity (atrophy of reproductive organs in males or females; Table of Macroscopic Observations p 141-142). We therefore assume for the purposes of this review that any elagolix toxicity is probably non-receptor mediated.

ADME of elagolix was fully characterized in the mouse. Bioavailability is 9.6% (much less than human, which is ~52%) and protein binding was 78.5% (equal to human). Metabolites were not quantified but were identified. Confusingly, M6x (NBI 54048) was not identified in the mouse in vivo metabolite study, but was identified in this carci study. Two other minor metabolites, M10 and M17 are present in humans but not in mice.

The test model was deemed appropriate.

Evaluation of Tumor Findings

Since no findings were deemed significant, no further evaluation of tumor findings was done.

Methods	
Doses:	0, 50, 50, 50 mg/kg/d Week 1 0, 50, 150, 300 mg/kg/d Week 2 0, 50, 150, 500 mg/kg/d Weeks 3-termination at Week 102 Dietary test article concentrations were adjusted weekly based on historical (Weeks 1 and 2) or actual study (Weeks 3 through termination) body weight and food consumption data. Due to the potential for poor consumption of test article-treated diet, the dietary test article concentration (dose levels) for the mid- and high-dose levels was increased gradually over the first 1 or 2 weeks of the study.
Frequency of dosing:	daily
Dose volume:	N/A
Route of administration:	Oral diet
Formulation/Vehicle:	(b) (4)
Basis of dose selection:	Range finding studies identified 500 mg/kg/d as the MTD for a carci study, based on decline in body weight gain. 500 mg/kg/d was also the NOAEL for the range-finding study.
Species/Strain:	Mouse ' Crl:CD1(ICR)
Number/Sex/Group:	N=60/sex/group
Age:	8-9 wks
Animal housing:	Animals were housed individually in stainless steel cages beginning on Day 8 of the predose phase. For health reasons, some animals were individually housed in polycarbonate cages with bedding
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	None
Satellite groups:	TK: N=57/sex/group. Three animals/sex/group were bled for each collection time point and discarded. Blood samples (~0.3 mL) were collected during weeks 4, 13 and 26 from unfasted animals at 6:00, 10:00, 14:00, 18:00, 22:00, and 06:00 (on the following day).
Deviation from study protocol:	Multiple minor deviations, but overall no impact on the study.

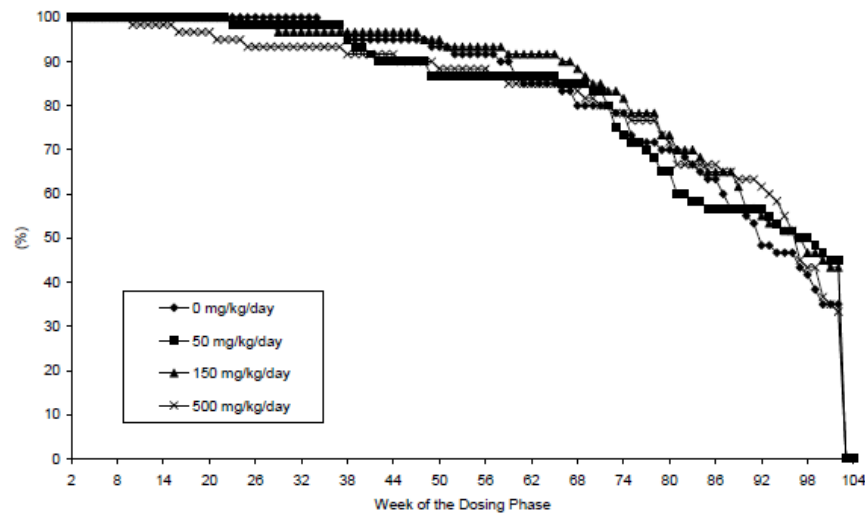
Observations and Results

Mortality

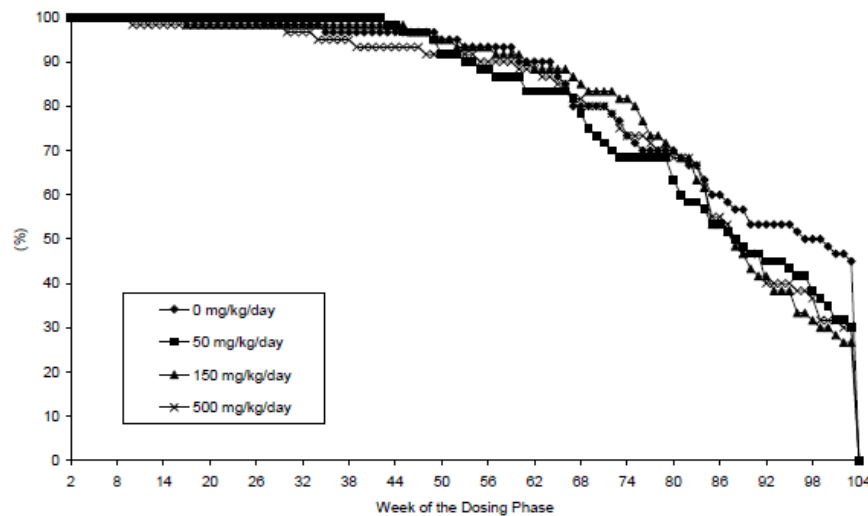
Survival was near or above 90% for all groups through Week 52 and began to decline progressively during the second year of the study as an expected aging effect. Mortality was not treatment/dose related as survival at study termination (Week 103 or 104) was in the 33 to 45% range for all male study groups including the controls. The survival for the female control group was slightly higher (45%) than treated female groups (27 to 30%) but there were no statistically significant differences in survival rates among the treatment groups (i.e., there was no dose response), or between treatment and control groups in either males or females.

All surviving males (Groups 1 through 4) were sacrificed on Day 720 (at least 102 weeks), and all surviving females (Groups 1 through 4) were sacrificed on Day 728 (104 weeks). This was done in accordance with the predetermined criteria to preserve an acceptable animal survival at termination and was discussed with the FDA/ Executive Carcinogenicity Assessment Committee (CAC).

Adjusted Survival Data (%) - Males



Adjusted Survival Data (%) - Females



Most Frequent Causes of Death

	Sex	Males				Females			
	Group	1	2	3	4	1	2	3	4
Dose Level (mg/kg/day)	0	50	150	500	0	50	150	500	
Number Examined	60	60	60	60	60	60	60	60	60
Terminal Sacrifice		20	27	26	19	27	18	14	18
Undetermined		4	2	6	5	8	4	2	3
Hepatocellular Neoplasia		6	5	5	11	0	0	0	0
Hematopoietic Neoplasia		3	0	4	1	6	11	13	11
Pulmonary Neoplasia		6	4	1	5	1	0	0	1
Amyloidosis		6	5	3	4	4	3	6	4
Inflammation, Skin/Subcutis		5	9	5	3	3	4	2	5
Cystic Endometrial Hyperplasia		NA	NA	NA	NA	0	5	2	2

NA = Not applicable.

Note: In this study, a death comment with an incidence of 5 or more in any dose group was considered most frequent for the purpose of inclusion for this table.

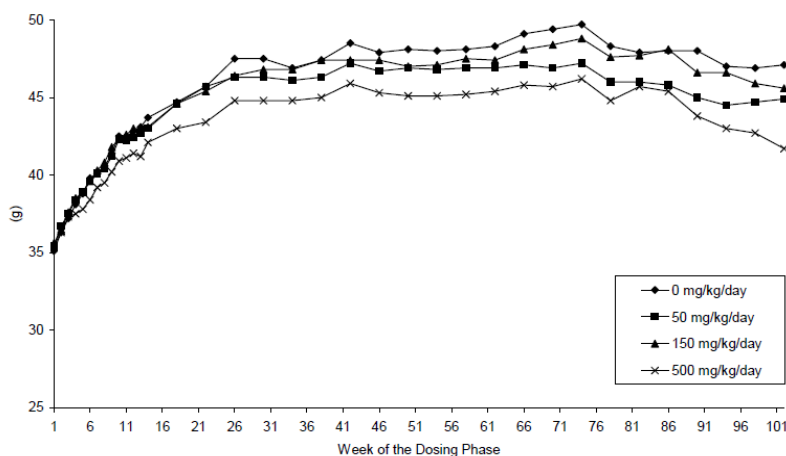
Clinical Signs

There were no treatment-related signs.

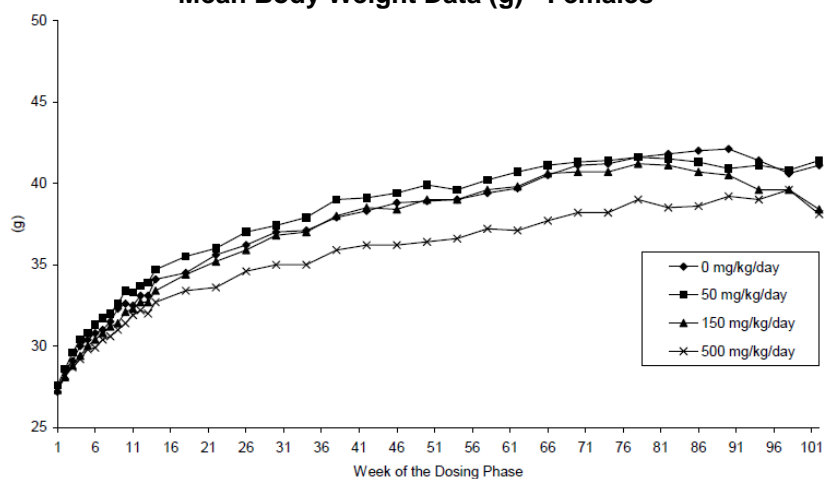
Body Weights and Feed Consumption

Slightly lower body weight gain was present in both sexes at 500 mg/kg/day. The study achieved an MTD as the percent difference in body weight change (g) for the 500 mg/kg/day group (males and females) was greater than 10% at Week 13 and at terminal necropsy. However, there was no clear effect of NBI-56418 on food consumption.

Mean Body Weight Data (g) – Males



Mean Body Weight Data (g) - Females



Gross Pathology

In 1/60 males and 1/60 females given 500 mg/kg/day, and in 1/60 females given 150 mg/kg/day, abnormal gall bladder content or calculus (stone) was observed. These macroscopic findings may have been associated with elagolix-related gall bladder bile concretions noted microscopically.

Histopathology Peer Review: Yes**Neoplastic:**

Liver: Incidence of hepatocellular adenoma / carcinoma did not reach significance in male mice. Table excerpted from CDER stat review below.

Incidence of Incidental Hepatocellular Carcinoma and/or Adenoma in Male Mice

Organ Name	Tumor Name	Control*	Low Dose**	Mid Dose**	High Dose**
Liver	Adenoma/Carcinoma incidence	15/60	15/60	13/60	21/60
	P-value	0.0854	0.6191	0.8161	0.1823
	M-Carcinoma incidence	15/60	14/60	12/60	21/60
	P-value	0.0703	0.7020	0.8714	0.1823

*p-value for trend

**p-value for pair-wise comparison compared to vehicle control

Uterus, Cervix, and Vagina

There was an increased incidence of cervical leiomyosarcoma in females at the high dose that was significant for trend but had no pairwise significance. Leiomyosarcomas correlated macroscopically with 2/5 cervical masses. Table excerpted from CDER stat review below.

Incidence of Incidental Leiomyosarcoma in the Distal Female Mouse Reproductive Tract

Organ Name	Tumor Name	Control*	Low Dose**	Mid Dose**	High Dose**
Cervix	M-Leiomyosarcoma	0/60 0.0176	0/60	1/58 0.4744	3/59 0.1067

*p-value for trend

**p-value for pair-wise comparison compared to vehicle control

Non Neoplastic: No significant findings**Gall bladder**

Nonproliferative, treatment-related microscopic findings were limited to an increased incidence of bile concretions within the lumen of the gall bladder of males and females at the high dose (see below). Although no correlations were established (possibly due to routine tissue processing), these microscopic findings may have correlated with the uncommon macroscopic finding of abnormal gall bladder contents or calculus.

Incidence and Average Severity of Elagolix-Related Bile Concretions in the Gall bladder

	Sex	Males				Females			
		Group	1	2	3	4	1	2	3
	Dose Level (mg/kg/day)	0	50	150	500	0	50	150	500
	Number Examined	51	57	52	57	57	56	58	58
Bile Concretion	Minimal	1	2	3	6	0	0	1	4
	Slight	1	1	3	11	0	0	0	5
	Moderate	0	0	0	2	0	0	0	6
	Average Severity	1.5	1.3	1.5	1.8	0	0	1.0	2.1
	Percent Affected	4	5	12	33	0	0	2	26

Liver

An increased incidence and/or severity of hepatocellular hypertrophy (centrilobular and/or diffuse) was inconsistently present in treated animals. In males given 150 or 500 mg/kg/day,

centrilobular hypertrophy was slightly increased in incidence; in females given 500 mg/kg/day diffuse hypertrophy was slightly increased; however, there was no consistent dose response.

Incidence and Average Severity of Hepatocellular Hypertrophy

	Sex	Males				Females			
		Group	1	2	3	4	1	2	3
	Dose Level (mg/kg/day)	0	50	150	500	0	50	150	500
	Number Examined	60	60	60	60	60	60	60	60
Hypertrophy, Hepatocyte, Centrilobular									
	Minimal	3	8	17	10	6	6	2	2
	Slight	5	3	5	2	1	0	0	1
	Moderate	0	0	1	2	0	0	0	0
	Average Severity	1.6	1.3	1.3	1.4	1.1	1	1	1.3
	Percent Affected	13	18	38	23	12	10	3	5
Hypertrophy, Hepatocyte, Diffuse									
	Minimal	4	2	0	1	2	1	3	8
	Slight	1	3	3	4	0	0	0	1
	Moderate	0	1	2	2	1	0	0	0
	Average Severity	1.2	1.8	2.4	2.1	1.7	1	1	1.1
	Percent Affected	8	10	8	12	5	2	5	15

Toxicokinetics (mouse)

TK data were collected during weeks 4, 13 and 26.

Mean Toxicokinetic Parameters for elagolix at Week 26

Treatment Group	Sex	Dose (mg/kg/day)		C _{max} (ng/mL)	AUC (ng*hr/mL)
		Designated	Actual ^a		
6	Male	50	49	21.4	341
	Female	50	42	22.7	395
7	Male	150	127	199	2900
	Female	150	141	255	3760
8	Male	500	518	2920	40500
	Female	500	448	5470	66500

^a Values calculated for Week 26 from carcinogenicity animal groups.

NBI-56418 (parent)

Exposure to NBI-56418 generally increased with the increase dose level. Values for C_{max} and AUC_{0-t} were generally similar during Weeks 4, 13, and 26, indicating that steady-state for NBI-56418 was generally reached by Week 4 of the study. The increases in C_{max} and AUC_{0-t} for males and females were greater than dose proportional. T_{max} values ranged from 12 - 24 hours during Week 4, from 0 - 16 hours during Week 13, and from 0 - 24 hours during Week 26. No consistent sex differences were observed

NBI-61962 (metabolite M3)

Limited data above the LOQ were available for the low-dose group and variability between individual animals at the different dose levels was large. Exposure to NBI-61962 generally increased with increased dose. T_{max} values were similar to the parent. Sex differences were greater than 2-fold at the mid-dose but generally similar at the high dose. The increases in C_{max} and AUC_{0-t} for males and females were greater than dose proportional. The AUC_{0-t} metabolite-to-parent ratios ranged from 0.00678 - 0.181, indicating that NBI-61962 was a minor circulating metabolite.

NBI-54048 (metabolite M6x)

Reviewer notes that NBI-54048 was not identified as being present in the mouse in the in vivo metabolite profiling study using radiolabeled elagolix.

Plasma levels were below the LOQ for the low-dose group and variability between individual animals at the different dose levels was quite large. Exposure to NBI-54048 generally increased with dose level. Tmax values ranged from 4.0 to 24 hours during Week 26. Sex differences were generally less than 2-fold. The increases in Cmax and AUC_{0-t} for males and females between 150 and 500 mg/kg/day were greater than dose proportional. The AUC_{0-t} metabolite-to-parent ratios ranged from 0.00827 to 0.0155, indicating that NBI-54048 was a minor circulating metabolite.

Stability and Homogeneity

Stability of the elagolix in basal diet was evaluated in (b) (4) Study No. 8213284, which was conducted concurrently with this study. Homogeneity was acceptable. Concentration was verified in feed and ranged from 89.7-106.7%.

Study title: 2-Year Dietary Carcinogenicity and Toxicokinetic Study with NBI-56418 (Elagolix) in Rats	
Study no.:	RD101103
Study report location:	Application 210450 - Sequence 0000 - RD101103 2-Year Dietary Carcinogenicity Rat
Conducting laboratory and location:	(b) (4)
Date of study initiation:	22 July 2009
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	Elagolix Na salt, lots 29001262 and 29001263, 99.7%, and 29001264 99.8%
CAC concurrence:	Yes

Key Study Findings

NBI-56418 administered via diet at dose levels of 150, 300, and 800 mg/kg/day resulted in reduction in survival of males at 300 and 800 mg/kg/day (33.3 and 31.7%, respectively). However, adequate number of animals survived in all dose groups to provide a valid study for statistical analysis. Survival was unaffected in females.

