CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214846Orig1s000

CLINICAL REVIEW(S)

Clinical Review
NDA 214826

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Reviewer Name(s)	Jennifer Lawrence, MD Linda Jaffe, MD
Review Completion Date	5/24/2021
Established/Proper Name	Relugolix, estradiol and norethindrone acetate
(Proposed) Trade Name	Myfembree
Applicant	Myovant Sciences, GmbH
Pharmacologic Class	Gonadotropin-releasing hormone (GnRH) antagonist
Dosage Form(s)	Oral tablet
Dosing Regimen	One tablet daily
Proposed Indication	Management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women
Intended Population	Premenopausal women
Regulatory Action	Approval
Recommended Indication	Management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women

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Glossary

AC	advisory committee
ABT	add-back therapy
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
ATE	arterial thromboembolism
BA	bioavailability
BE	bioequivalence
BMD	bone mineral density
BPD	Bleeding and Pelvic Discomfort (subscale of UFS-QoL)
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	clinical investigator
CMC	chemistry, manufacturing, and controls
COA	Clinical Outcome Assessment
COC	combination oral contraceptive
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DXA	dual-energy X-ray absorptiometry
E2	estradiol
ECG	electrocardiogram
eCTD	electronic common technical document
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDC	fixed-dose combination
FSH	follicle stimulating hormone

GCP	good clinical practice
GnRH	gonadotropin-releasing hormone
GRMP	good review management practice
HMB	heavy menstrual bleeding
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IQC	instrument quality control (used for BMD)
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LH	luteinizing hormone
LNG	levonorgestrel
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menorrhagia Impact Questionnaire
mITT	modified intent to treat
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NETA	norethindrone acetate
NME	new molecular entity
NRS	Numerical Rating Scale
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
ORA	Office of Regulatory Affairs
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBAC	Pictorial Blood Loss Assessment Chart
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PGA	Patient Global Assessment
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
R	relugolix
R+E2/NETA	relugolix + estradiol/norethindrone acetate
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event

SAP	statistical analysis plan
SGE	special government employee
SOC	system organ class
TEAE	treatment-emergent adverse event
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life
ULN	upper limit of normal
VTE	venous thromboembolism

1. INTRODUCTION

Uterine fibroids, also known as uterine leiomyomas, are benign smooth muscle tumors that arise primarily in three regions of the uterus (submucosal, intramural and subserosal). Their location in the uterus correlates roughly with symptomatology which occurs in approximately 25-30% of women with fibroids. Submucosal and intramural types are more likely to be associated with heavy menstrual bleeding (usually defined as > 80 mL per menstrual cycle). Heavy menstrual bleeding (HMB) in turn can result in iron-deficiency anemia.

Myfembree is a fixed-dose combination oral tablet containing relugolix (R) 40 mg, estradiol (E2) 1 mg, and norethindrone acetate (NETA) 0.5 mg. The proposed indication for Myfembree in this application is the treatment of HMB associated with uterine fibroids. The proposed dosing regimen is one tablet to be taken orally once daily.

Relugolix is an addition to the existing drug class of nonpeptide GnRH receptor antagonists that inhibit endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. This binding in turn suppresses the gonadotropins - luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Suppression of the gonadotropins results in decreased blood concentrations of the ovarian hormones estradiol and progesterone. Therapy designed to reduce the concentrations of these ovarian hormones is thought to aid in the treatment of fibroid-related HMB by reducing hormone-related proliferative effects on uterine fibroids and stabilization of the endometrium.

However, long-term treatment regimens designed to reduce ovarian hormones have side effects including among others, bone loss and vasomotor symptoms. To ameliorate these side effects, Myfembree also contains the add-back therapy (ABT) of E2/NETA. These hormonal components are identical to doses in a combination menopausal product (Activella) approved under NDA 020907.

Another GnRH receptor antagonist (elagolix) combined with E2/NETA received FDA approval in 2020 for the treatment of HMB associated with uterine fibroids. Based on bone mineral density studies to date, the elagolix combination product is presently limited to two years of use.

A GnRH agonist, leuprolide acetate, was approved in 1999 for the preoperative hematologic improvement of patients with anemia caused by uterine fibroids. However, leuprolide for this indication is limited to three months of use.

Other options for patients who have HMB from uterine fibroids include a range of surgical and interventional techniques. Excisional surgical options for removal of fibroids from the uterus includes abdominal and vaginal approaches (e.g. laparotomy, laparoscopy or hysteroscopy). Hysterectomy remains the only definitive treatment for HMB associated with fibroids.

Other interventional techniques available to patients in the U.S. include uterine artery

embolization and Magnetic Resonance Imaging (MRI)-guided focused ultrasound.

Medical therapies for HMB that do not include an indication for women with fibroids include:

- Antifibrinolytic tranexamic acid
- Levonorgestrel (LNG) intrauterine system
- Combination oral contraceptive (COC) containing dienogest/estradiol valerate

It is possible that some women with fibroid-related HMB have been treated off-label with these three products.

Finally, it is important to note that even though many of the therapies for fibroid-related bleeding are not definitive alone, they may allow for premenopausal women to transition into the menopause where fibroid symptomatology tends to regress naturally.

To establish the efficacy and safety of Myfembree, two replicate, 24-week, multi-national, randomized, double-blind, placebo-controlled Phase 3 trials were conducted in premenopausal women with HMB associated with uterine fibroids [Study MVT-601-3001 (NCT03049735), hereafter referred to as Study 3001 and Study MVT-601-3002 (NCT03103087), hereafter referred to as Study 3002]. Relugolix and E2/NETA add-back component therapy was administered in Phase 3 studies via an over-encapsulation process. Comparable bioavailability between the study preparation, hereafter designated as R+E2/NETA, and the to-be-marketed fixed-dose combination Myfembree tablet was demonstrated in a single-dose pharmacokinetic study (MVT-601-042). The primary endpoint for both Study 3001 and 3002 was the proportion of women in the R+E2/NETA group compared with women in the placebo group who achieved menstrual blood loss (MBL) volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method. Key secondary endpoints proposed by the Applicant for labeling are discussed in Section 6.1.2 of this review.

Important efficacy and safety review issues evaluated internally and discussed with the Applicant during the review cycle are found in Sections 5.1.3, 7.4.4 and 7.5.

1.1. Primary Reviewer's (Jennifer Lawrence) Conclusions on the Substantial Evidence of Effectiveness

Based on the totality of the clinical data submitted by the Applicant, R+E2/NETA significantly reduced HMB associated with uterine fibroids in premenopausal women. Substantial evidence of effectiveness was demonstrated in two replicate, adequately powered, placebo-controlled Phase 3 trials (Studies 3001 and 3002), which included 252 women treated with R+E2/NETA and 242 women treated with placebo. Objective alkaline hematin laboratory data supported the

conclusion that treatment with R+E2/NETA by 24 weeks reduced MBL volume to <80 mL (the threshold used to define HMB) and reduced MBL volume by at least 50% from pre-treatment baseline over the last 35 days of treatment in a greater proportion of participants compared to placebo. See Table A below of the primary endpoint efficacy findings:

Table A: Proportion of Responders at Week 24

	Treatments		Difference (95% CI)
	R+E2/NETA	Placebo	
MVT-601-3001	88 /122 (72.1%)	19 /113 (16.8%)	55.3% (44.2%, 65.6%)
MVT-601-3002	89 /125 (71.2%)	19/129 (14.7%)	56.5% (46.6%, 66.5%)

Source: Adapted from Table 6 of the Sponsor's response to information request sent on 02/08/2021
Participants from closed Site 1152 excluded from analysis.

The data from pivotal Studies 3001 and 3002 also support the efficacy and inclusion in labeling of the following key secondary endpoints in favor of R+E2/NETA, as demonstrated in Table B below:

Table B: Efficacy Results Key Secondary Endpoints Included in Labeling

Endpoints	MVT-601-3001		
	R+E2/NETA N=122	Placebo N=113	Difference (95% CI)
Proportion of women who achieved amenorrhea over the last 35 days of treatment	61/122 (50.0%)	7/113 (6.2%)	43.8% (33.9%, 53.7%)
Percent change from baseline to Week 24 in MBL volume [mean (SD)]	-82.0 (5.09)	-19.1 (5.2)	-62.9 (-76.4, -49.4)
Proportion of women with hemoglobin level ≤10.5g/dL at baseline who achieved an increase of >2 g/dL from baseline at Week 24 (based on mixed-effects model approach)	19/43 (44.2%)	5/29 (17.2%)	26.9% (6.7%, 47.2%)
Endpoints	**MVT-601-3002**		
	R+E2/NETA N=125	**Placebo N=129**	**Difference (95% CI)**
Proportion of women who achieved amenorrhea over the last 35 days of treatment	63/125 (50.4%)	4/129 (3.1%)	47.3% (38.0%, 56.6%)
Percent change from baseline to Week 24 in MBL volume [mean (SD)]	-84.3 (5.45)	-15.1 (5.47)	-69.2 (-84.1, -54.3)
Proportion of women with hemoglobin level ≤10.5g/dL at baseline who achieved an increase of >2 g/dL from baseline at Week 24 (based on mixed-effects model approach)	22/40 (55.0%)	3/53 (5.7%)	49.3% (32.7%, 66.0%)

Source: Adapted from Table 6 of the Sponsor's response to information request sent on 02/08/2021;
Participants from closed Site 1152 excluded from analysis.
Mean: Least-squares means; SD: Standard deviation.

The strong and consistent efficacy results across the two adequate, placebo-controlled Phase 3 clinical trials for the primary endpoint, provide substantial evidence of effectiveness for R+E2/NETA for management of HMB associated with uterine fibroids in the target population.

Based upon the substantial evidence of effectiveness of R+E2/NETA demonstrated by highly consistent results across the two adequate and well-controlled Phase 3 clinical trials, I recommend approval of Myfembree for the management of HMB associated with uterine leiomyomas (fibroids) in premenopausal women.

1.2. Primary Reviewer's (Linda Jaffe) Safety Assessment Conclusions

The safety population for this NDA from Phase 3 Studies 3001 and 3002, and the open-label (OLE) extension trial MVT-601-3003 (hereafter referred to as Study 3003) included 634 women who received at least one dose of R+E2/NETA. Of these women, 451 were exposed to R+E2/NETA for at least 6 months, and 130 were exposed for at least 12 months. The safety database is adequate to evaluate R+E2/NETA for the longterm treatment of HMB related to uterine fibroids in premenopausal women.

The safety of R+E2/NETA in the target population was assessed in these three Phase 3 studies.

- No deaths occurred in Phase 3 studies submitted to this NDA.
- Serious adverse events (SAEs) were generally not attributed to study drug. In the placebo-controlled trials, 11 SAEs were reported for 8 participants in the R+E2/NETA arm. AEs assessed by the investigator and/or this reviewer as probably/possibly related to drug included menorrhagia, uterine myoma expulsion, uterine leiomyoma prolapse and pelvic pain.
- For the majority of AEs leading to discontinuation in the R+E2/NETA arm, single events were reported. Discontinuation due to adverse events of special interest (AESIs) included menorrhagia, metrorrhagia, alanine aminotransferase (ALT) increase, and hot flush, occurring in one participant each in the R+E2/NETA arm while no participants in the placebo (PBO) arm discontinued for these AESIs.
- The most common AEs occurring in at least 3% of women treated with R+E2/NETA and greater than PBO were hot flushes (and related terms), abnormal uterine bleeding, alopecia, and libido decreased.
- Other than an increase in total cholesterol and low-density lipoprotein (LDL) cholesterol in a subset of participants, no safety signals in laboratory parameters were identified. Confounding factors were identified for all participants with elevations in liver enzymes ≥ 3-fold upper limit of normal (ULN).
- A greater proportion of participants treated in R+E2/NETA in Study 3001 experienced the AE of hypertension.
- A decline in bone mineral density (BMD) (mean of 0.8% at the lumbar spine) was demonstrated with 12 months of treatment with R+E2/NETA without clear evidence of a plateau.
- A greater incidence of mood disorders (including depression, mood swings, irritability and anxiety) occurred in R+E2/NETA treated women as compared to placebo. No suicidal ideation behavior was reported in these studies.

In summary, the severity and frequency of the overall safety findings identified during this review do not rise to a level that would preclude approval of Myfembree. The safety issues identified can be adequately mitigated through labeling, evaluated through enhanced Pharmacovigilance Program, or evaluated via postmarketing requirements.

1.3. Patient Experience Data

Patient experience data for this application is presented in Table 1.

Table 1: Patient Experience Data Relevant to this Application

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)	Section 5.1.1 Study Design; Section 5.1.2 Study Results; Section 5.1.3: Key Review Issues Relevant to Evaluation of Benefit
	□	Observer reported outcome (ObsRO)	
	□	Clinician reported outcome (ClinRO)	
	□	Performance outcome (PerfO)	
□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
□	Patient-focused drug development or other stakeholder meeting summary reports		
x	Observational survey studies designed to capture patient experience data (MVT-601-034)		Section 4.1: Key Clinical Studies; Section 7.5.2 Decline in Bone Mineral Density
□	Natural history studies		
□	Patient preference studies (e.g., submitted studies or scientific publications)		
x	Other: (Please specify) Patient exit interview study (MVT-601-037)		Section 4.1: Key Clinical Studies; Section 4.2 Review Strategy; Section 5.1.3: Key Review Issues Relevant to Evaluation of Benefit

The Applicant submitted the following patient-reported outcome (PRO) assessments grouped

according to the type of efficacy endpoint being measured. The above table indicates the sections in which the PROs are discussed.

1. Key secondary endpoints
    a. Uterine Fibroid Symptom and Health-Related Quality of Life – Bleeding and Pelvic Discomfort subscale (UFS-QoL BPD)
    b. Numerical Rating Scale (NRS) for pain
2. Other secondary endpoints
    a. UFS-QoL scale
    b. Patient Global Assessment (PGA) for Function/Symptom Severity
    c. Menorrhagia Impact Questionnaire (MIQ)
3. Exploratory endpoint
    a. European Quality of Life Five-Dimension Five-Level (EQ-5D-5L) scale

The Applicant also submitted the following studies:

1. A BMD observational study (MVT-601-034) in women with uterine fibroids or endometriosis who were not treated with concomitant therapy.
2. An exit interview study (MVT-601-037) to assess trial participants' perception of minimum meaningful improvement in PRO instrument scores.

Reviewer's comment: (b) (4) *(See Section 5.1.3 Key Review Issues Relevant to Evaluation of Benefit).*

2. Therapeutic Context

2.1. Analysis of Condition

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

2.2. Analysis of Current Treatment Options

Available medical and surgical treatments for the management of heavy menstrual bleeding related to uterine fibroids are shown in Tables 2 and 3. Oriahnn (elagolix/E2/NETA) was approved in May 2020 for management of heavy menstrual bleeding caused by uterine fibroids

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

and has a limitation of use of two years to mitigate the risk of bone loss. Leuprolide is approved for no more than three months duration as part of pre-operative care prior to hysterectomy. The recommended use of leuprolide injections is limited to one course (one injection of 11.25 mg for three months or three monthly injections of 3.75 mg) to improve anemia prior to myomectomy or hysterectomy. The selective progesterone receptor modulator ulipristal acetate was approved in Europe for the chronic medical treatment of uterine fibroids, but its use has since been suspended due to postmarketing cases of severe liver injury.

Table 2: Summary of Medical Treatment Armamentarium Relevant to Proposed Indication

FDA Approved Treatments for Abnormal Uterine Bleeding in Women with Uterine Fibroids			
Indication	**Dosage and Administration**	**Efficacy Information**	**Key Safety and Tolerability Issues**
Lupron ® (leuprolide Acetate depot Injection) Approved 1995			
Preoperative hematologic improvement in women with anemia caused by fibroids	Monthly injection of 3.75 mg for up to 3 months or one injection of 11.25 mg (Must use concomitantly with iron therapy)	Administration of Lupron depot and iron produced an increase of ≥6% hematocrit and ≥2 g/dL hemoglobin in 77% of patients at three months of therapy.	Duration of use is limited due to concern over bone safety.
Oriahnn® (elagolix/E2/NETA) Approved 2020			
Management of heavy menstrual bleeding associated with uterine leiomyomas in pre-menopausal women	Elagolix 300 mg/E2 1mg/ NETA 0.5 mg in the morning and elagolix 300 mg in the evening	Difference from placebo in the proportion of women with MBL volume <80 mL and ≥ 50% reduction in MBL volume from baseline to final month (up to 6 months): 60-66%	Boxed Warning for risk of thromboemoblic disorders and vascular events; Duration of use is limited due to concern over bone safety.
FDA Approved Treatments for HMB but not Specifically for Bleeding in Women with Uterine Fibroids			
Lysteda® (Tranexamic acid) Approved 2009			
Cyclic heavy menstrual bleeding	1,300 mg (two 650 mg tablets) three times a day (3,900 mg for a maximum of 5 days during monthly menstruation; Dose adjustment is needed in patients with renal impairment.	An antifibrinolytic, Lysteda is contraindicated in women who are using combined hormonal contraception and women with current or history of thromboembolic disease	Efficacy In women with HMB due to fibroids has not been established.
Natazia® (estradiol valerate+/-dienogest) Approved 2010			
Cyclic heavy menstrual bleeding	28 day cycle regimen 26 tablets active with either estradiol valerate alone (1 mg and 3 mg tablets) or	Secondary indication is a combination oral contraceptive	Efficacy in women with HMB due to fibroids has not

	estradiol valerate 2 mg in combination with dienogest (2 mg or 3 mg), and 2 inert tablets		been established.
Mirena® (levonorgestrel intra-uterine device) Approved 2000			
Cyclic heavy menstrual bleeding	Levonorgestrel (LNG) release (52 mg); initial LNG release rate is approximately 20 mcg/day, that declines to approximately 10 mcg/day at 5 years	LNG-releasing intra-uterine system approved for up to 6 years of use	Efficacy In women with HMB due to fibroids has not been established.
Non-FDA Approved Treatments for Menorrhagia			
Oral contraceptive agents Initial Approved in 1961[2]			
Contraception	An example of a more recently approved dosing regimen is ethinyl estradiol 20 mcg and levonorgestrel 100 mcg for 21 days and placebo for 7 days (NDA 209405, approved in 2020)	Peer-reviewed literature	Risk of thromboembolic events. Contraindicated in women 35 years or older and who smoke.

E2=estradiol; NETA=norethindrone acetate; HMB=heavy menstrual bleeding; MBL=menstrual blood loss

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

Table 3: Summary of Surgical & Other Interventional Treatments Relevant to Proposed Indication

Procedure (Year FDA-approved)	**Agents/Devices**	**Efficacy Information**	**Key Safety and Tolerability Issues**	**Comments**
Endometrial ablation (1997)	Multiple FDA-approved devices for global endometrial ablation (GEA), e.g., NovaSure, Minerva, Thermachoice	FDA approval is based on results of RCTs that compare the safety and effectiveness of the GEA device to the hysteroscopic roller ablation.[3]	Perforation of the uterus, burns to bowels, pulmonary edema	Can be done as an office procedure
Uterine artery Embolization (2000)	Multiple FDA approved Embolic agents (e.g., trisacryl gelatin microsphere, polyvinyl alcohol particles gelfoam,) used to occlude the artery		Embolism, loss of ovarian function and infertility, iatrogenic menopause, postembolization syndrome (pain, fever, nausea)	Requires specialized expertise; short hospital stay; Cutoff of 10 cm size of fibroid; Need good renal function
MRI-guided focused ultrasound (MRgFUS) (2004)	FDA-approved to treat uterine fibroids		Skin burns, sciatic nerve injury, vaginal discharge, focal abdominal wall edema	Require specialized expertise; outpatient procedure; Cutoff of 10 cm size of fibroid; Need acceptable renal function due to use of gadolinium
Myomectomy (hysteroscopic, laparoscopic, and abdominal)			Incurs surgical risks	Risk of recurrence
Hysterectomy		Definitive treatment	Incurs surgical risks	Loss of childbearing and potential loss of ovarian function

RCTs=randomized controlled trials

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

2.3. U.S. Regulatory Actions and Marketing History

Relugolix monotherapy (marketed as Orgovyx®) was approved by FDA in 2020 for the treatment of adults with advanced prostate cancer. The approved dosing regimen is 360 mg oral loading dose followed by 120 mg taken orally once daily. Relugolix in combination with estradiol and norethindrone acetate has not been approved by FDA is currently not marketed in the U.S.

Estradiol 1 mg/Norethindrone acetate 0.5 mg fixed combination product was approved by FDA in 1998 for the treatment of moderate to severe vasomotor symptoms due to menopause, prevention of postmenopausal osteoporosis and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. The drug is marketed in the U.S. under the tradename Activella®.

2.4. Summary of Presubmission/Review Cycle Regulatory Activity

(b) (4)

10-5-2016 – An End of Phase 2 meeting was held under PIND 131161. Agreement was reached on the need for a food effect study using the to-be-marketed formulation, the use of 3 arms in the Phase 3 studies [relugolix 40mg, relugolix 40mg plus add-back (to assess the impact on bone mineral density), and placebo], the inclusion and exclusion criteria, the primary endpoint as the proportion of participants with a menstrual blood loss volume of less than 80ml and at least a 50% reduction in menstrual blood loss volume from baseline to the last month of treatment, as measured by the alkaline hematin method, and the safety assessment and monitoring plan. FDA informed the sponsor that the difference in responder rates between treatment arms must be both statistically significant and clinically meaningful. The sponsor informed the FDA that a majority of participants enrolled would be from the U.S.

11-29-2016 – IND 131161 was submitted for the fibroid indication, (b) (4)

2-3-2017 – FDA issued an advice letter regarding the Phase 3 clinical trials.

2-17-2017 – Myovant submitted protocol revisions for the Phase 3 clinical trials.

4-7-2017 – FDA issues an Agreed iPSP letter for the fibroid indication.

7-13-2017- Final written responses were issued regarding proposed starting materials (FDA agreed but stated if changes occurred prior to commercialization, the issue would be revisited) and setting the limit of genotoxic impurities (FDA agreed).

2-15-2018 – Final written responses were issued regarding information to be submitted in the NDA to support a categorical exclusion from the requirement to submit an environmental assessment.

3-16-2018 – Myovant submitted the protocol for the extension study.

5-25-2018 – FDA issued an advice letter regarding safety measures and secondary endpoints for the extension study.

8-22-2018 – A teleconference was held during which FDA advised the sponsor to use the to-be-marketed product in the Phase 3 program, to conduct a drug interaction study using a strong CYP3A inhibitor that does not affect P-gp, that a dose separation strategy alone would not support administration with P-gp inhibitors, and that the sponsor should address potential interactions with CPY3A substrates, combined hormonal contraceptives, and a sensitive Breast Cancer Resistance Protein. The FDA also agreed with the plan not to study interactions with Proton Pump Inhibitors if the sponsor was able to confirm the estimated solubility of relugolix at pH 6.

12-17-2018 – Final written responses were issued regarding CMC issues. (b) (4)

1-31-2019 – A Type C guidance meeting was held to discuss the Statistical Analysis Plan for the Phase 3 trials.

4-2-2019 – FDA issued an advice letter regarding patient-reported outcomes.

4-26-2019 – FDA issued an advice letter regarding the Statistical Analysis Plan.

5-7-2019 – Myovant responded to the 4-26-2019 letter by agreeing that participants who withdraw for lack of efficacy or the need for surgery would be considered non-responders, but disagreed that the mixed-effects model may underestimate menstrual blood loss volume.

6-11-2019 – Myovant responded to the 4-2-2019 advice letter. The sponsor did not adopt many of the suggestions, often because the trial had been completed.

11-5-2019 – Executive CAC held a meeting and concluded that the mouse and rat carcinogenicity studies were adequate and that no drug-related neoplasms occurred.

11-11-2019 – Myovant submitted information to demonstrate equivalence between the U.S. and E.U. brands of estradiol/norethindrone acetate used in the Phase 3 trials.

3-9-2020 – Myovant submitted an information amendment outlining the plan for a fixed-dose combination product and its components.

3-25-2020 – A pre-NDA meeting was held. Agreement was reached on the need to address the potential interaction between calcium and/or Vitamin D supplementation and bone mineral density (BMD), that the original NDA submission would include final safety data from the extension trial, and that case report forms and narratives would be included for several adverse events, including alopecia. FDA outlined how to present post-treatment BMD results and that the 120-day safety update should include information from any studies (including endometriosis trials). The sponsor explained that they planned to submit a 505(b)(2) application relying on the Agency's finding of safety and effectiveness for Activella (estradiol/norethindrone acetate) tablets and to leverage the Guidance for Industry: Labeling for Combined Hormonal Contraceptives for language in the Pregnancy subsection of labeling. The FDA agree to consider this proposal. The FDA informed the sponsor that the NDA would not be granted a priority review. FDA offered additional advice on the content and format of the NDA which was not discussed at the meeting.

4-2-2020 – NDA 214621 was submitted to the Division of Oncology 1 proposing relugolix 120mg tablets for the treatment of patients with advanced prostate cancer. The application was granted priority review status.

6-1-2020 – NDA 214846 was received and classified as a new molecular entity (NME) in the program with a 12-month clock (standard review).

Reviewer Comment: on 12/18/2020, Orgovyx (relugolix 120 mg) was approved for the treatment of patients with advanced prostate cancer. Therefore, the fixed combination product relugolix/estradiol/norethindrone acetate was no longer classified as an NME.

6-2-2020 – A proposed proprietary name (Myfembree) submission was received.

2.5. Foreign Regulatory Actions and Marketing History

Relugolix monotherapy 40 mg daily was approved in January 2019 in Japan for the improvement of symptoms associated with uterine myoma (hypermenorrhea, lower abdominal pain, lower back pain and anemia). The drug has been marketed in Japan under the tradename Relumina ® since March 2019.

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

3.1. Office of Scientific Investigations (OSI)

Four Clinical Investigators (CIs) participating in pivotal Studies 3001 and 3002 and Extension Study 3003 were selected for clinical inspections:

1. Dr. Nelson Uzquiano (Site 1123, US; Studies 3001 and 3003)
2. Dr. Gregory Michael Swor (Site 1023, US; Studies 3002 and 3003)
3. Dr. Lydie Hazan (Site 1077, US; Study 3002)
4. Dr. Roberta Venturella (Site 3094, Italy; Study 3001)

The CIs were chosen because of the higher numbers of participants enrolled in their study treatment arms compared to other CIs and the potential for data integrity concerns that may impact data interpretation. Due to scheduling limitations of the Office of Regulatory Affairs (ORA) to conduct onsite inspections, particularly outside of the US, because of the ongoing COVID-19 pandemic, the Division decided to cancel inspection of Site 3094 in Italy. The Division determined that given safety risks of the pandemic, the ability to inspect the other three domestic sites, and the significant efficacy findings of the application, that findings at site 3094 would not have a significant impact on the interpretation of efficacy and safety data.

At the end of the inspection of Site 1123, a Form 483 (Inspectional Observations) was issued to Dr. Uzquiano due to failure to conduct an investigation in accordance with the signed statement of the investigator and investigational plan. The observations were as follows:

1. Lack of cardiology follow-up of an abnormal ECG in Participant # (b) (6) (Study 3001). Action: The abnormal ECG was reported as an AE. A cardiologist appointment for evaluation was made for the participant, who failed to follow-up. The participant had no cardiac symptoms throughout the study.
2. An abnormal ECG in Participant # (b) (6) (Study 3001) was not signed by the CI or reported as an AE in a timely fashion according to reporting in source records. Action: A review of the submission identified that an AE of prolonged QRS complex was appropriately reported for the participant.
3. An abnormally low blood pressure (BP) in Participant (b) (6) (Study 3001) on Week 8 of the study was not evaluated by the CI or reported as an AE. Action: The participant was noted to have a low normal BP at baseline. The reported BP during the study was within the normal range for the participant and did not meet the criteria for an AE.

Dr. Uzquiano responded satisfactorily to the Form 483 observations. No other Form 483 observations were issued for the inspected sites. Overall, the CI inspections of Sites 1123, 1023, and 1077 found that the sites appeared to be in compliance with Good Clinical Practice (GCP) and that any deficiencies observed were unlikely to have a significant impact on the overall efficacy and safety results of Studies 3001, 3002, and 3003.

Site 1152 in Poland which participated in Studies 3001 and 3003 was closed by the Applicant on February 25-26, 2020 for "multiple observations of GCP noncompliance." Due to COVID-19 pandemic restrictions, full data audit of the site was not feasible. OSI recommended that the data from Site 1152 be excluded from per protocol analysis. These recommendations were communicated to the Division of Urology, Obstetrics and Gynecology (DUOG) on March 4, 2021. The Agency had since determined that all efficacy data from Site 1152 would be excluded from analysis to evaluate the primary and secondary endpoints, and safety data would be included in analysis. Exclusion of efficacy data from Site 1152 did not have a significant impact on efficacy results. (See Key Benefit Review Issue #1 in Section 5.1.3 Key Review Issues Relevant to Evaluation of Benefit for further details.)

See the OSI Clinical Inspection Summary in DARRTS dated April 15, 2021 for complete details of site inspections.

3.2. Product Quality

See the CDTL-review for summary information and the April 7, 2021 integrated quality review in DARRTS.

3.3. Clinical Microbiology

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

3.4. Nonclinical Pharmacology/Toxicology

See the CDTL-review for summary information and the May 5th and 10th, 2021 Nonclinical Pharmacology/Toxicology Reviews in DARRTS.

3.5. Clinical Pharmacology

See the CDTL-review for summary information and the May 14, 2021 Nonclinical Pharmacology/Toxicology Reviews in DARRTS.

3.6. Devices and Companion Diagnostic Issues

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

3.7. Consumer Study Reviews

This section is not applicable; no consumer studies were submitted to this NDA.