The highest target dose of 800 mg/kg/day was associated with increased incidences of hepatic (males) and thyroid tumors (males and females) that were likely a rat-specific effect and were predominantly benign. No correlation was observed between survival and tumors.

The study achieved an MTD as the percent difference in body weight change (g) for the high dose group (M and F) was greater than 10% at terminal necropsy. Mean body weights were 17 and 13% lower than control for females and males, respectively.

The Week 26 AUC_{0-t} for NBI-56418 at the 800 mg/kg/day dose was 43.3 ug.hr/mL for males and 45.4 ug.hr/mL for females. This corresponds to an MOE of 12.4 and 13, respectively, as compared to the human AUC of 3.5 ug.hr/mL at the highest proposed therapeutic dose of 200 mg BID. Exposure to metabolites NBI-61962 (M3) and NBI-54048 (M6x) was minor.

Adequacy of Carcinogenicity Study

An adequate number of rats survived an appropriate duration (i.e., at least to Week 101 of the dosing phase) to result in acceptable exposure to the test article for a valid evaluation of the carcinogenic potential of NBI-56418 (see correspondence from ECAC dated June 21 2011 and SDN May 1 2011 with protocol amendment). There was sufficient histopathological data from the designated organs and tissues to evaluate both the non-neoplastic and neoplastic effects of NBI-56418 at all dose levels (and changes in control animals) for valid carcinogenicity evaluation.

Appropriateness of Test Models

Binding of elagolix to the GnRH receptor in the rat is several orders of magnitude weaker than human. In addition, there were no obvious pharmacodynamic signs of drug activity (atrophy of reproductive organs in males or females; Table of Macroscopic Observations p 137-146). We therefore assume for the purposes of this review that any elagolix-related findings are non-receptor mediated.

Bioavailability of elagolix in the rat and human are approximately the same (~52%). Protein binding is slightly greater in the rat (90.4%) than human (78.5%). Five minor metabolites, M2, M4b, M6, M10, and M17 that are present in humans were not detected in the in vivo metabolism study in the rat using radiolabeled elagolix.

The test model was deemed appropriate.

Evaluation of Tumor Findings

Liver

Increased incidences of hepatocyte hypertrophy were seen in males at 800 mg/kg/day and females at 300 or 800 mg/kg/day. The increase in numbers of liver tumors (hepatocellular adenomas and hepatocellular carcinomas) in males and eosinophilic foci in females were seen only at 800 mg/kg/day.

Other findings included an increased incidence of hepatocyte hypertrophy in males and at 800 mg/kg/day and females at ≥ 300 mg/kg/day; hepatocyte cytoplasmic vacuolation and pigmentation in females at 800 mg/kg/day as well as bile duct hyperplasia in males at 800 mg/kg/day and in females at ≥ 150 mg/kg/day.

Thyroid

At the high dose, there was an increase in the incidence of thyroid follicular cell tumors (adenomas and carcinomas) in males and females. Statistical significance was achieved only for adenomas. Increases in the incidence of thyroid follicular cell hypertrophy was evident at 300 (minimal) and 800 (minimal to slight) mg/kg/day dose levels in both males and females.

Gut

At the high dose, 15 males had granulomatous inflammation, involving the ileum and/or jejunum and/or mesenteric lymph node and/or bile duct. The inflammation was characterized by numerous macrophages, including multinucleate cells. The granulomatous inflammation in the ileum and/or jejunum or other areas could be test article-related, but it did not seem to affect food consumption or general health significantly.

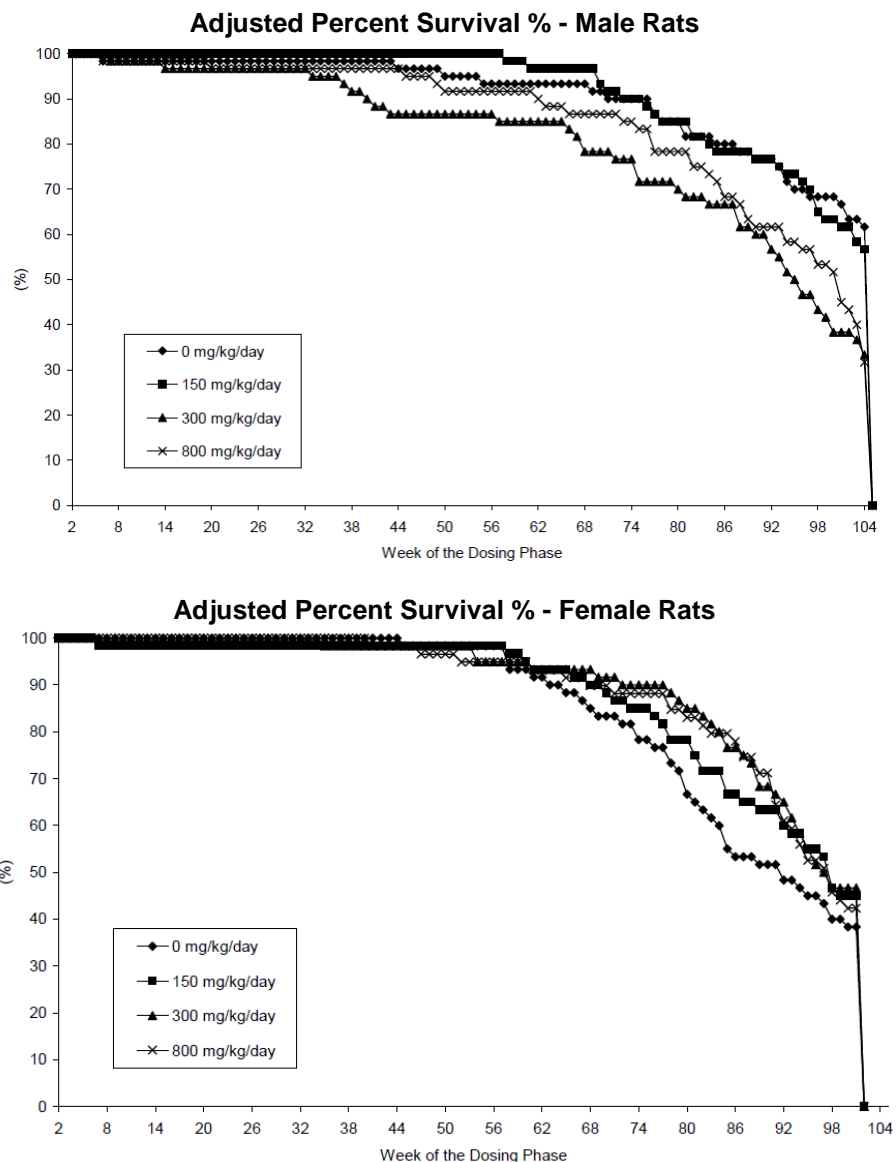
Methods	
Doses:	0, 150, 150, 150 mg/kg/d (Week 1) 0, 150, 300, 300 mg/kg/d (Week 2) 0, 150, 300, 800 mg/kg/d (Week 3 through termination) Dietary test article concentrations were adjusted weekly based on historical (Weeks 1 and 2) or actual study (Weeks 3 through termination) body weight and food consumption data. Due to the potential for poor consumption of test article-treated diet, the dietary test article concentration (dose levels) for the mid- and high-dose levels was increased gradually over the first 1 or 2 weeks of the study.
Frequency of dosing:	daily
Dose volume:	N/A
Route of administration:	Oral diet
Formulation/Vehicle:	(b) (4)
Basis of dose selection:	Range-finding studies. 600 mg/kg/d was the NOAEL in the range-finding studies. The 800 mg/kg dose was likely the MTD based on reduced body weight gain. The exposure at 800 mg/kg results in at least 16-fold the upper limit of the therapeutic human exposure in females. Higher doses (> 1200 mg/kg) resulted in decreased exposure at Weeks 8 and 15 presumably due to liver enzyme induction. The AUC ₀₋₄ at the 100 mg/kg/day dose is roughly equivalent to the expected therapeutic exposure (948 to 1581 ng·h/mL) and was deemed too low for the carci study.
Species/Strain:	Rat / CrI:CD(SD)
Number/Sex/Group:	60/sex/group
Age:	8-9 weeks
Animal housing:	Individual housing in stainless steel cages
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	None
Satellite groups:	5/sex/dose for TK Blood samples were collected via jugular vein from each nonfasted animal during Weeks 3, 13, and 26 at approximately 06:00, 10:00, 14:00, 18:00, 22:00, and 06:00 (on the following day).
Deviation from study protocol:	Multiple minor deviations, but overall no impact on the study.

Observations and Results

Mortality

For males, there was a significant increase in mortality rates ($p = 0.004$), with mid and high dose groups showing significantly higher mortality rates (66.7 and 68.3%, respectively) than the rate of the control group (38.3%). For females, no dose-response trend in mortality was detected, nor were NBI-56418 dose groups different in mortality from the control group.

In accordance with study termination criteria, all surviving females (Groups 1 through 4) were sacrificed during Week 102 since the number of females in the control group (Group 1) had reached a total of 20 animals. All surviving males (Groups 1 through 4) were sacrificed during Week 105 of the dosing phase.



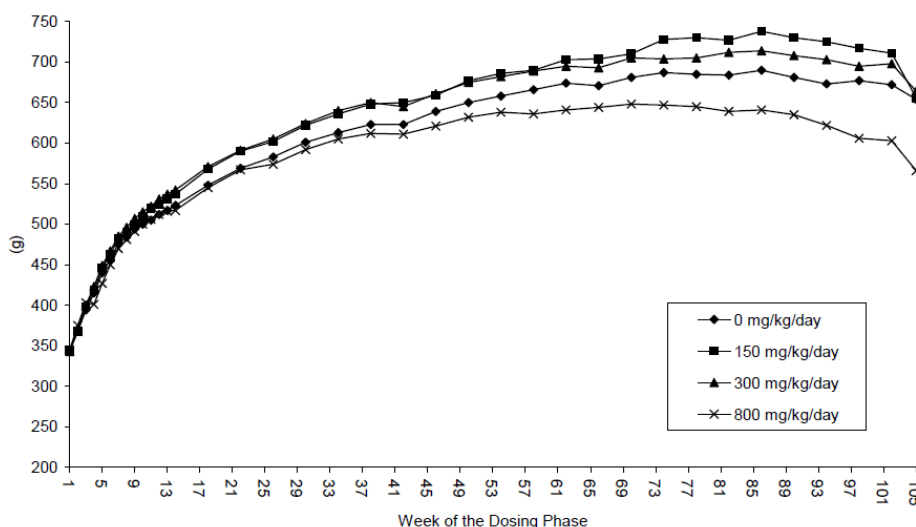
Clinical Signs

No treatment-related effects noted.

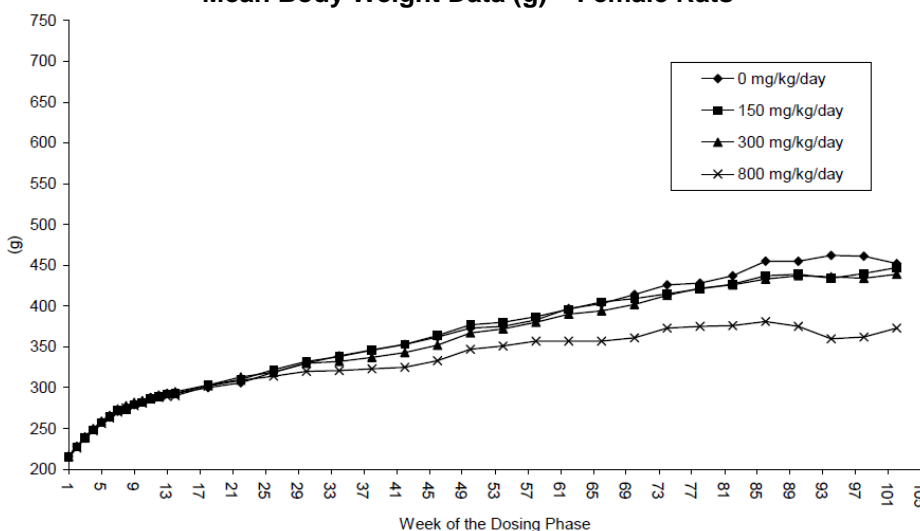
Body Weights and Food Consumption

Treatment-related lower mean body weight and body weight gain were noted at the high dose. Mean body weights were 17 and 13% lower than control for females and males, respectively, at the end of dosing phase. Percent difference in body weight change at the high dose was greater than 10%. However, food consumption was not affected in a dose-dependent way. The sponsor suggested that 'the lack of correlation between food consumption and decreased body weight may be attributed to the variability in the spillage of the feed by individual animals and assessment of food consumption over a short duration of 1-day period'.

Mean Body Weight Data (g) – Male Rats



Mean Body Weight Data (g) – Female Rats



Gross Pathology

Dose-dependent macroscopic findings were found in the thyroid and liver. Enlargement and/or mass were noted for 0, 1, 5, 12 thyroids in males and for 0, 2, 1, 8 thyroids in females given 0, 150, 300, or 800 mg/kg/day, respectively. Enlargement and/or mass were noted for 2, 0, 2, 13 livers in males and for 0, 3, 0, 5 livers in females given 0, 150, 300, or 800 mg/kg/day, respectively. Discolored liver was noted for 7, 12, 14, 12 males and for 3, 6, 14, 12 females given 0, 150, 300, or 800 mg/kg/day, respectively.

Histopathology

Peer Review: Yes

NeoplasticLiver:

Increased incidences of liver tumors (hepatocellular adenomas and hepatocellular carcinomas) were seen in males at the high dose. The combined incidence of adenoma/carcinoma was statistically significant. For females, no statistical significance was found for either tumor type. However, the incidence of eosinophilic foci appeared increased in the liver of females given 800 mg/kg/day. These foci varied from small, involving a few dozen cells, to areas larger than a lobule. Tables below are excerpted from the CDER statistical review.

Hepatocellular Adenomas and Carcinomas in Male Rat

Tumor	Control*	Low Dose**	Mid Dose**	High Dose**
Adenoma/Carcinoma incidence	2/60	1/60	0/60	15/60
P-value	<0.001	0.8788	1.0000	<0.001
B-Adenoma incidence	1/60	1/60	0/60	9/60
P-value	<0.001	0.7525	1.0000	0.0047
M-Carcinoma incidence	1/60	0/60	0/60	6/60
P-value	<0.001	1.0000	1.0000	0.0382

*p-value for trend

**p-value for pair-wise comparison compared to vehicle control

Thyroid:

In the thyroid, the high dose was associated with increased incidences of tumors of thyroid follicular cells (adenomas and carcinomas) in both males and females. The follicular cell adenomas were well differentiated and showed no atypia. Thyroid follicular cell carcinomas often showed invasion of the capsule but atypia was not prominent and distant metastases were not found.

Thyroid Follicular Cell Adenomas and Carcinomas in Male Rat

Tumor Name	Control*	Low Dose**	Mid Dose**	High Dose**
Adenoma/Carcinoma incidence	3/60	4/60	6/60	27/60
P-value	<0.001	0.5114	0.1619	<0.001
B-Adenoma incidence	2/60	4/60	6/60	23/60
P-value	<0.001	0.3485	0.0837	<0.001
M-Carcinoma	1/60	0/60	0/60	4/60
P-value	0.0132	1.0000	1.0000	0.1553

*p-value for trend

**p-value for pair-wise comparison compared to vehicle control

Thyroid Follicular Cell Adenomas and Carcinomas in Female Rat

Tumor Name	Control*	Low Dose**	Mid Dose**	High Dose**
Adenoma/Carcinoma incidence	0/60	2/60	1/60	19/60
P-value	<0.001	0.2719	0.5301	<0.001
B-Adenoma incidence	0/60	2/60	1/60	17/60
P-value	<0.001	0.2719	0.5301	<0.001
M-Carcinoma incidence	0/60	0/60	0/60	2/60
P-value	0.0636			0.2719

*p-value for trend

**p-value for pair-wise comparison compared to vehicle control

Nonneoplastic (rat)Liver:

In the liver, increased incidences of hepatocyte hypertrophy were seen in males at 800 mg/kg/day and females at 300 or 800 mg/kg/day and eosinophilic (possibly preneoplastic) foci in females at were seen at 800 mg/kg/day.