4. Sources of Clinical Data and Review Strategy

4.1. Key Clinical Studies (Tabular Summaries)

The key clinical study summaries for this application are shown in the following tables (**Tables 4-8**)

Table 4: Study MVT-601-3001 - Summary

Trial Identifier NCT # # Study Sites- Country	**Trial Population**	**Trial Design Duration of Treatment**	**Primary Endpoint**	**Study Arm**	**Participants Randomized/ Participants Treated**
MVT-601-3001 NCT=03049735 63 (sites)-US 3-Brazil 5-Italy 5-Poland 3-South Africa 1-UK	Premenopausal women between 18 and 50 years old with heavy menstrual bleeding associated with uterine fibroids	Phase 3 MC PC R DB 24 weeks	Primary: Proportion of women in relugolix Group A versus placebo Group C who achieve an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method.	Drug:Group A: Relugolix 40 mg QD for 24 wks plus E2/NETA (1 mg/0.5 mg) QD for 24 wks Number treated: 128 Drug:Group B: Relugolix 40 mg QD for 12 wks plus placebo, followed by relugolix 40 mg QD plus E2/NETA (1 mg/0.5 mg) QD for 12 wks+E2/NETA Number treated: 132 Drug:GroupC: Placebo QD for 24 wks Number treated: 127	Group A: 128 randomized/ 128 treated Group B: 132 randomized/ 132 treated Group C: 128 randomized/ 127 treated

Source: NDA 214846 Section 5.2 Tabulated Listing of all Clinical Studies
Abbreviations: PC, placebo-controlled; R, randomized; DB, double-blind; QD, daily; MC, multi-center; US, United States; UK, United Kingdom

Table 5: Study MVT-601-3002 - Summary

Trial Identifier NCT # # Study Sites - Country	**Trial Population**	**Trial Design Duration of Treatment**	**Primary Endpoint**	**Study Arm**	**Participants Randomized/ Participants Treated**
MVT-601-3002 NCT=03103087 67 (sites)-US 4-Belgium 4-Brazil 4-Chile 4-Czech Republic 7-Hungary 5-Poland 4-South Africa	Premenopausal women between 18 and 50 years old with heavy menstrual bleeding associated with uterine fibroids	Phase 3 MC PC R DB 24 weeks	Primary: Proportion of women in relugolix Group A versus placebo Group C who achieve an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method.	Drug:Group A: Relugolix 40 mg QD for 24 wks plus E2/NETA (1 mg/0.5 mg) QD for 24 wks Number treated: 128 Drug:Group B: Relugolix 40 mg QD for 12 wks plus placebo, followed by relugolix 40 mg QD plus E2/NETA (1 mg/0.5 mg) QD for 12 wks+E2/NETA Number treated: 132 Drug:GroupC: Placebo QD for 24 wks Number treated: 127	Group A: 126 randomized/ 125 treated Group B: 127 randomized/ 127 treated Group C: 129 randomized/ 129 treated

Source: NDA 214846 Section 5.2 Tabulated Listing of all Clinical Studies
Abbreviations: PC, placebo-controlled; R, randomized; DB, double-blind; QD, daily; MC, multi-center; US, United States

Table 6: Study MVT-601-3003 - Summary

Trial Identifier NCT # # Study Sites - Country	**Trial Population**	**Trial Design Duration of Treatment**	**Primary Endpoint**	**Study Arm**	**Participants Randomized/ Participants Treated**
MVT-601-3003 NCT= 03412890 106 sites-US 43 sites-Rest of world: EU, South America, Africa	Premenopausal women who completed MVT-601-3001 and MVT-601-3002	Phase 3 MC Single arm OLE 28 weeks	Safety Endpoints: Analysis of AEs, vital signs, clinical laboratory tests, ECG, endometrial biopsies, BMD Supportive Endpoints: There is supportive information for efficacy.	Drug: Relugolix 40 mg QD plus E2/NETA (1 mg/0.5 mg) QD for 28 wks	477 enrolled, 476 received Relugolix+E2/NETA Of these participants from studies MVT-601-3001 and MVT-601-3002: 163 originated from Group A (Relugolix+E2/NETA); 149 originated from Group B (Relugolix+delayed E2/NETA); 164 originated from Group C (placebo)

Source: NDA 214846 Section 5.2 Tabulated Listing of all Clinical Studies
Abbreviations: PC = placebo-controlled; R = randomized; DB = double-blind; QD = daily; MC = multi-center; US = United States; EU = European Union; OLE = open-label extension

Table 7: Study MVT-601-037 - Summary

Trial Identifier **# Study Sites - Country**	**Trial Population**	**Trial Design**	**Study Objective**	**Test Product**	**Participants Enrolled/Completed**
MVT-601-037 15 sites - US	Participants who completed MVT-601-3001 or MVT-601-3002 and had at least a 1-point improvement from baseline in PGA	Interviews of English-speaking patients as they complete their end of study visit of either MVT-601-3001 or MVT-601-3002	Objectives: Assess minimum meaningful improvement as perceived by patients on the UFS-QoL BPD subscale, pain NRS, PGA for symptoms/function, UFS-QoL revised activities subscale; assess 3-month recall; assess appropriateness of "distress"	N/A	31 enrolled/ 30 completed

Source: NDA 214846 Section 5.2 Tabulated Listing of all Clinical Studies
Abbreviations: PGA = Patient Global Assessment; UFS-QoL BPD = Uterine Fibroid Symptom and Health-Related Quality of Life Bleeding and Pelvic Discomfort subscale; NRS =Numerical Rating Scale

Table 8: Study MVT-601-034 - Summary

Trial Identifier NCT # **# Study Sites - Country**	**Trial Population**	**Trial Design Duration of Study**	**Study Objective**	**Test Product**	**Participants enrolled**
MVT-601-034 NCT=03744507 27 sites - US	Premenopausal women ages 18 to 50 years with uterine fibroids or endometriosis	Prospective Observational 52 weeks	Assess percent change from baseline to Week 52 in lumbar spine femoral neck and total hip BMD	N/A	262

Source: NDA 214846 Section 5.2 Tabulated Listing of all Clinical Studies
Abbreviations: BMD = bone mineral density

4.2. Review Strategy

The Phase 3 trials (Study 3001) and (Study 3002) as well as the 28-week uncontrolled extension trial (Study 3003) provided primary support for the efficacy and safety of R+E2/NETA for the management of HMB associated with uterine fibroids. The Applicant's Phase 2 study TAK-385/CCT-001 was reviewed in regard to dosage selection for relugolix. Dosage selection for this combination product had taken into account improvement in HMB in addition to mitigating safety concerns with relugolix, especially bone loss (for further details, see discussion of Dose Selection in Section 5.1.1).

The primary efficacy heavy menstrual bleeding endpoints (alkaline hematin determination) were assessed in Studies 3001 and 3002 for the to-be-marketed product versus placebo. Alkaline hematin quantitative analysis of HMB has been utilized in previous NDA submissions and is considered fit for purpose.

Ranked key secondary efficacy endpoints were reviewed for potential labeling claims. These secondary endpoints were reviewed in consultation with the Clinical Outcome Assessment (COA) team. The clinical and COA team reviewed past meeting recommendations as well as clinical results. Specifically, Study MVT-601-037 which provided results of an assessment in Patient Global Assessment (PGA) from baseline to end of treatment was reviewed as an anchor for other clinical outcomes.

This reviewer's approach to safety focused on the following:

- Review of safety findings for Studies 3001 and 3002 for the R+E2/NETA arm as compared to the placebo arm. The relugolix monotherapy (12 weeks) followed by combination therapy (12 weeks) arm was used primarily to compare changes in bone mineral density (BMD) with monotherapy to combination therapy. This arm also provided additional supportive safety information.
- Review of Study 3003 alone (open-label extension trial) for safety findings over an additional 28-week period. Review of BMD findings in this period was critical for the review.
- Review of a (b) (4)
- Review of pooled safety information from: 1) Study 3001 + Study 3002 and 2) Studies 3001, 3002 and 3003, as appropriate.
- Review of the 120-day safety update and additional information received from the Applicant in response to Agency information requests.

Section 4.1 provides a tabular summary of the key clinical trials conducted to support the benefit-risk assessment of R+E2/NETA. The key benefit and risk issues are addressed in Sections 5.1 and 7.5, respectively.

5. Review of Relevant Individual Trials Used to Support Efficacy

5.1. Review of Studies 3001 and 3002

The pivotal Phase 3 randomized, placebo-controlled trials for this application had identical study designs. The study titles only differed in that study number MVT-601-3001 was called LIBERTY 1 and study number MVT 601-3002 was called LIBERTY 2. Section 5.1.1 (Study Design) applies to both studies.

> LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids.
>
> LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids.

5.1.1. Study Design

Overview and Objective

The primary objective of these trials was to determine the safety, tolerability, and efficacy of R+E2/NETA compared with placebo for 24 weeks in the management of HMB associated with uterine fibroids.

Trial Design

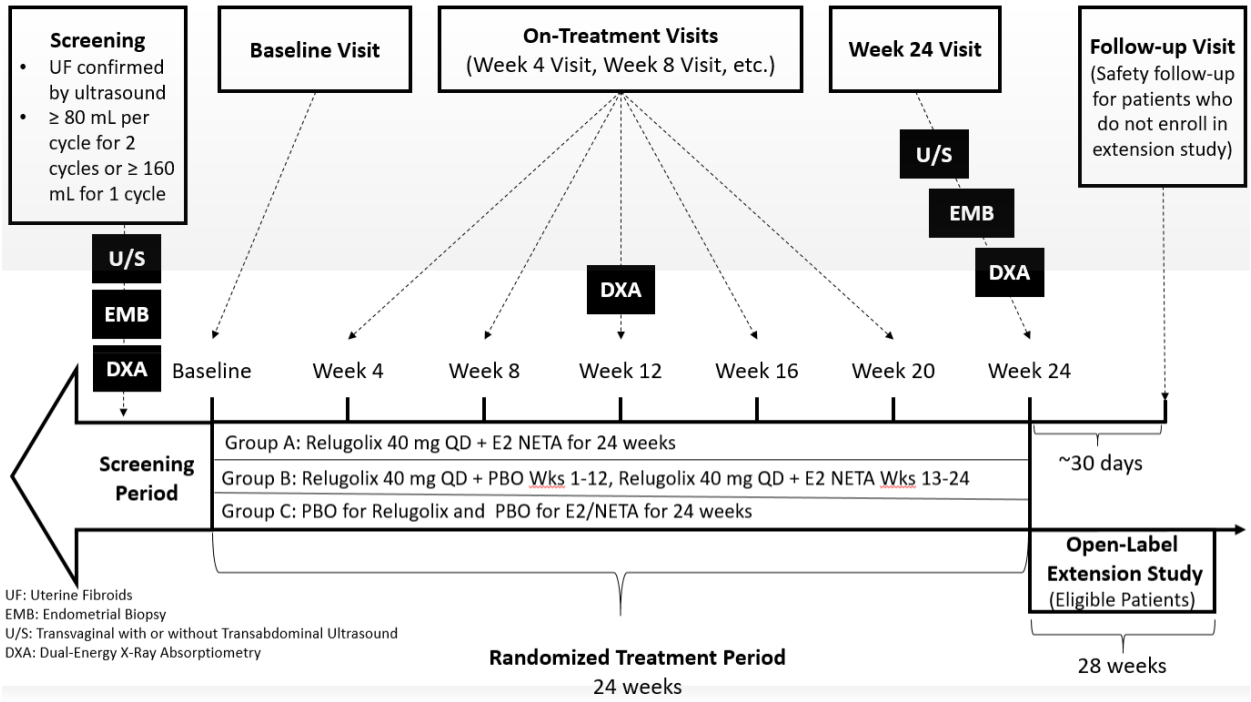
Both trials were multicenter, double-blinded, randomized, placebo-controlled studies. In both trials, a 1:1:1 randomization ratio was used for allocating eligible patients to three study treatment regimens:

- Relugolix 40 mg tablet co-administered orally with E2 1 mg and NETA 0.5 mg capsule (R+E2/NETA)
- Relugolix 40 mg tablet with E2/NETA placebo capsule orally for 12 weeks followed by relugolix 40 mg tablet co-administered orally with E2 1 mg and NETA 0.5 mg capsule for 12 weeks [R+delayed E2/NETA (delE2/NETA)]
- Relugolix placebo tablet co-administered orally with E2/NETA placebo capsule

The total duration of both trials was 24 Weeks. The trials had scheduled visits occurring at Screening, Baseline (Day 1), and every 4 weeks until Week 24 (Study Design Schema in Figure 1). Randomization was stratified by mean screening MBL volume (< 225 mL versus ≥ 225 mL) and by geographic region (North America versus Rest of World). The trial design was found

acceptable.

Figure 1: Study Design Schema



Source: Figure 4-1 of Protocol Amendment 2, Study 3001 and 3002. Abbreviations: E2 = estradiol; NETA = norethindrone acetate; PBO = placebo; QD = once a day; Wks = weeks; U/S = ultrasound; EMB = endometrial biopsy; DXA = dual-energy X-ray absorptiometry

Key Eligibility Criteria

Inclusion Criteria:

1. Voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Had regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least three months prior to the screening 1 visit;
4. Had a diagnosis of uterine fibroids that was confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid had to be verified by a central reader to meet at least one of the following criteria:
    a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or
    b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3
5. Had heavy menstrual bleeding associated with uterine fibroids as evidenced by an MBL volume of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as

measured by the alkaline hematin method during the screening period.
6. Had a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits.
7. Agreed to use non-hormonal contraception during the study and for 30 days following the last dose of study drug.

Exclusion Criteria:

1. Had transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could have been responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;
2. Had known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Had undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the screening 1 visit;
4. Had a weight that exceeded the weight limit of the dual-energy x-ray absorptiometry (DXA) scanner or had a condition that precluded an adequate DXA measurement at the lumbar spine and proximal femur (e.g., bilateral hip replacement or spinal hardware in the lumbar spine);
5. Had a baseline BMD Z-score < -2.0 at spine, total hip, or femoral neck;
6. Had a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face, and ankle fractures were allowed). Patients whose hyperparathyroidism or hyperthyroidism had been successfully treated or whose hyperprolactinemia had been successfully treated and/or who met BMD eligibility criteria for the study were allowed.
7. Had history of use of any medication other than calcium or vitamin D preparations to treat BMD loss;
8. Had any contraindication to treatment with low-dose estradiol and norethindrone acetate.
9. Had any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8 g/dL;
    b. Alanine aminotransferase (ALT)or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2;
    d. Hypocalcemia or hypercalcemia;
    e. Hypophosphatemia or hyperphosphatemia.
10. Had clinically significant cardiovascular disease or history of other clinically significant condition including, but not limited to:
    a. Untreated thyroid dysfunction;
    b. History of malignancy within the past 5 years;
    c. Any current psychiatric disorder that would impair the ability of the patient to

participate in the study or would impair interpretation of their data;
d. Had systemic autoimmune disease.
11. Was currently pregnant or lactating, intended to become pregnant during the study period through one month after the last dose of study drug;
12. Was currently using any prohibited medications;
13. Had a contraindication or history of sensitivity to any of the study treatments or components thereof;
14. Had received a blood transfusion within eight weeks prior to Screening Visit 1 or during the screening period;

Drug Class of Prohibited Medications

Drug class of prohibited medications includes bisphosphonates; GnRH analogues; anti-androgens; anti-convulsant drugs; aromatase inhibitors; progestins and progestin implants; estrogens; hormonal contraceptives, contraceptive patches and vaginal rings; selective estrogen receptor modulators; selective progesterone receptor modulators; over the counter and herbal products/teas with known hormonal activity; intrauterine devices; bone agents; anti-coagulants/platelets/fibrinolytics; glucocorticoids; p-glycoprotein inducers.

Study Endpoints

The primary efficacy endpoint of these trials was the proportion of responders at Week 24. Responders are women with an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment.

The two trials had the following key secondary efficacy endpoints:

1. Proportion of women who achieved amenorrhea over the last 35 days of treatment
2. Percent change from baseline to Week 24 in MBL volume
3. Change from baseline to Week 24 in Bleeding and Pelvic Discomfort (BPD) scale score as measured by the UFS-QoL (Question 1, Question 2, Question 5)
4. Proportion of women who achieved a maximum NRS score ≤ 1 for uterine fibroids associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization
5. Proportion of women with a hemoglobin ≤10.5 g/dL at baseline who achieved an increase of ≥2 g/dL from baseline at Week 24
6. Percent change from baseline to Week 24 in uterine fibroid volume
7. Percent change from baseline to Week 24 in uterine volume.

Reviewer's comment: Late in the development cycle of this product, the Applicant amended the statistical analysis plan (SAP) for Study 3002 changing the hierarchy of the secondary endpoints. In the SAP for Study 3002, the hemoglobin endpoint became the fourth key secondary endpoint and the NRS pain endpoint became the fifth endpoint in the hierarchy. See Key Benefit Review Issue #5 in Section 5.1.3 Key Review Issues Relevant to Evaluation of Benefit for further details.

Dose Selection

The Applicant selected the combination of relugolix 40 mg, E2 1 mg and NETA 0.5 mg for their Phase 3 uterine fibroid program.

The selection of the relugolix 40 mg dose was based on the following:

- Phase 1 single ascending dose (1 mg to 80 mg) and multiple dose escalation study (10-80 mg daily doses over 14 days) that demonstrated maximal suppression of E2 levels with 40 mg, and

- Phase 2 randomized, double-blind, placebo-controlled studies of 12 to 24 weeks in the uterine fibroid and endometriosis development programs investigating relugolix doses of 10 mg, 20 mg and 40 mg, that demonstrated dose-dependent reductions in HMB associated with uterine fibroids based on Pictorial Blood Loss Assessment Chart (PBAC) scores and reduction in endometriosis-associated pain, respectively. A dose-dependent decline in bone mineral density and increase in vasomotor symptoms was also *observed.*

The selection of E2 1mg and NETA 0.5 mg to mitigate bone loss and vasomotor symptoms was based on the following:

- Clinical data that supported the approval of Activella® (E2 1mg/NETA 0.5 mg fixed dose combination therapy) for the treatment of moderate to severe vasomotor symptoms (NDA 020907) and prevention of osteoporosis.

- A pharmacokinetic/pharmacodynamic (PK/PD) study (Study MVT-601-1001) of 6-weeks duration in healthy premenopausal women that demonstrated that the addition of E2 1mg/NETA 0.5 mg to relugolix 40 mg maintained E2 concentrations in the Applicant's target range of 20 to 50 pg/mL over a 24-hour dosing interval and reduced vasomotor symptoms as compared to relugolix 40 mg monotherapy. Additionally, the addition of E2/NETA to relugolix monotherapy blunted the increase in bone resorption markers (N-telopeptide and C-telopeptide) observed with relugolix monotherapy.

Statistical Analysis Plan

<u>Key Points from SAP Interaction with the Applicant</u>
The following are key decisions reached after discussion with the Applicant regarding efficacy analysis in the SAP. Details of discussion are found in Section 5.1.3 Key Review Issues Relevant to Evaluation of Benefit or the Biostatistical Review in DARRTS dated May 10, 2021.

1. Exclusion of data from closed Site 1152 from efficacy analysis of the primary and key secondary endpoints and inclusion of data from Site 1152 in safety analysis.
2. Amendment of the SAP for Study 3002 after the unblinding of Study 3001 and prior to unblinding of Study 3002 to reverse the hierarchal order of key secondary endpoints #4 hemoglobin and #5 pain NRS.

3. The use of the mixed-effects model approach to impute missing data in analysis of the primary efficacy endpoint.
4. The use of the mixed-effects model approach to impute missing data in analysis of the key secondary hemoglobin endpoint.
5. Exclusion [redacted] (b) (4)
6. Designation of BMD as a safety endpoint [redacted] (b) (4) and placement in Section 6 Adverse Reactions of the drug label.
7. The provision of confidence intervals in statistical analyses for each endpoint in which an inferential claim was made.

Analysis Populations

The following analysis populations were defined in the SAP:

- The safety population: Includes all treated participants (participants who received at least one dose of the study medications).
- The intent-to-treat (ITT): Includes all randomized participants.
- The modified intent-to-treat (mITT): Includes all randomized and treated participants
- The per-protocol (PP): Includes all randomized and treated participants who do not have protocol deviations that impact the primary efficacy variable.

Sample Size Calculation

In each trial, the Applicant planned to enroll a total of 390 participants. This sample size will provide approximately 99% power to detect a 30% difference in responder rates between R + E2/NETA and placebo. This calculation assumes that the tests will be conducted at 2-sided alpha level of 0.05 based on a chi-square test; a responder rate of 25% in the placebo group and a dropout rate of 20%.

Reviewers' Comments:
Study 3001 enrolled 388 participants [R+E2/NETA (N=128), R+delE2/NETA (N=132), and Placebo (N=128)]. Similarly, in Study 3002, 382 participants [R+E2/NETA (N=126), R+delE2/NETA (N=127), and Placebo (N=129)] were enrolled. For MVT-601-3001, the safety population included 387 participants R+E2/NETA (N=128), R+delE2/NETA (N=132), and Placebo (N=127)]. The difference in the placebo arm is explained by Participant [redacted] (b) (6) who was randomized to placebo but was recorded as discontinued prior to receiving treatment. In Study 3002, 381 participants [R+E2/NETA (N=126), R+delE2/NETA (N=126), and Placebo (N=129)] were included in the safety population. The difference from the ITT population is explained by the following participants: Participant [redacted] (b) (6) was enrolled in the R+E2/NETA group but did not received treatment due to a randomization error before eligibility was confirmed. Participant [redacted] (b) (6) was randomized to the R+del E2/NETA arm, received relugolix monotherapy for the first four weeks, and then received R+E2/NETA for the remainder of Study 3002. This participant was recorded as a participant in R+ E2/NETA arm for the safety analysis.

Handling of Missing Data

For participants with treatment ≥ 4 weeks, the responder status was determined based on the observed MBL data (for those who had complete information) or using imputed data from a mixed-effects model if data was missing. Participants with < 4 weeks of treatment who withdrew from the study prematurely due to lack of efficacy or withdrew prematurely to undergo surgical intervention for uterine fibroids were considered non-responders.

To account for missing data and define responder status, the Applicant took the duration of treatment exposure, the feminine product (FP) return rate, eDiary entry, and reasons for no FP collection into consideration. Participants who recorded no FP collection but reported amenorrhea, spotting, or negligible bleeding confirmed by eDiary entry were imputed as responders. Full details of handling of missing data and derivation of responder status are described in the Biostatistics Review in DARRTS dated May 10. 2021.

Analysis of the Primary Efficacy Endpoint

The primary efficacy analyses in both trials provided the treatment difference in the proportion of participants with an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment and the corresponding 2-sided 95% confidence interval (CI). The CIs were computed using the Cochran–Mantel–Haenszel (CMH) weighted method with the baseline MBL volume (< 225 mL versus ≥ 225 mL) and geographic region (North America versus Rest of World) used as stratification factors. The primary efficacy analysis was conducted based on the mITT population.

Participants who discontinued the study due to lack of efficacy or those who required surgical intervention for uterine fibroids were considered as non-responders in the primary efficacy analysis. A conclusion that R+ E2/NETA is superior to placebo is made if the lower bound for the 2-sided 95% confidence interval (CI) for the difference in proportions is greater than 0%. See Biostatistics Review in DARRTS dated May 10, 2021 for additional details on comparisons of the key secondary endpoints to placebo.

Analysis of the Key Secondary Efficacy Endpoints

As stated earlier, the trials had seven key secondary efficacy endpoints. The analysis of the binary secondary efficacy endpoints (amenorrhea, NRS pain score, hemoglobin) was conducted using the CMH based approach that was used for the primary efficacy analysis. For the secondary efficacy endpoints percent change in MBL volume and change in BPD scale score, which evaluated the change (absolute or % change) from baseline to Week 24, treatment comparisons were performed using a mixed model repeated measures approach. The model included treatment, visit, randomization stratification factors and treatment by visit interactions as fixed effects, and an unstructured variance-covariance matrix was used to account for within participant correlation. For the secondary efficacy endpoints uterine fibroid volume and uterine volume, an analysis of covariance (ANCOVA) model with treatment, randomization stratification factors and baseline value included as covariates was used.

Protocol Amendments

There were two amendments to the protocol for the replicate Studies 3001 and 3002. The purpose of the amendments was to simplify screening procedures; modify study eligibility requirements and the frequency of study procedures; clarify entrance of participants into the extension Study 3003 and follow-up assessments for those not entering the extension study; and modify secondary efficacy endpoints related to disease symptoms and impact on quality-of -life. Significant amendment changes included:

1. Requirement of additional safety procedures in patients not continuing into the extension Study 3003 such as:
    a. Contacting patients whose menses had not returned as of the Follow-up visit.
    b. Repeating endometrial biopsy in 3 to 6 months if biopsy at Week 24/Early Termination visit had findings of endometrial hyperplasia or endometrial cancer and contacting patients to obtain information about treatment the patient may have had for those conditions.
    c. Follow-up DXA scan for patients with a BMD loss of > 2% in 6 months after discontinuing study drug.
2. Modification of study eligibility by:
    a. Excluding patients with hypercalcemia/hypocalcemia or hyperphosphatemia/hypophosphatemia.
    b. Excluding patients with autoimmune disease.
    c. Excluding patients known to have rapidly enlarging uterine fibroids.
    d. Excluding patients who have migraine with aura or history of porphyria.
3. Removal of protocol references to analyses based on cut-offs for T-scores to align with the SAP.
4. Notification of Investigator by central radiology if 7% or greater decline in BMD at any time point to assess for patient withdrawal and future management.
5. Central reading of Papanicolaou test and endometrial biopsy specimens.
6. Requirements changed to recommendations for medication allowed for uterine fibroid pain, and restrictions on analgesics for other pain conditions removed.
7. Allowance of the use of calcium and vitamin D by trial participants.

5.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that pivotal studies 3001 and 3002 and extension study 3003 were conducted in accordance with the International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, applicable participant privacy requirements, and ethical principles that have their origin in the Declaration of Helsinki.

Financial Disclosure

Financial disclosures support the validity and reliability of the data generated to support the

proposed indication. Please see details in Appendices Section 12.2.

Patient Disposition

In Study 3001, 2279 participants were screened, and 388 were randomized (17.0%). Of the 388 randomized participants, 387 were treated. Of those treated, 62.9% continued into the 28-week open-label extension Study 3003 including 60.9% from the R+E2/NETA group, 59.8% from the R+delE2/NETA group, and 68.0% from the placebo group.

In Study 3002, 2899 participants were screened, and 382 were randomized (13.2%). Of the 382 randomized participants, 381 were treated. Of those treated, 60.8% continued into the open-label extension study including 67.5% from the R+E2/NETA group, 55.1% from the R+delE2/NETA group, and 59.7% from the placebo group.

The disposition of all randomized participants and reasons for premature discontinuation during the treatment period for Studies 3001 and 3002 are presented in Table 9. The proportion of participants who discontinued treatment prior to 24 weeks ranged from 17.2% to 22.8% across all treatment groups of both studies. The most common reasons for premature discontinuation across treatment groups were AE(s) and "Withdrawal by Patient." A greater proportion of participants in the R+delE2/NETA groups of each study discontinued the studies due to AE(s) compared with the R+E2/NETA and placebo groups. A greater proportion of participants in the R+E2/NETA groups of both studies prematurely discontinued treatment due to "Withdrawal by Patient" than in the R+delE2/NETA and placebo groups. An Information Request was sent to the Applicant on August 13, 2020 to provide reasons for discontinuation of treatment characterized by "Withdrawal by Patient" and "Other" categories. "Withdrawal by Patient" reasons for premature discontinuation were largely personal such as related to participants' employment, families, or relocation. The "Other" category reasons were mostly due to participants' noncompliance with study conduct. Relatively few participants withdrew prematurely to have surgery related to uterine fibroids.

Table 9: Patient Disposition

	MVT-601-3001			MVT-601-3002		
	R+E2/NETA	**R+del E2/ NETA**	**Placebo**	**R+E2/NETA**	**R+del E2/ NETA**	**Placebo**
Randomized	128	132	128	126	127	129
Treated[1]	128 (100%)	132 (100%)	127 (99.4%)	125 (99.2%)	127 (100%)	129 (100%)
Completed the Week 24	100 (78.1%)	103 (78.0%)	105 (82.0%)	102 (81.0%)	98 (77.2%)	102 (79.1%)
Discontinued the Study[2]	28 (21.9%)	29 (22.0%)	22 (17.2%)	23 (18.3%)	29 (22.8%)	27 (20.9%)
Reason for Participant Withdrawal						
Adverse Event(s)	7 (5.5%)	18 (3.6%)	5 (3.9%)	2 (1.6%)	15 (11.8%)	6 (4.7%)
Lack of Efficacy	4 (3.1%)	0 (0.0%)	3 (1.0%)	2 (1.6%)	1 (0.8%)	1 (0.8%)
Lost to Follow-Up	1 (0.8%)	5 (3.8%)	5 (3.9%)	4 (3.2%)	2 (1.6%)	7 (5.4%)
Withdrawal by Patient	10 (7.8%)	3 (2.3%)	7 (5.5%)	13 (10.3%)	6 (4.7%)	6 (4.7%)
Protocol Deviation	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (1.6%)	1 (0.8%)
Other	5 (3.9%)	3 (2.3%)	1 (0.8%)	1 (0.8%)	3 (2.4%)	5 (3.9%)
Pregnancy	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)

Source: Adapted from Figure 3 of the Applicant's Clinical Study Reports. Participants from closed Site 1152 are included in these summaries.
[1] Included in the mITT population.
[2] Discontinued the Study before Week 24.

Protocol Violations/Deviations

Important protocol deviations in Study 3001 numbered 39 (30.5%), 38 (28.8%), 34 (26.8%) in the R+E2/NETA, R+delE2/NETA, and placebo groups, respectively. The most common important protocol deviations in Study 3001 were missed key study procedures which were recorded when patient missed or declined required end-of-treatment assessments involving 23 (18.0%), 26 (19.7%), and 22 (17.3%) participants in the R+E2/NETA, R+delE2/NETA, and placebo groups, respectively. The most missed assessments included endometrial biopsies and DXA scans.

Important protocol deviations in Study 3002 numbered 40 (32.0%), 39 (30.7%), 40 (31.0%) in the R+E2/NETA, R+delE2/NETA, and placebo groups, respectively. The most common important protocol deviations in Study 3002 were also missed key study end-of-treatment procedures involving 25 (20.0%), 25 (19.7%), and 30 (23.3%) participants in the R+E2/NETA, R+delE2/NETA, and placebo groups, respectively. The most missed assessments included endometrial biopsies and transvaginal ultrasounds.

Despite the protocol deviations, the Applicant's sensitivity analysis results and supplemental analysis results conducted by the statistical reviewer, were consistent with the findings from the primary efficacy analyses. See the Biostatistical Review in DARRTS dated May 10, 2021.

Table of Demographic Characteristics

Table 10 demonstrates the baseline demographics and disease characteristics of the study population. The characteristics appear well-balanced among the treatment arms in both trials. A larger proportion of participants in all arms were older than 40 years with an average age of

around 42 years. Both trials enrolled a higher proportion of White and Black study participants compared with fewer Asian and women of other races. The majority of participants were enrolled in study sites located within the US and Canada (North American region).

Table 10: **Baseline Demographic and Clinical Characteristics**

	Study 3001			Study 3002		
	R+E2/NETA N=128	**R+delE2 /NETA N=132**	**Placebo N=127**	**R+E2/NETA N=125**	**R+delE2/ NETA N=127**	**Placebo N=129**
Age (years) Mean (SD)	42.5 (4.99)	41.3 (5.39)	42.2 (5.7)	42.4 (5.38)	42.1 (5.25)	41.8 (5.26)
Age Categories						
<40 years	30 (23.4%)	49 (37.1%)	36 (28.3%)	32 (25.6%)	39 (30.7%)	42 (32.6%)
≥40 years	98 (76.6%)	83 (62.9%)	91 (71.7%)	93 (74.4%)	88 (69.3%)	87 (67.4%)
Geographic Region						
North America	98 (76.6%)	101 (76.5%)	98 (77.2%)	93 (74.4%)	94 (74.0%)	96 (75.4%)
Rest of World	30 (23.4%)	31 (23.5%)	29 (22.8%)	32 (25.6%)	33 (26.0%)	33 (25.6%)
Race						
American Indian	2 (1.6%)	5 (3.8%)	1 (0.8%)	0 (0.0%)	2 (1.6%)	1 (0.8%)
Asian	0 (0.0%)	2 (1.5%)	2 (1.6%)	0 (0.0%)	3 (2.4%)	1 (0.8%)
Black/African American	59 (46.1%)	67 (50.8%)	65 (51.2%)	62 (49.6%)	66 (52.0%)	74 (57.4%)
Native Hawaiian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	64 (50.0%)	53 (40.2%)	56 (44.1%)	58 (46.4%)	50 (39.4%)	49 (38.0%)
Other	2 (1.6%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	2 (1.6%)	3 (2.3%)
Multiple	1 (0.8%)	4 (3.0%)	2 (1.6%)	1 (0.8%)	1 (0.8%)	0 (0.0%)
Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.4%)	3 (2.4%)	1 (0.8%)
Ethnicity						
Not Hispanic or Latino	92 (71.9%)	99 (75.0%)	103 (81.1%)	105 (84.0%)	91 (71.7%)	96 (74.4%)
Hispanic or Latino	34 (26.6%)	33 (25.0%)	23 (18.1%)	18 (14.4%)	34 (26.8%)	32 (24.8%)
Not reported	2 (1.6%)	0 (0.0%)	1 (0.8%)	2 (1.6%)	2 (1.6%)	1 (0.8%)
BMI (kg/m2)						
Mean (SD)	31.4 (7.6)	31.3 (7.3)	32.3 (7.5)	31.0 (6.6)	30.8 (5.7)	32.1 (7.6)
Median	30.3	31.0	31.1	31.4	30.4	30.8
Min, Max	17.0, 62.8	19.3, 52.0	19.4, 54.7	17.3, 48.8	19.1, 50.4	16.0, 60.1
MBL volume (mL)						
Mean (SD)	239.4 (180.2)	228.8 (159.6)	218.8 (125.0)	246.7 (186.0)	227.4 (134.3)	211.75 (129.9)
Median	193.5	193.5	185.67	184.1	192.8	177.4
Min, Max	88.3, 1365.1	81.2, 1036.5	84.7, 754.5	88.5,1045.5	87.6, 800.2	85.5, 839.6
MBL volume (mL)						
<225	84 (65.6%)	86 (65.2%)	85 (66.9%)	80 (64.0%)	80 (63.0%)	86 (66.7%)
≥225	44 (34.4%)	46 (34.8%)	42 (33.1%)	45 (36.0%)	47 (37.0%)	43 (33.3%)
Hemoglobin (g/dL)						
Mean (SD)	11.24 (1.56)	11.13 (1.65)	11.40 (1.36)	11.34 (1.46)	11.10 (1.63)	11.05 (1.57)
Min, Max	7.3, 14.9	6.1, 15.7	8.0, 14.6	7.9, 15.0	7.0, 15.4	7.3, 14.6
Hemoglobin < 10.5 (g/dL), n (%)	41 (32.0%)	43 (32.6%)	28 (22.0%)	39 (31.2%)	43 (33.8%)	46 (35.7%)
Index uterine fibroid volume (cm^3)						
n	127	131	127	125	127	129
Mean (SD)	71.9 (128.1)	93.8 (143.8)	71.8 (124.0)	73.7 (126.7)	78.9 (157.5)	74.1 (123.0)
Median	24.2	37.9	27.8	29.2	37.2	31.4
Min, Max	1.5, 989.0	1.0, 904.2	0.8, 1031.2	2.2, 944.0	0.8, 1378.3	1.3, 866.5
Uterine volume (cm^3)						
n	127	132	127	125	127	129
Mean (SD)	379.1 (316.8)	469.9 (427.9)	397.8 (324.8)	387.7 (344.0)	402.6 (371.1)	407.8 (402.0)
Median	265.1	329.9	293.2	274.3	266.8	295.9
Min, Max	56.6, 1580.1	46.5, 2555.6	65.5, 2015.1	79,4, 1907.6	52.3, 2381.8	58.2, 2625.0

Source: Source: Table 7.1.4.1 of the Study Reports. Participants from the closed Site 1152 included in these summaries.
Note: n= number of patients included in summary statistics for index uterine fibroid volume and uterine volume

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed by pill counts. In Study 3001, over 80% of patients in each treatment arm had an overall compliance rate of ≥ 80% to ≤ 100%. In Study 3002, over 76% of patients in each treatment arm had an overall compliance rate of ≥ 80% to ≤ 100%. According to the Applicant, there were no meaningful differences observed between treatment groups in the mean overall compliance rate.

During Study 3001, 374 patients (96.6%) took concomitant meds. The most commonly used medication was ibuprofen taken by 242 (62.5%) patients [76 (59.4%), 74 (56.1%), and 92 (72.4%) in the R+E2/NETA, R+delE2/NETA, and placebo groups, respectively]. Other concomitant medications taken in all treatment arms included: Ferrous sulfate 107 (27.6%), paracetamol 75 (19.4%), iron 60 (15.5%), vitamin D NOS (not otherwise specified) 51 (13.2%), vitamins NOS 46 (11.9%), and cholecalciferol 41 (10.6%).

A similar pattern was observed in Study 3002 with 360 patients (94.5%) taking concomitant medications. The most commonly used medication was ibuprofen taken by 242 (62.2%) patients [80 (63.5%), 76 (60.3%), and 81 (62.8%) in the R+E2/NETA, R+delE2/NETA, and placebo groups, respectively]. Other concomitant medications taken in all treatment arms included: Ferrous sulfate 98 (25.7%), iron 72 (18.9%), paracetamol 77 (20.2%), vitamins NOS 45 (11.8%), vitamin D NOS 44 (11.5%), and cholecalciferol 39 (10.2%).

Per protocol, all patients with a hemoglobin concentration ≥ 8 g/dL and ≤ 10 g/dL at baseline were required to receive iron supplementation to be eligible for the study. Supplementation with calcium and vitamin D was permitted but not required during the study.

The Applicant permitted analgesics to be used during the studies for uterine fibroid-associated pain as follows to evaluate the effects of R+E2/NETA on the secondary endpoint of uterine fibroid-related pain:

- First-line: ibuprofen
- Second-line: non-ibuprofen non-steroidal anti-inflammatory drug or acetaminophen
- Third-line: opioid or opioid-acetaminophen combination
- Fourth-line: Investigator discretion.

Reviewer's comment: These medications; however, were not clearly defined as rescue medications with parameters of quantity, timing, or dosage in relation to pain. The Applicant also did not clearly define the conditions under which analgesics should be used or what represented an increase, decrease, or no change in medication use. Further discussion of the uterine fibroid-associated pain endpoint is found in Section 5.1.1 Study Design, Section 5.1.2 Study Results, and Section 5.1.3 Key Review Issues Relevant to Evaluation of Benefit: Key Benefit Review Issue #3.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint is the percentage of responders defined as participants with an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment at Week 24; and evaluated in the mITT population for the primary analysis. The review team was able to replicate the Applicant's analysis of the primary efficacy endpoint. In both trials, the lower bound of the 95% CI for the treatment difference is greater than zero. Therefore, the results in both trials support a conclusion of superiority of R+E2/NETA over placebo. The secondary and sensitivity analyses all show similar robust findings and demonstrate the efficacy of R+E2/NETA in patients with HMB associated with uterine fibroids.

Table 11 summarizes the results of the primary efficacy endpoint. For MVT-601-3001, the responder rate is 72.1% for R+E2/NETA and 16.8% for placebo resulting in a treatment difference (95% CI) of 55.3% (44.2%, 65.6%). For MVT-601-3002, the responder rate is 71.2% for R+E2/NETA and 14.7% for placebo resulting in a treatment difference (95% CI) of 56.5% (46.6%, 66.5%).

Table 11: Percentage of Responders at Week 24

	Treatments		Difference (95% CI)
	R+E2/NETA	Placebo	
Study 3001	88 /122 (72.1%)	19 /113 (16.8%)	55.3% (44.2%, 65.6%)
Study 3002	89 /125 (71.2%)	19/129 (14.7%)	56.5% (46.6%, 66.5%)

Source: Adapted from Table 6 of the Sponsor's response to information request sent on 02/08/2021 (Study 3001); Table 7.2.1.1 of the Study reports (Study3002). Participants from closed Site 1152 excluded from analysis.

For detailed analysis of the primary efficacy endpoint, see the Biostatistical Review in DARRTS dated May 10, 2021.

Data Quality and Integrity

The Applicant's primary and sensitivity analyses and the statistical reviewer's additional analysis establish the efficacy of R+E2/NETA over placebo in reducing HMB. Data from Site 1152 were excluded from efficacy analysis due to the site being closed by the Applicant with notification of the Agency just after NDA submission. The safety data were included in the safety analysis. See Key Benefit Review Issue #1 in Section *5.1.3* Key Review Issues Relevant to Evaluation of Benefit.

Efficacy Results – Secondary and other relevant endpoints

Tables 12 and 13 summarize the results of the key secondary efficacy endpoints for Studies 3001 and 3002. Because the confidence intervals for the treatment differences excluded zero, statistically significant differences in favor of R+E2/NETA are observed in six of the seven key secondary efficacy endpoints. The treatment difference for the comparison of the percent change from baseline to Week 24 in uterine fibroid volume did not meet the threshold for statistical significance.

Table 12: Summary of Key Secondary Efficacy Endpoints (Study 3001)

Ranking	Endpoints	Treatments		
		R+E2/NETA	Placebo	Difference (95% CI)
1	Proportion of women who achieved amenorrhea over the last 35 days of treatment	61/122 (50.0%)	7/113 (6.2%)	43.8% (33.9%, 53.7%)
2	Percent change from baseline to Week 24 in MBL volume [mean (SD)]	-82.0 (5.09)	-19.1 (5.2)	-62.9 (-76.4, -49.4)
3	Change from baseline to Week 24 in UFS-QoL BPD scale score as measured by UFS-QoL (Q1, Q2, Q5) [mean (SD)]	-44.1 (3.13)	-16.4 (3.24)	-27.7 (-35.7, -19.7)
4	Proportion of women with hemoglobin level ≤10.5g/dL at baseline who achieved an increase of >2 g/dL from baseline at Week 24 (based on mixed-effects model approach)	19/43 (44.2%)	5/29 (17.2%)	27.0% (6.7%, 47.2%)
5	Proportion of women who achieved a maximum NRS score ≤1 for uterine fibroid-associated pain over the 35 days of treatment in the subset of women with a maximum pain score ≥4 during the 35 days prior to randomization	25/55 (41.8%)	7/61 (11.5%)	30.3% (15.1%, 45.6%)
6	Percent change from baseline to Week 24 in primary uterine fibroid volume [mean (SD)]	-12.6 (5.95)	-0.01 (6.19)	-12.6 (-27.7, 2.52)
7	Percent change from baseline to Week 24 in uterine volume [mean (SD)]	-12.9 (3.21)	2.2 (3.37)	-15.1 (-23.3, -6.9)

Source: Adapted from Table 6 of the Sponsor's response to information request sent on 02/08/2021. Participants from closed Site 1152 excluded from analysis. Mean: Least-squares means; SD: Standard deviation.

Table 13: Summary of Key Secondary Efficacy Endpoints (MVT-601-3002)

Ranking	Endpoints	Treatments		
		R+E2/NETA	Placebo	Difference (95% CI)
1	Proportion of women who achieved amenorrhea over the last 35 days of treatment	63/125 (50.4%)	4/129 (3.1%)	47.3% (38.0%, 56.6%)
2	Percent change from baseline to Week 24 in MBL volume [mean (SD)]	-84.3 (5.45)	-15.1 (5.47)	-69.2 (-84.1, -54.3)
3	Change from baseline to Week 24 in UFS-QoL BPD scale score as measured by UFS-QoL (Q1, Q2, Q5) [mean (SD)]	-51.7 (2.89)	-18.3 (2.93)	-33.4 (-41.2, -25.5)
4	Proportion of women who achieved a maximum NRS score ≤1 for uterine fibroid-associated pain over the 35 days of treatment in the subset of women with a maximum pain score ≥4 during the 35 days prior to randomization	32/68 (47.1%)	14/82 (17.1%)	30.0% (15.6%, 44.4%)
5	Proportion of women with hemoglobin level ≤10.5g/dL at baseline who achieved an increase of >2 g/dL from baseline at Week 24 (based on mixed-effects model approach)	22/40 (55.0%)	3/53 (5.7%)	49.3% (32.7%, 66.0%)
6	Percent change from baseline to Week 24 in primary uterine fibroid volume [mean (SD)]	-17.4 (5.9)	-7.4 (5.92)	-10.0 (-25.8, 5.8)
7	Percent change from baseline to Week 24 in uterine volume [mean (SD)]	-13.8 (3.4)	-1.5 (3.37)	-12.2 (-21.3, -3.2)

Source: Adapted from Table 6 of the Sponsor's response to information request sent on 02/08/2021. Participants from closed Site 1152 excluded from analysis. Mean: Least-squares means; SD: Standard deviation.

Reviewer's comment: Three (b) (4) *key secondary endpoints were determined adequate to support labeling claims:*

1. *Proportion of women who achieved amenorrhea over the last 35 days of treatment.*
2. *Percent change from baseline to Week 24 in MBL volume.*
3. *Proportion of women with hemoglobin level* ***≤10.5g/dL*** *at baseline who achieved an increase of >2 g/dL from baseline at Week 24.*

(b) (4)

(b) (4)

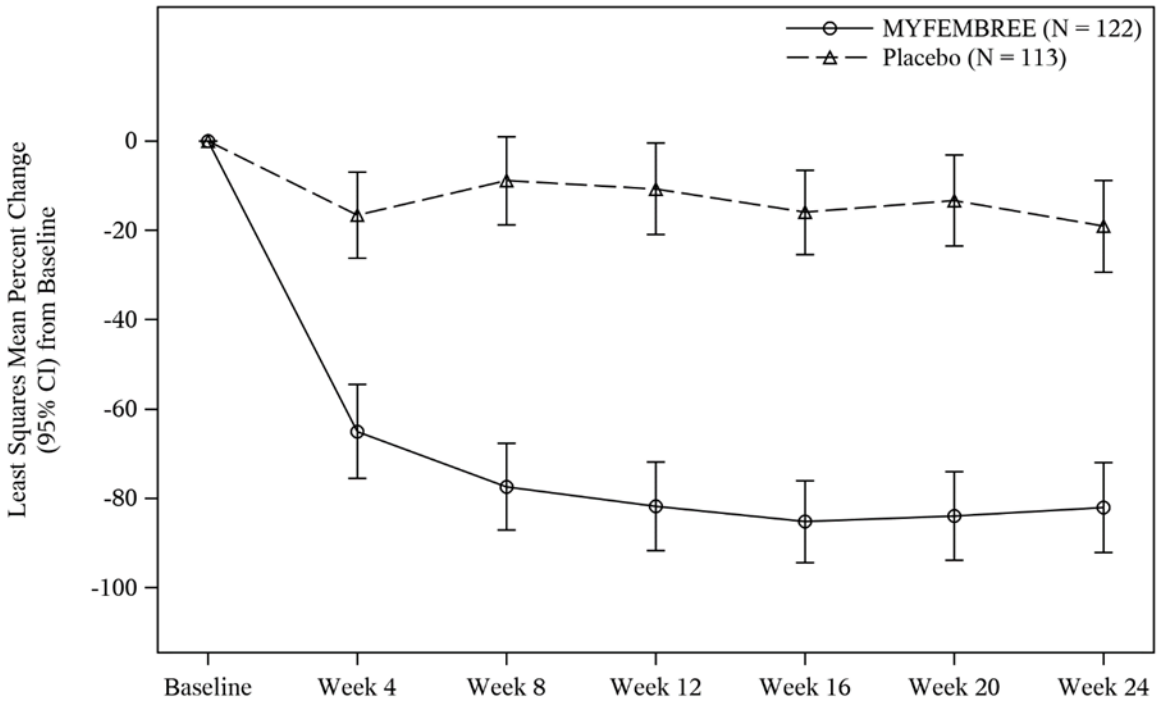
(b) (4)

For detailed analysis of the seven key secondary efficacy endpoints, see the Biostatistical Review in DARRTS dated May 10, 2021.

Durability of Response

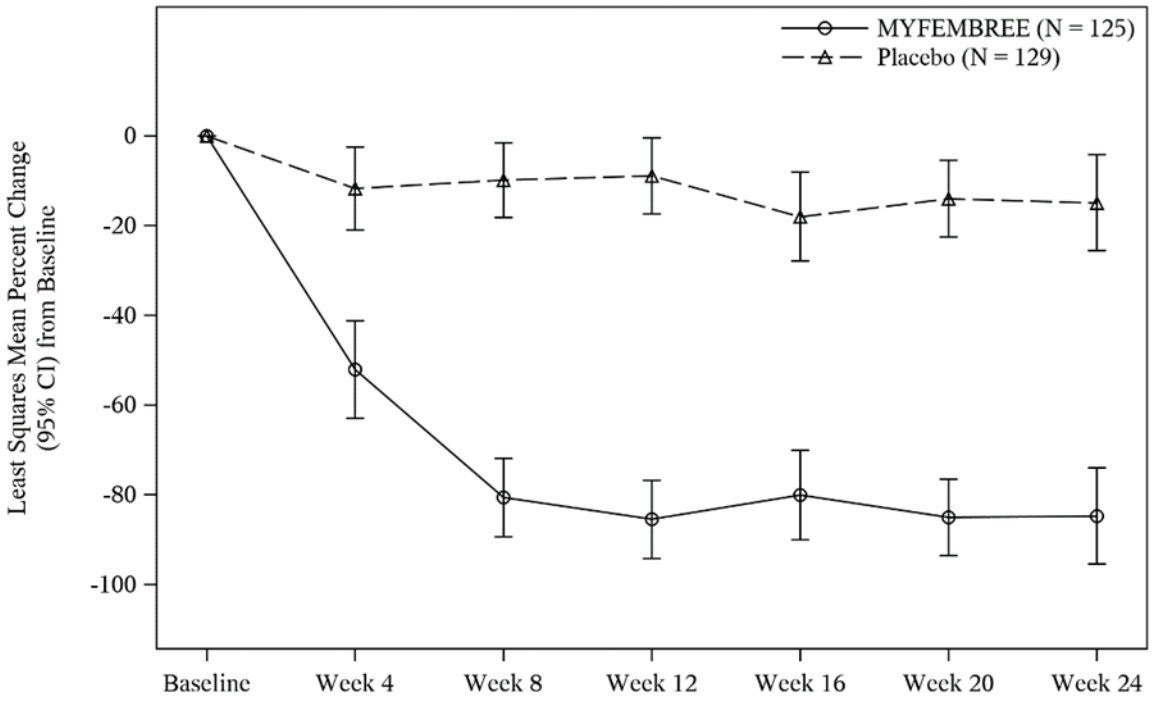
In Studies 3001 and 3002, the percent change from baseline in MBL volume by visit and time to achieve a response inform the onset and durability of the response. In both studies, a significant percent change in MBL volume as compared to placebo was seen in R+E2/NETA treated participants from baseline to Week 24 and was maintained throughout the 24-week treatment period (See Figure 2 and 3 below).

Figure 2: Percent Change from Baseline in Menstrual Blood Loss over Time (Study 3001)



Source: Applicant's Prescribing Information Label. Participants from closed Site 1152 excluded from analysis.

Figure 3: Percent Change from Baseline in Menstrual Blood Loss over Time (Study 3002)



Source: Applicant's Prescribing Information Label. Participants from closed Site 1152 excluded from analysis.

Persistence of Effect

An indicator of the persistence of effect of R+E2/NETA for the treatment of HMB associated with uterine fibroids is the time to resumption of menses after discontinuation of the drug product. After six months of study treatment in Study 3001, 143 participants either did not continue into the extension Study 3003 or discontinued study treatment prematurely. Post-treatment menstrual status was available in 100 of those participants. Resumption of menses was reported by 35 (100%), 39 (100%), and 23 (88.5%) of participants in the R+E2/NETA, R+ delE2/NETA, and placebo groups, respectively. The mean number of days to return to menses was 36.0, 33.6, and 24.3 in the R+E2/NETA, R+ delE2/NETA, and placebo groups, respectively.

In Study 3002 after six months of study treatment, 149 participants did not continue into the extension Study 3003 or discontinued study treatment prematurely. Post-treatment menstrual status was available in 110 of those participants. Resumption of menses was reported by 28 (93.3%), 43 (97.7%), and 35 (97.2%) of participants in the R+E2/NETA, R+ delE2/NETA, and placebo groups, respectively. The mean number of days to return to menses was 30.7, 35.7, and 24.2 in the R+E2/NETA, R+ delE2/NETA, and placebo groups, respectively.

After 12 months of treatment in the extension Study 3003, 248 participants did not continue into the randomized withdrawal study or discontinued study treatment prematurely.

Post-treatment menstrual status was available in 194 of those participants. Resumption of menses was reported by 61 (93.8%), 66 (97.1%), and 57 (93.4%) of participants originally in the R+E2/NETA, R+ delE2/NETA, and placebo groups, respectively. The mean number of days to return to menses was 40.5, 40.6, and 36.9 in participants from the R+E2/NETA, R+ delE2/NETA, and placebo groups, respectively. Mean time to resumption of menses was longer in participants who reported amenorrhea over the last 35 days of treatment compared with participants without amenorrhea of the last 35 days of treatment in the R+E2/NETA (45.6 vs. 32.6 days) and R+delE2/NETA (44.3 vs. 33.2 days) groups, respectively.

Additional details about resumption of menses after drug discontinuation are found in Section 7.5.3. Information regarding resumption of menses is included in Section 6 of the Prescribing Information label for R+E2/NETA.

Reviewer's comment: Quantitative analysis of resumed MBL post-treatment was not performed. It was not reported whether MBL volume after treatment discontinuation was decreased, increased, or equivalent compared to baseline.

Additional Analyses Conducted on the Individual Trial

The Applicant's sensitivity analysis results and supplemental analysis results conducted by the statistical reviewer for the primary endpoint, were consistent with the findings from the primary efficacy analyses. See the Biostatistical Review in DARRTS dated May 10, 2021.

5.1.3. Key Review Issues Relevant to Evaluation of Benefit

Key efficacy issues were identified and discussed with the Applicant during the course of this review and will be discussed in detail in this section. The key issues include closure of Site 1152, (b) (4) and the amendment of the statistical analysis plan for Study 3002 after unblinding Study 3001.

Key Benefit Review Issue #1

Issue

Appropriateness of including efficacy and safety data from closed Site 1152.

Background

On June 10, 2020, the Applicant informed the Agency that they closed study Site 1152 due to multiple observations of noncompliance with Good Clinical Practice (GCP). Site 1152 enrolled 27 patients in Study 3001 [R+E2/NETA (N=6), R+delE2/NETA (N=7), placebo (N=14)], of whom 23 enrolled in the extension Study 3003. The Applicant selected the site for an internal audit because of its high enrollment and high number of protocol deviations. Findings of GCP noncompliance included concerns related to protocol adherence, principal investigator oversight, training records, good documentation practices, and late data entry into electronic

data capture system (EDC). Based on the outcome of a visit to this site by the Myovant Clinical Operation staff and the medical monitor, coupled with adequate audit responses and corrective and preventative action (CAPA) plan, the site was allowed to remain open with enhanced monitoring and oversight. The Applicant reported that after the site visit, the CAPA was confirmed to be implemented in a timely manner and there was clear evidence of improvement in site performance including a lower protocol deviation rate, as well as timely EDC entry and query resolution. However, improvements were not sustained, and the Applicant made the decision to close the site. Although the site was referred for inspection by the Office of Scientific Investigations (OSI), the inspection could not be conducted due to the COVID-19 pandemic.

(b) (4) the Applicant (b) (4) indicated that they took several steps to address reliability of the data despite site closure. This included a targeted 100% review of safety data (i.e., concomitant medications, laboratory tests, vital signs, adverse events, etc.) which they state did not reveal safety concerns or underreporting of adverse events. Review of source documents for randomized patients during the Myovant January 2019 visit found them to be complete. Lastly, they stated that 100% of the EDC data was source data verified without higher than expected rates of discrepancies identified, and which were subsequently queried and resolved. (b) (4)

Assessment

(b) (4) Analyses of the efficacy data excluding Site 1152 were performed by the Agency. Although there was a slight change in the magnitude of the treatment effect, the overall conclusions remain consistent with the primary and secondary efficacy analyses conducted with participants from Site 1152 included (Table 14).

Table 14: Efficacy Analyses with and without Site 1152 (Study 3001)

Rank	Endpoint	With Site 1152			Without Site 1152		
		R+E2/NETA	PBO	Difference	R+E2/NETA	PBO	Difference
0	Primary	(b) (4)			88 /122 (72.1%)	19 /113 (16.8%)	55.3% (44.2%, 65.6%)
1	Proportion achieving amenorrhea				61/122 (50.0%)	7/113 (6.2%)	43.8% (33.9%, 53.7%)
2	Percent change in MBL volume				-82.0 (5.09)	-19.1 (5.2)	-62.9 (-76.4, -49.4)
3	Change in BPD scale score				-44.1 (3.13)	-16.4 (3.24)	-27.7 (-35.7, -19.7)
4*	Proportion with increase in hemoglobin				15/30 (50.0%)	5/22 (22.7%)	27.3% (2.24%, 52.3%)
5	Proportion with decrease in NRS score				25/55 (41.8%)	7/61 (11.5%)	30.3% (15.1%, 45.6%)

Source: Statistical review , SE: Standard error.
*Note that the hemoglobin endpoint analysis in the Table is using the Applicant's original method of study completers only.

Conclusion

The analysis results excluding data from Site 1152 will be used to evaluate the primary and secondary efficacy endpoints of R+E2/NETA in Study 3001. Safety data from Site 1152 will be included in safety analysis (See Section 7.3.1 for justification for keeping the safety data).

Key Benefit Review Issue #2

Issue

Adequacy of the key secondary endpoint regarding the Bleeding and Pelvic Discomfort (BPD) subscale of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) questionnaire (b) (4)

Background

(b) (4) . The BPD subscale was derived by the Applicant from the UFS-QoL Symptom Severity scale. The UFS-QoL is a 37-item questionnaire PRO instrument to assess

distress related to symptoms and impact on quality of life of uterine fibroids. The BPD subscale assesses 3 items of the UFS-QoL that pertain to distress due to uterine fibroid symptoms of heavy bleeding, passage of blood clots, and pelvic pressure/tightness in the pelvic area. Patients are asked to rate on a scale of 1 to 5 (1=not at all to 5=a very great deal) how distressed they were by each of these symptoms during the previous three months.

(b) (4)

the Applicant was informed during a Type C Meeting with the Agency on January 31, 2019 and in the formal Meeting Minutes sent February 22, 2019, that there was insufficient evidence that the UFS-QoL Symptom Severity scale including the BPD subscale, was fit-for-purpose (b) (4) . The Agency stated that it was not possible to interpret the quantitative findings without first establishing that the patient reported outcome (PRO) instrument was content valid. The Applicant responded that they would provide a PRO evidence dossier for the UFS-QoL after completing the planned exit interviews in Study MVT-601-037. In a post-meeting addendum, the Agency stated it planned to provide comments on the exit interview protocol in a separate communication.

The Agency reviewed the exit interview protocol and sent the Applicant an advice letter on April 2, 2019 with protocol recommendations; however, the study had already been completed. The PRO evidence dossier which included the results of the exit interview study was submitted with the NDA for review.

Assessment

The Division of Clinical Outcome Assessment (DCOA) was consulted to evaluate (b) (4) information submitted by the Applicant, including the PRO evidence dossier, (b) (4)

(b) (4)

After review of the exit interview evidence dossier (Study MVT-601-037) to evaluate the content validity of the UFS-QoL BPD subscale, the Agency found that insufficient evidence of content validity had been provided (b) (4) of the UFS-QoL BPD subscale for

the following reasons:

1. Distress is not a clinically relevant concept for the indication of management of HMB associated with uterine fibroids.
    a. Distress is not part of the clinical definition for this indication. It does not characterize the symptoms associated with uterine fibroids.
    b. Assessment of the disease symptoms rather than distress caused by the symptoms may be more clinically appropriate (i.e., distress does not reflect actual symptom improvement).
    c. In managing the disease symptoms, the distress caused by the symptoms will decrease as a consequence. Therefore, it is management of the disease symptoms that is meaningful from a clinical perspective.
2. Meaning of distress/tightness differs to patients.
    a. Distress is not a well-defined concept; it is difficult to interpret because it can mean different things across patients as demonstrated in the patient interviews (e.g., worried, aggravated, fearful, bothered, overwhelmed).
    b. Distress can have different etiologies (e.g., distress due to bleeding issues, cramping from clots, bladder and back discomfort).
    c. Based on the exit interview study, it is unclear whether "distress" is an important concept to patients. Participants in the interviews were queried about their experience with uterine fibroids in the context of their symptoms and impacts. Negative impacts on emotional wellbeing were reported spontaneously by nearly all patients (n=27, 90.0%); however, the use of the term "distress" did not seem to be utilized. Patients most commonly expressed feeling embarrassed; worried or anxious; sad or depressed; angry or irritable about their uterine fibroid signs/symptoms. Among those feeling worried or anxious, patients indicated that they felt this way due to concerns related to their symptoms.
    d. There are also items in the BPD subscale that may not be comprehended appropriately across patients. For example, based on the Applicant's qualitative data, a majority of patients (70%) were unable to distinguish the concept of "tightness/pressure" (i.e., item 5 of BPD subscale) in the pelvis from pelvic pain.
3. Three-month recall period.
    a. While most patients were able to accurately interpret the recall period, the UFS-QoL BPD subscale remains susceptible to recall error as it requires patients to reflect over three menstrual cycles.
4. Assessment of other measurement properties.
    a. The Applicant's proposed threshold for meaningful within-patient score change was not reviewed because of lack of content validity of the BPD subscale.
    b. There is also a lack of data regarding the reliability of the UFS-QoL BPD subscale (i.e., no test-retest reliability data). The testing of other measurement properties does not replace or rectify problems with content validity.

Conclusion

As stated during the Type C Meeting with the Agency on January 31, 2019 and in the formal Meeting Minutes sent February 22, 2019, there was insufficient evidence that the Uterine Fibroid Symptom and Health-Related Quality of Life Bleeding and Pelvic Discomfort (UFS-QoL BPD) subscale was fit-for-purpose (b) (4) Additional information submitted with the NDA, including the PRO evidence dossier discussed above, does not provide sufficient evidence of content validity (b) (4)

Key Benefit Review Issue #3

Issue

Adequacy of the key secondary endpoint regarding NRS pain score (b) (4).

Background

The Applicant proposed a key secondary endpoint of the proportion of women with a maximum NRS pain score of ≤ 1 (minimal to no pain) over the last 35 days of treatment in a subset of women with a maximum NRS score of ≥ 4 (at least moderate pain) during the 35 days prior to randomization. The pain NRS is a single item PRO instrument to rate the intensity of uterine fibroid-associated pain on an 11-point scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine) over the previous 24 hours. The pain-evaluable population was defined as participants with an NRS score of ≥4 prior to randomization and who had > 80% of pain score entries in the eDiary over the last 35 days of treatment. The Applicant conducted a substudy of Study 3001 and Study 3002 of patient exit interviews (MVT-601-037) to assess minimum meaningful improvement as perceived by patients of the PRO instruments in the studies including the pain NRS. According to the Applicant, the study found that at least a 3-point reduction in NRS pain score was meaningful to patients with moderate to severe pain at baseline.

Additional analyses which were not pre-specified in the list of ranked secondary endpoints included assessment of NRS scores of the pain-evaluable population during bleeding (i.e., dysmenorrhea) and non-bleeding days and analgesic use during bleeding and non-bleeding days. The Applicant was informed in the Type B pre-NDA meeting on March 25, 2020 that endpoints of these additional analyses were not pre-specified (b) (4)

Assessment

The Applicant stated that their analysis based on the pain-evaluable population in both trials met the responder definition of achieving a maximum NRS score of ≤ 1 during the last 35 days of treatment in favor of the R+E2/NETA arm. Among the pain-evaluable participants in Study 3001, 41.8% in the R+E2/NETA arm compared with 11.5% in the placebo arm had a maximum

NRS score of ≤1 during the last 35 days of treatment [Difference (95% CI): 30% (15.1%, 45.6%)]. In Study 3002, 47.1% in the R+E2/NETA arm compared with 17.0% in the placebo arm had a maximum NRS score of ≤1 during the last 35 days of treatment [Difference (95% CI): 30% (15.6%, 44.4%).

Review of the NRS pain endpoint in consultation with Biostatistics, the Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP), and the Division of Clinical Outcome Assessment (DCOA) revealed the following issues:

1. Not all patients in the pivotal studies who presented with uterine fibroids and HMB reported moderate to severe pain.

2. For women with uterine fibroids and HMB who reported moderate to severe pain, the primary source of pain was associated with menstrual bleeding. The Applicant's methodology of calculating the NRS score did not differentiate between pain during menstrual bleeding days versus non-menstrual bleeding days. Based on these results it appears that a more correct secondary endpoint would have been dysmenorrhea. Blood clots appear with HMB because the heavy flow outpaces the ability to produce enough anticoagulants. Passage of clots in turn leads to crampy pain consistent with dysmenorrhea.

   In an official copy of the Meeting Minutes from a Type C meeting on January 31, 2019, the FDA communicated to the Applicant that it planned to provide comments in a separate communication about the exit interview protocol (Study MVT-601-037) regarding PRO instruments used in the trials. The Applicant notified the Agency in a correspondence received March 4, 2019, that it may not be able to address the Agency's comments because the study had been completed and the data analyzed. Despite the study having been completed, the Agency still sent its recommendations on April 2, 2019 regarding the exit interview protocol for the Applicant's consideration. Amongst several recommendations, the Agency recommended the following regarding the NRS pain endpoint: "[w]e recommend you debrief this item in the exit interviews to determine whether patients were rating their pain intensity due to dysmenorrhea or the bulk of the fibroid. Given you are seeking an indication for heavy bleeding due to uterine fibroids, a measure of pain due to dysmenorrhea appears to be more meaningful."

   To address the Agency's comment while the baseline data was blinded, Myovant conducted additional analyses related to the key secondary NRS pain endpoint assessing pain recorded during menstrual and non-menstrual days. According to the Applicant, the analysis did indicate that patients' pain was mainly due to dysmenorrhea, and the Applicant (b) (4) The Applicant was told at the pre-NDA meeting on March 25, 2020 that these endpoints were not pre-specified in the list of ranked secondary endpoints that would be formally tested with multiplicity control over Type I error, (b) (4)

3. Non-menstrual pain associated with fibroids is multidimensional and can involve pressure against other organs in the pelvis and lower abdomen in addition to back pain. The Applicant did not adequately assess patients in this analysis to exclude other etiologies for non-menstrual pain such as adenomyosis, endometriosis, gastrointestinal disorders (e.g., constipation), and urologic disorders.

4. The Applicant did not require a total minimum pain score at baseline in the inclusion criteria, nor was randomization stratified by baseline pain score. Therefore, a single day with a score of 4 during menses would qualify.

5. As uterine fibroid-associated pain can be both chronic and intermittent, the Applicant's use of a single maximum NRS score at baseline was not acceptable to adequately capture the change in pain intensity over time.

6. The Applicant's methodology did not identify the location of the pain to confirm that the patient understood the concept and whether the pain they experienced was consistent with where their fibroids were located.