		Incidence and Severity of Test Article-Related Microscopic Findings in Liver							
		NBI-56418 mg/kg/day							
Sex		Males				Females			
Dose Level (mg/kg/day)		0	150	300	800	0	150	300	800
Liver									
	Number Examined	60	60	60	60	60	60	60	60
Hyperplasia, Bile Duct									
	Total number affected	17	16	12	28	8	20	25	45
	Minimal	16	14	11	27	7	20	22	23
	Slight	1	2	1	0	1	0	1	16
	Moderate	0	0	0	1	0	0	2	6
Vacuolation, Hepatocyte									
	Total number affected	3	7	6	7	20	19	26	45
	Minimal	2	3	4	5	18	17	20	39
	Slight	1	4	1	2	2	1	6	5
	Moderate	0	0	1	0	0	1	0	1
Hypertrophy, Hepatocyte									
	Total number affected	2	3	5	28	4	5	22	50
	Minimal	2	3	5	23	4	5	21	34
	Slight	0	0	0	5	0	0	1	16
Pigment									
	Total number affected	0	0	0	1	0	0	0	21
	Minimal	0	0	0	1	0	0	0	18
	Slight	0	0	0	0	0	0	0	3
Focus, Cellular Alteration, Eosinophilic									
	Total number affected	8	11	4	9	2	5	5	14
	Minimal	7	10	4	5	1	4	0	5
	Slight	0	1	0	2	0	1	2	4
	Moderate	1	0	0	2	1	0	3	4
	Marked	0	0	0	0	0	0	0	1

Other findings in the gut:

Fifteen males in the high dose group were noted to have granulomatous inflammation, most frequently involving the ileum and/or jejunum and, less frequently, the mesenteric lymph node and bile duct. The inflammation was characterized by numerous macrophages, including multinucleate cells. Other findings included hepatocyte cytoplasmic vacuolation and pigmentation in females at 800 mg/kg/day as well as bile duct hyperplasia in males at 800 mg/kg/day and in females at ≥ 150 mg/kg/day.

Thyroid:

In the thyroid, the high dose was associated with increased incidences of hypertrophy and hyperplasia. Increased incidences of thyroid follicular cell hypertrophy were evident in both sexes at 300 (minimal) and 800 (minimal to slight) mg/kg/day.

Incidence and Severity of Test Article-Related Microscopic Findings in Thyroid										
		NBI-56418 mg/kg/day								
		Sex	Males				Females			
Dose Level (mg/kg/day)			0	150	300	800	0	150	300	800
Thyroid										
Number Examined			60	60	60	60	60	60	60	60
Hypertrophy, Follicular Cell										
Total number affected			14	18	31	43	3	9	19	54
Minimal			14	18	31	40	3	9	19	42
Slight			0	0	0	3	0	0	0	12
Hyperplasia, Follicular Cell										
Total number affected			1	7	3	15	2	1	2	13
Minimal			0	4	3	9	2	1	1	4
Slight			0	1	0	3	0	0	1	3
Moderate			1	2	0	3	0	0	0	6

Uterus:

Cystic endometrial hyperplasia showed an apparent increased incidence in dosed animals. This change was not considered test article-related because it was generally of minimal severity, is a common age-related change in this strain, and severity was not dose-related because moderate severity was seen only in low dose and control females.

Toxicokinetics (rat)

Samples were collected via jugular vein during weeks 3, 13, and 26. Exposure increased with the increasing dose and was generally greater than dose proportional. C_{max} and AUC_{0-t} values were generally higher during Weeks 13 and 26 relative to Week 3, except at 800 mg/kg/day dose level for males, where exposures decreased approximately 2-fold from Week 3 to Weeks 13 and 26; indicating steady-state was reached by Week 3. Overall, maximum exposures were lower than for oral gavage. T_{max} values ranged from 4.0 - 17 hours during Week 3, from 3.2 - 17 hours during Week 13, and from 0 - 18 hours during Week 26. Sex differences were generally less than 2-fold.

Mean Toxicokinetic Parameters for NBI-56418 at Week 26

Treatment Group	Sex	Dose (mg/kg/day)		C _{max} (ng/mL)	AUC _{0-t} (µg*hr/mL)
		Designated	Actual ^a		
6	M	150	146	185	2880
	F	150	139	156	1960
7	M	300	279	768	10900
	F	300	285	933	10600
8	M	800	723	2950	43300
	F	800	848	5450	45400

^a Values calculated for Week 26 from carcinogenicity animal groups.

Sponsor's table: note apparent error in units for the AUC values – should be ng.hr/mL not ug.hr/mL

Control group exposures: Exposures during Week 3 were below the limit of quantitation (BLQ; <5.00 ng/mL). During Weeks 13 and 26, 8 control animals had a total of 10 measurable concentrations of NBI-56418 that 6.44 - 112 ng/mL. Exposures in the control animals were investigated at (b) (4), but could not be explained. The concentrations were confirmed upon reassay.

Metabolites: The low Week 26 AUC_{0-t} metabolite-to-parent ratios (approximately 3.6 and 0.8% for NBI-61962 (M3) and NBI-54048 (M6x), respectively) indicated that they were relatively minor circulating metabolites of NBI-56418 in rats following dietary administration.

NBI-61962 exposures increased with dose, but were not consistently dose proportional. T_{max} ranged from 4.8 to 19 hours during Week 26. Sex differences were generally less than 2-fold with the exception of males at the low dose that had values approximately 3-fold higher than females. The AUC_{0-t} metabolite-to-parent ratios ranged from 0.00930 to 0.0360.

NBI-54048 exposures increased with dose, and were generally greater than dose proportional. T_{max} ranged from 0 - 19 hours during Week 26. Males generally were greater than 2-fold those in females. The AUC_{0-t} metabolite-to-parent ratios ranged from 0.00281 to 0.00775.

Stability and Homogeneity

The stability analyses were performed under (b) (4) 8213284 and were acceptable.

Homogeneity: With the exception of the Week 1 samples for females in Groups 2 and 6 and Week 52 samples for Group 2 males homogeneity results for the remainder samples met acceptance criteria. Exceptions did not affect the outcome of the study.

Concentration was verified and ranged from 90.1 to 107.0% of target, with one exception: the Week 52 samples for males in Group 2 had mean concentration of 243.7% of target concentration. Exceptions did not affect the outcome of the study.

Follow up study to the 2-yr rat carcinogenicity study

Study title: 6-Week Dietary Study with A-1278823 (Elagolix) Sodium in Rats to Investigate Thyroid and Hepatic Effects	
Study no.:	RD12438
Study report location:	Application 210450 - Sequence 0000 - RD12438 6-Week Dietary Rat located in section 4.2.3.7.3.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	17 April 2012
GLP compliance / QA statement:	No /
Drug, lot #, and % purity:	Elagolix free acid, 03805YS00/03805YS10, 95.4%; 13617PP01, 95.2%

This study evaluated the thyroid and hepatic effects and the TK of elagolix sodium, when administered daily in the diet to rats for at least 6 weeks at doses higher than or equal to the highest dose of 800 mg/kg/day used in the rat carcinogenicity study. The objective was to investigate if the thyroid and liver effects observed in the carcinogenicity study were related to induction of specific hepatic enzyme activity. The activity of additional hepatic drug metabolizing enzymes was also evaluated to generate a mechanistic understanding of the hepatic histopathological changes observed following chronic dosing.

Key Study Findings

Dietary administration of elagolix at 800 or 1200 mg/kg/day for up to 6 weeks resulted in thyroid effects that included decreased serum T4 levels, increased serum TSH levels, increased thyroid gland weight (females), and thyroid follicular cell hypertrophy. These effects were considered to

be related to liver changes that included increased liver weights, and panlobular hepatocellular hypertrophy and increased in the activity of hepatic UDPGT enzyme. The liver pathological changes also correlated with induction of liver drug metabolizing enzymes including increased CYP3A, CYP2B (males), 4-MU UDPGT, and 4-NP UDPGT (females) activities.

The day 42 overall Cmax and AUC values were 3.39 µg/mL and 45.3 µg*hr/mL, respectively, for the 800 mg/kg/day dose level, and 3.62 µg/mL and 42.4 µg*hr/mL, respectively, for the 1200 mg/kg/day dose level. Exposure was roughly similar at the d22 and d42 time points.

Methods	
Doses:	Group 1: saline control (gavage) beginning on d13 Group 2: positive control (phenobarbital 75 mg/kg) beginning on d13 Group 3: vehicle control Group 4: 800 mg/kg/d (titration: 150 (d1-4), 300 (d5-8), 600 (d9-12), 800 (d13-end) Group 5: 1200 mg/kg/d (titration: 200 (d1-4), 400 (d5-8), 800 (d9-12), 1200 (d13-end)
Frequency of dosing:	Daily
Dose volume:	N/A
Route of administration:	Oral diet
Formulation/Vehicle:	(b) (4)
Basis of dose selection:	Doses were selected based on the 2 yr carcinogenicity study
Species/Strain:	Rat / CrI:CD(SD)
Number/Sex/Group:	30/sex/group for the dosed groups 15/sex/group for the saline and vehicle controls 30/sex/group for the positive control
Age:	6.9-7.4 weeks
Body weights:	110-192 g (M) 88-166 g (F)
Animal housing:	Individual housing in stainless steel cages
Satellite groups:	6/sex/dose for TK; samples taken on d22 and d42
Unique study design:	There were two interim sacrifices: one on Day 22 and one on Day 29 5/sex/group from controls, and 10/sex/group from positive control and treated groups Samples were taken for serum TSH, and T4 on d 22, d29, and d43
Deviation from study protocol:	Multiple minor deviations, but overall no impact on the study.

Observations and Results

Mortality

There were no treatment related deaths. 2 main study males were sacrificed on d13 and d26 due to clinical signs (head and shoulder sores). 8 TK animals died after serum collection and were replaced.

Clinical signs

None treatment related

Body weight

In positive control animals, no body weight changes were noted. For elagolix-treated animals, a decrease in mean body weight gain (actual loss for some intervals) was noted in males between Days 1 and 41 (18 and 23% decrease at 800 and 1200 mg/kg/day, respectively). In females given 1200 mg/kg/day, no significant change in body weight gain was noted overall between Days 1 to 41.

Food consumption

Positive control animals showed no change in food consumption. For elagolix-treated animals, a significant decrease in mean food consumption was noted between Days 1 and 42 (13 and 16% decrease in males given up to 800 or 1200 mg/kg/day, respectively, and 16 and 10% decrease in females given up to 800 or 1200 mg/kg/day, respectively). In males, decreased food consumption correlated with decreased body weight. The decreased food consumption in males was recovering towards the end of the study.

Thyroid hormone analysis

TSH:

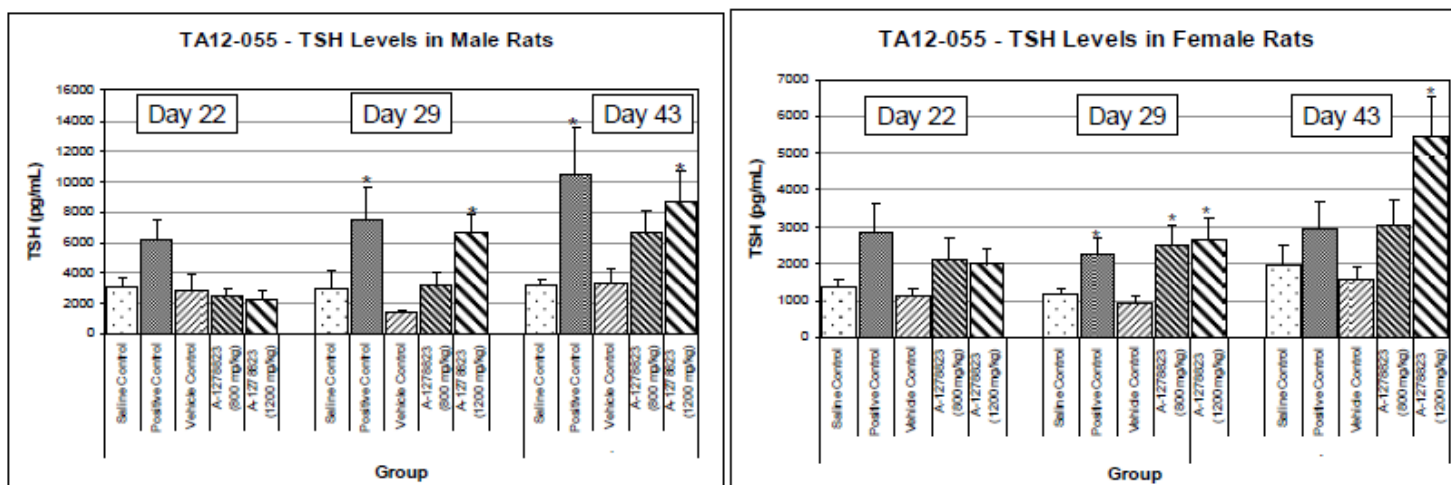
TSH levels increased as expected for the positive control animals.

Elagolix-treated male rats had a significant increase in serum TSH levels on days 29 and 43 at the high dose.

Elagolix-treated female rats had a significant increase in serum TSH levels on day 29 at 800 and 1200 mg/kg/day and on day 43 at 1200 mg/kg/day.

The increase in TSH levels is consistent with a hepatic uridine diphosphate glucuronosyltransferase (UDPGT) induction effect.

Groups 1-5 are shown L→R.



Error bars represent SEM.

n= 5 [saline control and vehicle control groups];

n= 9 [day 29 males dosed with 800 mg/kg/day and day 22 males dosed with 1200 mg/kg/day]

n=10 [all other groups]

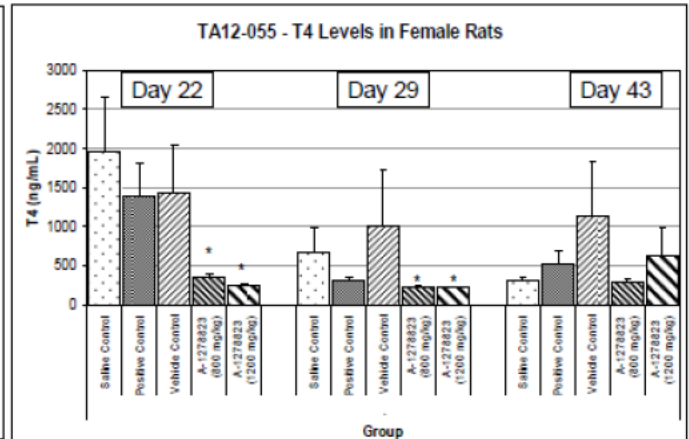
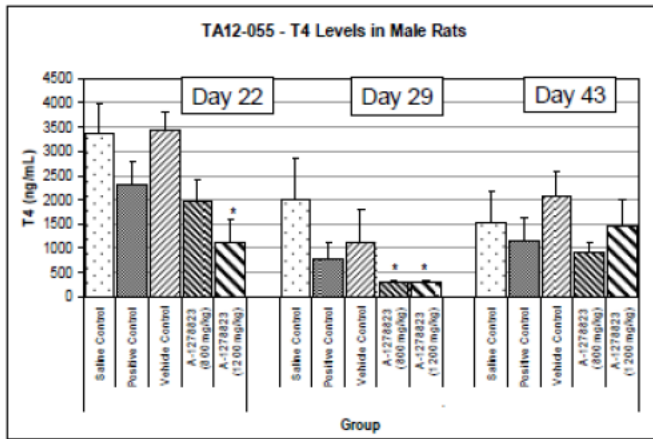
*p value < 0.05 is considered statistically significant

T4 / T3

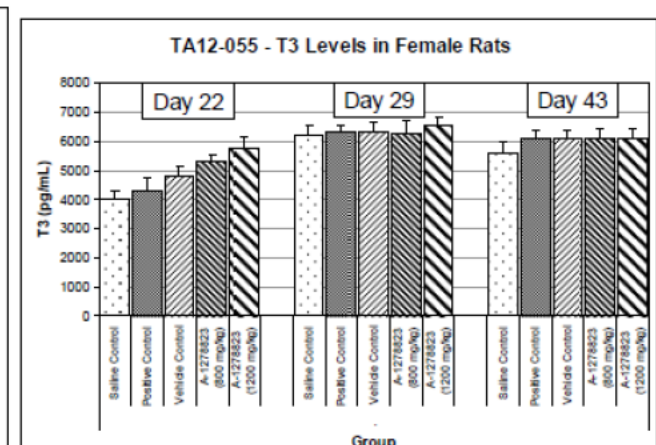
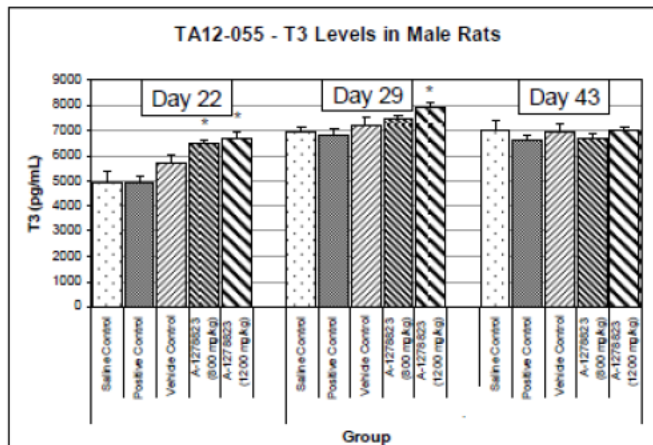
Decreased level of serum thyroid hormone (T4) has been associated with a compensatory increase in serum TSH levels.