7. In the advice letter sent to the Applicant on February 3, 2017, the following comment was included regarding the list of permitted medications, "[s]ubjects are allowed to take ibuprofen or other Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) for fibroid-related pain and allowed to use acetaminophen for non-fibroid pain. Justify this distinction and describe how participants could distinguish pelvic pain/menstrual pain that is or is not fibroid-related." In the response received March 29, 2017, the Applicant amended the protocol for participants' treatment of uterine fibroid pain only to include ibuprofen, acetaminophen, or opioid or opioid-acetaminophen combination depending on the severity of pain. The use of rescue medication in this manner was not adequate for evaluation of pain associated with uterine fibroids.

8. The Applicant's methodology did not provide appropriate anchor-based analyses (b) (4)

Conclusion

Given the numerous issues with methodology stated above, the key secondary endpoint of the proportion of women with a maximum NRS pain score of ≤ 1 over the last 35 days of treatment in a subset of women with a maximum NRS score of ≥ 4 during the 35 days prior to randomization, as analyzed, does not adequately inform the clinical meaningfulness of this endpoint (b) (4)

The data demonstrate that the pain decrease is primarily derived from reduction in dysmenorrhea. (b) (4)

(b) (4)

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A future trial to evaluate uterine fibroid pain would need to ensure that women with other causes of chronic pain are appropriately excluded, that pain assessment was correlated with menstrual and non-menstrual bleeding days, and that pain intensity criteria are specified as to when a rescue analgesic medication should be taken and timing of pain in relation to allowed rescue medication use. For this new trial, the Agency recommends that the Applicant provide a definition of what constitutes increased, decreased, or no change in pain medication use. In addition, rescue medication(s) would need to be specified in terms of their allowed use and dosage.

Key Benefit Review Issue #4

Issue

Acceptability of the Applicant's analysis results to support the proposed labeling for the hemoglobin endpoint.

Background

The Applicant proposed a key secondary endpoint of the proportion of women with a hemoglobin level ≤ 10.5 g/dL at baseline who achieved an increase of > 2 g/dL from baseline at week 24. The original analysis was conducted based on study completers only. Because missing data and noncompliance are post-randomization intercurrent events, analysis with only observed data may introduce selection bias. During the Mid-Cycle Meeting with the Applicant on November 16, 2020, the Agency requested that the Applicant submit analyses results for this endpoint based on all participants with baseline hemoglobin levels of ≤ 10.5 g/dL including participants who had missing data at Week 24 (non-responders). On November 23, 2020, the Agency received from the Applicant a submission including three approaches to sensitivity analyses to account for missing data including considering patients who did not have hemoglobin concentrations at Week 24 as non-responders. The other two approaches were a mixed-effects model approach and the last observation carried forward (LOCF) approach. Please see the Biostatistical Review in DARRTS dated May 10, 2021 for additional details about the analysis approach to the hemoglobin endpoint.

The Applicant concluded that the findings from the three sensitivity analyses supported the primary analysis of the hemoglobin endpoint. The Applicant also concluded that the analysis population of Week 24 completers for the hemoglobin endpoint was appropriate because it allowed a more accurate assessment of the effect of R+E2/NETA combination therapy and avoided the potential bias of incorporating the missing data. The Applicant stated that the non-significant results in Study 3001 observed in the non-responder approach were thought due to the smaller proportion of patients with anemia at baseline in the placebo group compared with

relugolix group. The Applicant concluded that the totality of the data of the primary and sensitivity analyses of the hemoglobin endpoint, overall, supported the clinically meaningful impact R+E2/NETA combination therapy had upon anemia and was adequate to support a labeling claim.

Because of the Agency's view that treatment comparison should be conducted by incorporating participants with missing data in the primary analysis of the hemoglobin endpoint, the Applicant proposed that data from the mixed-effects model approach be included in labeling rather than data from study completers only. The Applicant's rationale as presented in their Response to FDA Information Request, received February 22, 2021, module 1.11.4., page 35, was that the mixed-effects model to impute missing data took the variability of missing data into consideration, was the same methodology for assessing the primary endpoint, and better reflected the drug product's effect on hemoglobin over time.

Assessment

Our analysis of participants with missing hemoglobin data at Week 24 is as follows: As shown in Table 15, many participants did not have Week 24 data because they discontinued the study early for a variety of reasons including treatment related reasons such as adverse events and lack of efficacy.

Table 15: Patient Disposition for the Evaluation of Hemoglobin

	Study 3001		**Study 3002**	
	R+E2/NETA	**Placebo**	**R+E2/NETA**	**Placebo**
Randomized	122	113	126	129
Evaluable [1]	43/122 (35.2%)	29/113 (25.7%)	40/126 (32%)	53/129 (41.1%)
Completed the Week 24	30/43 (69.7%)	22/29 (75.9%)	31/40 (77.5%)	37/53 (69.8%)
Discontinued the Study[2]	13/43 (30.2%)	7/30 (23.3%)	9/40 (22.5%)	16/53 (30.2%)
Reasons				
Adverse Event(s)	0/43 (0.0%)	1/29 (3.4%)	1/40 (2.5%)	2/53 (3.8%)
Lack of Efficacy	3/43 (6.9%)	0/29 (0.0%)	2/40 (5.0%)	0/53 (0.0%)
Lost to Follow-Up	0/43 (0.0%)	1/29 (3.4%)	0/40 (0.0%)	1/53 (1.9%)
Withdrawal by Patient	5/43 (11.6%)	2/29 (6.9%)	3/40 (7.5%)	3/53 (5.7%)
Protocol Deviation	1/43 (2.3%)	0/29 (0.0%)	0/40 (0.0%)	0/53 (0.0%)
Other	2/43 (4.6%)	1/29 (3.4%)	1/40 (2.5%)	4/53 (7.5%)
No reason	2/43 (4.6%)	2/29 (6.9%)	2/40 (5.0%)	6/53 (11.3%)

Source: Statistical reviewer's analysis: [1] Participants with baseline hemoglobin levels of <10.5g/dL; [2] Participants with no Week 24 hemoglobin data either because they discontinued the study early or did not provide data and hence were excluded from the analysis. Participants from closed Site 1152 excluded from analysis.

Table 16 provides the results of our analysis where participants who did not have hemoglobin data at Week 24 are considered as treatment non-responders. This analysis provided treatment differences that are numerically favorable to R+E2/NETA in both trials. However, the treatment difference is not statistically significant in Study 3001.

Table 16: Proportion of Participants with a Hemoglobin **≤10.5** g/dL at Baseline who Achieved an Increase of **≥** 2 g/dL from Baseline at Week 24

	Treatments		**Difference (95% CI)**
	R+E2/NETA	**Placebo**	
Study 3001	15/43 (34.9%)	5/29 (17.2%)	17.6% (-2.2%, 37.4%)
Study 3002	19/40 (47.5%)	2/53 (3.8%)	43.7% (27.4%, 60.0%)

Source: Statistical reviewer's analysis.

Our analysis results of the hemoglobin endpoint using the mixed-effects model approach and excluding closed Site 1152 (see Key Benefit Review Issue #1) differed slightly from the Applicant's. In an advice letter sent March 17, 2021, we requested that the Applicant recalculate the hemoglobin endpoint using the mixed-effects model approach excluding closed Site 1152 and to submit their SAS program for the mixed-effects model. We were able to replicate the Applicant's results using the SAS codes submitted and following their mixed model approach. The results are acceptable.

Conclusion

We did not agree with the Applicant's original method of analysis of the key secondary endpoint of the proportion of women with a hemoglobin level ≤ 10.5 g/dL at baseline who achieved an increase of > 2 g/dL from baseline at week 24. The most conservative analysis of the data with participants who did not have a hemoglobin value at week 24 being considered as non-responders would not meet statistical significance in Study 3001, but trends in favor of the R+E2/NETA group. However, the endpoint does meet statistical significance in favor of R+E2/NETA in Study 3002. Other methods of analysis of this endpoint in Studies 3001 and 3002 including the mixed-effects model approach, meet statistical significance for a treatment difference in favor of R+E2/NETA compared with placebo.

With success of the primary endpoint of reduction of menstrual blood loss volume which extrapolates to an increase in hemoglobin, the significant results of other sensitivity analyses for the key secondary hemoglobin endpoint, and given the clinical importance of increasing hemoglobin in patients with anemia due to blood loss, we accept a labeling claim for the effectiveness of R+E2/NETA in increasing hemoglobin by greater than 2 g/dL in patients with a baseline hemoglobin less than or equal to 10.5 g/dL. The Applicant and Agency have agreed to use the results from the mixed-effects model analysis of the key secondary hemoglobin endpoint excluding closed Site 1152 in labeling.

Key Benefit Review Issue #5

Issue

Acceptability of amending the SAP for Study 3002 after the unblinding of Study 3001 late in the clinical development cycle of this NDA.

Background

The Applicant submitted a common SAP for analysis of its pivotal studies 3001 and 3002 on May 7, 2019. This SAP was reviewed and accepted by the Agency prior to the completion of the Study 3001. However, the Applicant submitted an amendment to their SAP for Study 3002 late in the clinical development cycle on June 14, 2019 prior to unblinding of Study 3002 but after unblinding of Study 3001. This amendment changed the order of testing of two key secondary efficacy endpoints in Study 3002 in which the hemoglobin endpoint became number five and the NRS pain score endpoint became number four instead of vice versa with testing per the Hochberg procedure.

The Applicant was asked about the rationale for amending the SAP and was requested to analyze the results of Study 3002 by the testing order of the original SAP. The Applicant stated in Responses to FDA Information Requests received September 24, 2020, November 30, 2020, and February 22, 2021, that based on the results of the fourth key secondary endpoint of hemoglobin in Study 3001, they wanted to increase the probability of technical success for Study 3002 by testing endpoint five NRS pain score before endpoint four hemoglobin. The Applicant stated that because the amendment occurred prior to unblinding of Study 3002 and the ICH E9 guidelines allow changes to SAPs prior to unblinding of a study using external data, that they were justified in making the amendment. The Applicant also stated that analysis of all endpoints for Study 3002 had been conducted per the amended SAP and were included in the NDA submission, and that they did not concur with analyzing the results using the testing order of the original SAP.

Conclusion

The Agency reviewed the Applicant's justification for the SAP amendment for Study 3002. Although learning from an early trial is a common practice and is allowed per the ICH guidelines, the Agency determined that to maintain the integrity of the study and to avoid unintended bias in study results, major changes to an SAP after a substantial number of study participants have completed safety and efficacy evaluations should be avoided. Because the Applicant was able to document the timeline that the unblinding of Study 3002 occurred after the SAP amendment, albeit late in the clinical development of cycle of this NDA, we did not require the Applicant to re-analyze their data using the testing hierarchy defined in the original SAP.

6. Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

The two replicate six-month Phase 3 trials (Study 3001 and Study 3002) submitted by the Applicant support the effectiveness of R+E2/NETA to reduce HMB associated with uterine fibroids. In these studies, HMB defined as MBL volume ≥ 80 mL, the accepted threshold

commonly used in clinical trials, was determined using the objective alkaline hematin method, which is considered the "gold-standard" method to assess MBL volume. The majority of participants in both studies were enrolled in North America and the study population was representative of the target population for whom the drug is intended. The demographic and baseline characteristics of study participants were similar across trials, and results from these trials were consistent.

6.1.1. Primary Endpoints

The results of data analysis from both replicate Studies 3001 and 3002 support a conclusion of superiority of R+E2/NETA over placebo. Although the results were not pooled, the percentage of responders and difference from placebo in the two studies were very similar as seen in Section 5.1.2, Table 11 (Percentage of Responders at Week 24).

6.1.2. Secondary and Other Endpoints

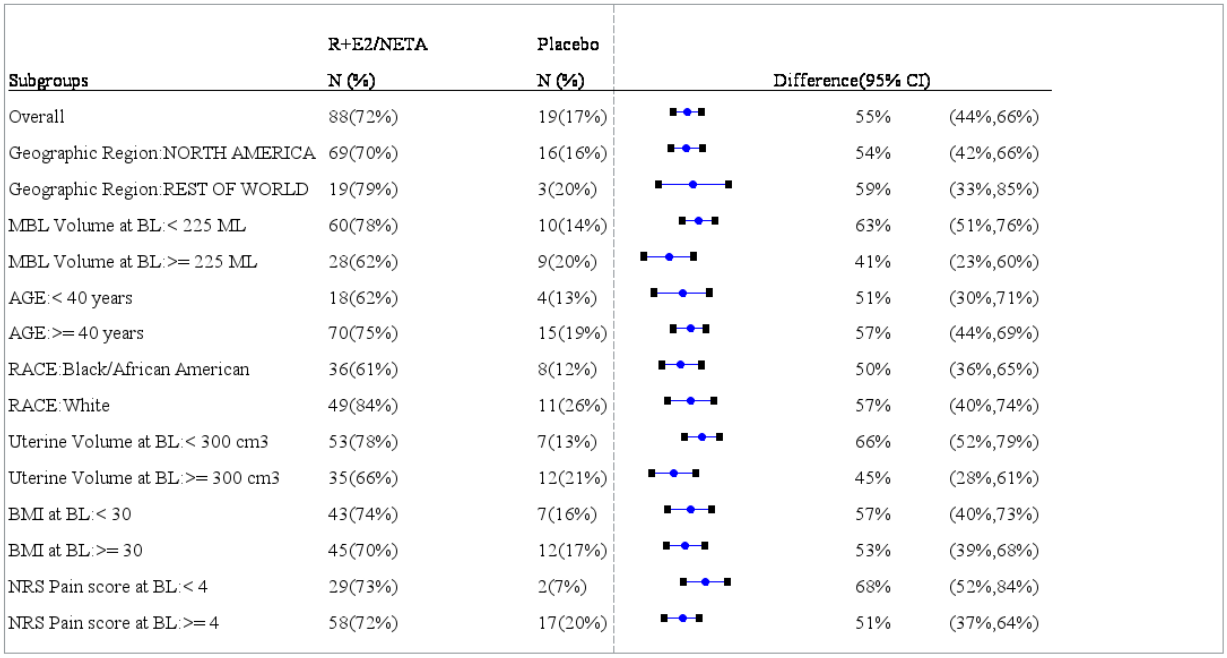
Three ranked secondary endpoints were met in Studies 3001 and 3002 and found adequate to support labeling claims including the proportion of women achieving amenorrhea, the percent change in MBL volume, and the proportion of women achieving an increase in hemoglobin. Results of data analysis for amenorrhea and percent change in MBL volume were consistent between the two studies and statistically significant in favor of R+E2/NETA as seen in Section 5.1.2, Tables 12 and 13. The results were not pooled. Although the hemoglobin endpoint was met in both studies using the mixed-effects statistical model, a greater difference in analysis results between the two studies was noted. See Section 5.1.3. Key Benefit Review Issue #4 for details about the analysis of the hemoglobin endpoint.

6.1.3. Subpopulations

The subgroup analyses results presented in Figure 4 and Figure 5 provided results that were consistent with the Applicant's primary efficacy findings. The results provided treatment differences in favor of R+E2/NETA across all categories including race, age, and BMI. In both trials, the proportion of responders was higher in participants with baseline NRS pain score of <4. Participants with baseline MBL volume <225 mL, participants with uterine volume <300 cm^3 (Study 3001) and participants enrolled in sites located outside the North American region (Study 3002) also had higher percentages of responders compared to the other subgroups.

Statistical reviewer's comment: For each subgroup, the Applicant presented the proportion of responders for each treatment. However, the treatment comparisons were done based on odds ratios as opposed to the difference in the proportion of responders. The statistical reviewer provided the difference in proportions and the associated 95% CI for each subgroup treatment comparison.

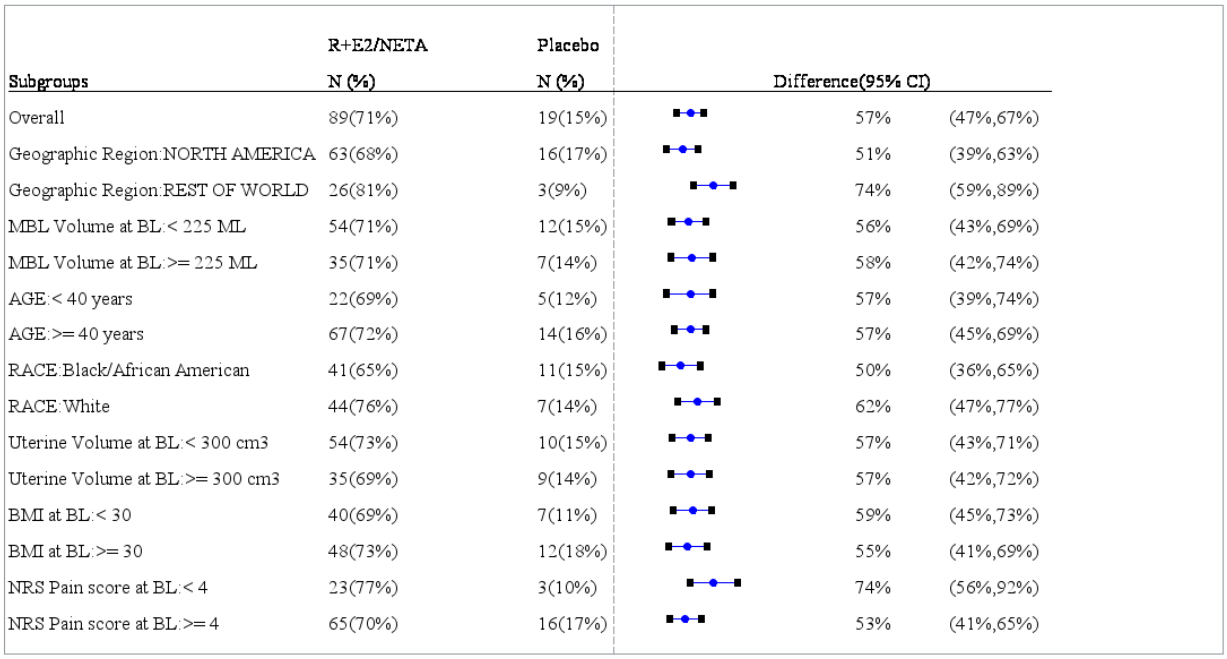
Figure 4: Proportion of responders at Week 24: Subgroup Analysis (MVT-601-3001)



Subgroups	R+E2/NETA N (%)	Placebo N (%)	Difference(95% CI)	
Overall	88(72%)	19(17%)	55%	(44%,66%)
Geographic Region:NORTH AMERICA	69(70%)	16(16%)	54%	(42%,66%)
Geographic Region:REST OF WORLD	19(79%)	3(20%)	59%	(33%,85%)
MBL Volume at BL:< 225 ML	60(78%)	10(14%)	63%	(51%,76%)
MBL Volume at BL:>= 225 ML	28(62%)	9(20%)	41%	(23%,60%)
AGE:< 40 years	18(62%)	4(13%)	51%	(30%,71%)
AGE:>= 40 years	70(75%)	15(19%)	57%	(44%,69%)
RACE:Black/African American	36(61%)	8(12%)	50%	(36%,65%)
RACE:White	49(84%)	11(26%)	57%	(40%,74%)
Uterine Volume at BL:< 300 cm3	53(78%)	7(13%)	66%	(52%,79%)
Uterine Volume at BL:>= 300 cm3	35(66%)	12(21%)	45%	(28%,61%)
BMI at BL:< 30	43(74%)	7(16%)	57%	(40%,73%)
BMI at BL:>= 30	45(70%)	12(17%)	53%	(39%,68%)
NRS Pain score at BL:< 4	29(73%)	2(7%)	68%	(52%,84%)
NRS Pain score at BL:>= 4	58(72%)	17(20%)	51%	(37%,64%)

Source: Statistical reviewer's analysis. Participants from closed Site 1152 excluded from analysis. BL: Baseline

Figure 5: Proportion of responders at Week 24: Subgroup Analysis (MVT-601-3002)



Subgroups	R+E2/NETA N (%)	Placebo N (%)	Difference(95% CI)	
Overall	89(71%)	19(15%)	57%	(47%,67%)
Geographic Region:NORTH AMERICA	63(68%)	16(17%)	51%	(39%,63%)
Geographic Region:REST OF WORLD	26(81%)	3(9%)	74%	(59%,89%)
MBL Volume at BL:< 225 ML	54(71%)	12(15%)	56%	(43%,69%)
MBL Volume at BL:>= 225 ML	35(71%)	7(14%)	58%	(42%,74%)
AGE:< 40 years	22(69%)	5(12%)	57%	(39%,74%)
AGE:>= 40 years	67(72%)	14(16%)	57%	(45%,69%)
RACE:Black/African American	41(65%)	11(15%)	50%	(36%,65%)
RACE:White	44(76%)	7(14%)	62%	(47%,77%)
Uterine Volume at BL:< 300 cm3	54(73%)	10(15%)	57%	(43%,71%)
Uterine Volume at BL:>= 300 cm3	35(69%)	9(14%)	57%	(42%,72%)
BMI at BL:< 30	40(69%)	7(11%)	59%	(45%,73%)
BMI at BL:>= 30	48(73%)	12(18%)	55%	(41%,69%)
NRS Pain score at BL:< 4	23(77%)	3(10%)	74%	(56%,92%)
NRS Pain score at BL:>= 4	65(70%)	16(17%)	53%	(41%,65%)

Source: Statistical reviewer's analysis. Participants from closed Site 1152 excluded from analysis. BL: Baseline

6.1.4. Dose and Dose-Response

Based on the consistent primary endpoint findings in both placebo-controlled trials, the dose selection and response appear appropriate.

6.1.5. Onset, Duration, and Durability of Efficacy Effects

The efficacy effects over time were previously shown in Figures X and X.

6.2. Additional Efficacy Considerations

6.2.1. Considerations on Benefit in the Postmarket Setting

The primary benefit anticipated in the postmarket setting is reduction in HMB and the reduction of anemia. The impact on surgical management for uterine fibroids remains to be seen.

6.3. Integrated Assessment of Effectiveness

Based on the totality of the clinical data submitted by the Applicant, R+E2/NETA reduced HMB associated with uterine fibroids in premenopausal women. The Applicant provided data from two replicate, adequately powered, placebo-controlled Phase 3 trials (Studies 3001 and 3002), which included 252 women treated with R+E2/NETA and 242 women treated with placebo. These data support the following conclusions:

- Treatment with R+E2/NETA by 24 weeks reduced MBL volume to <80 mL (the threshold used to define HMB) and reduced MBL volume by at least 50% from pre-treatment baseline over the last 35 days of treatment.
- Compared to placebo, 55% of women in Study 3001 and 56% of women in Study 3002 responded to treatment with R+E2/NETA by reduction in HMB as defined above.
- Compared to placebo, 44% of women in Study 3001 and 47% of women in Study 3002 treated with R+E2/NETA achieved amenorrhea over the last 35 days of treatment.
- By Week 24, women treated with R+E2/NETA had a 63% mean reduction from baseline in MBL volume in Study 3001 and a 69% mean reduction from baseline in MBL volume in Study 3002 compared to women treated with placebo.
- Compared to placebo, 27% of women in Study 3001 and 49% of women in Study 3002 with baseline Hgb ≤10.5 g/dL who were treated with R+E2/NETA had an increase in Hgb of more than 2 g/dL at Week 24.

Reviewer Comment:
The highly consistent results across the two adequate placebo-controlled Phase 3 clinical trials, establish substantial evidence of effectiveness for R+E2/NETA as a treatment for HMB associated with uterine fibroids in the target population.

7. Review of Safety

7.1. Safety Review Approach

Individual and pooled data from two replicate Phase 3 randomized, double-blinded, placebo-controlled trials of 24-weeks duration (Study 3001 and Study 3002) form the basis of the safety review for R+E2/NETA. A summary of the design of the 24-week placebo-controlled trials can be found in Section 5.1.1. In addition, the safety data from one open-label extension (OLE) trial of 28-weeks duration (Study 3003) is reviewed.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

The safety database is adequate to evaluate the fixed-dose combination R+E2/NETA for the treatment of heavy menstrual bleeding related to uterine fibroids for premenopausal women in the US.

As of the January 7, 2020 data cut-off date for ongoing studies, the overall extent of exposure to relugolix alone or in combination with E2/NETA (relugolix combination therapy) in the uterine fibroid, endometriosis and prostate cancer clinical development programs includes 3,258 participants who received at least one dose, 1,509 participants exposed for at least 6 months, and 326 participants exposed for at least a year.

Of the participants exposed to relugolix ≥ 40 mg, 2,787 received at least one dose (942 participants in phase 1 studies), 1,414 were exposed for at least 6 months, and 326 participants were exposed for at least one year.

Study MVT-601-3201, which supported the approval of relugolix monotherapy for the treatment of advanced prostate cancer (NDA 214621), investigated relugolix 360 mg single oral loading dose followed by 120 mg daily for 48 weeks. A total of 622 males were exposed to at least one dose of relugolix and 563 males were exposed to relugolix 120 mg daily for the full 48 weeks (see Officer Director Review dated December 18, 2020).

Exposure to R+E2/NETA combination therapy included 888 participants (fibroid and endometriosis programs) who received at least one dose.

In the uterine fibroid clinical development program, a total of 1,006 women with uterine fibroids participated in Phase 2 or Phase 3 studies, 588 of whom received relugolix monotherapy and 634 received relugolix combination therapy. In Phase 2 studies TAK-385/CCT-002, TAK-385-3008 and TAK 385/CCT-001 combined, 226 females with uterine fibroids were treated with relugolix monotherapy for up to 12 weeks. In Study TAK-385/CCT-002, 138 females with uterine fibroids were treated with relugolix 40 mg for up to 24 weeks.

The primary safety population for this application is derived from Phase 3 Studies 3001, 3002, and 3003. The safety population is comprised of 634 participants from Studies 3001 and 3002 who received at least one dose of R+E2/NETA (see SAP, Section 5.1.1). A total of 451 participants were treated with R+E2/NETA for at least 6 months (24 weeks) and 130 participants for at least 12 months (52 weeks) (see Table 17).

Additional safety information for 321 premenopausal women who received at least 6 months of combination therapy in Phase 3 studies in the endometriosis clinical development program is included in the 120-day Safety Update. Pertinent findings are included in this review.

Table 17: Number of Patients Treated with Relugolix+E2/NETA During the Parent Study and OLE Period, Safety Population, Studies 3001, 3002 and 3003

Participants Treated, by Duration	3001 R+delayed E2/NETA N=132 n (%)	3001 R+E2/NETA N=128 n (%)	3001 PBO N=127 n (%)	3002 R+delayed E2/NETA N=126 n (%)	3002 R+E2/NETA N=126 n (%)	3002 PBO N=129 n (%)	Total N=768 n (%)
Participants treated for at least 1 dose	113 (85.6)	128 (100.0)	87 (68.5)	103 (81.7)	126 (100.0)	77 (59.7)	**634** (82.6)
< 24 weeks	38 (28.8)	31 (24.2)	19 (15.0)	52 (41.3)	26 (20.6)	17 (13.2)	183 (23.8)
≥ 24 weeks	75 (56.8)	97 (75.8)	68 (53.5)	51 (40.5)	100 (79.4)	60 (46.5)	**451** (58.7)
≥ 24 to < 36 weeks	11 (8.3)	24 (18.8)	68 (53.5)	5 (4.0)	18 (14.3)	60 (46.5)	186 (24.2)
≥ 36 to < 52 weeks	64 (48.5)	12 (9.4)	0 (0.0)	46 (36.5)	13 (10.3)	0 (0.0)	135 (17.6)
≥ 52 weeks	0 (0.0)	61 (47.7)	0 (0.0)	0 (0.0)	69 (54.8)	0 (0.0)	**130** (16.9)

Source: adsl.xpt; Software: R
Abbreviations: N, number of participants in treatment arm; n, number of participants with given treatment duration; OLE, open-label extension; PBO, placebo.

7.2.2. Relevant characteristics of the safety population:

The demographics of the Phase 3 trials is presented in Section 5.1.2 (see Table 10). The U.S. population was well represented in the three Phase 3 clinical trials such that the safety findings are generalizable to the target population for whom this drug is intended.

7.2.3. Adequacy of the safety database:

The adequacy of the safety database was assessed using summaries generated by the Clinical Data Scientist and Core Datafit Services for Studies 3001 and 3002. AEs were coded using MedDRA version 22.0. No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. Handling of safety data from Site 1152, which was closed because of non-compliance with GCP is addressed in Section 7.3.1. There were no major issues identified with respect to recording, coding, and categorizing AEs. The clinical reviewer assessed the Applicant's translations of verbatim terms to the MedDRA preferred

terms (PTs) for the events reported in the Phase 3 trials as well as requested narrative reports, and determined that coding of AEs was generally acceptable. A few AEs were re-coded (abdominal pain for Participants (b) (6) and (b) (6) in Study 3001 and hot flushes for Participant (b) (6) in Studies 3001 and 3003).

The safety database is adequate to evaluate R+E2/NETA for the longterm treatment of HMB related to uterine fibroids in premenopausalwomen. Exposure to relugolix alone or in combination with E2/NETA meets the ICH E1 guidelines for long-term treatment.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

Safety Data Quality Assessments for Studies 3001 and 3002 did not reveal any concerns regarding data integrity.

On June 10, 2020, the Applicant informed the Agency that they closed study Site 1152 due to multiple observations of noncompliance with GCP. Site 1152 enrolled 27 patients in Study 3001 [R+E2/NETA (N=6), R+delE2/NETA (N=7), PBO (N=14)], of whom 23 enrolled in the extension Study 3003. Study Site 1152 was closed due to non-compliance with GCP (see Section 5.3. Key Benefit Review Issue #1 for further background information). Data from this site were excluded from the efficacy analysis. The rationale for including data from Site 1152 in the clinical safety is presented here.

The clinical review team based the decision to include Site 1152 in the safety analysis on several factors. Safety data from Site 1152 for Study MVT-601-3001 was examined. All participants from the site completed Study 3001. In this study, Site 1152 had the highest number of SAEs of any site (3). Two SAEs pertained to a single ankle fracture in one participant in the R+E2/NETA arm (Participant (b) (6)) that was reported with two preferred terms. The third SAE was a wrist fracture experienced by one participant in the R+delE2/NETA arm (Participant (b) (6)) that occurred during the screening period, prior to first dose of study drug.

As compared to the rate for the study as a whole, this site had fewer nonserious AEs (1.33% vs. 1.85%). However, the rate was within 25-75% of the mean, and therefore, was not considered an outlier. In the R+E2/NETA arm, 5 unique participants experienced 12 AEs; in the PBO arm, 8 unique participants experienced 17 AEs, and in the R+delE2/NETA arm, 5 unique participants experienced 10 AEs. AE terms were reviewed and no unusual or unexpected patterns with respect to preferred terms or frequency of AEs were identified. We also conducted a sensitivity analysis and re-calculated the incidence of AEs in the pivotal trials excluding Site 1152. The site exclusion did not alter the adverse reactions that would have been included in labeling nor our conclusions with respect to AEs.

The frequency of laboratory safety assessments was also examined as an indicator of study protocol compliance for Site 1152. Most participants adhered to the laboratory safety

assessment schedule, with 6/7 in the R+delE2/NETA arm, 5/6 in the R+E2/NETA arm, and 12/14 in the PBO arm having laboratory assessments at all study time points per protocol. Furthermore, all participants in the R+E2/NETA and R+delE2/NETA arms had baseline and Week 24 safety laboratory assessments.

DXA scan frequency and BMD data for both Study 3001 and Study 3003 was also considered, since these data contributed to the Limitations of Use labeling considerations for the product. DXA scans were generally obtained in the specified window for each visit. BMD results for each participant in the R+E2/NETA and PBO arms were examined for both Study 3001 and Study 3003. No unusual trends were noted in percent change from baseline in lumbar spine BMD for these participants. In addition, longitudinal DXA scanner quality control and blinded DXA scan reads were performed by a central imaging center, increasing the likelihood of reliable BMD measurements. In their DXA instrument quality control (IQC) reports, no concerns about this site were raised.

Overall, our examination of the safety information from Site 1152 discussed above (AEs, compliance with laboratory and BMD assessments, and lumbar spine BMD results) did not raise concerns about the integrity of the safety data. In addition, we considered that the definition of the safety population is all randomized participants who took at least one dose of investigational drug. While the clinical review team recognizes that noncompliance at the site could have potentially led to under-reporting of AEs, we concluded that safety information obtained at Site 1152 should be included in the safety assessment for this product.