Elagolix-treated male rats had decreased serum T4 levels on day 22 at 1200 mg/kg/day and on day 29 at 800 and 1200 mg/kg/day.

Elagolix-treated female rats had decreased serum T4 levels on day 22 and 29 at both 800 and 1200 mg/kg/day.



Males had a statistically significant increase in serum T3 levels (data not shown) on day 22 at 800 and 1200 mg/kg/day and on day 29 at 1200 mg/kg/day. Levels of serum T3 were consistently higher in male rats when compared to female rats. This could be due to extra-thyroid conversion of T4 to T3.



Gross Pathology

No treatment-related observations.

Organ Weights

Absolute and relative liver (M/F) and thyroid (F) organ weights were increased in the positive controls and in the elagolix treated groups (both doses). Increased liver weights correlated with hepatocellular hypertrophy. Increased thyroid weights in females correlated with follicular cell hypertrophy.

Relative organ weights (% body weight) terminal sacrifice

Group	Liver		Thyroid / Parathyroid		Pituitary	
	M	F	M	F	M	F
1 Saline	3.07	3.18	0.0070	0.0073	0.0036	0.0060
2 Phenobarbitol	4.31	4.15	0.0073	0.0091	0.0034	0.0060
3 Vehicle	3.05	3.18	0.0074	0.0086	0.0034	0.0066
4 800 elagolix	3.28*	3.79*	0.0075	0.0106*	0.0035	0.0064
5 1200 elagolix	4.27*	5.38*	0.0088	0.0119*	0.0034	0.0064

*P≤0.05

Histopathology

Administration of A-1278823 or the positive control (phenobarbital) was associated with histopathological changes in liver and thyroid glands. In the liver, increased incidence and severity of hepatocellular hypertrophy was dose- and duration-dependent. In the thyroid, increased incidence and severity of follicular cell hypertrophy was also dose- and duration dependent.

There were no elagolix-related microscopic changes were identified in pituitary or parathyroid glands.

Hepatic Microsomal Enzyme Analysis

Microsomal protein yield: no change

At terminal sacrifice, there were no changes in the overall microsomal protein yield for either the positive control or the elagolix-treated animals.

Total cytochrome P450 content: no change

No change was observed with elagolix treatment. Phenobarbital increased total P450 content 2-2.7-fold.

CYP2B activity – very slight increase

Elagolix treatment produced only a very slight (1.3-1.7 fold) increase in CYP2B activity in males and none in females. Phenobarbital increased CYP2B activity 60-135-fold.

CYP3A activity - increased

Elagolix treatment produced increased activity of 1.9-5.2-fold in males and 2.4-7.8-fold in females. Phenobarbital increased CYP3A activity 2.2-3.5-fold in males and 6.8-11.1-fold in females.

4-MU UDPGT activity - increased

Elagolix also increased UDPGT activity 1.7-3.0-fold (M/F) – potency similar to the positive control. Phenobarbital increased 4-MU UDPGT activity 1.5-2.4-fold (M/F).

4-NP UDPGT activity – increased in females only

Elagolix produced no increased enzyme activity in males, but in females, 4-NP UDPGT activity was increased 1.2-2.1-fold. Phenobarbital increased 4-NP UDPGT activity 2.1-2.7-fold (M/F).

Toxicokinetics

The day 42 overall C_{max} and AUC values were 3.39 µg/mL and 45.3 µg*hr/mL, respectively, for the 800 mg/kg/day dose level, and 3.62 µg/mL and 42.4 µg*hr/mL, respectively, for the 1200 mg/kg/day dose level. Exposure was roughly similar at the d22 and d42 time points.

Stability and Homogeneity

Homogeneity and concentration were verified and found acceptable.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Fertility and early development to implantation in rats after oral administration of NBI-56418.	
Study no.:	RD101081 ((b) (4) 6944-272)
Study report location:	\\cdsesub1\evsprod\nda210450\0000\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev\rd101081\c-tox-6944272-rd101081-seg1-po-rat.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	23 May 2006
GLP compliance and QA statement:	Yes / yes
Drug, lot #, and % purity:	NBI-56418 elagolix, 17BN02.HQ00001, 98.9%

Key Study Findings

Unscheduled deaths (9M/13F) were dose-related and occurred between 2 and 30 days post-dosing. One high dose male had convulsions prior to dying. There were dose-related clinical signs of nasal discharge, salivation, labored breathing and hypoactivity, and necropsy findings of mottled lungs and material in the thoracic cavity. The sponsor proposed that the deaths were related to aspiration of test article and that aspiration became more likely with higher dose because the animals had a taste aversion to the formulation.

High dose males showed a slightly reduced body weight gain. There were no necropsy findings. There was slight to no effect on estrous cycle or reproductive performance, fertility parameters in males or females, or cesarean section (implantation or embryo/fetal viability) parameters. However, NBI-56418 has very low affinity for the rat GnRH receptor, and so there was correspondingly little effect on gonadotropins or sex steroid production.

Formulation analysis showed that the low dose group received a reduced dose (about 1/3 less) during week 6.

Regarding TK, the C_{max} and AUC of the metabolites NBI-61962 (M3) and NBI-54048 (M6x) were approximately 10% and 6%, respectively of the corresponding measures for the parent NBI-56418, with most values less than 5% of parent. Metabolite NBI-54048 has ~6 fold higher affinity for the rat GnRH receptor than the parent compound.

The sponsor's NOAEL for maternal and paternal toxicity was 150 mg/kg/day due to respiratory distress leading to excessive mortality at the 300 mg/kg/day dose. However, given the dose dependence of the mortality, reviewer feels that the **NOAEL** is more accurately set at **50 mg/kg/day**. We note that other repeat dose studies had similar mortality due to aspiration but had higher NOAELs. TK values at the 50 mg/kg/day dose were:

Males: C_{max} = 0.7 µg/mL and AUC = 1.8 µg.h/mL on Day 28.

Females: C_{max} = 0.8 µg/mL and AUC = 2.3 µg.h/mL on Day 14.

The **NOEL** for reproductive performance, fertility, and embryo/fetal viability was **300 mg/kg/day**, the highest dose tested. TK values at this dose were:

Males: C_{max} = 2.8 µg/mL and AUC = 41.6 µg.h/mL on Day 28.

Females: C_{max} = 2.2 µg/mL and AUC = 16.1 µg.h/mL on Day 14.

With respect to the AUC at the MRHD, the exposure multiple for women based on the AUC at the NOEL of 300 mg/kg/day for the fertility effects in the female rat study is approximately 4.6-

fold. However, the sponsor carried out a calculation that showed that, when adjusted for the difference in affinity of elagolix for the rat and human GnRH receptor, this exposure multiple is reduced to 0.007-fold.

The sponsor has correctly concluded that, because the elagolix binds so poorly to the rat GnRH receptor, this study cannot effectively assess the effect of elagolix on fertility. *That is, even though rats were exposed at a reasonable multiple of the human MRHD based on AUC, the lack of pharmacodynamic effect renders the study not applicable to human risk assessment.*

Methods	
Doses*:	0, 50, 150, 300 mg/kg/d
Frequency of dosing:	Once daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water
Species/Strain:	CrI:CD(SD) rats
Number/Sex/Group:	25/sex/gp
Satellite groups:	9/sex/gp
Study design:	Dosing schedule: Males were dosed for at least 28 days prior to mating and throughout the mating period through the day prior to termination (at least 10 weeks prior to sacrifice). Females were dosed for at least 14 days prior to mating, throughout the mating period and through GD 7. Females were necropsied on GD13. Females that were not confirmed for mating at the end of breeding period were dosed for an additional 8 days.
Deviation from study protocol:	Group 2 dosing in week 6 was 65.8%

*Dose selection was based on an EFD rat study conducted in 2004 ([Application 210450 - Sequence 0000 - RD101075 Seg II DRF Rat](#)) where maternal and in-utero toxicity was assessed in pregnant rats at dose levels of 300, 600 and 1200 mg/kg/day. There were 6 unscheduled deaths (1 in the 300, 4 in the 600 and 1 in the 1200 mg/kg/day groups). Treatment-related clinical observations included excessive salivation immediately following dosing and labored/audible respiration at dose > 600 mg/kg/day. There was significant decreased maternal body weight gain and food consumption during dosing in all treated groups. Caesarean section data indicated increased post-implantation loss and decreased fetal weight at 600 mg/kg/day. Also in the 6-month toxicology study (RD101044) there was over 50% mortality in the 600 mg/kg/day dosing group and over 25% mortality in the 300 mg/kg/day dosing group. Based on these observations, 300 mg/kg/day was selected as the highest dose.

Observations and Results

Parameters and endpoints evaluated: Clinical observations, body weight, food consumption, mating incidence, estrus cycling, drug plasma levels, GD 13 cesarean section data, macroscopic observations including male reproductive organ weights, and sperm motility and count.

Mortality

Sponsor's text: "There were numerous (13) unscheduled deaths (see Table below) that were dose-dependent: 1 control female, 2 at the low-dose (1 male and 1 female), 6 at the mid-dose (2 males and 4 females), and 13 at the high-dose (6 males and 7 females or ~25%).

The clinical sign of clear or discolored oral and/or nasal discharge occurred immediately following dosing had an incidence and severity that increased with dose. Also, a 300 mg/kg/day

male (B04671) was observed with convulsions immediately following dosing on the day of death (Day 30). Necropsy findings were remarkable in almost half of the unscheduled-death males and included mottled/discolored lungs, some with material in the thoracic cavity. None died on the day of initiation of treatment, but it is believed that these clinical observations and deaths are attributed to some undetermined characteristic of the dosing formulation (causing taste aversion) that resulted in the aspiration of the dose preparation into the lungs (i.e., excessive salivation produced by the dosing formulation resulting in aspiration of saliva leading to the respiratory signs [and the convulsions in the 300 mg/kg/day male], as well as clear discharge from the nose).

In an attempt to overcome this problem, the use of cherry syrup to coat the outside of the dosing needle was initiated to coincide with the third week of dosing in the males and the initiation of dose administration for the females. Immediately, upon the use of the cherry syrup the incidence of oral discharge and audible respiration decreased in the males. Although the use of the cherry syrup helped alleviate the excessive salivation in the males, the problem was not completely alleviated in the females. Remarkable clinical signs included clear or discolored oral and/or nasal discharge immediately following dosing. Again, the incidence and severity of these finding increased with dose. Nearly half of these females had a clinical observation with pulmonary involvement similar to the males, and although their deaths cannot be definitively determined, it is believed that they are associated with stress related to the dosing procedure, or aspiration of excessive salivation or residual dosing formulations.”

Sponsor's Table Section 2.6.7.12 p 108 Tox Tabulated Summary

Daily Dose (mg/kg)	0 (Control)	50	150	300
Females				
Toxicokinetics - AUC (µg·hr/mL)				
Day 1	BLQ	1.81	7.66	36.4
Day 14	BLQ	2.31	12.6	16.1
No Evaluated	25	25	25	25
No. Died or Sacrificed Moribund	1	1 ^a	4 ^a	7 ^a
Premating Clinical Observations				
clear or discolored oral and/or nasal discharge	-	+	+	++
audible/labored respiration	-	-	+	+
Gestation Clinical Observations				
clear or discolored oral and/or nasal discharge	-	-	+	++
audible/labored respiration	-	-	-	+
Necropsy Observations^b				
material in trachea	0	0	1	1
fluid and/or material filled thoracic cavity	0	0	3	2
esophagus perforation	0	0	0	1
uterus distended	0	0	0	2
uterus nongravid	0	0	0	1

- No noteworthy findings; + Slight; ++Moderate; BLQ = Below the limit of quantitation of 5 ng/mL. TK analyses not done.

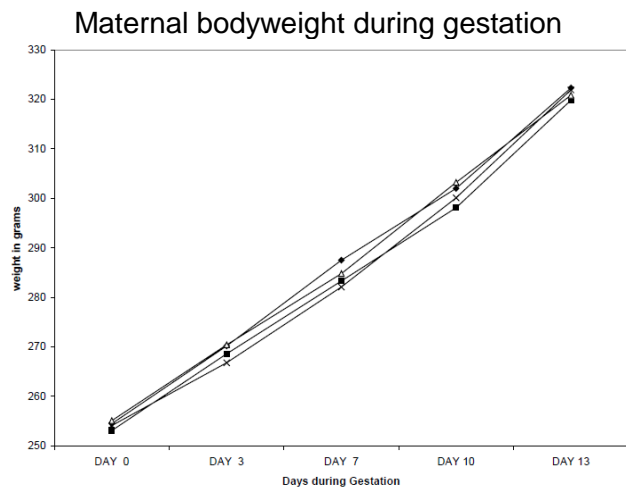
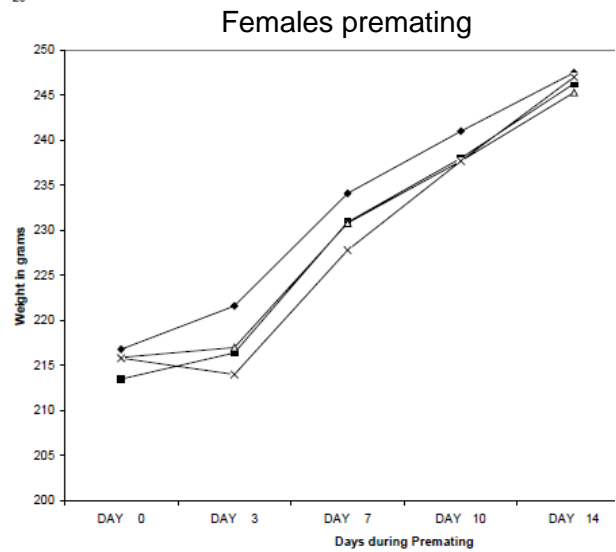
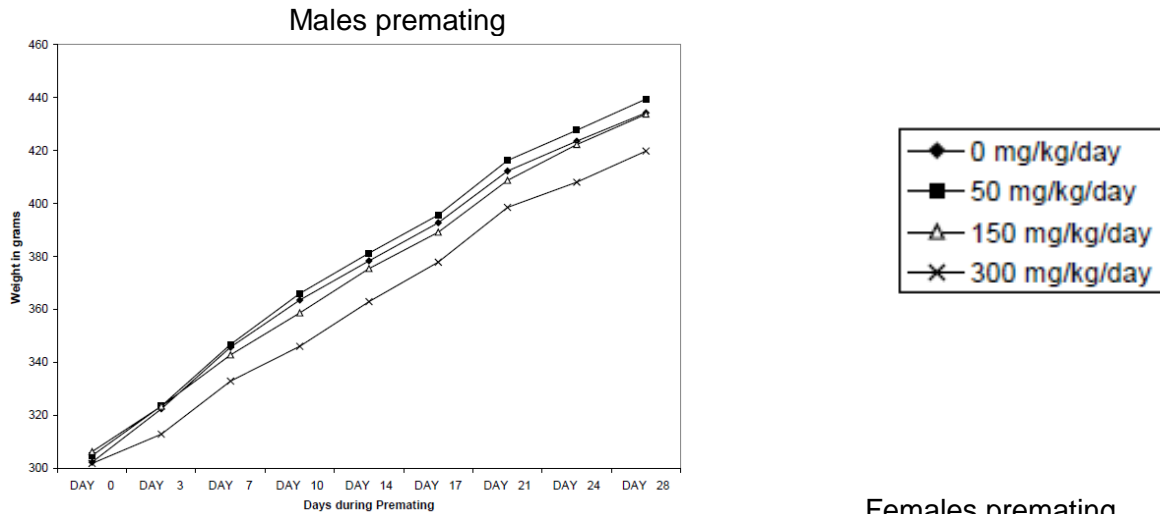
- These deaths, with the exception of the 1 female in the vehicle group (Gavage error), were attributed to secondary effects associated with the test article (i.e. clear oral/nasal discharge leading to aspiration of saliva and/or residual dosing formulation).
- Remarkable necropsy findings primarily associated with unscheduled deaths.

Clinical Signs

For the surviving animals, remarkable clinical signs included primarily clear oral/nasal discharge in the low dose group and audible/labored respiration and hypoactivity in the mid and high dose groups, the incidence and severity of which increased with dose. Other clinical observations were sporadic and considered unrelated to treatment.

Body Weight

There was a slightly reduced body weight in high dose males attributable to reduced body weight gain over the first few days of dosing.



Feed Consumption

Consistent with body weights.

Toxicokinetics

All animals were systemically exposed to NBI-56418, the metabolite NBI-61962 (M3) and the metabolite NBI-54048 (N6x) at all dose levels on the sampling days evaluated (Day 1 and Day 28 for males; Day 1 and 14 for females). See Appendix A pp 12-14 for concentration vs time plots.

Generally, dose dependent increase of both total exposure (AUC) and peak exposure (C_{max}) of NBI-56418 was observed on the sampling days evaluated. Relatively little or no accumulation was observed upon repeated once daily administration. There were no consistent or substantial gender differences observed in this study. The C_{max} and AUC of the metabolites NBI-61962 and NBI-54048 were approximately 10% and 6%, respectively of the parent, with most values less than 5%.

Sponsor's Table 7. p 365 of the study report

NBI-56418								
Dose (mg/kg)	Route/Formulation	Gender/Strain	Study Day	t _{max} (Hr)	C _{max} (ng/mL)	AUC _{last} (Hr*ng/mL)	AUC _{all} (Hr*ng/mL)	N
50	Oral/Solution	Female	1	0.5	784	1810	1810	3
			14	0.3	818	2120	2310	3
		Male	1	0.5	568	1060	1250	3
			28	0.5	695	1590	1840	3
150	Oral/Solution	Female	1	0.5	1410	7660	7660	3
			14	1.0	1460	12600	12600	3
		Male	1	0.5	1080	8040	8040	3
			28	1.0	1270	4190	4190	3
300	Oral/Solution	Female	1	8.0	2650	36400	36400	3
			14	0.5	2230	16100	16100	3
		Male	1	4.0	1890	25800	25800	3
			28	8.0	2770	41600	41600	3

NM: Not measurable.

With respect to the AUC at the MRHD, the exposure multiple for women based on the AUC at the NOEL of 300 mg/kg/day for the fertility effects in the female rat study is approximately 4.6-fold. *When adjusted for the difference in affinity of elagolix for the rat and human GnRH receptor, this exposure multiple translates to 0.007-fold.*

Stability and Homogeneity

The NBI-56418 concentrations in formulation samples from Groups 2, 3, and 4 ranged from 65.8 to 115.0%, 97.7 to 112.3%, and 93.8 to 99.8% of the theoretical concentration, respectively (Appendix 4). Specifically, analytical results for week 6 showed that concentration value for Group 2 was 65.8%, which was outside the acceptable deviation of $\pm 15\%$. This value held up with repeat sampling.

Necropsy

Necropsy findings in the treated males were primarily associated with the unscheduled deaths. In addition, remarkable necropsy findings for a low dose male (B04608) consisted of small testes and epididymides. This male was confirmed to have mated with its paired female (B04744), but the female was not pregnant at necropsy. These findings were not observed at the higher dose levels.

Similar to the males, remarkable necropsy findings in the females were primarily associated with the unscheduled deaths. In addition, a single incidence of distended uterus was observed in a high dose female (B04825). This female was confirmed to have mated (male B04687), but was not pregnant at necropsy.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

The pregnancy rates were 100, 96, 95, and 89% for the 0 (control), 50, 150, and 300 mg/kg/day groups, respectively.

Pregnancy rate Study report Text table 2 p 19

Indices	0 mg/kg	50 mg/kg	150 mg/kg	300 mg/kg
No. of males paired with one female	25	24	21	19
No. of females paired with one male	25	24	21	19
No. (%) of animals mated (Male/Female Copulation Index)	100	100	100	100
No. of females successfully mated	25	23	20	16
No. (%) of animals successfully mated (Male/Female Fertility Index)	100	96	95	89

Confirmed-mated Group 4 Female (B04810) was euthanized on GD 4 (prior to probable date of implantation); pregnancy status cannot be determined and thus, this female was excluded from the group mean percent pregnant (successful mating) calculation.

Male fertility parameters 2.6.7.12 p 109 Tox Tabulated Summary p 107

Daily Dose (mg/kg)	0 (Control)	50	150	300
Males				
Toxicokinetics - AUC (µg•hr/mL)				
Day 1	BLQ	1.25	8.04	25.8
Day 28	BLQ	1.84	4.19	41.6
No. Evaluated	25	25	25	25
No. Died or Sacrificed Moribund	0	1 ^a	2 ^a	6 ^a
Clinical Observations				
clear or discolored oral and/or nasal discharge	-	+	++	+++
audible/labored respiration and hypoactivity	-	-	+	++
Necropsy Observations^b				
material in trachea	0	0	1	1
fluid filled thoracic cavity	0	0	1	1
lungs dark and/ or mottled	0	0	0	3
stomach & intestines distended	0	0	0	1
Body Weight (% ^c)	434.3 g	1.2	-0.1	-3.3
Food Consumption (% ^c)	31.3 g	1.6	2.6	1.0
No. of males paired with one female	25	24	21	19
Sperm Motility (%)	96	89	80	85
Epididymal Count (million sperm/gram)	1017.5	1048.6	1028.2	1306.2

- No noteworthy findings; + Slight; ++Moderate; +++Marked; BLQ = Below the limit of quantitation of 5 ng/mL

- These deaths, were attributed to secondary effects associated with the test article (i.e., clear oral/nasal discharge leading to aspiration of saliva and/or residual dosing formulation).
- Remarkable necropsy findings primarily associated with unscheduled deaths.
- At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls were calculated and are shown. Statistical significance is based on actual data (not on the percent differences).

The group mean sperm motility values were 96, 89, 80 and 85% for the 0 (control), 50, 150, and 300 mg/kg/day group, respectively with no statistically significant or biologically meaningful differences observed (Appendix 7). One male from each of the treated groups had remarkably low percent sperm motility values (i.e., 50 mg/kg/day male B04608, 0%; 150 mg/kg/day male B04640, 14%; and 300 mg/kg/day male B04677, 1%). No significant differences were observed in the epididymal sperm count data across groups.

Remarkable necropsy findings were observed only in the low dose male and were limited to small testes and epididymides; there were no remarkable necropsy findings for the other two males. All three males were confirmed to have mated with their female pair within the first three days of mating and the mating of both the mid and high dose males resulted in successful pregnancies with viable fetuses. The necropsy findings and the unsuccessful mating of the low dose male were not attributed to treatment with NBI-56418.

Reproductive indices 2.6.7.12 p 109 Tox Tabulated Summary

Daily Dose (mg/kg)	0 (Control)	50	150	300
Females				
Premating Body Weight (% ^a)	247.5 g	-0.5	-0.9	-0.2
Gestation Body Weight (% ^a)	322.3 g	-0.8	-0.5	-0.1
Premating Food Consumption (% ^a)	22.5 g	-1.3	-1.8	-0.9
Gestation Food Consumption (% ^a)	29.1 g	-2.4	-1.4	-1.0
Females with pre mating prolonged diestrus	0	3	4	3
Females with Confirmed Mating Day	25	24	21	18 ^b
No. females successfully mated	25	23	20	16 ^b
No. of Pregnant Females	24	23	20	16
No. Aborted or with Total Resorption of Litter	0	0	0	0
Mean No. Corpora Lutea	15.8	16.6	15.8	15.6
Mean No. Implantations	14.9	15.8	14.4	15.3
Mean % Preimplantation Loss	5.5	5.2	10.3	2.1
Mean No. Live Fetuses	14.4	15.1	14.2	14.8
Mean No. Resorptions	0.5	0.7	0.2	0.5
No. Dead Fetuses	0	0	0	0
Mean % Postimplantation Loss	3.6	4.5	0.9	3.2

a. At end of pre mating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls were calculated and are shown. Statistical significance is based on actual data (not on the percent differences).

b. Confirmed-mated female B04810 was euthanized on GD 4 (prior to probable date of implantation); thus, this female was excluded from group mean pregnant as it was too early to determine pregnancy status.

There were no abortions or early deliveries. The mean number of corpora lutea, implantation sites, and preimplantation loss were generally similar across groups. A slight decrease in mean number of implantation sites and an increase in mean preimplantation loss were observed in the mid-dose group. This was due to a single female (B04792); although this female had 10 corpora lutea, it only had one implantation site. Effects were not noted at the higher dose level. Therefore, the slight differences in these two Caesarean section parameters were not attributed to treatment. The mean number of early resorptions (there were no late resorptions), mean postimplantation loss, and mean percent live fetuses were similar across groups, indicating NBI-56418 had no effects on embryo/fetal viability.

9.2 Embryonic Fetal Development

RAT

RD 101075: Oral gavage dose range-finding developmental toxicity and TK study with NBI-56418 in rats. 2006. [Application 210450 - Sequence 0000 - RD101075 Seq II DRF Rat](#). Excerpted comments from the review by Dr. Krishan Raheja are given below, updated for the 2017 NDA submission.

Methods: Time-mated female SD rats were dosed at 300, 600, and 1200 mg/kg/d on days 6-17 of gestation. N = 6/dose in the main study and 6/dose in the TK study. Assessment of maternal and embryo/fetal toxicity and teratogenic potential was based on mortality, body weight, food consumption, clinical observations, Caesarean section data and fetal external examination.

Results: There were 2 unscheduled deaths in the mid dose group, one on GD 9 and the other on GD 17. Prior to death both had excessive salivation and labored and audible respiration. Significant necropsy findings for the first rat were pale spleen and pale glandular mucosa of the stomach. Distended stomach containing thick grainy white material and distended cecum and small intestine with dark red fluid were reported for the second rat. Both rats were pregnant. Similar findings were not observed in the rest of the mid-dose group and in only one of the high dose group.

Treatment-related clinical observations included excessive salivation immediately following dosing in the mid and high dose groups. There was a slight decrease in body weight associated with slightly decreased food intake in the high dose group. Necropsy findings were limited to the 2 rats found dead. Mean uterine weight and mean terminal body weights were similar across groups.

Predose LH, FSH, estradiol and progesterone were not significantly different between groups. As expected for pregnant rats, the levels of LH, FSH and estradiol were suppressed by pregnancy (LH:1 ng/mL, FSH:5 ng/mL and estradiol not detectable on GD 6). Levels of progesterone were elevated as expected in pregnancy (~50-350 ng/mL). At 2 hrs post dose on GD 6, there were no remarkable changes from predose values or notable differences between groups. Two hrs post dose on GD 17, there was an expected increase in estradiol from predose values consistent with progressing pregnancy and no remarkable changes in LH, FSH and progesterone.

The pregnancy rates were 83% for the control and low dose groups, and 100% for the mid and high dose groups. There were no abortions or early deliveries. At Caesarean section, one high dose dam had no viable fetuses, which resulted in increased values for mean postimplantation loss and decreased mean number of live fetuses in this group. Fetal weights were higher for all treated groups when compared to the controls. There were no fetal external findings. Based on the results of this study, 1200 mg/kg/day was chosen as the high dose for the definitive study.

TK data (Female rat)

Group	GD	Tmax (hr)	Cmax (ng/ml)	AUC (0-24hr) (ng.hr/ml)	Dose adjusted Cmax (ng/ml)/(mg/kg)	Dose adjusted AUC(0-24hr) (ng.hr/ml)/(mg/kg)
300	6	8	2430	16500	8.1	55.1
600	6	24	3310	45700	5.52	76.1
1200	6	8	5510	6010	4.59	50.1
300	17	8	2290	30900	7.63	103
600	17	12	6260	74200	10.4	124
1200	17	1	10100	104000	8.42	86.8

Study title: Oral gavage study for effects on embryo-fetal development and toxicokinetics with NBI-56418 in rats.	
Study no:	RD101078. NBI 06-56418-001-TX.
Study report location:	Application 210450 - Sequence 0000 - RD101078 Seq II Oral Rat
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 20, 2004
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418, 01NBI04-05-82, 98.9%

Key Study Findings

Mortality: There were 6 unscheduled deaths occurring between GD13 and 18: 1 each in the low and high dose groups and 4 in the mid dose group. The cause of death was not determined and there were minimal clinical signs.

Recall that distribution studies indicated complete penetration of NBI-56418 across the placental barrier. Fetal exposures can therefore be assumed to be equal to maternal exposures.

The **NOEL for maternal toxicity was ≤ 300 mg/kg/day**, based on the likelihood that unscheduled deaths were related to aspiration of the test article.

The **NOEL for fetal viability and growth was 300 mg/kg/day** based on increased post-implantation loss and decreased fetal weight at 600 mg/kg/day (MOE = 20). These effects were attributed to decreased food consumption and excessive body weight loss at 600 mg/kg/day and not to a direct effect of the test article.

The **NOAEL for fetal teratogenicity was 1200 mg/kg/day**, the highest dose tested in this study.

Using rat AUC values obtained on GD17 compared to the AUC at the MRHD of 3.5 ug.hr/mL: **At 300 mg/kg/day**, the MOE for the MRHD based on AUC is **6.5**. **At 1200 mg/kg/day**, the MOE for the MRHD based on AUC is **39.4**.

Methods	
Doses:	300, 600, 1200 mg/kg/d
Frequency of dosing:	Daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water
Species/Strain:	Rat / SD
Number/Sex/Group:	25 F/group
Satellite groups:	6 F/group for TK
Study design:	Animals were dosed on GD6-GD17
Deviation from study protocol:	None significant

Observations and Results

Assessment of maternal and embryo/fetal toxicity and teratogenic potential was based on mortality, body weights, food consumption, clinical observations, Caesarean section data, and fetal external, visceral, and skeletal examinations.

Mortality

Mortality: There were 6 unscheduled deaths as given in the table below. All were confirmed pregnant.

Dose	GD	Clinical observations	Necropsy
300	15	Found dead, no remarkable clinical observations	None
600	18	Found dead, no remarkable clinical findings	None
	16	Found dead, excessive salivation and labored respiration post dose	None
	17	Found dead, excessive salivation post dose	None
	13	Found dead, excessive salivation post dose, labored and audible respiration	None
1200	16	Found dead, thin, distended abdomen, labored and audible respiration, urine stains, red hair around mouth, few or no feces, soft feces, excessive salivation post dose.	None

Clinical Signs

Clinical observations included labored and audible respiration in all treated groups (with the highest incidence at the mid dose) and a dose related increase in urine stains, thin appearance and few or no feces. An increased alopecia was observed at 1200 mg/kg/day. Significant post-dose observations included excessive salivation and an increased incidence of labored and audible respiration at the mid and high doses.

Body Weight and Feed Consumption

NBI-56418 produced significantly decreased mean maternal body weight gain (up to ~33% below control) in all treated groups. The decreased body weights (up to ~13% below control) correlated with significantly decreased food consumption (up to 19% below control for the treatment period). Effects on food consumption appeared to be reversible during the postdose phase (GD 18-20).

Toxicokinetics

AUC and C_{max} on GD 17 were 1.5 to 3.5 times higher than those on GD 6. Values were roughly similar to those obtained in the range-finding study.

Dose mg/kg/d	GD	T _{max} (hr)	C _{max} (ng/ml)	AUC _(0-24hr) (ng.hr/ml)	Dose adjusted C _{max} (ng/ml)/(mg/kg)	Dose adjusted AUC _(0-24hr) (ng.hr/ml)/(mg/kg)
300	6	4	1790	22500	5.97	75
600	6	8	3150	45700	5.25	76.1
1200	6	8	2490	39200	2.08	32.6
300	17	4	5110	55500	16.7	185
600	17	8	5210	68600	8.68	114
1200	17	8	6180	138000	5.15	115

Stability and Homogeneity

Adequate. Dosing formulations were adequate.

Necropsy

Maternal necropsy findings: A single mid dose dam had discolored amniotic fluid. The slight decrease in mean gravid uterine weight in the mid dose group was not dose-related. All animals were pregnant.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no abortions or early deliveries. All surviving dams had litters with viable fetuses. There was a slight increase in postimplantation loss at the mid dose (8.9% versus 3.5% for control), which resulted in a slight decrease in the mean number of live fetuses in this group (12.8% versus 13.6% for control). This was attributed primarily to an increase in the late resorption in a single litter and decreased food consumption and excessive body weight loss in this group. Covariant adjusted mean fetal weight was significantly decreased (~10%) at the mid dose. (See Table 7 p 35 of the study report for the complete summary of Cesarean section data.)

Offspring (Malformations, Variations, etc.)

Fetal observations: There were no fetal external anomalies, or soft tissue or skeletal malformations in treated groups. Fetal skeletal variations consisted of unossified bones, which included the following:

- Fetal incidence of unossified vertebral arches at 1200 mg/kg/d (9.1% vs 4.0% in control)
- Fetal incidence of unossified vertebral centrum at 600 mg/kg/day (5.2% vs 0% in control)
- Fetal and litter incidence of 6th sternebra unossified at 600 mg/kg/day (30% vs 10% in control)
- Fetal incidence of other sternebra unossified at 600 and 1200 mg/kg/day (9.7% and 6.1%, respectively versus 0.6% in control)
- Litter incidence of other sternebra unossified at 600 mg/kg/day (29% vs 4% in control)
- Fetal and litter incidence of 13th rudimentary rib at 600 mg/kg/day (3.7% vs 0% and 19% vs 0% in control)
- Fetal and litter incidence of less than four metatarsals ossified at 600 mg/kg/day (4% vs 0% and 14% vs 0% in control)
- Fetal and litter incidence of incomplete ossification of ischium at 600 mg/kg/day (8.2% vs 1.7% and 29% vs 12% in control)
- Fetal and litter incidence of unossified pubis at 600 mg/kg/day (5.2% vs 0% and 24% vs 4% in control)

Although the type of fetal skeletal variations observed were those commonly seen in this strain of rat, an increased fetal incidence occurred in all treated groups (up to 90% of fetuses versus 62% of fetuses in the control group). These increases correlated with decreased fetal weight and were considered to represent a delay in fetal development and not a direct effect of NBI-56148.