7.3.2. Categorization of Adverse Events

Treatment-emergent AEs (TEAEs) were protocol-defined as AEs occurring during the period of time from the first dose date of the randomized study drug treatment through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, or the date and time of the first dose of open-label extension (Study 3003) study drug, whichever occurred first. All AEs in the reviewed trials were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). The Applicant provided defined terms used for grading that were not specified with the CTCAE. These were deemed acceptable by the review team.

Adverse events of special interest (AESIs) were identified based on the mechanism of action of relugolix (suppression of estrogen levels), clinical safety concerns identified for another approved GnRH antagonist, and known adverse drug reactions for E2/NETA. AESIs included bone loss, fractures, vasomotor symptoms, liver enzyme elevations, hypertension, mood disorders, breast and liver tumors, arterial and venous thromboembolic events, abnormal lipids and glucose, gallbladder disease, hypersensitivity reactions and alopecia.

The 120-day Safety Report included a final report of recovery of bone loss post-treatment in Phase 3 studies and is presented in Section 7.5.2. The Phase 3 studies from the endometriosis development program (Studies MVT-601-3101 and MVT-601-3102) in which premenopausal women were treated with the same dose of R+E2/NETA used in the fibroid program were unblinded, and safety information from these studies were included in the 120-day Safety Update.

7.3.3. Routine Clinical Tests

During the pivotal trials, clinical safety laboratory assessments were performed at screening, baseline (Day 1), 4-week intervals throughout the treatment phase, early termination (if applicable), and approximately 30 days after last dose of study drug by a central laboratory. Samples were obtained after an overnight fast of ≥ 8 hours at baseline and Week 24 for lipids, hemoglobin A1c (HgbA1c), and prolactin, in addition to routine chemistries and complete blood count. Vitamin D was measured at baseline and thyroid stimulating hormone (TSH) at Week 24.

7.4. Safety Results

Safety results are presented here for pivotal Studies 3001 and 3002. Relevant AEs that occurred in Study 3003 are also presented in this section as appropriate. A comprehensive review of Study 3003 follows in Section 7.7.

7.4.1. Deaths

No deaths occurred in Studies 3001, 3002 or 3003.

7.4.2. Serious Adverse Events

Serious adverse events (SAEs) were infrequent. SAEs are shown in Table 18. Aside from two cases of ankle fracture, only single events occurred for each preferred term (PT) reported.

Table 18: Serious Adverse Events, Safety Population – Studies 3001 and 3002 and Pooled

Preferred Term	3001 R+del E2/NETA N=132 n (%)	3001 R+ E2/NETA N=128 n (%)	3001 PBO N=127 n (%)	3002 R+del E2/NETA N=126 n (%)	3002 R+ E2/NETA N=126 n (%)	3002 PBO N=129 n (%)	Pooled R+del E2/NETA N=258 n (%)	Pooled R+ E2/NETA N=254 n (%)	Pooled PBO N=256 n (%)	Risk Difference (95% CI)
Any SAE	3 (2.3)	7 (5.5)	2 (1.6)	2 (1.6)	1 (0.8)	4 (3.1)	5 (1.9)	8 (3.1)	6 (2.3)	0.8 (-2.0, 3.6)
Ankle fracture	1 (0.8)	1 (0.8)	0	0	0	0	1 (0.4)	1 (0.4)	0	0.4 (-0.4, 1.2)
Avulsion fracture	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Cholecystitis	0	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Haematemesis	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Hypothyroidism	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Menorrhagia	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Pelvic pain	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Rhabdo-myolysis	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Uterine leiomyoma	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Uterine myoma expulsion	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Vitreous detachment	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Appendicitis	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0	0.0 (0.0, 0.0)
Panic attack	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0	0.0 (0.0, 0.0)
Cholecystitis acute	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0	0.0 (0.0, 0.0)
Intervertebral disc degeneration	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0	0.0 (0.0, 0.0)
Intervertebral disc protrusion	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0	0.0 (0.0, 0.0)
Acute psychosis	0	0	1 (0.8)	0	0	0	0	0	1 (0.4)	-0.4 (-1.2, 0.4)
Anaemia	0	0	0	0	0	1 (0.8)	0	0	1 (0.4)	-0.4 (-1.2, 0.4)
Necrotising fasciitis	0	0	0	0	0	1 (0.8)	0	0	1 (0.4)	-0.4 (-1.2, 0.4)
Pneumonia	0	0	1 (0.8)	0	0	0	0	0	1 (0.4)	-0.4 (-1.2, 0.4)
Radius fracture	0	0	0	0	0	1 (0.8)	0	0	1 (0.4)	-0.4 (-1.2, 0.4)
Road traffic accident	0	0	0	0	0	1 (0.8)	0	0	1 (0.4)	-0.4 (-1.2, 0.4)
Syncope	0	0	0	0	0	1 (0.8)	0	0	1 (0.4)	-0.4 (-1.2, 0.4)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as any adverse event that occurred after administration of the first dose of study treatment.
Abbreviations: N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event
Risk difference is estimated using the pooled relugolix+E2/NETA minus pooled placebo (with 95% confidence interval).

Eleven SAEs were reported for 8 participants in the R+E2/NETA arm, the majority of which occurred in Study 3001. The following SAEs were assessed by the investigator as probably/possibly related to drug: menorrhagia and uterine myoma expulsion experienced by one participant and pelvic pain that occurred in another participant. This reviewer concurs. In addition, this reviewer assesses uterine leiomyoma (prolapsed) as possibly related to drug (see Narratives below). The rare, but serious adverse drug reactions of uterine myoma expulsion and prolapse will be included in the Warnings and Precautions section of the label.

Although estrogen has been associated with cholelithiasis and cholecystitis, it is uncertain albeit possible that the SAE cholecystitis (Participant (b) (6) in Study 3002) was related to study drug. This participant was described in the study report as having pre-existing cholelithiasis and right upper quadrant abdominal pain for “months”.

The event of acute cholecystitis that occurred for a participant in the R+delE2/NETA arm (Participant (b) (6) in Study 3002) was unlikely related to relugolix monotherapy because the participant had a history a cholelithiasis and experienced the event on Day 15.

Reviewer Comment: In addition to the SAEs discussed above, a nonserious AE of biliary colic was reported for one participant in the R+delE2/NETA during relugolix monotherapy. No cases of cholecystitis or gallbladder disease were reported for participants randomized to PBO. Gallbladder disease will be including in the Warnings and Precautions section of the label, consistent with class labeling.

Narrative reports for the three additional SAEs experienced by R+E2/NETA-treated participants and assessed as related (defined as probably or possibly related) to study drug are presented below:

Participant (b) (6) (Study 3001) was reported to have had the SAEs of menorrhagia and uterine myoma expulsion. She was noted to have a 7.84 cm submucosal fibroid on the ultrasound obtained at screening. On Day 125 days she experienced bleeding, cramping, and a prolapsed fibroid protruding from her vagina. An endoloop excision was performed under anesthesia. The event resolved and no action was taken with study drug. The event was assessed as related to study drug by the investigator and the Applicant. This reviewer concurs with the causality assessment.

Participant (b) (6) (Study 3001) was reported to have had the SAE of uterine leiomyoma (verbatim, prolapsed submucosal leiomyoma). The participant was noted to have a 2.6 cm hypoechoic mass in the endocervical canal assessed by the central reader to be a probable small fibroid close to the cervix on screening ultrsound. At the Week 24 visit, 169 days after initiating study drug, she was noted to have a 0.5 cm endocervical polyp protruding from the cervix. The same day she enrolled in study MVT-601-3003. The “possible polyp” was subsequently removed by her gynecologist as an outpatient procedure and pathology confirmed a submucosal leiomyoma. The event resolved, and no action was taken with study drug. The event was assessed as not related to study drug by the investigator and possibly related by the Applicant. It is difficult in this case to explain the discrepancy in size between the mass described by ultrasound and the visible polypoid lesion protruding from the cervix. However, this reviewer concurs with the Applicant’s assessment.

Participant (b) (6) (Study 3001) was reported to have had a serious adverse event of pelvic pain 87 days after initiating study drug. The patient was seen in the emergency room and underwent ultrasound imaging which showed a fibroid uterus and no other abnormal findings. She received analgesic therapy and was discharged the same day. The event resolved; no action was taken with study drug. This SAE of pelvic pain was assessed by the investigator and the Applicant as related to study drug. This reviewer concurs that a causal relationship cannot be ruled out.

SAEs reported for participants in the R+delE2NETA and PBO arms are shown in Table 18 above, and were assessed by the investigators as not related to study drug. This reviewer concurs.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

AEs leading to study drug discontinuation for participants in the R+E2/NETA arm are shown in Table 19. For the majority of AEs leading to discontinuation in the R+E2/NETA arm, single events were reported. Discontinuation due to adverse events of special interest (AESIs) included menorrhagia (verbatim term: prolonged menstrual bleeding), metrorrhagia, ALT increase, and hot flush, occurring in one participant each in the R+E2/NETA arm as compared to no participants in the PBO arm. One participant in the PBO arm discontinued due to alopecia and no participants in either arm discontinued due to bone loss (see Section 7.4.4) for further discussion of alopecia).

Only one participant discontinued study drug due to an SAE. Participant (b) (6) was a 46-year-old female randomized to PBO in Study MVT-601-3002 and experienced the SAE of necrotizing fasciitis on Day 113. The event was assessed as not related to study drug.

Table 19: Adverse Events Leading to Discontinuation, Safety Population – Studies 3001 and 3002* and Pooled

Preferred Term	3001 R+del E2/NETA N=132 n (%)	3001 R+ E2/NETA N=128 n (%)	3001 PBO N=127 n (%)	3002 R+del E2/NETA N=126 n (%)	3002 R+ E2/NETA N=126 n (%)	3002 PBO N=129 n (%)	Pooled R+del E2/NETA N=258 n (%)	Pooled R+ E2/NETA N=254 n (%)	Pooled PBO N=256 n (%)	Risk Difference (95% CI)
Any AE leading to discontinuation	16 (12.1)	7 (5.5)	5 (3.9)	14 (11.1)	3 (2.4)	6 (4.7)	30 (11.6)	10 (3.9)	11 (4.3)	-0.4 (-3.8, 3.0)
Menorrhagia	2 (1.5)	1 (0.8)	0	0	1 (0.8)	0	2 (0.8)	2 (0.8)	0	0.8 (-0.3, 1.9)
Alanine aminotransferase increased	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Anxiety	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Breast cyst	0	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Fatigue	3 (2.3)	1 (0.8)	0	2 (1.6)	0	0	5 (1.9)	1 (0.4)	0	0.4 (-0.4, 1.2)
Headache	0	1 (0.8)	0	2 (1.6)	0	0	2 (0.8)	1 (0.4)	0	0.4 (-0.4, 1.2)
Hot flush	4 (3.0)	1 (0.8)	0	2 (1.6)	0	0	6 (2.3)	1 (0.4)	0	0.4 (-0.4, 1.2)
Irritability	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Metrorrhagia	1 (0.8)	1 (0.8)	0	0	0	0	1 (0.4)	1 (0.4)	0	0.4 (-0.4, 1.2)
Mood swings	0	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Muscle twitching	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Vomiting	0	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0.4 (-0.4, 1.2)
Asthenia	1 (0.8)	1 (0.8)	1 (0.8)	0	0	0	1 (0.4)	1 (0.4)	1 (0.4)	0.0 (-1.1, 1.1)
Paraesthesia	0	1 (0.8)	1 (0.8)	0	0	0	0	1 (0.4)	1 (0.4)	0.0 (-1.1, 1.1)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as any adverse event that occurred after administration of the first dose of study treatment.
Abbreviations: AE, adverse event; N, number of participants in treatment arm; n, number of participants with adverse event
Risk difference is estimated using the pooled relugolix+E2/NETA minus pooled PBO (with 95% confidence interval).
*This table includes all of the adverse events leading to drug discontinuation for participants in the R+E2/NETA arm.

Discontinuations due to AEs were also assessed using FDA MedDRA Queries (FMQs) (Narrow). This analysis highlighted abnormal uterine bleeding as a cause for discontinuation for 3/254 participants (1.2%) in the R+E2/NETA arm as compared to none in the PBO arm. The rate of discontinuation due to abnormal uterine bleeding in the R+delE2/NETA arm was similar to the R+E2/NETA arm. In addition, this analysis demonstrated that in the R+delE2/NETA arm, 2/258 participants (0.8%) discontinued due to hypertension and 2/258 participants (0.8%) discontinued due to alopecia. One participant in the PBO arm (0.4%) also discontinued due to alopecia.

7.4.4. Adverse Events of Special Interest

Venous thromboembolism (VTE) Venous and arterial thromboembolic events (VTEs and ATEs) are discussed in Section 8.5.1 and bone loss is discussed in Section 8.5.2. Elevated transaminases are addressed in Section 7.4.6 (Laboratory Findings). The adverse event of alopecia is discussed in this section.

Alopecia

Issue

An imbalance in alopecia (PTs hair loss and hair thinning) was observed in the placebo-controlled trials. We consider this adverse drug reaction (ADR) of clinical importance to females. Therefore, we will issue a postmarketing requirement (PMR) to better characterize alopecia and assess for post-treatment recovery.

Background

The combination GnRH-antagonist/E2/NETA product previously approved for the treatment of HMB in females with uterine fibroids was associated with alopecia in placebo-controlled trials. In addition, hair loss is listed as a common side effect in the Patient Information section of the label for NETA, and loss of scalp hair is noted in the Postmarketing Experience section of the label for E2/NETA (Activella). Alopecia in women with HMB related to uterine fibroids treated with R+E2/NETA is likely multifactorial and may be related to changes in levels of endogenous gonadal steroids, the effects of E2 and NETA on the phases of the hair cycle, as well as underlying iron deficiency. At the pre-NDA teleconference held on March 25, 2020 (see Meeting Minutes dated April 16, 2020), the imbalance in alopecia with R+E2/NETA treatment as compared to PBO was noted, and the Agency requested additional information including narrative reports for participants who experienced the AE of alopecia.

Assessment

In Studies 3001 and 3002 combined, an imbalance in the TEAE of alopecia was observed, with events reported in nine females in the R+E2/NETA arms (3.5%) as compared to two in the PBO arm (0.8%).

Narrative reports for cases in which the AE of alopecia were reviewed and are summarized here. During the pivotal trials, the onset of alopecia occurred from Study Days 9-148 in the R+E2/NETA arm and Days 1-31 in the PBO arm. The severity grading of alopecia according to CTCAE is as follows:

- Grade 1: hair loss of <50% of normal for that individual, not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss, but does not require a wig or hair piece to camouflage.
- Grade 2: hair loss ≥ 50% of normal for that individual that is readily apparent to others; a wig or hair piece is necessary to completely camouflage the hair loss and is associated with psychosocial impact.

Alopecia was characterized as Grade 1 for all but one participant in the R+E2/NETA arm and for both participants in the PBO arm. One participant in the R+E2/NETA arm had Grade 2 alopecia. However, in their labeling comments dated February 22, 2021, the Applicant indicated that the study was not specifically designed to assess alopecia and grading of alopecia may not have been strictly adherent to CTCAE.

Anemia with or without iron deficiency was documented at baseline for 5/9 participants in the R+E2/NETA arm and 1/2 participants in the PBO arm. None of the nine affected women treated with R+E2/NETA discontinued study drug during the pivotal studies because of alopecia; one of the two participants in the PBO arm discontinued because of both alopecia and acne. Alopecia resolved in 2/9 participants in the R+E2/NETA arm while on continued therapy and in 2/2 participants in the PBO arm after study drug was stopped.

Hair loss was ongoing at the end of the study for 7/9 women in the R+E2/NETA arm, all of whom enrolled in the open-label extension study MVT-601-3003. Nine additional participants in the R+delE2/NETA arm also had the AE of alopecia in the pivotal trials, 5 of whom were on relugolix monotherapy at that point, and 3 who were later on combination therapy. The study day the event occurred was not reported for one participant.

During the OLE, eight participants reported the AE of alopecia. Onset was earlier for participants in the parental R+E2/NETA arm than for participants in the parental PBO arm (from Days 170-206 vs. Days 207-231, respectively). One participant (Participant (b) (6)) in the PBO arm had the onset of alopecia during the pivotal trials (Day 109) but reported the event during Study 3003. Participant (b) (6) who was randomized to parental R+E2/NETA arm reported Grade 1 alopecia in the pivotal trial (Day 148) followed by resolution and then reported a recurrence during the OLE (Day 260). She withdrew on Day 291 and reported resolution of alopecia on Day 306.

Anemia at pretreatment baseline in the parent study was observed in 5/8 of the participants who reported alopecia during Study 3003. Severity was reported as Grade 1 for six participants and Grade 2 for two participants. From the three Phase 3 trials combined, 3/11 (27.3%) participants in the R+E2/NETA arm with alopecia reported Grade 2 severity. Resolution of alopecia was reported for 4/8 participants, one during the treatment phase, and three post-treatment. Of the seven participants from the R+E2/NETA arm who experienced alopecia during the pivotal trials and enrolled in the OLE study, six completed the study and four entered the randomized withdrawal study MVT-601-035 in which participants who completed Study 3003 and were responders to R+E2/NETA (defined as MBL < 80 mL and ≥ 50% reduction in MBL from pretreatment baseline) were randomized to R+E2/NETA or PBO for an additional 52 weeks.

In their response to the midcycle meeting discussion (Meeting Minutes dated November 16, 2020 and submitted on November 30, 2020), the Applicant proposed that a predisposition to telogen effluvium related to iron deficiency may be accentuated by the decrease in estrogen/progestin with R+E2/NETA treatment in premenopausal women with HMB due to uterine fibroids. We concur that this is a plausible explanation for the observed increase in alopecia with R+E2/NETA. They also suggest acute stress may be a contributing factor, but provide no additional information regarding how stress was assessed or why an imbalance in stress may have occurred. They further hypothesize that (b) (4)

This claim, however, is not supported by clinical trial data of up to 12 months duration. (b) (4)

Conclusion

Alopecia is an ADR of clinical importance to premenopausal women. It is important for prescribers and patients to understand the risk of alopecia with R+E2/NETA. Therefore, in addition to including the observed imbalance in Section 6 (Clinical Trials) of the label, this ADR will be including in the Warnings and Precautions section. Furthermore, if MYFEMBREE is approved, a PMR will be issued to obtain more detailed information on the time to onset, pattern, severity and reversibility of hair loss.

Fractures

Fractures, excluding hands, feet and face/skull were adverse events of special interest. Low trauma fractures, or fragility fractures are of particular interest in situations related to decreased estrogen levels and bone loss. Fragility or low trauma fractures are defined as fractures that result from a fall of standing height or less. Fractures that are not considered low trauma or osteoporotic fractures that occurred during Studies 3001, 3002 and 3003 include a facial fracture and a traumatic wrist fracture that occurred in two placebo treated subjects, and traumatic fractures of the wrist/radius and forearm that occurred in a single subject randomized to the R+delE2/NETA arm.

For a comprehensive review, low trauma fractures that occurred during both the placebo-controlled trials and the long-term OLE trials are discussed here.

Four low trauma fractures occurred in subjects while on R+E2/NETA, two of whom were randomized to the R+delE2/NETA arm during the pivotal trials. All subjects experienced bone loss.

- Subject (b) (6) (Study 3001)- 42 year-old (yo) white female (WF) randomized to R+E2/NETA experienced the SAE ankle fracture/avulsion fracture after tripping on a ball and falling. At baseline, BMD was normal (Z-score 0.67). At Week 24, percent change from baseline in BMD was +078, -0.3 and -2.3% at the lumbar spine (LS), total hip (TH) and femoral neck (FN), respectively. The Investigator and Applicant assessed the fracture as not related to study drug.
- Subject (b) (6) (Study 3002)- 48 yo WF randomized to R+E2/NETA and experienced a wrist fracture after a fall on ice. She had a normal BMD at baseline (Z-score -0.33) At Week 24, percent change from baseline in LS BMD , FN BMD and TH BMD was - 2.84%, -2.1% and -1.0%, respectively. Z-score at Week 24 was -0.51. No action was taken with the study drug and the subject completed the study.
- Subject (b) (6) (Study 3003)- 40 yo WF who was randomized to R+delE2/NETA in Study 3001 followed by participation in the OLE study experienced a tibia fracture [verbatim term: non-displaced fracture of lateral condyle of tibia (left knee)] on Day 259 while on R+E2/NETA as a result of a fall caused by stepping into a hole covered by water. At baseline, her BMD Z-score was at the lower end of the normal range (-1.64), and confounders included Type I Diabetes Mellitus and glucocorticoid use. During the study she experienced bone loss at all 3 anatomic sites. Maximum documented bone loss occurred at Week 36 (after 24 weeks of R+E2/NETA combination therapy), with percent change from baseline in BMD of -3.0%, -5.7% and -6.8% at the LS, TH, and FN,

respectively. At Week 52, Z-score was -1.92 (lower end of the expected range for age). Although she had multiple confounders, this reviewer assesses the event as possibly related to R+E2/NETA.

- Subject (b) (6) (Study 3003)- 43 yo black female (BF) who was randomized to R+delE2/NETA in Study 3001 followed by participation in the OLE experienced an ankle fracture as a result of slipping on a wet floor on Day 228. Baseline BMD was above the expected range for age (Z-score +2.37). Maximum bone loss at the occurred at Week 12 with percent change from basely in LS BMD of -3.1% and FN BMD of -5.8%. BMD increased thereafter. Confounders included history of vitamin D and omeprazole use. Study drug was held for 3 days, and she completed the study. The event was assessed by the investigator as not related to study drug.

It is possible that R+E2/NETA contributed to accelerated bone loss in these cases. The extent to which the observed accelerated bone loss contributed to fractures in these females, and particularly in the three with normal BMD (Z-score > -1.0) is uncertain.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAEs occurring in at least 2% of participants and at least in 1% in the R+E2/NETA arm as compared to PBO are shown in Table 20. See the Appendix for a full listing of AEs by System Organ Class occurring in at least 2% of participants in any treatment arm.

Table 20: Treatment-Emergent Adverse Events Occurring in at Least 2% of Participants in Any Treatment Arm and at Least 1% Higher Frequency in the R+E2/NETA Arm Than PBO Arm, Phase 3 Safety Population – Study 3001, 3002 and Pooled

Preferred Term	3001 R+del E2/NETA N=132 n (%)	3001 R+ E2/NETA N=128 n (%)	3001 PBO N=127 n (%)	3002 R+del E2/NETA N=126 n (%)	3002 R+ E2/NETA N=126 n (%)	3002 PBO N=129 n (%)	Pooled R+del E2/NETA N=258 n (%)	Pooled R+ E2/NETA N=254 n (%)	Pooled PBO N=256 n (%)	Risk Difference (95% CI)
Any AE	96 (72.7)	79 (61.7)	84 (66.1)	90 (71.4)	76 (60.3)	76 (58.9)	186 (72.1)	155 (61.0)	160 (62.5)	-1.5 (-9.9, 6.9)
Hypertension	3 (2.3)	7 (5.5)	0	7 (5.6)	5 (4.0)	4 (3.1)	10 (3.9)	12 (4.7)	4 (1.6)	3.1 (0.1, 6.1)
Alopecia	4 (3.0)	4 (3.1)	2 (1.6)	5 (4.0)	5 (4.0)	0	9 (3.5)	9 (3.5)	2 (0.8)	2.7 (0.2, 5.2)
Hot flush	47 (35.6)	14 (10.9)	10 (7.9)	44 (34.9)	7 (5.6)	5 (3.9)	91 (35.3)	21 (8.3)	15 (5.9)	2.4 (-2.0, 6.8)
Libido decreased	2 (1.5)	3 (2.3)	1 (0.8)	3 (2.4)	4 (3.2)	0	5 (1.9)	7 (2.8)	1 (0.4)	2.4 (0.2, 4.6)
Menorrhagia	2 (1.5)	3 (2.3)	0	4 (3.2)	4 (3.2)	1 (0.8)	6 (2.3)	7 (2.8)	1 (0.4)	2.4 (0.2, 4.6)
Irritability	0	5 (3.9)	0	1 (0.8)	1 (0.8)	0	1 (0.4)	6 (2.4)	0	2.4 (0.5, 4.3)
Breast cyst	0	2 (1.6)	0	0	3 (2.4)	0	0	5 (2.0)	0	2.0 (0.3, 3.7)
Abdominal pain	1 (0.8)	4 (3.1)	3 (2.4)	4 (3.2)	5 (4.0)	1 (0.8)	5 (1.9)	9 (3.5)	4 (1.6)	1.9 (-0.8, 4.6)
Dyspepsia	2 (1.5)	2 (1.6)	0	0	3 (2.4)	1 (0.8)	2 (0.8)	5 (2.0)	1 (0.4)	1.6 (-0.3, 3.5)
Metrorrhagia	1 (0.8)	3 (2.3)	0	5 (4.0)	2 (1.6)	1 (0.8)	6 (2.3)	5 (2.0)	1 (0.4)	1.6 (-0.3, 3.5)
Hyperhidrosis	3 (2.3)	3 (2.3)	2 (1.6)	2 (1.6)	2 (1.6)	0	5 (1.9)	5 (2.0)	2 (0.8)	1.2 (-0.8, 3.2)
Night sweats	4 (3.0)	3 (2.3)	0	3 (2.4)	0	0	7 (2.7)	3 (1.2)	0	1.2 (-0.1, 2.5)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as any adverse event that occurred after administration of the first dose of study treatment.
Abbreviations: AE, adverse event; N, number of participants in treatment arm; n, number of participants with adverse event

Reviewer's comment (menorrhagia): All of these TEAEs may be related to changes in levels of estrogens and progestogens and therefore, are considered adverse drug reactions (ADRs) that will be included in Section 6 of the label. While all participants were required to have HMB for study enrollment, review of available narratives from both the pivotal trials and Study 3003, suggest a change in menstrual bleeding pattern for most cases reporting menorrhagia (or similar terms), prolonged menstrual bleeding *or persistence of HMB* (particularly for participants in the PBO arm). *See additional discussion of Hypertension in Section 7.4.7 and further discussion of Alopecia in Section 7.4.4.*

Reviewer's comment (abdominal/pelvic pain); We examined the apparent imbalance in the AE of abdominal/pelvic pain in depth and determined that this AE did not represent an ADR. In response to IRs dated August 13, 2020 and October 14, 2020, the Applicant provided a re-analysis of abdominal/pelvic pain, which included re-coding two events that were erroneously coded as upper abdominal pain to the term abdominal pain lower (Participants (b) (6) *and* (b) (6) *in Study 3001), and one event of abdominal tenderness that was re-coded to the term abdominal pain upper (Participant* (b) (6) *in Study 3002). Additionally, the clinical review team's approach was to assess dysmenorrhea, upper abdominal pain and dyspepsia separately from the other PTs for abdominal/pelvic pain. Of note, most of the uterine fibroid pain reported by participants using the NRS pain scale occurred during bleeding days,*

consistent with dysmenorrhea (see Benefit Review Issue #3). After re-coding the events and modifying the approach to the analysis, the imbalance in abdominal/pelvic pain was no longer apparent. Additionally, in the cases coded to the general PT abdominal pain, participants were not specifically evaluated for abdominal pain and the pain resolved while on continued treatment. The etiology of abdominal pain in these cases is unknown. None of these participants discontinued study drug or withdrew from the study due to abdominal pain. Overall, we are in agreement with the Applicant's assessment that abdominal pain is not an ADR (submitted on February 22, 2021 as Supplemental Table 1 in response to FDA label comments dated February 8, 2021), and abdominal/pelvic pain will not be included as an ADR in labeling.

Table 21: Adverse Events of Abdominal and Pelvic Pain, Studies 3001 and 3002

Preferred Term	R+delE2/NETA (N=-258)	R+E2/NETA (N=254)	PBO (N=256)
Patients with at least one AE of abdominal/pelvic pain	11 (4.3%)	17 (6.7%)	16 (6.3%)
Abdominal pain	5 (1.9%)	9 (3.5%)	4 (1.6%)
Pelvic pain	3 (1.2%)	5 (2.0%)	6 (2.3%)
Abdominal pain lower	2 (0.8%)	2 (0.8%)	6 (2.3%)
Uterine pain	1 (0.4%)	1 (0.4%)	0

Source: Adapted from Table 1 submitted by the Applicant in their Response to the Information Request dated October 14, 2020. Note, abdominal tenderness was excluded from the Agency's analysis because review of the narrative report indicates that the pain was upper abdominal pain which was assessed separately.
AE=adverse event

TEAEs were also analyzed using FMQs (narrow and broad) and led to the detection of additional PTs reported for the AEs listed below. These PTs will be included in the ADRs listed in Section 6 of the label.

- Abnormal uterine bleeding: The following PTs were identified: menorrhagia, metrorrhagia, menstruation irregular and Vaginal haemorrhage. In addition, this analysis identified one participant in the PBO arm with the AE of polymenorrhea.
- Depression: Excluding overdose of study medication [which were unintentional (see description of cases in Section 7.8.4)], an imbalance in depression (PTs included mood swings, depression, and depressed mood) was observed and will be included in Sections 5 and 6 of the label. Additionally, although no cases of suicidal ideation were reported in the uterine fibroid program, (b) (4) given the importance of this information for patients and

prescribers, the information that suicidal ideation occurred in another clinical development program for the R+E2/NETA combination product for a different indication will be included in the Warnings and Precautions section of the label.

- Libido decreased: An additional case of decreased libido that was coded to the PT Loss of libido was identified.

7.4.6. Laboratory Findings

Laboratory parameters of interest included increases in transaminases, glucose/hemoglobin A1c, and lipids as well as corresponding AEs. These are presented below. No safety signals were identified in other routine chemistry and hematology assessments. Favorable changes in hemoglobin are presented in the efficacy section (see Section 5.1.3).

Transaminases

Participants were monitored for liver injury with liver function tests at each visit. Increase in ALT and/or AST ≥ 3X ULN was an adverse event of clinical interest. Of the laboratory assessments performed in the central laboratory per protocol, the number and percentage of participants meeting criteria for a worsened grade in liver enzymes postbaseline are summarized in Table 22. Two additional participants in the R+E2/NETA arm (Participants (b) (6) experienced grade 2 elevations in AST that are not included in Table 22. These elevations were detected during point-of-care management for rhabdomyolysis associated with uncontrolled hypothyroidism and in the postoperative setting following cholecystectomy, respectively, and were reported as AESIs (see brief narrative summary in Table 50 in the Appendix). An additional participant (Participant (b) (6)) had an ALT elevation ≥ 3X ULN that occurred on study Day 1. This was prior to the initiation of treatment and therefore, her results are also not included in Table 22.

Table 22: Participants Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade[1] From Baseline Through Week 24, Safety Population, Studies 3001, 3002 and Pooled

Laboratory Test	3001 R+del E2/NETA N=132 n (%)	3001 R+ E2/NETA N=128 n (%)	3001 PBO N=127 n (%)	3002 R+del E2/NETA N=126 n (%)	3002 R+ E2/NETA N=126 n (%)	3002 PBO N=129 n (%)	Pooled R+del E2/NETA N=258 n (%)	Pooled R+ E2/NETA N=254 n (%)	Pooled PBO N=256 n (%)
Alanine Aminotransferase (U/L)	15 (11)	12 (9)	15 (12)	15 (12)	7 (6)	9 (7)	30 (12)	19 (7)	24 (9)
Increased to Grade 1 (>ULN to 3X ULN Increased to	14 (11)	11 (9)	15 (12)	14 (11)	7 (6)	9 (7)	28 (11)	18 (7)	24 (9)
Grade 2 (>3-5X ULN) Increased to	0	1 (1)	0	1 (1)	0	0	1 (0)	1 (0.4)	0
Grade 3 (>5-20X ULN) Increased to	1 (1)	0	0	0	0	0	1 (0)	0	0
Grade 4 (>20X ULN)	0	0	0	0	0	0	0	0	0
Aspartate Aminotransferase (U/L)	13 (10)	6 (5)	7 (6)	11 (9)	5 (4)	10 (8)	24 (9)	11 (4)	17 (7)
Increased to Grade 1 (>ULN to 3X ULN	12 (9)	6 (5)	6 (5)	11 (9)	5 (4)	10 (8)	23 (9)	11 (4)	16 (6)
Increased to Grade 2 (>3-5X ULN)	1 (1)	0	1 (1)	0	0	0	1 (0.4)	0	1 (0.4)
Increased to Grade 3 (>5-20X ULN)	0	0	0	0	0	0	0	0	0
Increased to Grade 4 (>20X ULN)	0	0	0	0	0	0	0	0	0

Source: ad b.xpt; Software
CTCAE Version 5.0
Abbreviations: LLN, lower limit of normal; N, number of participants with relevant laboratory data; n, number of participants with abnormality; ULN, upper limit of normal

Worsened grade in postbaseline elevations in ALT was reported for 30/258 (12%), 19/254 (7%) and 24/256 (9%) of participants in the R+delE2/NETA, R+E2/NETA, and PBO arms, respectively. All elevations were ≤3X ULN except for one participant (0.4%) in each the R+E2/NETA and R+delE2/NETA arms with elevation in the range of >3- to 5-fold ULN, and one participant in the R+delE2/NETA arm with elevation in the range of > 5- to 20-fold ULN. No participants in the PBO arm had elevations > 3-fold.