RABBIT

RD 101074. Oral gavage dose range-finding developmental toxicity and TK study with NBI-56418 in rabbits. 2004. [Application 210450 - Sequence 0000 - RD101074 Seq II DRF Rabbit](#)

Methods: Premated female NZW rabbits were dosed at 30, 100, 300, and 600 mg/kg/d from GD7-GD20 (N=6/group). Additional predated rabbits were used for TK analysis and effects on hormone levels (N=3/group). As in the rat study, assessment of maternal and embryo-fetal toxicity and teratogenic potential of NBI-56418 was based on mortality, body weight, food consumption, clinical observations, cesarean section data, and fetal external examination.

Results:

Mortality: A low dose rabbit was found dead on GD 9 and death was attributed to dosing. Four 300 mg/kg/day rabbits aborted and were subsequently euthanized. These abortions were attributed to decreased food consumption. Only one rabbit in the 300 mg/kg/day group survived past GD 22.

Clinical observations in the surviving rabbits included few or no feces at doses of 300 mg/kg/day or greater. Thin appearance and increased incidence of alopecia was observed in the 600 mg/kg/day rabbits. Wheezing was reported in two mid dose and one high dose animal. Another high dose animal had a swollen, discolored vagina.

Body weight: Treatment with NBI-56418 produced a dose-related body weight loss during GD 7 to 9. During the dosing interval of GD 7-21, decreased mean body weight gain was observed at 300 mg/kg/day and mean body weight loss was observed at 600 mg/kg/day. During the dosing interval (GD 7-21), food consumption was decreased at doses of 100 mg/kg/day and above.

Necropsy findings: There were no necropsy findings attributed to NBI-56418. Mean uterine weights and corrected maternal body weights were similar across groups up to 100 mg/kg/day. There were no fetal external findings.

There was a dose-related decrease in pregnancy rates. The pregnancy rates were 100% for the control and two low dose groups, 83% for the 300 mg/kg/day group, and 50% for the 600 mg/kg/day group. Four 300 mg/kg/day rabbits aborted and were subsequently euthanized.

There were no early deliveries. Mean preimplantation loss was unaffected at doses up to 100 mg/kg/day. Due to the high abortion rate, this parameter could not be adequately assessed at 300 mg/kg/day. None of the pregnant 600 mg/kg/day rabbits had litters with viable fetuses. All were early resorptions (postimplantation loss was 100% at 600 mg/kg/day). Based on the sole surviving 300 mg/kg/day dam, mean fetal weight was decreased by more than 10% compared to controls.

TK: Female Rabbit

Dose mg/kg	GD	Tmax (hr)	Cmax (ng/ml)	AUC _(0-24hr) (ng.hr/ml)	Dose adjusted Cmax (ng/ml)/(mg/kg)	Dose adjusted AUC _(0-24hr) (ng.hr/ml)/(mg/kg)
30	7	0.5	77.2	121	2.57	4.05
30	20	0.5	1130	1340	37.7	44.6
100	7	0.667	501	1990	5.01	19.9
100	20	0.667	5430	15200	54.3	153
300	7	3.33	10200	39300	34	131
300	20	3.33	18700	87100	62.5	290
600	7	2.83	17100	83700	17.1	83.7
600	20	4.67	21300	112000	21.3	112

It should be noted that exposures in the two lower dose groups increased roughly 10-fold between GD7 and GD20, a striking increase. We also note that dose adjusted Cmax and AUC values were much higher than in the rat.

Hormone analysis: There were no relevant differences between groups at predose for LH, FSH, estradiol and progesterone. As expected in pregnancy, the production of LH, FSH and estradiol were suppressed (LH not measurable, FSH < 1 ng/mL and estradiol not measurable) and

progesterone was elevated (4 to 8 ng/mL). One of the high dose animals had atypically low progesterone levels (F61828 measured 0.29 ng/mL) suggestive of a nonviable pregnancy, but since necropsies were not performed on satellite animals, a non-viable pregnancy was not confirmed. There were no relevant differences between predose on GD 7, 2 hours postdose on GD 7 and 2 hours postdose on GD 20 or between groups on any of these days.

Conclusion: Based on the high abortion rate at 300 mg/kg/day, a dose between 100 and 300 mg/kg/day was recommended as the high dose for the definitive developmental toxicity study.

Study title: Oral gavage study for effects on embryo-fetal development and toxicokinetics with NBI-56418 in rabbits.	
Study no:	RD101080 (b) (4) study No. 6944-173
Study report location:	Application 210450 - Sequence 0000 - RD101080 Seg II Oral Rabbit
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4 Aug 2004 Amended report issued 02 Feb 2017
GLP compliance / QA statement:	Yes / Yes
Drug, lot #, and % purity:	NBI-56418, 01NBI04-05-82, 98.9%

Key Study Findings

There were 6 unscheduled deaths: 2 at the mid-dose (1 of these was a gavage error) and 4 at the high dose. Other than a gavage error in one animal at the mid-dose, cause of death was not established. Of the 4 deaths at the high dose, 3 were euthanizations following abortion.

The pregnancy rate was unaffected by treatment. Fetal growth was retarded in the high dose group as reflected by decreased gravid uterine weight gain. This was attributed to maternal toxicity in the form of reduced feed consumption and reduced body weight gain.

One mid-dose and one high dose dam had litters with no viable fetuses, which resulted in an increase in postimplantation loss and a decrease in number of live fetuses in these groups. There was no treatment related teratogenicity.

The **NOAEL for maternal toxicity was 150 mg/kg/day** based on reduced maternal weight gain and decreased feed consumption.

The sponsor's NOEL for embryo/fetal toxicity was 150 mg/kg/day based on significantly decreased fetal weights at 200 mg/kg/day. However, the reviewer disagrees, based on the finding of increased postimplantation loss at both the mid and high doses. Postimplantation loss was a factor in setting the NOEL in the rat EFD study, but for some reason was discounted by the sponsor in this rabbit study.

Reviewer's NOEL for embryofetal toxicity is thus set at 100 mg/kg/d.

The **NOEL for teratogenicity was 200 mg/kg/day**, the highest dose used in this study.

At 100 mg/kg/day on GD20:

Cmax = 3.5 ug/mL and AUC = 9.3 ug.hr/mL. MOE based on AUC relative to MRHD is **2.7**.

At 150 mg/kg/day on GD20:

Cmax = 8.4 ug/mL and AUC = 23.3 ug.hr/mL. MOE based on AUC relative to MRHD is **6.6**

At 200 mg/kg/day on GD20:

Cmax = 9.1 ug/mL and AUC = 40.5 ug.hr/mL. MOE based on AUC relative to MRHD is **11.6**.

Methods	
Doses:	0, 100, 150, 200 mg/kg/d
Frequency of dosing:	Daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sterile water
Species/Strain:	Rabbit / Hra(NZW)SPF
Number/Sex/Group:	20 F/group
Satellite groups:	5 F/group for TK
Study design:	Dosing on Days 7-20 of gestation
Deviation from study protocol:	None significant

Observations and Results

Assessment of maternal and embryo/fetal toxicity and teratogenic potential of NBI-56418 was based on mortality, body weight, food consumption, clinical observations, cesarean section data, fetal external, visceral, and skeletal examinations.

Mortality

There were 6 unscheduled deaths:

Dose level	GD	Clinical observations	Necropsy findings
100 mg/kg/day	14	Gavage error; red fluid coming from mouth	Perforated trachea; confirmed pregnant
	15	Found dead; no remarkable clinical observations	No necropsy findings; confirmed pregnant
200 mg/kg/day	16	Found dead, no remarkable clinical findings	No necropsy findings Confirmed pregnant
	22	Aborted / euthanized; thin, few or no feces	No necropsy findings
	22	Aborted / euthanized; thin, few or no feces	No necropsy findings
	23	Aborted / euthanized; thin, soft , few or no feces	No necropsy findings

Clinical Signs

Increased incidence of few or no feces at the mid and high dose.

Body Weight and Feed Consumption

NBI-56418 produced significantly decreased (-28%) mean body weight gain at the high dose, which was largely attributable to reduced gravid uterine weight. Effects on food consumption correlated with body weight changes. Effects on food consumption and body weight change were reversible.

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 100 MG/KG/DAY	GROUP 3 150 MG/KG/DAY	GROUP 4 200 MG/KG/DAY
GRAVID UTERUS	MEAN	543.44	529.44	468.02	428.56*
	S.D.	90.70	123.19	161.25	126.67
	N	18	18	20	15
CORRECTED WEIGHT	MEAN	3331.39	3335.84	3365.03	3313.58
	S.D.	184.06	219.27	228.21	222.67
	N	18	18	20	15
NET CHANGE FROM DAY 0	MEAN	73.61	75.34	82.28	16.91
	S.D.	143.89	157.43	194.92	186.30
	N	18	18	20	15

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
CORRECTED WEIGHT = TERMINAL BODY WEIGHT MINUS GRAVID UTERINE WEIGHT
NET WEIGHT CHANGE FROM DAY 0 = CORRECTED WEIGHT MINUS DAY 0 BODY WEIGHT

Toxicokinetics: Female Rabbit

Exposure increased with duration of dosing. C_{max} and AUC_{all} increased with greater than dose proportionally from 100 to 200 mg/kg on GD7 and GD20.

Dose Group mg/kg	GD	T _{max} (hr)	C _{max} (ng/ml)	AUC all (ng.hr/ml)	Dose adjusted C _{max} (ng/ml)/(mg/kg)	Dose adjusted AUC _(0-24hr) (ng.hr/ml)/(mg/kg)
100	7	1.4	669	2240	6.69	22.4
150	7	2	1290	5180	8.6	34.5
200	7	3	3870	15100	19.3	75.3
100	20	1.3	3490	9300	34.9	93
150	20	1.8	8380	23200	55.9	155
200	20	2	9110	40500	45.5	203

Stability and Homogeneity

Formulation analysis showed adequate concentration

Necropsy

Necropsy findings: no treatment-related necropsy findings were reported.

Mean gravid uterine weight was significantly decreased (-21%) at the high dose and was attributed to the decreased maternal weight and food consumption during the dosing period. When corrected for body weight the weights were similar in all groups.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

The pregnancy rate was 90% for the control group, 100% for the 100 and 150 mg/kg/day groups, and 95% for the 200 mg/kg/day group.

Three high dose rabbits aborted and were subsequently euthanized. None of the rabbits delivered early.

At the high dose, 3 rabbits aborted and one had a litter with no viable fetuses. At the mid-dose, one rabbit had a litter with no viable fetuses. This resulted in an increase in postimplantation loss and a decrease in number of live fetuses in these groups. The two rabbits with no viable fetuses also had the lowest number of corpora lutea within their respective group. When the litters with no viable fetuses were excluded from calculation, postimplantation loss and the mean number of live fetuses were generally similar across groups.

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 100 MG/KG/DAY	GROUP 3 150 MG/KG/DAY	GROUP 4 200 MG/KG/DAY
Females Mated	N	20	20	20	20
Pregnant	N	18	20	20	19
	%	90	100	100	95
Aborted	N	0	0	0	3
	%	0.0	0.0	0.0	15
Died	N	0	1	0	1
	%	0.0	5.0	0.0	5.0
Delivered Early	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pregnant at C-section	N	18	18	20	15
Dams with Viable Fetuses	N	18	18	19	14
	%	100	100	95	93
Dams with no Viable Fetuses	N	0	0	1	1
	%	0.0	0.0	5.0	6.7
Corpora Lutea	MEAN	11.4	10.3	10.4	9.3
	S.D.	1.9	2.3	2.1	2.0
	N	18	18	20	15
	TOTAL	205	186	208	139
Implantation Sites	MEAN	9.7	8.9	8.6	7.9
	S.D.	1.4	2.4	2.7	1.9
	N	18	18	20	15
	TOTAL	175	161	171	118
Preimplantation Loss	MEAN%	13.9	14.1	18.7	15.3
	S.D.	9.4	16.0	21.4	9.7

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 100 MG/KG/DAY	GROUP 3 150 MG/KG/DAY	GROUP 4 200 MG/KG/DAY
Pregnant at C-section	N	18	18	20	15
Resorptions: Total	MEAN	0.6	0.2	0.7	0.3
	S.D.	1.1	0.4	1.4	0.8
	N	18	18	20	15
	TOTAL	11	3	14	4
	MEAN%	5.9	1.6	10.4	7.6
	S.D.	11.7	3.7	24.1	25.8
Early	MEAN	0.4	0.1	0.5	0.3
	S.D.	1.0	0.2	1.4	0.8
	N	18	18	20	15
	TOTAL	7	1	9	4
	MEAN%	3.9	0.6	7.3	7.6
	S.D.	11.0	2.4	22.7	25.8
Late	MEAN	0.2	0.1	0.2	0.0
	S.D.	0.6	0.3	0.6	0.0
	N	18	18	20	15
	TOTAL	4	2	5	0
	MEAN%	1.9	1.1	3.1	0.0
	S.D.	5.6	3.1	7.0	0.0
Dead Fetuses	TOTAL	0	0	0	0
Postimplantation Loss	MEAN%	5.9	1.6	10.4	7.6
	S.D.	11.7	3.7	24.1	25.8

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

Cesarean section data were generally unremarkable and indicated that fetal viability was unaffected by NBI-56418. However, mean fetal weight was significantly decreased (-9%) in the high dose group (more pronounced in female fetuses). This finding was attributed to the decreased maternal food consumption and subsequent decreased body weight in this group.

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 100 MG/KG/DAY	GROUP 3 150 MG/KG/DAY	GROUP 4 200 MG/KG/DAY
FETAL WEIGHTS	UNITS: GRAMS				
	of all Viable Fetuses				
	MEAN	41.69	42.75	42.73	39.92
	S.D.	4.25	4.85	7.87	4.41
	N	18	18	19	14
	Covariate Adjusted MEAN	42.70	43.11	42.09	39.04*
of Male Fetuses	MEAN	41.39	43.17	41.89	40.65
	S.D.	4.54	5.05	7.76	4.31
	N	18	18	18	14
	Covariate Adjusted MEAN	42.22	43.34	41.74	39.56
of Female Fetuses	MEAN	42.00	42.44	42.80	39.15
	S.D.	4.92	4.93	8.09	5.40
	N	18	18	19	14
	Covariate Adjusted MEAN	42.97	42.78	42.18	38.30*

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

Offspring (Malformations, Variations, etc.)

There were no treatment-related fetal external, visceral, or skeletal findings.

9.3 Prenatal and Postnatal Development

Study title: A Dietary Study of the Effects of NBI-56418 on Pre- and Postnatal Development, Including Maternal Function in Rats	
Study no:	RD13581
Study report location:	<u>Application 210450 - Sequence 0000 - RD13581</u> <u>Seg III Oral Rat</u>
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 2012
GLP compliance: / QA statement:	Yes / yes
Drug, lot #, and % purity:	NBI-56418, 29001264, 99.8%

Key Study Findings

One animal was found dead, but clinical findings were otherwise minimal. At the high dose, two dams had total litter loss, and one failed to deliver. There were no effects on the mean number of F1 pups born, live litter size, percentage of males at birth, or pup necropsy findings at any exposure level.

Due to lower F1 postnatal survival and lower F1 birth weights and pre-weaning body weights and body weight gains at 300 mg/kg/day, the **NOEL for F1 neonatal/early postnatal toxicity was 100 mg/kg/day.**

Lower mean maximum startle response (MAX) and average response (AVE) values were noted on PND 20 for F1 males and females in the high dose group. These effects were considered to be in part secondary to the effects on F1 body weights noted during the pre- and post-weaning periods and were attributable to F0 maternal test article exposure. Therefore, **the NOEL for F1 developmental toxicity, including neurobehavioral development was 100 mg/kg/day.**

No toxicity was observed in the F0 maternal animals, in F1 animals during the post-weaning period, or in the F2 pups. Therefore, the **NOEL for F0 systemic toxicity, F1 post-weaning systemic toxicity, F1 reproductive toxicity, and F2 neonatal/early postnatal toxicity was 300 mg/kg/day.**

The maternal plasma concentration (measured 2 hours after the initiation of light cycle) for NBI-56418 on LD 21 was 47.2 and 125 ng/mL for the 100 and 300 mg/kg/day dose groups, respectively. These values are roughly **10 fold lower** than oral gavage at the same doses.

Methods	
Doses:	0, 100, 300 mg/kg/d The 100 mg/kg/day group was offered the test diet beginning on GD 2. The 300 mg/kg/day group was offered the test diet on an escalating schedule as follows: 100 mg/kg/day on GD 2 and 3, 200 mg/kg/day on GD 4 and 5, and 300 mg/kg/day from GD 6 onward.
Frequency of dosing:	Daily in the diet
Dose volume:	N/A
Route of administration:	Oral
Formulation/Vehicle:	(b) (4) Formulation analysis verified concentration and homogeneity
Species/Strain:	SD rat
Number/Sex/Group:	25/F/group
Satellite groups:	On LD/PND 21, blood samples (for plasma analysis of the parent drug) were collected from 4 F ₀ females/group and 1 F ₁ pup/sex/litter from the same 4 F ₀ females
Study design:	Exposure from GD2 through LD20; F ₀ animals were ~14 wks of age at the beginning of exposure
Deviations:	None significant

Doses were chosen based on findings from a dose-range finding study conducted at 400 and 1500 mg/kg/d. Mortality at the high dose and incidences of total litter loss at both doses led to a reduction in dosing for the definitive study.

Observations and Results

Maternal Feed consumption:

Target Dietary Level (mg/kg/day)	Actual NBI-56418 consumed (mg/kg/day)			
	Gestation (GD 2-4) ^a	Gestation (GD 4-6) ^a	Gestation (GD 6-20)	Lactation (LD 1-20)
100	108	105	96	122
300	104	206	297	345

a = The 100 mg/kg/day group was offered the test diet beginning on GD 2. The 300 mg/kg/day group was offered the test diet on an escalating schedule as follows: 100 mg/kg/day on GD 2 and 3, 200 mg/kg/day on GD 4 and 5, and 300 mg/kg/day from GD 6 onward.

Daily Dose (mg/kg)	0 (Control)	100	300
<u>F₀ Females:</u>			
No. Evaluated	25	25	25
Not pregnant	3	0	2
No. Pregnant	22	25	23
No. Died or Euthanized in Extremis	0	0	1 ^d
No. Aborted or with Total Resorption of Litter	0	0	0
Females with total litter loss	0	0	2
Failed to deliver	0	0	1
Females with viable pups	22	25	19

F1 observations (sponsor's text):

Postnatal survival was decreased from birth to PND 4 (pre-selection) at the highest dose of 300 mg/kg/day, with a corresponding increased number of pups found dead or missing prior to weaning (total of 39 pups) compared with controls (total of 2 pups). There were no effects on postnatal survival at 100 mg/kg/day.

Daily Dose (mg/kg)		0 (Control)	100	300
F₁ Litters:	No. Litters Evaluated	22	25	21
Pre-weaning	Mean No. of Implantations	15.1	15.9	15.4
	Mean No. of Pups Born/Litter	14.3	15.2	13.6
	Mean No. Live born Pups/Litter	14.3	14.9	13.3
	Postnatal Survival Birth to PND 4 (% per litter)	99.5	96.6	84.5
	Postnatal Survival PND 4 to PND 21 (% per litter)	100.0	99.5	97.4

There were lower mean birth weights and lower mean body weight gains for F1 males and females at the high dose, resulting in mean body weights that were generally lower than the control group throughout the pre-weaning period. Furthermore, a higher incidence of small stature (which is defined as small body size in relation to littermates) was noted for the F1 pups in the high dose group (4 pups from 4 litters affected compared to 1 pup from 1 litter in the control group), which corresponded to the lower pup weights in this group. Mean pup body weights and body weight gains for the low dose group were similar to the control group during the postnatal period.

Developmental landmarks (balanopreputial separation and vaginal patency) in the F1 offspring were unaffected by F0 maternal test article exposure at all exposure levels. In addition, there were no test article-related effects on behavior, including startle response on PND 20 and 60, locomotor activity on PND 21 and 61, and learning and memory assessments on PND 22 and 62. Lower mean overall maximum startle response (MAX) and average response (AVE) values were noted on PND 20 for F1 males and females in the 300 mg/kg/day group. Although these effects on startle response were in part attributed to the lower body weights noted in the males and females at this exposure level, they were considered test article-related effects (Błaszczuk and Tajchert, 1996).

There were no effects on survival, clinical condition, or mean body weights or body weight gains were noted for F1 males and females at any exposure level. F1 reproductive endpoints (pre-coital intervals, estrous cycle lengths, and mating, fertility, and copulation/conception indices) were unaffected by F0 maternal test article exposure. Furthermore, there were no effects on the F1 gestation lengths or parturition. There were no macroscopic findings in the F1 males and females in any group or effects on the mean numbers of implantation sites, unaccounted-for sites, and corpora lutea at any exposure level.

F2 observations:

There were no effects of F0 maternal exposure on the mean number of F2 pups born, viability on PND 0, postnatal survival, physical condition, mean body weights, body weight gains, or necropsy findings of F2 pups that were found dead or euthanized due to the death of the dam.

Toxicokinetics: Female rat dietary

Mean Plasma Concentrations of NBI-56418 for Dams on LD 21

Day	Dose Group (mg/kg/day)	Plasma Concentration (ng/mL)
LD 21	100	47.2
LD 21	300	125

Mean Plasma Concentrations of NBI-56418 for Male and Female F1 Pups on PND 21

Day	Dose Group (mg/kg/day)	Plasma Concentration (ng/mL)
PND 21	100	30.4
PND 21	300	139

Pup/Dam Concentration Ratios of NBI-56418 on LD/PND 21

Day	Dose Group (mg/kg/day)	Pup/Dam Ratio
LD/PND 21	100	0.644
LD/PND 21	300	1.112

10 Special Toxicology Studies

Local tolerance:

A study on local tolerance of elagolix was submitted to IND 64802 but not to NDA 210450. This study was conducted in 2006 and reviewed by Dr. Raheja in 2007. His summary is given below.

Assessment of contact hypersensitivity to NBI-56418 (sodium salt) in the mouse (local lymph node assay). NBI Report No. 06-56418-008-TX. GLP. NBI-56418 lot No. 17BNo2.HQ00002).

Experimental design: Four groups of 5 female CBA mice were treated with vehicle (dimethyl formamide) or 10, 25, or 50% NBI-56418 on the dorsal surface of both ears at a dose of 25 ul/ear for 3 consecutive days. Three days after the last exposure, all animals were injected with ³H-methyl thymidine and after 5 hours the draining (auricular) lymph nodes were excised. After precipitating the lymph node cells, radioactivity was measured and expressed as DPM. A stimulation index (SI) = ratio of DPM/treated group compared to DPM/vehicle control was calculated. An SI value of 3 or greater is regarded as a skin sensitizer.

Results:

There was no mortality, no systemic toxicity and no body weight changes.

Clinical observations: Erythema was noted for both ears of animals treated with 10 (2 of 5 animals), 25 (2 of 5 animals) and 50% (all animals) concentration of NBI-56418. No edema was observed. A majority of lymph nodes were normal in size except for one animal in the high dose which had enlarged lymph nodes.

DPM values: Mean DPM/animal values for the experimental groups treated with 10, 25, and 50% concentration of NBI-56418 were 243, 405, 307 and 619, respectively. The calculated SI values for NBI-56418 concentration of 10, 25, and 50% were 1.7, 1.3, and 2.5, respectively. NBI-56418 is thus regarded not a skin sensitizer.

Dr. Raheja's review included the following comment:

The mean DPM/animal of 619 in the 50% concentration group is based on the following 5 values: 977, 785, 597, 567 and 171. Apparently the last value does not belong to this group and if it is taken out, the mean will be 732 with decreased variation and SI value will exceed 3, suggesting that NBI-576418 at 50% concentration is a potential skin sensitizer.

This reviewer notes that the standard deviation on these 5 numbers was very high, and that there are no statistical criteria for excluding the low value. In addition, the study director concluded that the findings were negative, and the Division did not follow up with any further requests to characterize the potential for skin sensitization.

Phototoxicity Risk Evaluation:

The sponsor presented a risk evaluation for phototoxicity as follows:

- (1) A distribution study of radiolabeled elagolix in the rat showed no accumulation in the pigmented part of the eye or skin.
- (2) The absorption spectrum for elagolix showed peaks at 201 and 274 nm (see Table 19 Section 2.6.6.8.7.1. Molar absorptivity at 290 nm (the lower cutoff for evaluation of phototoxicity) was 6290 L/Mol/cm) but declined to near zero at 305 nm.

Phototoxicity testing is required (ICH S10) for compounds with absorption coefficients >1000 between 290 and 700 nm. The sponsor estimated risk of phototoxicity to be negligible and the Division did not request phototoxicity testing during development.

11 Integrated Summary

Cmax and AUC values are given for the doses that are in bold, which are usually the NOAEL. Values in repeat dose study correspond to the last day of the study, except for the monkey, where they correspond to day 1 of the study. Values are the average of males and females.

Study #	Species	Route	Duration (weeks)	Doses mg/kg/d	Cmax ug/mL M/F avg	AUC ug.hr/mL M/F avg	Cmax MOE	AUC MOE
Single dose								
RD10104	Rat	Gavage	-	300, 600, 1200, 2000	2.5	22.8		
RD101072	Monkey	Gavage	-	300, 600, 1200, 2000	10.2	75.8		
Genetox In vivo micronucleus	Mouse	Gavage	-	500, 1000, 2000				
Repeat dose								
	Mouse	Gavage	13	30, 100, 300				
	Mouse	Diet	15	30, 500, 1700				
RD101086	Rat	Gavage	2	300, 600, 1200	3.8	28.4		8
RD101089	Rat	Gavage	6	150, 300, 600	4.9	65.4		19
RD101077	Rat	Gavage	13	100, 300, 600	4.4	38.9		11
RD101045 (b)(4) salt	Rat	Gavage	13	100, 300, 600	2.8	13.8		
RD101044	Rat	Gavage	26	50, 100, 300, 600	1.9	7.1		2
RD12556 Impurities	Rat	Diet	6	650	2.5	31.3		9
RD101047 Carci range finding	Rat	Diet	15	100, 600, 2000	2.1	22.0		
RD11756 Bridging	Rat	Diet	28	600, 800	4.8	29.9		8.5
RD101083	Dog	Gavage	6	50, 150, 300	11.6	34.2		10
RD101093	Dog	Gavage	26	50, 75, 150	22.4	80.1		23
RD101101	Dog	Capsule	39	10, 30, 150	9.4	28.7		8
RD101085	Monkey	Gavage	2	50, 150, 300	6.7	26.3		7.5
RD101088	Monkey	Gavage	6	75, 150, 300, 600	18.9	136.8		39
RD101076	Monkey	Gavage	13	75, 150, 300	19.2	172		49
Carci								
RD101102	Mouse	Diet	104	50, 150, 500	4.2	53.5		
RD101103	Rat	Diet	104	150, 300, 800	4.2	44.4		
RD12438	Rat	Diet	6	800, 1200	3.4	45		
Reprotox								
Fertility and EED	Rat	Gavage	M: 28d prior - d70 F: 14 d prior-GD7	50, 150, 300 overall 50, 150, 300 reproductive	0.8 2.5	2.1 28.8		
Embryofetal development								
	Rat	Gavage	GD6-GD17	300, 600, 1200	2.4	23.7		
	Rat	Gavage	GD6-GD17	300, 600, 1200	5.1	55.5		
	Rabbit	Gavage	GD7-GD20	30, 100, 300, 600	5.4	15.2		
	Rabbit	Gavage	GD7-GD20	100, 150, 200	5.2	23.2		
Pre and postnatal development								
	Rat	Diet	GD6-LD20	400, 1500				
	Rat	Diet	GD6-LD20	100, 300				

References

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Appendix 2 Executive CAC Final Study Minutes

Date of Meeting: January 23, 2018

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Ron Wange, PhD, OND IO, Member
Todd Palmby, PhD, DHOT, Alternate Member
Mukesh Summan, PhD, DBRUP, Pharm Tox Supervisor
Leslie McKinney, PhD, DBRUP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #210450

INDs 64802, (b) (4)

Drug Name: Elagolix, NBI56418, A-1278823.5

Sponsor: Abbvie, Inc.

Background: Elagolix is a GnRH antagonist being developed for treatment of endometriosis and uterine fibroids. GnRH antagonists cause a suppression of LH and FSH secretion from the pituitary, and a subsequent reduction in levels of sex steroids. In the rat, binding of elagolix to the GnRH receptor ($K_i = 1-4 \mu\text{M}$) is several orders of magnitude weaker than in human. Receptor binding was not measured in the mouse. Exposure was adequate in both species. Elagolix was found not genotoxic by the standard genotox battery.

Mouse Carcinogenicity Study

CD1 mice (60/sex/dose) were orally administered elagolix in the diet at 0 (vehicle (b) (4)), 50, 150, and 500 mg/kg/day. The study was conducted in accordance with the dose levels recommended by the Executive CAC. Survival was unaffected in all dosed groups. All male and female groups were terminated in Week 104. There were no drug-related neoplasms in the mouse.

Rat Carcinogenicity Study

SD rats (60/sex/dose) were orally administered elagolix in the diet at 0 (vehicle (b) (4)), 150, 300, and 800 mg/kg/day. The study was conducted in accordance with the dose levels recommended by the Executive CAC. There was reduced survival in males at the mid and high dose (33.3 and 31.7%, respectively) when compared to the control group. Survival was unaffected in females. An adequate number of animals survived in all dose groups to provide a valid study. All male groups were terminated at 105 weeks and female groups were terminated at Week 102.

The high dose of 800 mg/kg/day was associated with significantly increased incidences of hepatic (males) and thyroid adenomas/carcinomas (males and females) by both trend and pairwise analysis.

Hepatocellular Adenomas and Carcinomas in Male Rat

Tumor	Control*	Low Dose**	Mid Dose**	High Dose**
Adenoma/Carcinoma incidence	2/60	1/60	0/60	15/60
P-value	<0.001	0.8788	1.0000	<0.001
B-Adenoma incidence	1/60	1/60	0/60	9/60
P-value	<0.001	0.7525	1.0000	0.0047
M-Carcinoma incidence	1/60	0/60	0/60	6/60
P-value	<0.001	1.0000	1.0000	0.0382

Thyroid Follicular Cell Adenomas and Carcinomas in Male Rat

Tumor Name	Control*	Low Dose**	Mid Dose**	High Dose**
Adenoma/Carcinoma incidence	3/60	4/60	6/60	27/60
P-value	<0.001	0.5114	0.1619	<0.001
B-Adenoma incidence	2/60	4/60	6/60	23/60
P-value	<0.001	0.3485	0.0837	<0.001
M-Carcinoma	1/60	0/60	0/60	4/60
P-value	0.0132	1.0000	1.0000	0.1553

Thyroid Follicular Cell Adenomas and Carcinomas in Female Rat

Tumor Name	Control*	Low Dose**	Mid Dose**	High Dose**
Adenoma/Carcinoma incidence	0/60	2/60	1/60	19/60
P-value	<0.001	0.2719	0.5301	<0.001
B-Adenoma incidence	0/60	2/60	1/60	17/60
P-value	<0.001	0.2719	0.5301	<0.001
M-Carcinoma incidence	0/60	0/60	0/60	2/60
P-value	0.0636			0.2719

*p-value for trend

p-value for pair-wise comparison compared to vehicle control

Statistical review of tumor incidence data was provided by Steve Thompson, CDER statistician, and agrees with the sponsor's analysis.

Executive CAC ConclusionsMouse

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 2-year mouse carcinogenicity study in either males or females.

Rat

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that the incidence of hepatocellular adenomas and the combined incidence of hepatocellular adenomas and carcinomas in male rats was increased at 800 mg/kg/day and was drug related.
- The Committee concurred that the incidence of thyroid follicular cell adenoma and the combined incidence of thyroid follicular cell adenomas and carcinomas in male and female rats was increased at 800 mg/kg/day and was drug related.

Karen Davis Bruno, PhD
Chair, Executive CAC

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LESLIE C MCKINNEY
05/10/2018

MUKESH SUMMAN
05/10/2018
I concur

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Full Review Template version: November 29, 2017

COA ID	C2017343
NDA #	210450
Referenced IND for NDA/BLA	(b) (4)
Established Name/Trade Name	Elagolix sodium
Applicant	AbbVie
Indication	Management of endometriosis associated pain
Meeting Type/Deliverable	COA Consult Review for the NDA
SDN #	1
Date of Consult Request	October 31, 2017
Review Completion Date	January 23, 2018
Review Division	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Clinical Reviewer/Clinical Team Leader(CTL)	Gerald Willet, MD Abby Anderson, MD
Review Division PM	Maria Wasilik
COA Reviewer	Nikunj Patel, PharmD
COA TL/Secondary Reviewer	Selena Daniels, PharmD, MS
COA Associate Director	Elektra J. Papadopoulos, MD, MPH
Instrument 1	Electronic Daily Diary (eDiary)
Instrument 2	Patient Global Impression of Change (PGIC)
Instrument 3	
COA Type 1 and Endpoint Concepts	Disease-specific signs and symptoms; analgesic use
COA Type 2 and Endpoint Concepts	Patient global
COA Type 3 and Endpoint Concepts	
Intended Population	Adult female patients (≥18 years) with endometriosis associated pain
Internal Meeting	N/A
Sponsor Meeting/WRO	N/A

Please check all that apply:

Rare Disease/Orphan Designation

Pediatric

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

NDA 210450

Elagolix oral tablets

eDiary (dysmenorrhea, non-menstrual pelvic pain, dyspareunia, endometriosis pain)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Bone, Reproductive, and Urologic Products (DBRUP) regarding NDA 210450. The Applicant (AbbVie Inc.) is seeking an FDA approval for elagolix sodium oral tablets for management of endometriosis with associated pain in adult female patients (≥ 18 years). The Applicant completed two phase 3, pivotal, randomized, double-blind, placebo-controlled, multi-center, clinical trials to assess safety and efficacy of elagolix (Clinical Trials M12665 and M12671). The following select patient-reported outcome (PRO) instruments were implemented in the phase 3 clinical trials:

PRO Instrument Name	Concept(s)	Endpoint ¹	Copy of Instrument and scoring
Electronic Daily Diary (eDiary)	Dysmenorrhea pain (DYS), non-menstrual pelvic pain (NMPP)	Co-primary	Appendix A
	Dyspareunia (DYSP)	Secondary	
	Worst endometriosis pain (NRS)	Secondary	
	Uterine bleeding	Secondary	
	Analgesic use	Secondary	Not included
Patient Global Impression of Change	Patient global	Exploratory	Appendix B

The Division had previously agreed on the acceptability of the eDiary before COA Staff consultation. Specifically, there was agreement that the DYS and NMPP scores was acceptable for use as a co-primary endpoint. Therefore, this review focused on whether the eDiary was fit-for-purpose in the context of this particular drug development program to assess endometriosis associated pain (menstrual and non-menstrual pain) in the target patient population. Of note, the Applicant is seeking marketing application approval and relevant PRO labeling claims. Refer to the NDA 210450, eCTD Module 1, for information on proposed prescribing information.