Worsened grade in post-baseline elevations in AST occurred in 24/259 (9%), 11/254 (4%) and 17/256 (7%) of participants in the R+delE2/NETA, R+E2/NETA, and PBO arms, respectively. One participant (0.4%) in each the R+delE2/NETA and PBO arms had AST elevation in the range of >3-5-fold ULN.

No participants had total bilirubin elevations ≥ 2-fold ULN, and no Hy's law cases were detected.

Narrative reports for participants with any postbaseline ALT and/or AST ≥ 3X ULN in the pivotal placebo-controlled trials are summarized in Table 50 in the Appendix. For completeness, cases of elevated ALT and/or AST that occurred in Study 3003 are also included in this table.

Confounders were present in all cases of transaminase elevations of ≥ 3-fold upper limit of normal. Creatine kinase (CK) elevations occurred in 3 cases (1 participant in each treatment arm) suggesting the source of the enzyme elevation was skeletal muscle rather than liver. Other confounders included obesity, diabetes mellitus, pre-diabetes, fatty liver, alcohol, liver biopsy during laparoscopic cholecystectomy, acetaminophen, and mild elevation in liver enzymes at baseline. Resolution of liver enzyme elevations occurred in 5 cases within 4 to 36 days, 3 in whom no action with study drug was taken, and 2 in whom drug was held for 1-3 days. Study drug was discontinued in one participant and liver enzyme elevations improved. The elevation was detected in one participant post-treatment, and subsequent assessments showed improvement.

Overall, an increased risk for serious drug-induced liver injury with R+E2/NETA was not demonstrated in these clinical trials. All these participants had confounding factors. Most cases of transaminase elevation (AST and/or ALT ≥ 3-fold ULN) improved or resolved with ongoing treatment or with only a brief disruption in treatment. Some elevations were likely of skeletal muscle origin. However, because clearance of the drug is primarily hepatic, patients should be educated on signs and symptoms of liver dysfunction and prescribers should be instructed to discontinue study drug in participants who are found to have hepatic enzyme elevations or liver impairment of any etiology. This information will be included in labeling.

Carbohydrate Metabolism

Fasting blood glucose (FBG), HgbA1c and lipids were measured at baseline and week 24/EOS. The shift analyses for glucose, HgbA1c and lipids presented here were conducted by the FDA Clinical Data Scientist. Shifts in categories of FBG were examined as a function of baseline FBG. The distribution of baseline FBS in the range of normal (<100 mg/dL), pre-diabetes [(pre-DM)≥ 100 to < 126 mg/dL) and diabetes mellitus [(DM) ≥ 126 mg/dL] were generally similar across treatment arms[4] (Source: modified from ISS Table 104).

Glucose:

In the pooled analysis, mean (SD) FBG at baseline was 91.4 (18.4) mg/dL and 94.0 (23.8) mg/dL in the R+E2/NETA and PBO arms, respectively. At Week 24, mean (SD) change from baseline in FBS was +4.9 (24.0) mg/dL and +0.27 (14.9 mg/dL), in the R+E2/NETA and PBO arms, respectively (Source: ISS Table 102). All of the participants who experienced last observed FBS ≥ 200 mg/dL had baseline FBG in the range of DM (≥ 126 mg/dL) (Source: ISS Table 103).

[4] Note that while the diagnostic categories are used to summarize glucose data, in the clinical setting, typically two consistent glucose values are required to establish a clinical diagnosis of IGT or DM in asymptomatic individuals.

Shifts in categories of fasting blood glucose are summarized for the R+E2/NETA arm vs. PBO arm below:

- Shift from normal to pre-DM: 12.7% (28/220) vs. 11.9% (25/210)
- Shift from normal to DM: 1.8% (4/220) vs. 1.9% (4/210)
- Shift from pre-DM to DM: 12.0% (3/25) vs. 9.1% (3/33)
- Shift from DM to pre-DM or normal: 11.1% (1/9) vs. 46.2% (6/13)

Overall, for participants with normal FBG at baseline, an increase in the development of pre-DM or DM with R+E2/NETA treatment as compared to PBO was not observed. Of the participants with pre-DM at baseline, however, a slightly greater proportion had a shift in FBS into the range of DM in the R+E2/NETA arm as compared to PBO, but the number of participants in this category is too small to draw definitive conclusions. Additionally, as compared to the R+E2/NETA arm, a greater proportion of participants in the PBO arm with baseline FBS in the range of DM had improvement with a shift into the range of pre-DM or normal. These results, however, should be viewed with caution. First, in labeling comments submitted on February 22, 2021, the Applicant indicated that they could not ensure that all participants were fasting at the time of the glucose assessment. In addition, the number of participants with pre-DM or DM at baseline was small, and data was missing for approximately 30% of participants.

Hemoglobin A1c:

Mean hemoglobin A1c was in the upper end of the normal range (≤ 5.6%) and comparable across treatment arms at baseline [5.46 (0.69) and 5.5 (0.86) in the R+E2/NETA and PBO arms, respectively]. Minimal mean (SD) increases from baseline in HgbA1c were observed at Week 24 [0.17 (0.34) and 0.06 (0.34)] in the R+E2/NETA and PBO arms, respectively (Source: ISS Outputs Table 5.8.1). The pre-defined categories of HgbA1c that were used for the shift analysis included normal (HbgA1c ≤ 5.6%), pre-DM(HgbA1c 5.7 to 6.4%) and DM (HgbA1c ≥ 6.5%). Last on treatment HgbA1c ≥ 6.5% and an increase from baseline was observed in 3.1% of participants in the R+E2/NETA arm and 1.6% of participants in the PBO arm. Three (1.2%) and one (0.4%) of participants in the R+E2/NETA and PBO arms, respectively had an increase in HgbA1c of >1.0 from baseline (Source: ISS Table 103).

Shifts in categories of HgbA1c are summarized for the R+E2/NETA arm vs. PBO arm below:

- Shift from normal to pre-DM: 20.7% (38/184) vs. 13.0% (23/177)
- Shift from pre-DM to DM: 7.6% (4/53) vs. 0%
- Shift from pre-DM to normal: 22.6% (12/53) vs. 35.1% (20/57)
- Shift from DM to pre-DM: 10.0% (1/10) vs. 25.0% (3/12)

These data may be confounded by the presence of HMB, anemia and/or improvements in anemia with associated reticulocytosis, all of which could reduce HgbA1c levels.

In the placebo-controlled trials, AEs related to carbohydrate metabolism (PTs included Type 2 diabetes mellitus, diabetes mellitus, hyperglycaemia, glucose tolerance impaired, and glycosylated haemoglobin increased) were reported for 5 participants (2%) (1 participant with

each PT) in the R+E2/NETA arm and 2 participants (0.8%) in the PBO arm (one with diabetes mellitus and one with hyperglycaemia) (Source: ISS Table 71). None were reported as SAEs. The risk was greater for participants with a medical history of carbohydrate and lipid metabolic abnormalities (Source: ISS Table 72). Of the participants without a medical history of events, all had risk factors at baseline including elevated BMI, baseline hyperglycemia or baseline elevation in HgbA1c. Analysis of the extension trial indicates that overall 2.5% of participants exposed to any R+E2/NETA reported an AE related to carbohydrate metabolism (Source: ISS Table 73).

Although some results are consistent with unfavorable alterations in carbohydrate metabolism, given the limitations discussed above, we agree with the Applicant that it is reasonable to exclude these clinical trial data from labeling. However, a warning regarding the risk of impaired carbohydrate metabolism will be included in the Warnings and Precautions section of the label for consistency with class labeling for other estrogen/progestin-containing products.

Lipids

Exogenous estrogens and progestins have been associated with increases in cholesterol and triglycerides. Therefore, changes in lipids were a laboratory assessment of interest. In addition, a dose-related increase in mean total cholesterol, LDL, and HDL that was greater than placebo was observed in pooled 12-week relugolix monotherapy studies in the uterine fibroid program TAK-385/CCT-002, TAK-385-3008, TAK-385/CCT-001). For example, the mean (SD) change from baseline for total cholesterol at week 12 for the PBO, and relugolix 10 mg, 20 mg and 40 mg arms was 3.5 (22.0), 5.4 (22.1), 13.3 (24.6) and 21.2 (22.4) mg/dL, respectively. The trend for an increase in triglycerides was less clear, with the greatest increase observed in the relugolix 20 mg arm (0.26 mmol/L).

In the 24-week placebo-controlled trials combined, small declines in mean total cholesterol were observed in the R+E2/NETA and PBO arms at Week 24 [mean (SD) change from baseline of -0.4 (25.02) mg/dL and -0.5 (24.39) mg/dL, respectively]. Similar results were seen in mean change from baseline in triglycerides, with mean (SD) changes of -0.071 (0.5805), and -0.057 (0.5487) observed in the relugolix + E2/NETA and placebo groups, respectively.

Shifts in categories of lipids [total cholesterol, LDL, HDL and triglycerides (TGs)] from baseline to Week 24 were examined. A summary of results for the R+E2/NETA arm vs. the PBO arm is presented here.

Total Cholesterol (R+E2/NETA vs. PBO)

- shift from normal to borderline high (200 to <240 mg/dL): 13.7% (24/175) vs. 7.7% (13/170)
- shift from normal to high (≥ 240 mg/dL): 1.7% (3/175) vs. 0.6% (1/170)
- shift from borderline high to high: 9.3% (5/54) vs. 6.5% (4/62)
- shift from high to borderline high: 57.1% (27/54) vs. 23.8% (5/21)
- shift from high to normal: 14.3% (3/21) vs. 9.5% (2/21)

Assessment of shifts toward improvement in these latter categories are limited by the relatively small number of participants with high total cholesterol at baseline.

LDL (R+E2/NETA vs. PBO)

- shift from normal (<130 mg/dL) to borderline high (130 to <160 mg/dL): 9.3 % (19/204) vs. 6.5% (13/201)
- shift from normal to high (160 to 190 mg/dL): 1.5% (3/204) vs. 0.5% (1/201)
- shift from normal to very high (≥ 190 mg/dL) , 0.5% (1/204) vs. 0%

For participants with borderline high LDL at baseline, shifts toward worsening categories or toward improvement were similar in the R+E2/NETA and PBO arms. Of the participants with high LDL at baseline, as compared to the R+E2/NETA arm, a greater proportion in PBO arm experienced shifts to lower (more favorable) categories of LDL; however, these data are limited by the small number of participants in this category (7 participants in the R+E2/NETA arm and 18 participants in the PBO arm).

HDL (R+E2/NETA vs. PBO)

A reduction of HDL is considered unfavorable. Oral estrogens and relugolix monotherapy have been associated with increases in HDL while some progestins have been associated with declines. Shifts in categories of HDL are summarized below:

- shift from normal HDL (50 to < 60 mg/dL) to low HDL (< 50 mg/dL): 26.9% (18/67) vs. 12.8% (10/78)
- from normal to high HDL (≥ 60 mg/dL) 19.4% (13/67) vs. 12.8% (17/78)
- shift from low HDL (< 50 mg/dL) to normal: 10.6% (9/85) vs. 18.3% (13/71)
- shift from low to high HDL: 5.9% (5/85) vs. 2.8% (2/71)

The number of participants with low HDL at baseline, however, is relatively small.
A similar proportion of participants in the R+E2/NETA and PBO arms had a shift from high HDL to lower categories.

Triglycerides (R+E2/NETA vs. PBO)

Oral estrogen has been associated with elevations in triglycerides. No participants had very high TGs (≥ 500 mg/dL) at Week 24/EOT in the placebo-controlled trials. A similar proportion of participants in the R+E2/NETA and PBO arms had shifts from normal TGs (< 150 mg/dL) to borderline high (150 to < 200 mg/dL) [5.7% (11/194) vs. 5.6% 12/215), respectively] or to high (200 to < 500 mg/dL) [3.6% (7/194) vs. 2.3% (5/215), respectively]. A similar proportion of participants (21% in each the R+E2/NETA and PBO arms) with borderline high TGs at baseline shifted to the category of high TGs.

Adverse events related to changes in lipids

No adverse events related to lipid metabolism were reported for participants treated with R+E2/NETA combination therapy during the pivotal trials (Source: ISS Table 71). One participant in the R+delE2/NETA arm (Participant (b) (6) in Study MVT-601-3002) experienced Grade 3 elevation in triglycerides. Baseline triglycerides were elevated at 3.97 mmol/L (352.3 mg/dL)

and increased to 6.05 mmol/L (535.4 mg/dL) 4 weeks later while on relugolix monotherapy. The participant withdrew at that time due to work constraints. No participants experienced marked hypertriglyceridemia (≥ 1000 mg/dL) or hypertriglyceridemia associated pancreatitis, which has been reported in association with estrogen. In the OLE study, 0.3% of participants with any R+E2/NETA exposure reported AEs related to lipid effects (one hypercholesterolemia and one hypertriglyceridemia).

Overall, of the participants with normal baseline measurements, a greater proportion of participants treated with R+E2/NETA as compared to PBO had shifts to worsening categories for each of these of the individual cholesterol assessments (total cholesterol, LDL and HDL). An imbalance in shifts in categories of TGs was not observed. Elevations in lipids is included in the Warnings and Precautions section of labeling for estrogen and progestin-containing products and therefore, will be included in labeling for this product. In addition, the unfavorable shifts observed in the placebo-controlled trials for total cholesterol and LDL will be useful to providers and patients and will be included in Section 6 of the label. The clinical consequence of the decline in HDL is less clear and will not be included in labeling. Although marked elevations in triglycerides was not observed in clinical trials, the risk for this potentially serious complication, particularly for women with pre-existing hypertriglyceridemia will also be included in the Warnings and Precautions section of the label. The increase in HDL and triglycerides and decrease in LDL described for E2/NETA will also be included in the Pharmacodynamics section of the label (Section 12.2).

Hyperkalemia

In Studies 3001 and 3002, post-baseline elevations in potassium of grade 2 or higher (>5.5 mmol/L) were seen in 12 participants, with an imbalance in the R+E2/NETA (2%) and R+delE2/NETA (1.9%) arms as compared to PBO (0.8%). In response to an IR from the Agency dated October 14, 2020, the Applicant provided additional information as requested. Most potassium elevations were grade 2 (>5.5-6.0 mmol/L), except for two grade 3 elevations (>6.0-7.0 mmol/L) in one participant each in the relugolix + E2/NETA (Patient (b) (6)) and relugolix + delayed E2/NETA (Patient (b) (6)) groups, and one grade 4 elevation (>7.0 mmol/L) in the placebo group (Patient (b) (6) In each case, potassium concentrations returned to within the laboratory reference range at the next study visit while the patient remained on study drug. Three participants, all in the R+E2/NETA arm, had fluctuations in potassium levels with transient elevations throughout the study, including at screening/baseline and at the safety follow-up visit in two participants. Two of these participants also had transient grade 2 elevations during Study 3003 that returned to and remained in the normal range in the latter weeks of the study. In Study 3003, there were 11 episodes of grade 2 increases in potassium observed in 10 participants. All but 3 were isolated elevations that returned to the normal range at the next visit while participants remained on study drug. Elevations were detected at the safety follow-up visit in two participants for whom no further values are available. In all 3 studies, most participants with hyperkalemia reported use of nonsteroidal anti-inflammatory medications on an as-needed basis. One participant in the R+E2/NETA arm had a medical history of hyperkalemia and had grade 2 hyperkalemia at screening. In the IR response, the Applicant indicated that no other potential factors were identified as contributing to the

elevations, including specimen handling issues, hemolysis, or use of other concomitant medications. No episodes were associated with abnormalities in other chemistry parameters and none were reported as an AE. These data do not suggest a safety signal. Rather, some participants appear to have hyperkalemia at baseline and intermittent hyperkalemia, and others had a single transient elevation that appears to have been spurious.

Creatine Kinase Elevations

An imbalance in creatine kinase (CK) elevations of Grade 3 or higher was noted in the R+E2/NETA and R+delE2/NETA arms as compared to PBO. The proportion of participants with CK elevations during pivotal trials is shown in Table X.

Table 23: Grade 3 or Grade 4 Elevations in Creatine Kinase in Phase 3 Trials 3001, 3002, and 3003

R+delE2/NETA*	R+E2/NETA	PBO
Studies 3001 and 3002		
N=258	N=254	N=256
6 (2.3%)	4 (1.6%)	1 (0.4%)
Study 3003		
N=149	N=163	N=164
4 (2.7%)	2 (1.2%)	5 (3.0%)

Source: Applicant response to Information Request submitted February 18, 2021 Table 4.
*Two additional participants in the R+delE2/NETA arm had elevations that occurred after the last dose of study drug.

In response to an information request, the Applicant provided narrative reports for participants with elevations in creatine kinase (submission dated February 18, 2021). Of the 4 participants in the R+E2/NETA arm, two had Grade 1 CK elevations at screening/ baseline. One participant (b) (6) had rhabdomyolysis associated with untreated hypothyroidism (Thyroid stimulating hormone (TSH) 79 mIU/L). CK improved to Grade 1 with treatment of hypothyroidism and hydration. Study drug was stopped soon after for unrelated reasons. Participant (b) (6) reported muscle soreness. She continued in the OLE study and had two subsequent Grade 1 CK elevations. Participant (b) (6) had Grade 1 elevation at screening/baseline and had fluctuations in CK from normal to Grade 2 through 44 weeks of treatment in the extension study. Her final (Week 44) assessment was normal. Participant (b) (6) had Grade 1 CK elevation at screening/baseline and periodic Grade 1-2 elevations. She had a Grade 3 CK elevation at Week 24 and did not have a follow-up assessment. Participant (b) (6) in the PBO arm also had a Grade 1 CK elevation at screening/baseline. She reported weekly physical therapy, daily stretching, and alcohol prior to her Grade 4 CK elevation. She enrolled in the extension study, and CK was normal on R+E2/NETA treatment until Week 52 when she again had Grade 1 elevation.

Two of the six participants with CK elevations in the R+delE2/NETA arm had Grade 1-2 CK elevations at screening/baseline. These two participants also had other potential confounders [exercise (b) (6) and concomitant medications (b) (6). Participant (b) (6) had recurrent

Grade 3-4 elevations at Weeks 32 and 40 while participating in the extension study. CK levels normalized on continued therapy in 3 of the six participants and declined in 3 others, two of whom had confounders. One participant (b) (6) with Grade 2 elevation at screening/baseline also had Grade 4 elevation at the 30 day post-treatment follow-up visit.

Five of the eleven participants who presented with new Grade 3-4 CK elevations during Study 3003 had Grade 1-2 elevations at screening/baseline. CK normalized in 9 participants on continued treatment and improved in the others. Potential confounders (concomitant medications, dehydration and strenuous exercise) were identified in two participants (b) (6) and (b) (6).

Overall, approximately 43% of the 23 participants with Grade 3 CK elevations had Grade 1-2 CK elevations detected during screening/baseline. All but three participants were asymptomatic; two reported myalgias and one was hospitalized with the SAE of rhabdomyolysis associated with hypothyroidism. None permanently discontinued study drug due to CK elevations. Activity and exercise were not specifically assessed in these participants. CK levels improved/normalized in all participants on continued therapy who had follow-up data. Only one participant had a recurrence of Grade 3-4 CK elevation while on therapy but was taking two medications reported to be associated with CK elevations.

This reviewer concurs with the Applicant that given the transient nature of these Grade 3-4 CK elevations during treatment with R+ E2/NETA coupled with the improvement or resolution with continued study drug and the rare recurrence of this degree of CK elevation with continued treatment, CK elevations are not suggestive of an adverse drug reaction and will not be included in labeling.

7.4.7. Vital Signs

Blood Pressure

Single blood pressure measurements were obtained in the seated position after 5 minutes of rest at baseline and at 4-week intervals during the treatment phase of all three Phase 3 trials, as well as 30 days after treatment at the safety follow-up visit.

In the placebo-controlled trials combined, only minor increases in blood pressure were observed in the R+E2/NETA arm as compared to the PBO arm. The maximum increase in DBP during the treatment phase occurred at Week 24, with a mean (SD) increase from baseline of 1.7 (10.66) mm Hg in the R+E2/NETA arm and mean (SD) change from baseline of 1.0 (10.91) mm Hg in the PBO arm. At the safety follow-up visit, mean (SD) change in SBP was 2.7 (11.31) and 3.6 (10.14) in the R+E2/NETA and PBO arms, respectively. The maximum increase in DBP during the treatment phase occurred at Week 16 for the R+E2/NETA arm with a mean (SD) increase of 0.9 (8.04) mmHg as compared to 0.6 (8.52) for placebo. At Week 24 mean (SD) changes were 0.1 (8.89) and 0.2 (9.05) for each arm, respectively. At the 30-day safety visit, corresponding values were 1.1 (9.34) mm Hg and -0.3 (8.85), respectively.

The proportion of participants who experienced any potentially clinically meaningful BP reading defined as SBP ≥140 mm Hg and ≥180 mm Hg or DBP ≥90 mm Hg and ≥105 mm Hg, as well as incremental changes in SBP ≥20 mm Hg and DBP ≥15 mm Hg are shown in Table 24 below. While a slight imbalance in the proportion of participants with any readings in SBP ≥140 mm Hg was observed in study MVT-601-3001, this was not the case for Study 3002, such that overall, in the studies combined, there was no imbalance. One participant had an increase in SBP ≥180 mm Hg (narrative for Participant (b) (6) is reviewed with SAEs for Study 3003). A greater proportion of participants in the R+E2/NETA arm experienced an increase from baseline in SBP ≥20 mm Hg as compared to the placebo arm. However, there were no meaningful differences in the proportions of participants having two or more consecutive values of increases in systolic or diastolic blood pressure above these predefined thresholds.

Table 24: The Proportion of Participants Meeting Thresholds for Increases in Systolic and Diastolic Blood Pressure in 24-week placebo-controlled Studies 3001 and 3002

	Study 3001		Study 3002		Studies 3001+3002	
Assessment	R+E2/NETA N=128	PBO N=127	R+E2/NETA N=126	PBO N=129	R+E2/NETA N=254	PBO N=256
Systolic Blood Pressure						
≥140 mm Hg	39 (30.5%)	33 (26.0%)	31 (24.6%)	38 (29.5%)	70 (27.6%)	71 (27.7%)
≥180 mm Hg	1 (0.8%)	0	0	0	1 (0.4%)	0
≥20 mm Hg increase from baseline	23 (18.0%)	17 (13.4%)	26 (20.6%)	18 (14.0%)	49 (19.3%)	35 (13.7%)
Diastolic Blood Pressure						
≥90 mm Hg	33 (25.8%)	35 (27.6%)	37 (29.4%)	42 (32.6%)	70 (27.6%)	77 (30.1%)
≥105 mm Hg	2 (1.6%)	4 (3.1%)	1 (0.8%)	2 (1.6%)	3 (1.2%)	6 (2.3%)
≥15 mm Hg increase from baseline	19 (14.8%)	22 (17.3%)	18 (14.3%)	19 (14.7%)	37 (14.6%)	41 (16.0%)

Source: MVT-601-3001 CSR Table 7.3.10.1, MVT-601-3002 CSR Table 7.3.10.1, ISS Table 7.2.1
Abbreviations: R=relugolix; E2 = estradiol; NETA = norethindrone; acetate; PBO=placebo; N = number of patients in the treatment group; bpm=beats per minute. Most extreme postbaseline treatment-emergent values. Patients can be summarized in more than one row. Baseline value is defined as the last measurement on or before the first administration (date and time) of study drug.

In the placebo-controlled trials of 24-weeks treatment duration, the AEs of hypertension (PT: hypertension, blood pressure increased, essential hypertension, BP diastolic increased, and hypertensive crisis) were reported in a greater proportion of participants in the R+ E2/NETA arm (14/254, 5.5%) as compared to PBO (7/256, 2.7%) (Source: ISS Table 82, Table 4.26.1.8). Hypertensive crisis was reported for 1 participant in the PBO arm. No events were reported as SAEs. No participants in the R+E2/NETA or PBO arms discontinued study drug due to hypertension, while two events led to study drug discontinuation for participants in the R+delE2/NETA arm, one while the participant was on relugolix monotherapy and the other while on R+E2/NETA.

The imbalance in hypertension AEs is primarily driven by Study MVT-601-3001, in which the AE of hypertension was reported for 7.0% of women in the R+E2/NETA arm (9/128) as compared to 0.8% in the placebo arm (1/127). In contrast, in study MVT-601-3002, AEs of hypertension were balanced [(4.0% (5/126) vs. 4.7% (6/129) in the R+E2/NETA and PBO arms, respectively]. See Tables 46, 47 and 48 in the Appendix for narrative summaries of participants with the AE of hypertension. In Study 3001, a greater proportion of participants in the R+E2/NETA arm had hypertension at baseline as compared to the PBO arm, but this was not the case for Study MVT-601-3002. This imbalance in baseline characteristics may provide a partial explanation for the difference in hypertension AEs observed in the two studies. However, both new onset hypertension and exacerbation of pre-existing hypertension are clinically important, and will be included in the Warnings and Precautions section of the label, consistent with class labeling for estrogen-containing products.

7.4.8. Electrocardiograms (ECGs)

Study 3001 and Study 3002
In the 24-week placebo-controlled trials, ECGs were obtained at baseline, Week 12, and Week 24 or early termination.

The following participants were noted to have abnormal ECG postbaseline:
Participant (b) (6) (Study 3001) Randomized to R+E2/NETA:

- Week 12 QTcF 478 msec, repeated 436 msec, 448 msec, biphasic/flat T-waves
- Week 24-flat T-waves, technical problem-artifact, unable to measure QT/QTc

Participant (b) (6) (Study 3001) Randomized to R+E2/NETA

- Week 12 sinus bradycardia Heart Rate (HR) 46 bpm

Participant (b) (6) (Study 3002) Randomized to R+E2/NETA

- Week 12-flattened T-waves, normalized at the safety follow-up visit

Study 3003
In the OLE study, ECGs were obtained at Week 52 or early termination.

The following participants had post-baseline ECG abnormalities:

- Participant (b) (6) Week 12 QTcF 478 msec
- Participant Week 12 sinus tachycardia with heart rate (HR) 101 bpm; Week 24 sinus tachycardia with heart rate (HR) 106 bpm
- Participant (b) (6): Week 24 QTcF 451-467 msec (QTcF was normal at 441 msec at Week 52)

Reviewer Comment: Changes in the QT interval are summarized in Section 7.4.9. Other ECG changes included tachycardia (1 participant) with heart rate in the low 100s, bradycardia (1 participant) with heart rate in the 40's, and non-specific T-wave changes (3 participants). No

safety signals related to ECG changes emerged.

7.4.9. QT

Thorough QT Study

A thorough QT study (Study TAK-385_106), entitled "A Randomized, Double-Blind, Placebo- and Positive-Controlled (Open-Label Moxifloxacin), 4-Arm Parallel-Group Study to Evaluate the Effect of TAK-385 on Cardiac Repolarization in Healthy Participants" was conducted in 280 healthy females (48.6%) and males (51.4%). (b) (4) Participants were randomized to receive single doses of TAK-385 (relugolix) 60 mg or 360 mg, placebo, or moxifloxacin 400 mg (positive control).QT intervals were assessed using three different correction methods: QT interval with Fridericia correction method (QTcF), QT interval with Bazett correction method (QTcB), and individual QT interval correction (QTcI). The review team concluded that no significant QTc prolongation effect of TAK-385 (60 mg and 360 mg) was detected in the study. Assay sensitivity was demonstrated in this study by confirming the QT prolongation effect of moxifloxacin 400 mg.

Studies 3001 and 3002

In the 24-week placebo-controlled trials, ECGs were obtained at baseline, Week 12, and Week 24 or early termination. A signal for a clinically concerning increase in QTcF was not observed. In the pivotal 24-week trials, no participant had QTcF >501 msec. At any time during the 24-week treatment period, change from baseline QTcF ≥ 30 msec was seen in 8.6%, 3.8% and 3.1% of participants in the R+E2/NETA, R+delE2/NETA and PBO arms, respectively in study MVT-601-3001, and in 3.2%, 6.3% and 5.4% of participants for each treatment arm, respectively in study MVT-601-3002. Only one participant of the 24 week pivotal studies had a change from baseline ≥ 60 msec (Participant (b) (6) in study MVT-601-3001 randomized to R+delE2/NETA).

Study 3003

In the open-label extension study, ECGs were obtained at week 52 or early termination. Mean QTcF did not increase with up to 52 week of treatment with R+E2/NETA. In the open-label extension trial, no participant had QTcF >500 msec. In the open-label extension study, at any time during the 52-week treatment period, 1.2% of participants in the R+E2/NETA arm experienced QTcF in the range of 480-500 msec while no participants in the other 2 treatment arms had QTcF ≥ 480. At any point during the 52-week treatment period, the proportion of participants with change from baseline in QTcF ≥ 30 msec was 7.4%, 5.4% and 4.3% for each treatment arm, respectively. One participant (0.6%) in the R+E2/NETA arm had change from baseline in QTcF ≥ 60 msec.

7.4.10. Immunogenicity

In Studies 3001 and 3002, the Applicant's search for events per the MedDRA Hypersensitivity SMQ (narrow) identified hypersensitivity-related AEs for 2% (5/254) of participants in the R+E2/NETA arm as compared to 3.9% (10/256) of participants in the PBO arm. In the R+del E2/NETA arm, 0.8% (2/258) reported a hypersensitivity-related AE. In the R+E2/NETA arm, one participant each reported the non-serious AE of dermatitis, blepharitis allergic, rash generalized, and rash pruritic. All events were reported as nonserious and none led to study drug discontinuation. In addition, one participant (b) (6) randomized to R+E2/NETA in Study 3002 experienced the non-serious AE of ocular angioneurotic edema on Study day 29. The event resolved on the same day. No action was taken with the study drug and the event did not recur. The event was assessed as not related to study drug. Nonserious hypersensitivity AEs that occurred in participants randomized to PBO included eczema (2), allergic rhinitis (2), urticaria (2), acneiform dermatitis (1), drug hypersensitivity (1), and hypersensitivity (1). One participant in the PBO arm of Study 3001 (Participant (b) (6) discontinued study drug due to the AE of urticaria.

In Study 3003, hypersensitivity-related AEs were reported in four additional participants in the R+ E2/NETA arm, and one in the PBO arm and four in the R+del E2/NETA arm. Other PTs reported for participants with any R+E2/NETA exposure in study MVT-601-3003 include three participant experiencing dermatitis, and one participant experiencing each dermatitis allergic, rash generalized, rash maculo-papular, dermatitis contact, vulval ulceration, vulvovaginal rash, and vulvovaginitis allergic.

Hypersensitivity reactions were also reported in trials of relugolix monotherapy. In study TAK-385/CCT-002 (24-week monotherapy), two events of urticaria were reported with relugolix monotherapy whereas no events were reported for participants in the active control arm (leuprorelin). In each case, no action was taken with study drug and the events were assessed as not related to study drug.

In the 120-day safety report, the Applicant described three postmarketing reports for Relumina 40 mg (relugolix monotherapy) of serious adverse reactions described below:

- 47-yo female was reported to have developed edema that extended from the face to the back of the hands associated with a pruritic skin eruption, with onset within 3 days after initiation of relugolix monotherapy, and after having taken 2 doses of drug. Vital signs were stable, and upper body edema and a mild skin eruption were the only signs reported. Relugolix was discontinued (last dose was on the day prior to onset of symptoms). The patient was hospitalized for observation and treated with dexamethasone sodium phosphate 6.6 mg, dexchlorpheniramine maleate 5 mg, famotidine 20 mg and Lactated Ringer's solution. On the following day, two doses of oral fexofenadine hydrochloride 60 mg were administered. On an unknown date, the event resolved.

- 49-year-old female patient with a past medical history of drug-induced anaphylactic reaction (drug unknown) developed "respiratory discomfort" and abdominal pain 1.5 hours after taking the first dose of relugolix monotherapy; the symptoms were reported

to resolve with rest, without treatment. The following day, 1.5 hours after taking the second dose of relugolix, the patient developed the same symptoms, which led to emergency room treatment with dexchlorpheniramine maleate and famotidine. Relugolix was discontinued on that day. Treatment with fexofenadine hydrochloride was started on the following day and the event was reported to resolve 24 days later (26 days after onset). Information is incomplete in this case to make a determination as to whether the patient had an anaphylactic reaction. Although the nature of "respiratory discomfort" was not provided, the recurrence of symptoms with the second dose is concerning for a serious hypersensitivity reaction. On the other hand, duration of 24 days would be unusual for a hypersensitivity reaction.

- 40-year-old female patient was reported to have drug eruption, described as red eczema, and malaise. Relugolix was dispensed 3 days prior to the event onset, and the exact start date of relugolix monotherapy was unknown. Relugolix was discontinued (last dose on Day 4 after relugolix dispensed). The patient was treated with diphenhydramine, and the event resolved on Day 4 after relugolix dispensed.

Although an imbalance in hypersensitivity-related AEs was not observed in placebo-controlled trials, the postmarketing reports for relugolix monotherapy are concerning for serious hypersensitivity reactions. Therefore, the Division concurs with the Applicant's proposal to include hypersensitivity as a contraindication (Section 4). In addition, we will require hypersensitivity reactions to be included in the Warnings and Precaution section (Section 5.14) and anaphylactoid reactions to be included in postmarketing experience (Section 6.2) of the PI.

7.4.11. Visual Acuity

Data from nonclinical studies in rats and monkeys showed histological changes consistent with phospholipidosis (PLD). In the prostate cancer development program, no systematic increases in a biomarker for PLD were detected and no eye safety signals emerged in Studies C27002 and C27003 using slit lamp examinations. In Studies 3001 and 3002 in the uterine fibroid program, visual acuity was assessed at baseline and week 24/EOT using an eye chart. Overall, excluding participants whose deterioration in visual acuity was attributed to inconsistent use of corrective lenses, a total of 3/258 (1.2%), 7/254 (2.8%), and 5/256 (2.0%) of participants in the R+delE2/NETA, R+E2/NETA, and PBO arms, respectively had a decline in visual acuity score by ≥ 10 points. No abnormal eye findings were reported for 6/7 participants in the R+E2/NETA arm and 4/5 participants in the R+DelE2/NETA arm who underwent ophthalmologic examination by a specialist.

Reviewer Comment: A decline in visual acuity from relugolix or R+E2/NETA was not apparent in clinical Studies C27002 and C27003 for the prostate program and Studies 3001 and 3002 in the uterine fibroid program. Furthermore, PLD was not reported for the participants with a decline in visual acuity who were evaluated by a specialist.

7.5. Analysis of Submission-Specific Safety Issues

7.5.1. Boxed Warning for venous and arterial thromboembolic events (VTEs and ATEs)

Issue

The Agency will require a boxed warning in the label to inform prescribers of the potential risk of venous and arterial thromboembolic events (VTEs and ATEs). (b) (4)

Background

Estradiol (E2) 0.5 mg in combination with norethindrone acetate (NETA) 1 mg (Activella) is approved for postmenopausal women for the treatment of moderate to severe vasomotor symptoms and moderate and severe vulvar and vaginal atrophy due to menopause. Labeling for this approved combination product contains a boxed warning regarding the risk of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and myocardial infarction (MI) based upon results of the Women's Health Initiative (WHI) conducted in postmenopausal women 50 to 79 years of age. No product containing only E2 and NETA is currently approved for use in premenopausal women. However, another GnRH antagonist in combination with E2/NETA is approved for the treatment of heavy menstrual bleeding due to uterine fibroids in premenopausal women. Labeling for this approved GnRH antagonist/E2/NETA combination product also includes a boxed warning regarding the risk of venous and arterial thrombotic or thromboembolic events, "especially in women at increased risk for these events." Additionally, although there are no available CHCs that include E2/NETA, DUOG believes that the Draft Guidance for Industry on Labeling for Combined Hormonal Contraceptives which provides recommendations for class labeling of VTE/ATE risk for these estrogen/progestin combination products in premenopausal women is relevant for labeling for R+E2/NETA. The Draft Guidance advises inclusion of a boxed warning for the increased risk of serious cardiovascular events, particularly in women over 35 years of age who smoke.

In the current marketing application, the Applicant proposes (b) (4)

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(b) (4)

Conclusion

(b) (4)

VTE/ATE are serious and potentially life-threatening events that meet the statutory requirement for a boxed warning in labeling. In addition, a boxed warning for VTE/ATE is consistent with 1) current box warning labeling for the E2/NETA product (Activella) which is being utilized as add-back; 2) the Draft Guidance for Industry on Labeling for Combined Hormonal Contraceptives and 3) the labeling for another oral GnRH antagonist combined with the same E2/NETA combination. Therefore, we have concluded that the label for R+E2/NETA should align with class labeling and include the boxed warning regarding the risk of VTE/ATE.

7.5.2. Decline in Bone Mineral Density (BMD)

Issue

DUOG and the Applicant differ with respect to the interpretation of BMD data from Phase 3 clinical trials. DUOG concluded that BMD declined over 52 weeks of R+E2/NETA treatment without evidence of a plateau while the Applicant concluded that (b) (4) loss occurred.

Background

(b) (4) To assess the extent to which E2/NETA mitigates bone loss when combined with relugolix, BMD was measured at the lumbar spine, total hip and femoral neck by dual energy X-ray absorptiometry (DXA) at baseline, Week 12 and Week 24 during the two Phase 3 placebo-controlled trials and at Weeks 36 and 52 in the OLE. BMD results for the uterine fibroid cohort in Study MVT-601-034 (heretofore, referred to as Obs-UF), an observational BMD study of women with uterine fibroids and endometriosis who were not treated with hormonal therapy was submitted as a comparator as agreed upon with the Division (see Meeting Minutes for End-of-Phase 2 meeting held on October 5, 2016 under IND 131161).

The Applicant proposed (b) (4)

(b) (4)

Assessment

BMD Protocol

BMD was measured by DXA at the lumbar spine (L1-L4), total hip and femoral neck at baseline and Weeks 12 and 24 in the pivotal trials, and at Weeks 36 and 52 in the OLE trial. A central imaging center was responsible for longitudinal calibration and quality control of scanners and for treatment-blinded readings. A correction factor, based on site-specific calibration data was applied to BMD data as appropriate. A DXA scan was not performed for participants who terminated study drug before treatment Week 6. Participants were not prescribed vitamin D or calcium as part of the protocol, but their use was permitted. In studies 3001 and 3002, investigators were notified if a participant had a decline in BMD of ≥ 7% at any of the 3 reported anatomic sites and action taken, if any, was determined by the investigator. However, participants with decline in BMD of ≥ 7% or Z-score < -2.0 were prohibited from entering Study 3003. During Study 3003, DXA scans were performed at Weeks 36 and 52/early termination. Study drug was discontinued for participants who experienced a decline in BMD of ≥ 7%. Decline in BMD of ≥ 7% and fractures were captured as AESIs.

The requirements for post-treatment follow-up DXA scans to assess for recovery of bone loss for participants who did not enter MVT-601-035 (randomized withdrawal study) varied according to treatment duration. The criteria for DXA scan 6 months post-treatment was

decline from pretreatment baseline of >2% at the lumbar spine or total hip for participants treated for < 36 weeks and decline >3% at the lumbar spine or total hip for participants treated for ≥ 36-52 weeks. At post-treatment month 6, participants who had a decline of > 1.5% in the lumbar spine or > 2.5% in the total hip were "encouraged" to have another scan at post-treatment month 12. Participants with a decline at either site of ≥ 3% at the post-treatment month 12 scan were referred to a bone specialist.

Results

Percent Change from Baseline in BMD

In Studies 3001 and 3002, baseline BMD was normal and comparable across treatment arms. Mean percent change (95% CI) from pretreatment baseline in BMD at 12 and 24 weeks for each anatomic site for each treatment arm is shown in Table 26. Because BMD changes tend to occur more rapidly in the lumbar spine in response to a reduction in estrogen levels, this anatomic site will be the focus of the remainder of this review. It is noteworthy, however, that changes in the femoral neck were generally similar to the lumbar spine. In a pre-specified statistical analysis of pooled data from Studies 3001 and 3002 at Week 12, treatment difference in the mean change in lumbar spine (LS) BMD at Week 12 in the R+E2/NETA as compared to the R+delE2/NETA arm (which compared relugolix monotherapy to R+E2/NETA combination therapy) was 1.34 [(95% CI 0.82, 1.85), p< 0.0001] (b) (4)

Table 26: Least Square Mean Percent Change (95% CI) from Pretreatment Baseline in Bone Mineral Density at Treatment Weeks 12 and 24 According to Treatment Arm in Studies 3001, 3002 and Combined

	MVT-601-3001			MVT-601-3002			Combined Safety Population		
Visit	**R+ E2/NETA N=128**	**R+del E2/NETA N=132**	**PBO N=127**	**R+ E2/NETA N=126**	**R+del E2/NETA N=126**	**PBO N=129**	**R+ E2/NETA N=254**	**R+del E2/NETA N=258**	**PBO N=256**
Lumbar Spine									
Week 12									
n	101	103	103	103	95	104	204	198	207
% change (95% CI)	-0.47 (-1.04, 0.10)	-2.0 (-2.56, -1.43)	0.20 (-0.36, 0.76)	-0.82 (-1.35, -0.29)	-1.92 (-2.46, -1.37)	0.51 (-0.01, 1.03)	-0.63 (-1.02, -0.24)	-1.96 (-2.35, -1.57)	0.34 (-0.04, 0.72)
Trt Diff vs. delayed (95% CI)	1.53 (0.79, 2.26)			1.10 (0.38, 1.82)			1.34 (0.82, 1.85) p< 0.0001		
Trt Diff vs. placebo (95% CI)	-0.67 (-1.40, 0.07)	-2.19 (-2.92, -1.47)		-1.33 (-2.03, -0.63)	-2.43 (-3.14, -1.71)		-1.00 (-1.48, -0.46)	-2.30 (-2.81, -1.79)	
Week 24									
n	100	100	102	95	94	95	195	194	197
% change (95% CI)	-0.36 (-0.93, 0.22)	-1.82 (-2.39, -1.25)	0.05 (-0.52, 0.62)	-0.13 (-0.71, 0.46)	-2.12 (-2.71, -1.54)	0.312 (-0.26, 0.89)	-0.23 (-0.64, 0.18)	-1.97 (-2.39, -1.57)	0.18 (-0.22, 0.58)
Trt Diff vs. delayed (95% CI)	1.46 (0.71, 2.21)			2.00 (1.21, 2.79)			1.74 (1.20, 2.28)		

Trt Diff vs. placebo (95% CI)	-0.41 (-1.16, 0.34)	-1.87 (-2.61, -1.13)		-0.44 (-1.23, 0.34)	-2.44 (-3.23, -1.65)		-0.42 (-1.00, 0.12)	-2.16 (-2.70, -1.62)	
Total Hip									
Week 12									
n	102	100	104	104	93	102	206	193	206
% change (95% CI)	0.01 (-0.44, 0.46)	-0.95 (-1.40, -0.50)	0.41 (-0.03, 0.85)	0.051 (-0.35, 0.45)	-1.07 (-1.48, -0.65)	-0.16 (-0.56, 0.24)	0.014 (-0.29, 0.32)	-1.02 (-1.32, -0.71)	0.12 (-0.17 0.42)
Trt Diff vs. delayed (95% CI)	0.96 (0.37, 1.54)			1.12 (0.57, 1.66)			1.03 (0.63, 1.43) P < 0.0001		
Trt Diff vs. placebo (95% CI)	-0.40 (-0.98, 0.18)	-1.36 (-1.94, -0.78)		0.21 (-0.32, 0.74)	-0.91 (-1.45, -0.36)		0.11 (-0.50, 0.28)	-1.14 (-1.54, -0.740)	
Week 24									
n	100	98	103	98	92	95	198	190	198
% change (95% CI)	0.02 (-0.46, 0.51)	-1.04 (-1.52, -0.56)	0.55 (0.08, 1.02)	-0.17 (-0.61, 0.26)	-1.16 (-1.60, -0.71)	-0.04 (-0.48, 0.39)	-0.08 (-0.40, 0.25)	-1.12 (-1.45, -0.79)	0.25 (-0.07, 0.57)
Trt Diff vs. delayed (95% CI)	1.07 (0.43, 1.70)			0.98 (0.38, 1.58)			1.04 (0.60, 1.48)		
Trt Diff vs. placebo (95% CI)	-0.53 (-1.15, 0.10)	-1.59 (-2.22, -1.0)		-0.13 (-0.72, 0.46)	-1.11 (-1.71, -0.51)		-0.33 (-0.76, 0.10)	-1.37 (-1.80, -0.94)	
Femoral Neck									
Week 12									
n	102	100	104	104	93	102	206	193	206
% change (95% CI)	-0.83 (-1.67, 0.01)	-0.97 (-1.8, -0.14)	0.09 (-0.72, 0.91)	-0.58 (-1.24, 0.08)	-1.21 (-1.90, -0.52)	0.24 (-0.42, 0.89)	-0.72 (-1.25, -0.19)	-1.08 (-1.62, -0.54)	0.15 (-0.37, 0.69)
Trt Diff vs. delayed (95% CI)	0.14 (-0.94, 1.22)			0.63 (-0.28, 1.54)			0.36 (-0.34, 1.07) p=0.3156		
Trt Diff vs. placebo (95% CI)	-0.92 (-1.99, 0.15)	-1.06 (-2.13, 0.01)		-0.82 (-1.70, 0.07)	-1.44 (-2.36, -0.53)		-0.87 (-1.56, -0.18)	-1.231 (-1.93, -0.53)	
Week 24									
n	100	98	103	98	92	95	198	190	198
% change (95% CI)	-0.26 (-1.14, 0.62)	-1.35 (-2.23, -0.47)	0.31 (-0.56, 1.17)	-0.68 (-1.42, 0.05)	-1.37 (-2.12, -0.62)	0.02 (-0.71, 0.75)	-0.48 (-1.05, 0.09)	-1.37 (-1.95, -0.80)	0.15 (-0.41, 0.71)
Trt Diff vs. delayed (95% CI)	1.09 (-0.07, 2.25)			0.68 (-0.32, 1.69)			0.89 (0.13, 1.66)		
Trt Diff vs. placebo (95% CI)	-0.57 (-1.71, 0.58)	-1.66 (-2.80, -0.51)		-0.70 (-1.70, 0.29)	-1.39 (-2.40, -0.38)		-0.63 (-1.39, 0.13)	-1.53 (-2.29, -0.76)	

Source: MVT-601-3001 CSR Tables 7.3.12.2, 7.3.12.6, 7.3.12.7; MVT-601-3002 CSR Tables 7.3.12.2, 7.3.12.6, 7.3.12.7;
ISS Table 56
CI=confidence interval; trt diff=treatment difference

The effect of the to-be-marketed drug combination (R+E2/NETA) on BMD is the focus of the remainder of the review. As compared to PBO, treatment difference in mean (95% CI) percent change from baseline in LS BMD for the R+E2/NETA arm at Weeks 12 and 24 were - 1.00% (-1.48, -0.46) and -0.42 (-1.00, 0.12), respectively.

Seven participants treated with in the R+E2/NETA arm during the pivotal trials (3 from Study 3001 and 4 from Study 3002) experienced bone loss ≥ 7% at any anatomic site at Week 24 and were therefore ineligible to enroll in the OLE study. In all cases, the site involved was the femoral neck and in one case, the total hip was also affected. All but one had low vitamin D levels at baseline and two participants also had other potential risk factors for bone loss, including moderate to heavy alcohol, smoking, elevated parathyroid hormone (PTH) and fluticasone treatment. Their exclusion may underestimate the risk of bone loss reported with 52 weeks of treatment with R+E2/NETA.

In Study 3003, a further decline in BMD was observed. Mean percent change from baseline in LS BMD through Week 52 is shown in Table 27. Although six participants in the R+E2/NETA arm experienced bone loss ≥ 7% at any anatomic site at Week 36 and should have been discontinued, four of the six went on to have Week 52 DXA scans due to the delay in notification of the investigator. Two participants terminated early, one with decline in LS BMD of 7.4% and one with decline in femoral neck BMD of 8.8%. These two exclusions are unlikely to have impacted the Week 52 BMD results substantially.

Table 27: Least Square mean percent change (95% CI) from Pretreatment Baseline in Lumbar Spine Bone Mineral Density According to Treatment Arm for Participants of Study MVT-601-3003

Visit	**R+E2/NETA N=163**	**PBO * N=164**
Week 12		
n	145	146
% change (95% CI)	-0.34 (-0.81, 0.08)	0.40 (-0.08, 0.87)
Week 24		
n	153	156
% change (95% CI)	-0.23 (-0.69, 0.24)	0.24 (-0.23, 0.72)
Week 36		
n	145	138
% change (95% CI)	-0.73 (-1.23, -0.22)	-0.25 (-0.79, 0.30)
Week 52		
n	132	120
% change (95% CI)	-0.80 (-1.36, -0.25)	-0.78 (-1.32, -0.23)

Source: ISS Table 8.5.1.2.
*Week 36 reflects 12 weeks of treatment with R+E2/NETA and week 52 reflects 28 weeks of R+E2/NETA for this treatment arm.

Overall, mean (95% CI) percent change in LS BMD at Week 52 was -0.80 (-1.36, -0.25). While the magnitude of bone loss at the lumbar spine in the R+E2/NETA arm are similar at Weeks 36 and 52 , the number of participants included in each assessments differs, and the interval of 12-16 weeks is too short to detect small declines in BMD by DXA. Therefore, the Week 36 and Week 52 results cannot be relied upon to definitively determine whether bone loss has plateaued.

Studies of longer duration are necessary in order to determine whether bone loss progresses or plateaus with treatment beyond 52 weeks.

Changes in BMD observed for the PBO arm provide additional evidence of a decrease in BMD with R+E2/NETA treatment. These participants experienced a slight increase in BMD over the first 24 weeks of PBO treatment [mean percent change from baseline 0.24 (-0.23, 0.72)]. Subsequently, after switching to open-label R+E2/ENTA, mean (95% CI) percent change from baseline in lumbar spine BMD at Week 36 (i.e., after 12 weeks of treatment with R+E2/NETA) and Week 52 (i.e., after 28 weeks of R+E2/NETA treatment), was -0.25 (-0.79, 0.30) and -0.78 (-1.32, -0.23), respectively.

Categorical Analysis

The number and proportion of participants experiencing no change/gains in LS BMD as well as declines of >2% and >3% at all study timepoints is shown in Table 28.

Table 28: Categorical Summary of Change in Lumbar Spine Bone Mineral Density in Studies 3001, 3002 and for the R+E2/NETA Arm with up to 52 Weeks of Treatment in Study 3003

	R+E2/NETA N=254	Placebo N=256
Studies 3001+ 3002		
Week 12		
N	204	207
No change or increase in BMD n (%)	80 (39.2%)	111 (53.7%)
≥2% to ≤8%	60 (29.5%)	33 (15.9%)
>3% to ≤8% n (%)	35 (17.2%)	21 (10.1%)
Week 24		
N	195	197
No change or increase in BMD n (%)	92 (47.2%)	103 (52.3%)
≥2% to ≤8%	48 (24.6%)	45 (22.8%)
>3% to ≤8% n (%)	31 (15.9%)	18 (9.1%)
Study 3003		
Week 36		
N	145	
No change or increase in BMD n (%)	59 (40.7%)	
≥2% to ≤8%	52 (35.9%)	
>3% to ≤8% n (%)	34 (23.4%)	
Week 52		
N	132	
No change or increase in BMD n (%)	51 (38.6%)	
≥2% to ≤8%	51 (38.6%)	
>3% n (%)	30 (22.8%)**	

Source: ISS Outputs Table 8.3.1.
Percentages calculated based on the number of participants with a BMD measurement at that time point.
**At week 52, one participant in the R+E2/NETA group experienced a decline in lumbar spine BMD >8%.

While acknowledging that bone loss < 3% may represent a true biological change, using a threshold of bone loss of >3%, an imbalance in the proportion of participants in the R+E2/NETA arm with decline in LS BMD > 3% as compared to PBO was observed (16% vs. 9% for the R+E2/NETA and PBO arms, respectively at Week 24. In the R+E2/NETA arm, the proportion of participants experiencing bone loss >3% at the lumbar spine increased over time from 16% at Week 24 to approximately 23% at Weeks 36 and 52. Additionally, In the PBO arm of the extension trial (data not included in Table 28 above), 24% of participants who were initially treated with PBO in the pivotal trials had a decline of >3% after 28 weeks of treatment with R+E2/NETA, including 2 (1.7%) with lumbar spine bone loss >8%. Overall, these data demonstrate that treatment with R+E2/NETA is associated with accelerated bone loss in a subset (nearly one-quarter) of women.

Study MVT-601-034

The Applicant submitted BMD results for the untreated uterine fibroid cohort of Study MVT-601-034 (Obs-UF) as a comparator. This study was a prospective observational study conducted in 27 sites across the U.S. that enrolled age-matched premenopausal women with uterine fibroids or endometriosis who were not treated with hormonal therapy and assessed changes in BMD over 52 weeks. The Applicant submitted the final results for the Obs-UF cohort to this NDA to provide information on the natural history of BMD in women with uterine fibroids. The study enrolled 262 women with uterine fibroids, of which 224 (85.5%) completed the study. The majority who did not complete the study were lost to follow-up or withdrew.
Formal statistical comparisons between the results of this study and Study 3003 should not be made because they are separate studies that differ in design, and differences in methodology may have introduced bias. Nonetheless, for ease of comparisons and discussion in this review, results for the R+E2/NETA arm of Study 3003 are shown alongside results for the Obs-UF cohort.

Demographic and baseline characteristics for the Obs-UF cohort of Study MVT-601-034 and the R+E2/NETA arm of Study 3003 for comparison are shown in Table 29. The two populations are similar with respect to baseline age, mean BMI (although a greater proportion in Study 3003 had BMI ≥30 kg/m2), ethnicity, smoking status and baseline LS BMD. Discrepancy with respect to geographic region, race, and moderate alcohol use are noted. In Study MVT-601-034, 6 participants (2.3%) reported use of combination oral contraception. Likewise, few participants reported use of medications that could contribute to bone loss, such as medroxyprogesterone therapy (2 participants [0.8%]) and glucocorticoids (prednisone in 1 participant [0.4%]). None reported use of GnRH agonists or antagonists.

Table 29: Demographic and Baseline Characteristics for R+E2/NETA in Study 3003 and Uterine Fibroid Cohort of Study MVT-601-034

	MVT-601-034 Obs-UF Cohort (N=262)	**MVT-601-3003 R+E2/NETA Arm (N=163)**
Age (years) Mean (SD)	41.8 (5.5)	42.6 (5.08)
Geographic Region n (%) • North America • Rest of World	262 (100%) 0	113 (69.3%) 50 (30.7%)
Race n (%) • Black • White • Other	152 (58.0%) 98 (37.4%) 12 (4.6%)	69 (42.3%) 85 (52.1%) 9 (5.5%)
Ethnicity n (%) • Not Hispanic or Latino • Hispanic or Latino	196 (74.8) 66 (25.2)	122 (74.8%) 38 (23.3%)
BMI (kg/m2) Mean (SD)	BMI 31.6 (7.95)	31.4 (7.05)
BMI Category n (%) • < 30 kg/m2 • ≥30 kg/m2	109 (41.6) 111 (42.4)	70 (42.9%) 92 (56.4%)
Alcohol Use n (%) None Moderate Heavy	153 (58.4%) 107 (40.8%) 1 (0.4%)	87 (53.4%) 75 (46.0%) 1 (0.6%)
Smoking n (%) Current Past Never	38 (14.5%) 23 (8.8%) 200 (76.3%)	25 (15.3%) 16 (9.8%) 122 (74.8%)
LS BMD (g/cm2) mean (SD)	1.207 (0.181)	1.186 (0.160)

Source: CSR MVT-601-034 Tables 5 and 6; CSR MVT-601-3003 Tables 10 and 11.
Abbreviations: BMD = bone mineral density; BMI = body mass index; n = number of patients in subset; N = number of patients in treatment arm; Obs-UF= uterine fibroid cohort from the observation study; R=relugolix; E2 = estradiol; NETA = norethindrone acetate; SD = standard deviation; LS BMD=lumbar spine

Mean percent change from baseline in LS BMD in the Obs-UF cohort and the R+E2/NETA arm of Study 3003 are shown in Table 30. Based on descriptive statistics, participants treated with R+E2/NETA for 52 weeks experienced bone loss at the lumbar spine that was twice that of the Obs-UF cohort.

Table 30: Change from Baseline in Least Square Mean Lumbar Spine BMD in the Uterine Fibroid Cohort of Study MVT-601-034 and the R+E2/NETA Arm of Study 3003

	MVT-601-034 Obs-UF Cohort (N=262)	**MVT-601-3003 R+E2/NETA Arm (N=163)**
Week 24		
n	222	153
% change (95% CI)	0.00 (-0.32, 0.31)	-0.23 (-0.69, 0.24)
Week 52		
n	213	132
% change (95% CI)	-0.41 (-0.77, -0.05)	-0.80 (-1.36, -0.25)

Source: CSR MVT-601-034 Table 9 ; ISS Table 8.5.1.2. Abbreviations: BMD = bone mineral density; = number of patients in treatment arm; Obs-UF= uterine fibroid cohort from the observation study; R=relugolix; E2 = estradiol; NETA = norethindrone acetate; CI=confidence interval; LS=lumbar spine

The categorical analysis of mean percent change from baseline in LS BMD at Week 52 in the two groups is shown in Table 31. A greater proportion of participants treated with R+E2/NETA for 52 weeks had bone loss at the lumbar spine of 2% or more, and conversely, fewer bone loss of less than 2% or gains in LS BMD compared to the Obs-UF cohort. Approximately 17% of participants had a decline in LS BMD of more than 3% in the UF-Obs cohort as compared to 23% in the R+E2/NETA arm of Study 3003. The imbalance between the R+E2/NETA group and the Obs-UF cohort in categories of bone loss provides additional supportive evidence of bone loss associated with R+E2/NETA treatment over 52 weeks.

Table 31: Categorical Analysis of Percent Change from Baseline in Lumbar Spine BMD at Study Week 52 in Uterine Fibroid Cohort of Study MVT-601-034 and the R+E2/NETA Arm of Study 3003

Categories of mean percent change from baseline in LS BMD	**MVT-601-034 Obs-UF Cohort[1] (N=213)**	**MVT-601-3003 R+E2/NETA Arm[2] (n=132)**
>-2%[3]	158 (74.2%)	84 (63.6%)
≤ -2% to ≥ - 3%	18 (8.5%)	18 (13.6%)
< -3 to ≥ -5%	28 (13.1%)	22 (16.7%)
< -5 to ≥ -8%	7 (3.3%)	7 (5.3%)
< -8%	2 (0.9%)	1 (0.8%)

[1] Modified from CSR MVT-601-034 Table 14.2.1.1
[2] Source: CSR MVT-601-3003 Table 8.3.12.
[3]Includes no change or increase in BMD
Abbreviations: LS=lumbar spine; BMD = bone mineral density; N=number of participants with Week 52 BMD; Obs-UF= uterine fibroid cohort from the observation study; R=relugolix; E2 = estradiol; NETA = norethindrone acetate; CI=confidence interval.

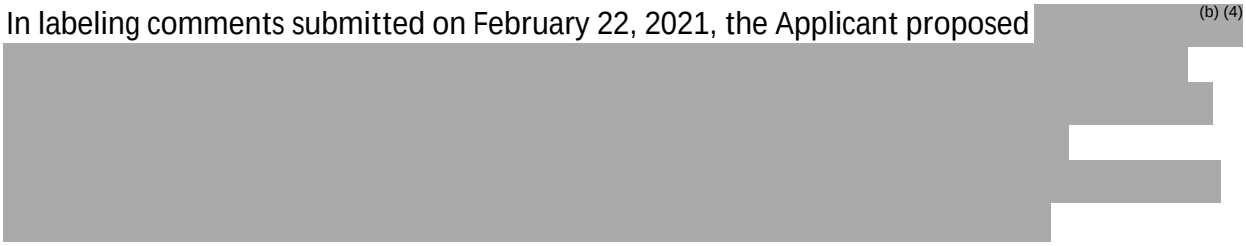
Z-score Analysis

In Phase 3 clinical trials, mean Z-scores at baseline were above the mean for the reference population and remained within the expected range for age for the duration of the trials. This is

not unexpected given the higher than average baseline BMD and the magnitude of bone loss observed in the clinical trials.

In response to IRs dated December 15, 2020 and February 18, 2021, the Applicant conducted a post-hoc exploratory analysis of categorical changes in Z-score (submissions January 11, 2021 and February 26, 2021). In the pivotal trials, a greater proportion of participants in the R+E2/NETA arm had declines in Z-score in the range of 0.25 to 0.5 SD as compared to PBO (16.4% vs. 11.7%) and this imbalance was driven by Study 3001. In the R+E2/NETA arm during Study 3003, the proportion of participants that had a decline in Z-score of more than 0.25 SD at Weeks 24 and 52 was 17% and 21.2%, respectively. In the Obs-UF cohort of Study MVT-601-034, the proportion of participants that had a decline in Z-score of more than 0.25 at Weeks 24 and 52 was 13.6% and 17.2%, respectively. Additionally, at Week 52, a greater proportion of participants in the Obs-UF cohort had no change or an increase in Z-score as compared to the R+E2/NETA arm in Study 3003 (57.1% vs. 43.2%) These results are consistent with and complement the categorical analysis of percent change from baseline in BMD.

In labeling comments submitted on February 22, 2021, the Applicant proposed (b) (4)



Recovery of Bone Loss Post-Treatment

Indications for post-treatment DXA scans are presented in the Section above entitled “BMD Protocol”. In the 120-Day Safety Update, the Applicant submitted an analysis of available data on post-treatment recovery of bone loss (Table 32). Data are limited, but after 52 weeks of treatment with R+E2/NETA these data demonstrated full recovery at the lumbar spine in 19%, ongoing bone loss in 25% and partial recovery in the remainder of participants. Given the limited number of participants, definitive conclusions should not be made. Additionally, whether a decline in BMD on treatment and/or lack of full recovery post-treatment increases the risk for fracture later in life cannot be determined from the available data.

Table 32: Summary of Percent Recovery of Bone Loss from End of Treatment to Final Post-Treatment Recovery Scan for Participants Treated with R+E2/NETA for up to 52 Weeks in Study 3003

		Percent Recovery from End of Treatment BMD					
Anatomic Site	N	<0% n (%)	0-25% n (%)	>25-50% n (%)	>50-75% n (%)	>75-100% n (%)	>100% n (%)
Lumbar Spine	16	4 (25.0%)	2 (12.5%)	2 (12.5%)	4 (25.0%)	1 (6.3%)	3 (18.8%)
Total Hip	16	5 (31.3%)	1 (6.3%)	0	3 (18.8%)	4 (25.0%)	3 (18.8%)
Femoral Neck	15	5 (33.3%)	1 (6.7%)	1 (6.7%)	3 (33.3%)	1 (6.7%)	4 (26.7%)

Source: 120-Day Safety Update Table 7.2.4.3

Mixed Effect Model

The Applicant used a mixed effect model to compare the rate of change in BMD according to age for each individual that received R+E2/NETA in the pivotal trials and OLE and for untreated participants in the observational cohort. This analysis was reviewed with the Clinical Pharmacology, Pharmacometrics and Biostatistics teams. The analysis showed that at each age, participants in the R+E2/NETA arm experienced a rate of decline that was approximately twice that of the observational cohort. One limitation of this model is the assumption that bone loss is linear. The model also implicitly imputed Week 52 results for participants who terminated the study early, some of whom terminated because of excessive bone loss per protocol. Although this model has several limitations, the results of this analysis are consistent with the BMD data that showed mean percent change from baseline in LS BMD for the R+E2/NETA arm was twice that of the observational cohort at Week 52.

QSP (Quantitative Systems Pharmacology) Model

The BMD model submitted by the Applicant, a modified version of a published QSP (quantitative systems pharmacology) model, was reviewed by the Clinical Pharmacology and Pharmacometrics team. The model describes E2 concentration-related effects on bone remodeling. The relationship between E2 suppression and BMD change over time was described using two latent variables as defined in the QSP model, i.e., a bone formation marker, bone specific alkaline phosphatase (BSAP), and a bone resorption marker, serum c-telopeptide (CTx). The team concluded that the model does not directly predict bone loss rate. They concluded that the model is not validated with data beyond one year, resulting in the uncertainty about model's ability to predicted bone loss or the bone loss rate beyond one year. Therefore, they recommend the inclusion of a limitation of use in labeling.