The submission did not include an evidence dossier describing the development of the eDiary. This review concludes the following based on face validity:

- The DYS, NMPP, DYSP, and NRS pain scales (part of the daily eDiary) measure the appropriate key symptoms of endometriosis and appear fit-for-purpose for this drug development program.
- DYS, NMPP, DYSP, and NRS results from the M12665 and M12671 clinical trials appear to demonstrate clinical benefit in the target patient population.

This reviewer recommends using anchor-based methods as the primary approach supplemented with cumulative distribution function to derive specific threshold(s) to help interpret PRO data in future clinical trials.² Refer to the Clinical and Statistical reviews for additional relevant discussion and analysis of PRO measures and results.

¹ Please see Section D 1.3 for a complete endpoint hierarchy.

² FDA PRO Guidance (2009)

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

NDA 210450

Elagolix oral tablets

eDiary (dysmenorrhea, non-menstrual pelvic pain, dyspareunia, endometriosis pain)

B. BACKGROUND

Materials reviewed:

- Study M12665 Clinical Study Report
- Study M12671 Clinical Study Report
- NDA 210450 Proposed Labeling

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

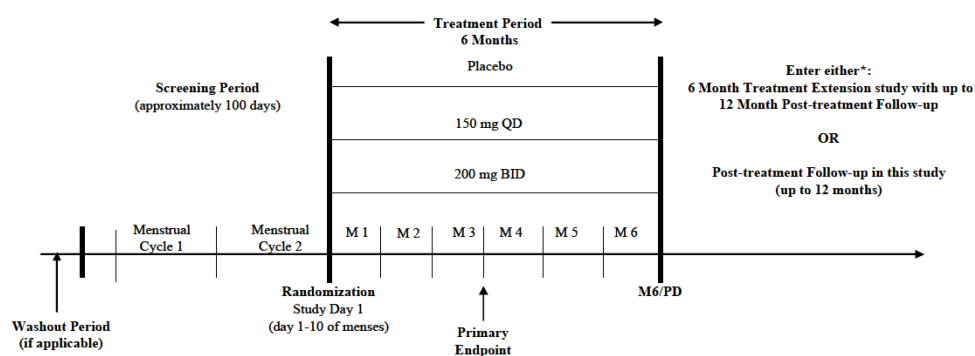
1.1 Clinical Trial Population

The Applicant conducted two phase 3 pivotal clinical trials in adult premenopausal women 18 to 49 years of age with moderate to severe endometriosis-associated pain. Patients were required to have presence of endometriosis associated pain at baseline. Refer to the Clinical review and relevant clinical study protocols for specific inclusion and exclusion criteria.

1.2 Clinical Trial Design

The Applicant completed two 6-month, phase 3, pivotal, randomized, double-blind, placebo-controlled, multi-center, clinical trials to assess safety and efficacy of elagolix (Studies M12665 and M12671). Patients were randomly assigned to receive placebo, elagolix 150mg once daily, or elagolix 200mg twice daily in a 3:2:2 ratio. Refer to the Clinical and Statistical reviews for further discussion on clinical trial design. Figure 1 below shows study schematic for both trials. Note: Both studies used the same trial design.

Figure 1. Study Schematic



* After completing the Treatment Period, subjects entered the PTFU Period (up to 12 months) or, if eligible, a separate continuous-use extension study. Subjects only entered the PTFU Period in this study if they prematurely discontinued from treatment, did not qualify, or declined to participate in the separate continuous-use extension study.

(Source: M12665 Clinical Study Report, Page 142)

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

NDA 210450

Elagolix oral tablets

eDiary (dysmenorrhea, non-menstrual pelvic pain, dyspareunia, endometriosis pain)

1.3 Endpoint Hierarchy and Definition

This reviewer provides an overview of select efficacy endpoints in the phase 3 clinical trials. Refer to the Clinical and Statistical reviews and corresponding clinical study reports for complete information on efficacy and safety endpoints.

Study M12665: Select Efficacy Endpoints

(1) Primary Endpoint

- Proportion of responders at Month 3 based upon the mutually exclusive scales for daily assessments of dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) measured by the Daily Assessment of Endometriosis Pain; use of analgesic medication for endometriosis-associated pain was included in the responder definition).

(2) Secondary Endpoints:

- Change from Baseline to Month 3 in numeric rating scale (NRS) for worst pain in the past 24 hours?
- Change from Baseline to Month 6 in DYS
- Change from Baseline to Month 6 in NMPP
- Change from Baseline to Month 3 in analgesic use across both classes of rescue analgesics based on total pill counts
- Change from Baseline to Month 6 in analgesic used across both classes of rescue analgesics based on total pill counts
- Change from Baseline to Month 3 in dyspareunia pain (DYSP)
- Change from Baseline to Month 3 in use of opioids class of medication based on pill counts

(3) Additional Endpoints:

- Change from Baseline to each visit in the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 6a.
- Change from Baseline to each visit in the control and powerlessness, emotional well-being, social support and self-image domains of Endometriosis Health Profile-30 (EHP-30) questionnaire scores.

Study M12671: Select Efficacy Endpoints

(4) Same select primary and secondary endpoints as in Study M12665 above.

(5) Additional Endpoints:

- Change from Baseline to each visit in the EQ-5D-5L.
- Change from Baseline to each visit in the control and powerlessness, emotional well-being, social support and self-image domains of EHP-30 questionnaire scores.

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

NDA 210450

Elagolix oral tablets

eDiary (dysmenorrhea, non-menstrual pelvic pain, dyspareunia, endometriosis pain)

1.4 Labeling or promotional claim(s) based on the COA

The Applicant proposes marketing approval and PRO labeling texts in Section 14 of the prescribing information (PI) based on relevant COA instruments. Refer to NDA 210450, eCTD Module 1 for proposed labeling texts.

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

This reviewer created the following conceptual framework based on copies of relevant COA instruments. Refer to Study M12665 Sample Case Report Form for copies of relevant COA measures. Refer to Appendix A for relevant pain and uterine bleeding scales included in the eDiary.

Items	Domain	General Concept
• Did you have your period in the last 24 hours? • Choose the item that best describes your pain during the last 24 hours when you had your period	Dysmenorrhea pain during menses	Disease specific sign and symptoms
• Did you have your period in the last 24 hours? • Choose the item that best describes your pain during the last 24 hours without your period	Non-menstrual pelvic pain	
• Choose the item that best describes your pain during sexual intercourse during the last 24 hours	Dyspareunia	
• Did you have any uterine bleeding in the last 24 hours? • Rate the flow of uterine bleeding.	Uterine bleeding	
• Select the one number that describes your endometriosis pain over the last 24 hours at its worst.	Overall endometriosis pain at its worst	
Endometriosis Health Profile-30 (EHP-30): Q 1-11	Pain	Disease impacts
EHP-30: Q 12-17	Control and Powerlessness	
EHP-30: Q 18-23	Emotional Well-Being	
EHP-30: Q 24-27	Social Support	
EHP-30: Q 28-30	Self-Image	
PROMIS Fatigue Short Form 6a items (Q 1-6)	Fatigue	Disease impact
Health Related Productivity Questionnaire – Q 1-9	Productivity	Health resource productivity

3 CLINICAL OUTCOME ASSESSMENT(S)

Endometriosis Daily Pain Impact Scales (Endometriosis eDiary): The Endometriosis eDiary included the following assessments: (1) Dysmenorrhea (DYS); (2) Non-Menstrual Pelvic Pain (NMPP); (3) Dyspareunia Assessment (DYSP); (4) overall endometriosis-associated pain on the numeric rating scale (NRS); (5) uterine bleeding; (3) time for study drug dosing; and (6) the use of allowed analgesic medications for endometriosis-associated pain. Refer to Appendix A for a copy of relevant pain and uterine bleeding scales included in the eDiary.

Prior Versions: There are no prior versions or user manuals provided by the Applicant.

User Manual: The Applicant did not provide a corresponding user manual for review.

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

NDA 210450

Elagolix oral tablets

eDiary (dysmenorrhea, non-menstrual pelvic pain, dyspareunia, endometriosis pain)

Timing, Data Collection Method, and Mode of Administration: The eDiary electronically administered daily at approximately same time using an ePRO device by patients until end of study period by Month 6 or at the time of premature discontinuation from the study.

Training method/materials: The Applicant provided training to patients and clinical investigators on eDiary administration.

The Applicant also administered the Patient Global Impression of Change (PGIC) in both clinical trials to facilitate evaluation of meaningful change for pain scales included in the eDiary. The PGIC asks patients to evaluate the change in their endometriosis-associated pain since initiation of study drug by choosing 1 of 7 responses. The PGIC was administered monthly. Refer to Appendix B for a copy of the instrument.

Reviewer Comments: While PGIC is one anchor measure that may be useful to evaluate meaningful change for a PRO instrument of interest; however, this reviewer offers following considerations for anchor measures in future clinical development programs for endometriosis:

- *Selected anchor(s) should be plainly understood in context, easier to interpret than the PRO itself, and sufficiently correlated to the target PRO.*
- *Multiple anchors should be explored to provide an accumulation of evidence to help interpret meaningful within-patient score change which can also be a range.*
- *The following anchors are recommended to generate appropriate improvement threshold(s) that represent a meaningful within-patient change in the target patient population:*
 - *Well established clinical outcomes*
 - *Static, current-state global impression of severity scale (e.g., Patient Global Impression of Severity or PGIS)*
 - *Global impression of change scale (e.g., Patient Global Impression of Change or PGIC)*
- *A static, current state global impression of severity scale is recommended at minimum, when appropriate, since these anchor measures such as PGIS are less likely to be subject to recall error than global impression of change such as PGIC.*
- *Optimize the frequency and timing of anchor measure administration as appropriate. For example, consider administering anchor measures at multiple time points throughout a clinical trial to maximize the amount of data available in both the investigational and control arms, particularly for patients who withdraw early.*

4 SCORING ALGORITHM

Electronic Daily Diary (eDiary):

- (1) **DYS:** This is a single item question with four categorical severity responses (none, mild, moderate and severe). “None” response corresponds to no discomfort while “Severe” to

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eDiary (dysmenorrhea, non-menstrual pelvic pain, dyspareunia, endometriosis pain)

severe pain causing greater difficulty doing routine things. Response of None, Mild, Moderate, and Severe were assigned a score of 0, 1, 2, 3, respectively.

- (2) NMSS: This is a single item question with four categorical severity response options (none, mild, moderate and severe). “None” response corresponds to no discomfort while “Severe” to severe pain causing greater difficulty doing routine things. Response of None, Mild, Moderate, and Severe were assigned a score of 0, 1, 2, 3, respectively.
- (3) DYSP: This is a single item question with five categorical severity responses (not applicable, none, mild, moderate, and severe). A not applicable response corresponds to responder not being sexually active for reasons other than endometriosis. “None” response corresponds to no discomfort with sexual intercourse while a “Severe” response option represented avoiding sexual intercourse because of pain. Response of None, Mild, Moderate, and Severe were assigned a score of 0, 1, 2, 3, respectively. Not Applicable responses were excluded from analysis.
- (4) Uterine Bleeding: This is a single item question with four response categories (spotting, light, medium, and heavy). A “Spotting” response corresponds to a light amount of bleeding while a “Heavy” response represents >4 tampons or pads required in 24 hours.
- (5) Overall endometriosis-associated NRS: This is a single item NRS asking patients to rate their overall endometriosis pain over the last 24 hours at its worst. A score 0 represents no pain while a score of 10 represents worst pain ever.
- (6) Analgesic use: The eDiary allowed patients to enter daily analgesic use (opioid and non-opioid) throughout the clinical trials.

5 CONTENT VALIDITY

The Applicant did not provide relevant information in the NDA submission to facilitate the review of content validity of the eDiary. However, the review division agreed to assessing endometriosis associated pain (dysmenorrhea, non-menstrual pelvic pain, and dyspareunia) and uterine bleeding using the eDiary prior to initiation of phase 3 clinical trials.

Reviewer Comments:

- *Dysmenorrhea, non-menstrual pelvic pain, dyspareunia, and uterine bleeding are considered clinically relevant and meaningful signs and symptoms associated with endometriosis in the target patient population. Assessment of these signs and symptoms using the eDiary were agreed upon by the review division prior to initiation of the phase 3 clinical trials.*
- *On face validity, individual pain scales for dysmenorrhea (DYS), non-menstrual pelvic pain (NMPP), dyspareunia (DYSP), and overall endometriosis pain (NRS) appear fit-for-purpose. Each pain scale question stem, pertinent response options, and recall period appear reasonable.*
- *This reviewer recommends patient input in future clinical trials to ensure and document the assessment meaningful concepts and patient understanding of the PRO instruments.*

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6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant did not provide relevant information for review.

7 INTERPRETATION OF SCORES

The threshold for reduction in pain was determined based on a receiver operating characteristic (ROC) analysis using the PGIC at Month 3 as an anchor. The response of “much improved” and “very much improved” on the PGIC were used to define responders, and the threshold for response was chosen to balance sensitivity and specificity. That is, it was the value that corresponds to the point on the ROC curve that is closest to the upper left corner, i.e., closest to 100% sensitivity and 100% specificity. The ROC analyses for DYS and NMPP were conducted separately. The optimal threshold obtained from the ROC analysis using PGIC at Month 3 and change from baseline to Month 3 in DYS was fixed and used for all responder analyses involving change from baseline in DYS (including responder analyses) taking into consideration of both pain reduction and analgesic use and responder analyses solely based on pain reduction at all time points such as Months 1-6 and final visit. Same applies to NMPP and dyspareunia.

The ROC analyses using percent change from baseline in pain scores were conducted separately from using change from baseline for both DYS and NMPP. The optimal threshold obtained from the ROC analysis using PGIC at Month 3 and percent change from baseline to Month 6 in DYS was fixed and used for all responder analyses involving percent change from baseline in DYS (including responder analyses) taking into consideration of both percent pain reduction and analgesic use and responder analyses solely based on percent pain reduction at all tie points such as Months 1-6 and final visit. Same applies to NMPP and dyspareunia.

Reviewer Comments: ROC methods used by the Applicant to derive meaningful change threshold is generally considered supportive. Instead, FDA recommends using anchor-based methods as the primary approach supplemented with cumulative distribution function (CDF) to derive specific threshold(s) to interpret PRO data. Refer to reviewer comments in Section C3 for comments related to selection/development of anchor measures.

The biostatistical reviewer conducted anchor-based analysis using the PGIC to facilitate interpretation of PRO results related to DYS and NMPP scales in both clinical trials. These internal analyses appeared to provide consistent evidence of improvement in pain severity associated with endometriosis in the treatment vs. placebo arms across both phase 3 clinical trials. Refer to the Statistical and Clinical review for additional relevant discussion and analysis.

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The Applicant did not provide relevant information for review.

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Reviewer Comments: This was a multinational drug development program. However, no information was given regard to the process of translation of the eDiary. Ideally, COAs should be culturally adapted and adequately translated for all intended study populations for use in multinational trials following best practices (e.g., ISPOR principles for the translation and cultural adaptation process)³.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

The Applicant did not provide relevant information for review.

10 REVIEW USER MANUAL

The Applicant did not provide a corresponding user manual for review.

11 KEY REFERENCES FOR COA

³ Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

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eDiary (dysmenorrhea, non-menstrual pelvic pain, dyspareunia, endometriosis pain)

E. APPENDICES

Appendix A: Endometriosis Daily Pain Impact Scales for DYS, NMPP, and DYSP (eDiary)

Appendix B: Patient Global Impression of Change (PGIC)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NIKUNJ B PATEL
01/23/2018

SELENA R DANIELS
01/23/2018

ELEKTRA J PAPADOPOULOS
01/23/2018