Decline in BMD ≥ 7%

Decline from pre-treatment baseline in BMD ≥ 7% at any anatomic site was an AESI. In Study 3001, 19 participants had BMD decline ≥7% at any anatomic site, 3 participants in the R+E2/NETA arm, 10 participants in the R+delE2/NETA, and 6 participants in the PBO arm. The site reported most frequently was the femoral neck. All 3 participants in the R+E2/NETA arm had vitamin D deficiency at baseline, and one had hyperparathyroidism, which may have been secondary to vitamin D deficiency. Four of the six participants in the PBO arm also had vitamin

D deficiency. One participant also had use of glucocorticoids that may have been a contributing factor. Most participants were white.

In Study 3002, 16 participants had BMD decline ≥7% at any anatomic site, 4 in the R+E2/NETA arm, 9 in the R+delE2/NETA, and 3 in the PBO arm. Overall, the site reported most frequently was the femoral neck, however, in the R+delE2/NETA arm, the lumbar spine was the most frequent site. Eleven of the sixteen participants had vitamin D deficiency at baseline. Most participants in the R+E2/NETA arm were white, while overall, more participants were black (9 black, 6 white). In the R+E2/NETA arm, one participant also reported heavy alcohol use and current smoking No risk factors were identified in another participant. Two participants in the PBO arm had technical factors that may have impacted the BMD assessment (artifact and hip rotation). In the R+delE2/NETA arm, most participants reported moderate alcohol use, two participants had elevated PTH in association with low vitamin D, and one participant reported glucocorticoid use. No fractures were reported for any of these participants. Fracture is an AESI that is discussed in Section X.

During Study 3003, six participants in the R+E2/NETA arm experienced bone loss ≥ 7% at any anatomic site at Week 36. Although the protocol specified that these participants were to discontinue study drug, four went on to have Week 52 DXA scans due to the delay in notification of the investigator. Two participants did terminate study drug early, one with decline in lumbar spine BMD of 7.4% and one with decline in femoral neck BMD of 8.8%. These two exclusions are unlikely to have impacted the Week 52 BMD results. At Week 52, three additional participants experienced bone loss ≥7%, one at the femoral neck, one at the lumbar spine, and one at both the femoral neck and lumbar spine. Eight of the nine participants had vitamin D deficiency. One also had elevated PTH. None reported fractures. Although the impact of vitamin D treatment on mitigating bone loss was not studied, the label will include the recommendation for adequate vitamin D and calcium intake, consistent with general health guidelines and the approach to labeling for other medications associated with bone loss.

Interpretation of Results

The Applicant (b) (4) This analysis was not pre-specified nor was it agreed upon with the Division. On November 30, 2020, in response to DUOG's request at the mid-cycle teleconference (Meeting Minutes dated November 16, 2020), they submitted information to support their position that included references from the 1990s in which the technology and the approach to the analysis are no longer used [i.e, dual photon absorptiometry (Pouilles JM et al. 1993) and BMD assessments using the lateral spine and Ward's triangle (Arlot ME et al. 1997)]. Additionally, it is not appropriate to rely on cross-sectional data to interpret longitudinal clinical trial data.

The Applicant also referenced the label for Lupaneta (NDA 020708) that contains clinical trial data for leuprolide acetate depot plus norethindrone acetate (LD/N) (Labeling Supplement approved on September 21, 2001). The label states that "For the open label study, success in

mitigating BMD loss was defined as the lower bound of the 95% confidence interval around the change from baseline at one year of treatment not to exceed -2.2%." Although trial results for LD/N met this condition [mean (95% CI) change from baseline in lumbar spine BMD was -0.2% (-0.6, 0.2) and -1.1% (-1.6, -0.5) at Week 24 and Week 52, respectively], bone loss associated with the GnRH antagonist was not completely prevented with the addition of NETA, and this safety concern contributed to the a Limitation of Use of no more than 12 months (two 6-month treatment courses) for Lupaneta (LD/N). Similarly, the data submitted to the current marketing application demonstrated that the addition to of E2/NETA to relugolix mitigates bone loss, but does not completely prevent it. The Division does not believe the lower limit of the confidence interval indicates that significant bone loss over 12 months did not occur. Furthermore, it is unknown whether bone loss will continue with use beyond 12 months. Therefore, considering the benefit/risk profile for R+E2/NETA, we have proposed a limitation of use of 2 years (see conclusions below).

We also disagree with (b) (4) As noted above, in the placebo-controlled trials, BMD increased in the PBO arm and declined in the R+E2/NETA arm over 24 weeks, such that the treatment difference in mean percent change in lumbar spine BMD at Week 24 was -0.4, and the mean percent change from baseline for the R+E2/NETA treatment arm was -0.2%. After 52 weeks of treatment, mean percent change in lumbar spine BMD was -0.8% and a similar degree of decline was observed at the femoral neck. Additionally, the rate of bone loss over 52 weeks was twice that of the observational cohort from Study MVT-601-034, which provides supportive evidence that R+E2/NETA is associated with bone loss. The Applicant proposed (b) (4)

The Applicant also proposed (b) (4) We do not agree with this hypothesis and the proposed analysis several reasons. First, baseline BMD by definition is the BMD measurement obtained prior to drug exposure; a different timepoint cannot be selected based on results of a post-hoc analysis. Secondly, in their proposal, the Applicant (b) (4) The clinical review team in consultation with the biostatistics, clinical pharmacology and pharmacometrics teams determined that this approach to the analysis is not acceptable. We concluded that the Applicant's initial analysis of rate of

change in BMD demonstrates that the rate of bone loss over 52 weeks in the R+E2/NETA arm occurs at a rate that is about twice that of the Obs-UF cohort. Additionally, given the limitations noted above, this analysis cannot be relied upon to predict bone loss beyond 52 weeks of treatment. Therefore, a postmarketing study will be required to characterize bone loss with R+E2/NETA treatment over a longer period of time, as well as recovery of bone loss post-treatment.

Conclusions

Overall, the totality of evidence indicates that while the addition of E2/NETA to relugolix mitigates bone loss, it does not completely prevent bone loss in a subset of women. This conclusion is based on the following trial results:

- Mean percent change from baseline in lumbar spine BMD of -0.80% at Week 52.
- Lack of a clear plateau in bone loss. Intervals of 12-16 weeks is too short to detect slow ongoing bone loss or to determine with confidence that bone loss has plateaued.
- Although a direct statistical comparison cannot be made between these two separate studies, the observed rate of bone loss over 52 weeks in the R+E2/NETA treated cohort was twice that of participants in the uterine fibroid cohort from the observational Study MVT-601-034, in which women received no treatment or non-hormonal therapy for HMB related to uterine fibroids (mean change from baseline in lumbar spine BMD of -0.8% and -0.4%, respectively).
- The categorical analysis of changes in BMD after 52 weeks demonstrated that 23% of participants treated with R+E2/NETA experienced a decline in lumbar spine BMD >3% as compared to 17% of participants in the uterine fibroid cohort from the observational Study MVT-601-034.
- Limited data are available to assess recovery of bone loss post-treatment.
- Whether the rate of bone loss for individuals treated with R+E2/NETA changes over time is unknown. Therefore, a linear decline in BMD for all participants over time cannot be assumed.
- Whether a decline in BMD and lack of full recovery increases the risk for fracture later in life is uncertain, and cannot be determined from the available data.

Bone loss is concerning both for younger premenopausal women who may have not yet attained peak bone mass, as well as for older premenopausal women who may be approaching menopause, a time when rapid bone loss is anticipated. Physicians and patients should be informed of this risk and risk mitigation strategies as outlined below should be implemented. To mitigate risk, DUOG proposes to include the following in labeling:

- Limitation of use of no more than 2 years.
- Contraindication for women with a history of osteoporosis.
- Recommendation for obtaining a baseline DXA scan to avoid use of R+E2/NETA in women with low bone mass and for periodic monitoring during treatment.
- Recommendation for adequate calcium and vitamin D intake.

- We will require a postmarketing BMD study to assess changes in BMD over 4 years in order to clarify whether bone loss plateaus with treatment beyond 52 weeks and to better characterize recovery of bone loss after cessation of treatment.

7.5.3 Endometrial Biopsies

In Study MVT-601-3001, endometrial biopsies were performed at baseline and end-of-treatment for all subjects who completed at least 6 weeks of study drug. In Study MVT-601-3002, endometrial biopsies were required for inclusion in extension study MVT-601-3003 and for subjects not enrolling in the extension study if the Week 24/EOS transvaginal ultrasound showed endometrial thickness measured ≥ 4 mm or if any other endometrial abnormality. Samples were submitted to one central laboratory (b) (4) for the initial blinded read and to a second central laboratory (b) (4) for a confirmatory blinded read. Discordant results were assessed by a third blinded pathologist and concordance between two of the three readings constituted the consensus diagnosis. In cases where the three readings were discordant, the worst diagnosis was used. In addition to the consensus procedure outlined in the protocol and CSRs, in their response to an Information Request dated December 15, 2020 that the Applicant submitted on January 11, 2021, they clarified that cases with a single reviewer designation of hyperplasia or worse or cases with significant disagreements were referred to another pathologist who was not involved in the review of that specific case to mediate agreement among the reviewers.

Because of the different indications for Week 24 endometrial biopsy for each pivotal trial, results are presented separately for Study 3001 and 3002. Consensus endometrial biopsy results submitted by the Applicant as dataset Addendum 2 ADEMB were summarized by FDA's Clinical Data Scientists are summarized.

Study 3001

Endometrial biopsies at baseline were generally similar across treatment arms. For the R+E2/NETA and PBO arms, consensus baseline endometrial biopsy results showed that approximately 40-50% had proliferative, 55% secretory/menstrual, and 2-5% atrophic/inactive endometrium. Additionally, 2% were identified as having a polyp. In the PBO arm, one subject (0.8%) had simple hyperplasia without atypia (Subject (b) (6)) and two subjects (1.6%) had inadequate samples.

At Week 24/EOT, 80.5% of subjects in the R+E2/NETA arm and 85.8% of subjects in the PBO arm had endometrial biopsy results. Consensus endometrial biopsy results for the R+E2/NETA arm and PBO arm, respectively were as follows: proliferative (14.1% vs. 40.2%), secretory/menstrual (7.8% vs. 30.7%), atrophic/inactive (46.9 vs. 6.3), reactive/inflammatory (0.8 vs. 0%), simple hyperplasia without atypia (0% vs. 1.6%), polyp (0.8% vs. 0%), Other non-physiologic epithelial changes (0.8 vs. 0%), and inadequate (9.4 vs. 7.1%). Results for the R+delE2/NETA arm were generally similar to the R+E2/NETA arm.

Study 3002
Baseline endometrial biopsies were generally similar to those of Study 3001.

Week 24/EOT consensus endometrial biopsy results for the R+E2/NETA arm and PBO arm, respectively were as follows: proliferative (6.3% vs. 24.8%), secretory/menstrual (8.7 vs. 28.7), atrophic/inactive (30.2 vs. 1.6), reactive/inflammatory (0% vs. 0%), hyperplasia (0% vs. 0.8%), polyp (0% vs. 0.8%), and inadequate(7.9% vs. 6.1%). Results for the R+delE2/NETA arm were generally similar to the R+E2/NETA arm.

Two subjects in the R+E2/NETA arm that had simple hyperplasia without atypia at baseline are described below.

- Subject (b) (6) had a baseline consensus diagnosis of simple hyperplasia without atypia. The subject was randomized to R+E2/NETA and completed Study 3002. The consensus reading of the biopsy obtained at Week 24 was atrophic endometrium.

- Subject (b) (6) had a baseline consensus diagnosis of simple hyperplasia without atypia. The subject was randomized to R+E2/NETA and completed the study. The consensus diagnosis on the Week 24 biopsy was non-secretory endometrium with breakdown.

The subject in the PBO arm with a consensus diagnosis of simple hyperplasia on the Week 24 endometrial biopsy is described below:

- Subject (b) (6) had secretory cyclic type endometrium on the primary clinical reading and simple hyperplasia without atypia on the Week 24 consensus reading. She enrolled in Study 3003. A repeat biopsy was obtained at approximately Week 48 when the consensus diagnosis was communicated to the investigator. The consensus diagnosis of the repeat biopsy was secretory cyclic type endometrium.

Overall, in Studies 3001 and 3002, a greater proportion of patients in the R+E2/NETA (and R+delE2/NETA) arm had consensus diagnoses of atrophic/inactive endometrium compared with the PBO arm. Conversely, in the PBO arms, a larger proportion of patients had proliferative and mixed/secretory/menstrual findings compared with both relugolix treatment arms. These findings are consistent with the mechanism of action of the combination of R+E2/NETA on the hypothalamic-pituitary-gonadal axis and the known effects of NETA on the endometrium. No cases of endometrial hyperplasia or carcinoma were identified post-baseline for subjects in the R+E2/NETA or R+delE2/NETA arms in these trials.

In Study 3003, one subject had a final read of endometrial hyperplasia. The Applicant submitted this narrative report on January 11, 2021 in response to an Information Request dated December 15, 2020. Subject (b) (6) was randomized to R+E2/NETA in MVT- 601-3002 and continued on therapy through Week 52. She had a Week 52 biopsy read of complex hyperplasia without atypia, based on the worst diagnosis of three discordant reads. However, given the discordant assessment by three pathologists, the timing of the biopsy 28 days after the last

dose of study drug and 4 days prior to menses, as well as the expected biological effect of 1 year of treatment with R+E2/NETA on the endometrium, an additional, independent assessment of all endometrial biopsies obtained from this patient was conducted in a blinded fashion by an academic expert, and the read was benign late proliferative endometrium without evidence of hyperplasia or malignancy. The subject had menses 4 days after this biopsy (See the safety review of Study 3003 below for complete summary of endometrial biopsy results for this study).

The totality of evidence indicates that treatment with R+E2/NETA was not associated with endometrial hyperplasia, except for one case described above where a single reviewer identified hyperplasia and additional blinded read outside of the protocol refuted that minority assessment. Overall, the endometrial biopsy data do not raise any endometrial safety concerns with R+E2/NETA treatment in this population.

7.5.3. Resumption of Menses After Drug Discontinuation

In Study 3001, menstrual status post-treatment was available for 100/143 participants who prematurely discontinued or did not continue into the OLE study (source: CSR for Study 3001 Addendum 1, Table 3). Of these participants, return of menses was observed in 100% (35/35) in the R+E2/NETA and R+delE2/NETA (39/39) arms and 88.5% (23/26) in the PBO arm. Mean time from last dose of study drug to onset of menses was 36 days in the R+E2/NETA arm as compared to 24 days for the PBO arm. For participants in the R+E2/NETA arm, mean time to onset of menses was longer for the 14 participants who achieved amenorrhea (40.6 days) as compared to the 21 without amenorrhea (33.0 days) in the last 35 days of treatment.

In Study 3002, menstrual status post-treatment was available for 110/149 participants who prematurely discontinued or did not continue into the OLE study. In this study, menses resumed in 93.3% (28/30), 97.7% (43/44) and 97.2% (35/36) of participants in the R+E2/NETA, R+delE2/NETA and PBO arms, respectively (CSR for Study 3002 Addendum 1, Table 3). Mean time from last dose of study drug to onset of menses was 30.7 days in the R+E2/NETA arm as compared to 24.2 days for the PBO arm. All of the 8 participants in this cohort with amenorrhea in the last 35 days of the study resumed menses post-treatment. Time to onset of menses was longer for the 8 participants who achieved amenorrhea with R+E2/NETA (41.1 days) as compared to the 20 without amenorrhea (26.6 days) in the last 35 days of treatment. Four participants (two, one, and one in the R+ E2/NETA group, R+del E2/NETA group, and PBO groups, respectively) who were not amenorrhoeic over the last 35 days of treatment reported not having a return of menses post-treatment due to treatment with surgery (3) or medication (1). Information regarding return of menses post-treatment is helpful for providers and patients and will be included in Section 6 of the label.

7.6. Safety Analyses by Demographic Subgroups

The Applicant provided a subgroup analysis of AEs according to geographic region (North America vs. Rest of World), race (Black/African American vs. Others), ethnicity (Hispanic/Latino vs. not Hispanic/ Latino), age (< 40 years old vs. ≥ 40 years old), and BMI (< 30 kg/m^2 vs. ≥ 30 kg/m^2) for the safety population from Studies 3001 and 3002 combined. No major safety concerns were identified in this exploratory subgroup analyses that change the conclusions with respect to the safety of R+E2/NETA.

Geographic region – North America vs. Rest of World (Source: ISS Table 119)
AEs were reported more frequently in the Rest of the World as compared to North America in all treatment arms (71.0% vs. 57.8% in the R+E2/NETA arm. 71.0% vs. 59.8% in the PBO arm, and 81.3% vs. 69.1% in the R+delE2/NETA arm). Treatment discontinuation occurred more frequently in females from North America as compared to the Rest of the World in the R+E2/NETA arm (4.7% vs. 1.6%), but not for the other treatment arms.

Race – Black/African American vs. Others (Source: ISS Table 120)
In the R+E2/NETA arm, a smaller proportion of Black/African American females reported any AE as compared to females of other ethnicities (56.6% vs. 64.3%, respectively). AEs leading to drug discontinuation and SAEs related to study drug were similar in this treatment arm.

Ethnicity – Hispanic/ Latino versus not Hispanic/ Latino (Source: ISS Table 121)
In the R+E2/NETA arm, AEs were more frequently reported in Hispanic /Latino females compared to females of other ethnicities (67.9% vs. 58.4%). An imbalance in AEs leading to study drug discontinuation or SAEs related to study drug was not seen in this treatment arm.

Age < 40 years old versus ≥ 40 years old (Source: ISS Table 122)
AEs were similar in these two age categories across all 3 treatment arms. Study drug discontinuation occurred in a greater proportion of participants ≥ 40 years old as compared to < 40 years old in the all 3 treatment arms. In the R+E2/NETA arm, SAEs occurred more frequently in participants ≥ 40 years old, as compared to the PBO arm; however, an imbalance in SAEs related to study drug was not seen.

DUOG performed a subgroup analysis for the AEs of hypertension and vasomotor symptoms according to categories of BMI and age because hypertension is associated with higher BMI and older age, and vasomotor symptoms is more common in perimenopausal women who are typically older than age 40.

BMI
Overall, AEs occurred with similar frequency across treatment arms and categories of BMI (Table 33). Although hypertension occurred more frequently in the R+E2/NETA arm as compared to PBO, as expected, hypertension was more frequent in females with BMI ≥ 30

kg/m^2 in all three treatment arms. Although SAEs were also more frequent in females with BMI ≥ 30 kg/m^2, the imbalance in SAEs assessed as treatment related for those in the R+E2/NETA arm was minimal.

Table 33: Adverse Events by BMI, Safety Population of the Studies 3001 and 3002

	R + Delayed N2/NETA N=258		**R+E2/NETA N=254**		**Placebo N=256**	
Event Category	**< 30 kg/m^2 N=120 n (%)**	**≥ 30 kg/m^2 N=138 n (%)**	**< 30 kg/m^2 N=119 n (%)**	**≥ 30 kg/m^2 N=134 n (%)**	**< 30 kg/m^2 N=115 n (%)**	**≥ 30 kg/m^2 N=141 n (%)**
Any AE	86 (71.7)	100 (72.5)	71 (59.7)	83 (61.9)	70 (60.9)	90 (63.8)
Hypertension	3 (2.5)	7 (5.1)	4 (3.4)	8 (6.0)	0	4 (2.8)
Vasomotor symptoms	44 (36.7)	50 (36.2)	14 (11.8)	12 (9.0)	7 (6.1)	10 (7.1)
Any SAE	2 (1.7)	3 (2.2)	1 (0.8)	7 (5.2)	2 (1.7)	4 (2.8)
Treatment-related SAE	0	0	0	2 (1.5)	0	0

Source: adae.xpt; Software: R.
Abbreviations: AE, adverse event; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event; BMI: body mass index.
Vasomotor symptoms: hot flushes, night sweats, and hyperhidrosis.
In the Relugolix+E2/NETA group, one BMI missing value was observed for the patient (b) (6) who had a treatment-related and non-serious AE of hot flush.

Age

No association between age ≥ 40 vs. < 40 years was seen with the frequency of overall AEs, hypertension, vasomotor symptoms or treatment-related SAEs in the R+E2/NETA arm (Table 34).

Table 34: Adverse Events by AGE subgroup, Safety Population of Studies 3001 and 3002

	R+Delayed N2/NETA N=258		R+E2/NETA N=254		Placebo N=256	
Event Category	< 40 years N=88 n (%)	≥ 40 years N=170 n (%)	< 40 years N=62 n (%)	≥ 40 years N=192 n (%)	< 40 years N=78 n (%)	≥ 40 years N=178 n (%)
Any AE	65 (73.9)	121 (71.2)	38 (61.3)	117 (60.9)	49 (62.8)	111 (62.4)
Hypertension	3 (3.4)	7 (4.1)	3 (4.8)	9 (4.7)	1 (1.3)	3 (1.7)
Vasomotor symptoms	35 (39.8)	59 (34.7)	7 (11.3)	20 (10.4)	4 (5.1)	13 (7.3)
Any SAE	3 (3.4)	2 (1.2)	1 (1.6)	7 (3.6)	1 (1.3)	5 (2.8)
Treatment-related SAE	0	0	1 (1.6)	1 (0.5)	0	0

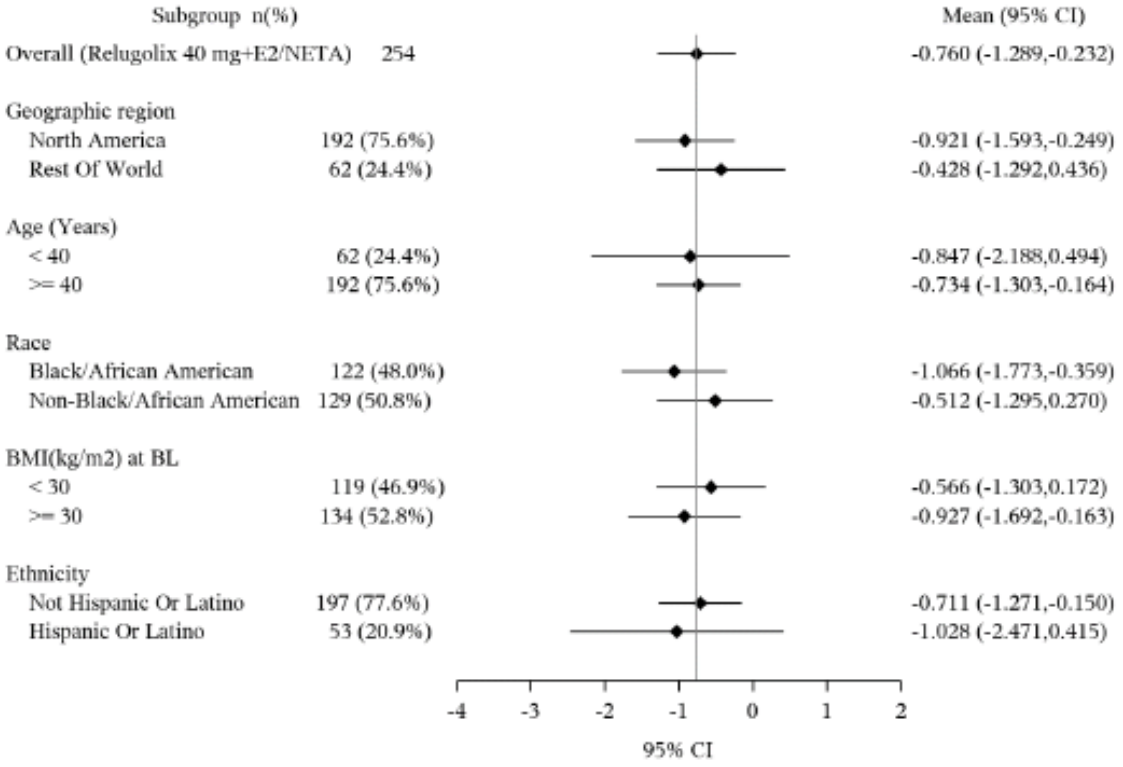
Source: adae.xpt; Software: R.
Abbreviations: AE, adverse event; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event.
Vasomotor symptoms: hot flushes, night sweats, and hyperhidrosis.

BMD

Subgroup analysis for change in BMD was performed for the following categories: geography (North America vs. Rest of World), race (Black/African American vs. other), ethnicity (Hispanic/Latino vs. other), age (< 40 years old vs. ≥ 40 years old), and BMI (< 30 kg/m^2 vs. ≥ 30 kg/m^2). Figure 6 shows the forest plot for the subgroup analysis for change in lumbar spine BMD for participants treated with RE2/NETA for up to 52 weeks. Trends in mean percent

change from baseline in BMD in each subgroup were generally comparable with the overall population in the lumbar spine and the total hip at Week 24 and Week 52.

Figure 6: Subgroup Analysis for Mean Percent Change from Baseline in Lumbar Spine Bone Mineral Density, Safety Population, Studies 3001, 3002 and 3003



Abbreviations: BL = baseline; BMI = body mass index; CI = confidence interval; E2 = estradiol; n = number of patients in the summary statistics; NETA = norethindrone acetate.
Summary is based on corrected bone mineral density data.
Clopper-Pearson confidence intervals.
Source: ISS Table 8.1.1, ISS Table 8.1.2, ISS Table 8.1.3, ISS Table 8.1.4, ISS Table 8.1.5, ISS Table 8.1.6, ISS Table 8.1.7, ISS Table 8.1.8, ISS Table 8.1.9, ISS Table 8.1.10, ISS Table 8.1.11.

7.7. Specific Safety Studies/Clinical Trials

7.7.1. Study 3003

Study Design

Trial MVT-601-3003 (Study 3003) was a 28-week open-label extension (OLE) study of the two pivotal trials conducted in North America, Europe and South Africa. The primary safety

objectives were to assess AEs and to monitor BMD for up to 52 weeks of treatment with R+E2/NETA. BMD results are presented in Section 7.5.2 along with results from the pivotal trials.

Participants who completed the pivotal trials and met eligibility criteria assessed at the week-24 visit were eligible to enroll in the OLE study.

Participants who experienced any of the following during the pivotal trials were ineligible for the extension study:

- Decline in BMD of ≥ 7% or a Z-score < -2.0 at any anatomic site
- Either of the following abnormalities in LFTs at Week 20 or later:
  a. ALT or AST > 2.0 times the ULN; or
  b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome)
- Decline in presenting visual acuity score, defined as:
  a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; OR
  b. The presenting visual acuity score has decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study Baseline visit
- Met a withdrawal criterion in the parent study (3001 or 3002).

Approximately 600 participants were planned to enroll and 477 participants actually enrolled (note the safety population was comprised of 476 participants because one participant enrolled in error and did not receive treatment).

In this safety analysis, the treatment arms are designated according to treatment arm in the parent study, and reflect differences in exposure to R+E2/NETA (i.e., up to 52 weeks, 40 weeks and 28 weeks in the R+E2/NETA, R+delE2/NETA and PBO arms, respectively). Exposure to study drug is shown above in Table 17 above. The parameters assessed as a part of safety monitoring were the same as those assessed in the pivotal trials, with the exception of visual acuity which was not assessed. Most of the AEs and clinical parameters of interest for the safety population are presented for the first 24 weeks of treatment in the pivotal trials followed by the latter 28 weeks during the OLE study to assess whether safety issues identified during the first 24 weeks appear to progress with increasing duration of use of R+E2/NETA and whether new safety signals emerge.

Changes in BMD are analyzed separately and presented in Section 7.5.2. No other new safety signals emerged during this study.

Overall Treatment-Emergent Adverse Event Summary - Study 3003

The occurrence of TEAEs is summarized for participants of Study 3003 for the first 24 weeks of treatment in the parent study (Table 35) and then for the subsequent 28 weeks of open-label treatment with R+E2/NETA (Table 36). A reduction in the proportion of participants experiencing any AE was most prominent for the R+delE2/NETA arm, and is attributed to the

substantial reduction in vasomotor symptoms associated with adding E2/NETA to relugolix monotherapy in this treatment arm. The study was not designed to assess efficacy with respect to vasomotor symptoms. The assessment of the AE of vasomotor symptoms (hot flushes) for therapy R+E2/NETA as compared to PBO in the pivotal trials is presented in Table 20 above.

Table 35: Overview of Treatment-Emergent Adverse Events Prior to the OLE Period (First 24 Weeks), Safety Population, Study 3003

Event Category	R+Delayed E2/NETA N=149 n (%)	R+E2/NETA N=163 n (%)	Placebo N=164 n (%)	Total N=476 n (%)
Any AE	110 (73.8)	97 (59.5)	108 (65.9)	315 (66.2)
Grade 3-4	10 (6.7)	5 (3.1)	11 (6.7)	26 (5.5)
Any SAE	3 (2.0)	4 (2.5)	4 (2.4)	11 (2.3)
SAE with fatal outcome	0	0	0	0
AE leading to discontinuation of study drug	1 (0.7)	1 (0.6)	0	2 (0.4)
AE leading to interruption of study drug	3 (2.0)	3 (1.8)	3 (1.8)	9 (1.9)

Source: adae.xpt; Software: SAS.
Adverse events prior to the OLE period: If adverse event onset date was prior to the first dose date in the open-label extension study period.

Table 36: Overview of Adverse Events During the OLE Period (28 Weeks), Safety Population, Study 3003

Event Category	R+Delayed E2/NETA N=149 n (%)	R+E2/NETA N=163 n (%)	Placebo N=164 n (%)	Total N=476 n (%)
Any AE	75 (50.3)	96 (58.9)	105 (64.0)	276 (58.0)
Grade 3-4	11 (7.4)	7 (4.3)	19 (11.6)	37 (7.8)
Any SAE	5 (3.4)	2 (1.2)	11 (6.7)	18 (3.8)
SAE with fatal outcome	0	0	0	0
AE leading to discontinuation of study drug	4 (2.7)	4 (2.5)	9 (5.5)	17 (3.6)
AE leading to dose modification of study drug	4 (2.7)	5 (3.1)	5 (3.0)	14 (2.9)
AE leading to interruption of study drug	4 (2.7)	5 (3.1)	5 (3.0)	14 (2.9)

Source: adae.xpt; Software: SAS
AEs during the OLE period: If adverse event onset date is on or after the first dose date in open-label extension period.
In the OLE period, all participants received the treatment of relugolix+E2/NETA. Adverse events are tabulated by the treatment group from the parent study.

Deaths – Study 3003
No deaths occurred in Study 3003.

Serious Adverse Events - Study 3003
SAEs experienced by the safety population for Study 3003 that occurred during either the parent study or the OLE are shown in Table X. Those SAEs that occurred during the 28-week OLE are bolded.

Table 37: Serious Adverse Events, Safety Population, Study 3003

Preferred Term	Relugolix (52W) + Delayed E2/NETA (40W) N=149 n (%)	Relugolix + E2/NETA (52W) N=163 n (%)	Placebo (24W) & Relugolix+ E2/NETA (28W) N=164 n (%)	Total Participants (52W) N=476 n (%)
Any SAE	8 (5.4)	6 (3.7)	15 (9.1)	29 (6.1)
Ankle fracture	**1 (0.7)**	1 (0.6)	0	2 (0.4)
Cholecystitis	1 (0.7)	1 (0.6)	0	2 (0.4)
Uterine leiomyoma	**1 (0.7)**	1 (0.6)	0	2 (0.4)
Appendicitis	1 (0.7)	0	**2 (1.2)**	3 (0.6)
Cholecystitis acute	**1 (0.7)**	0	**1 (0.6)**	2 (0.4)
Cholelithiasis	**1 (0.7)**	0	0	1 (0.2)
Forearm fracture	**1 (0.7)**	0	0	1 (0.2)
Panic attack	1 (0.7)	0	0	1 (0.2)
Wrist fracture	**1 (0.7)**	0	0	1 (0.2)
Menorrhagia	0	1 (0.6)	**2 (1.2)**	3 (0.6)
Avulsion fracture	0	1 (0.6)	0	1 (0.2)
Uterine haemorrhage	0	**1 (0.6)**	0	1 (0.2)
Uterine myoma expulsion	0	1 (0.6)	0	1 (0.2)
Vitreous detachment	0	1 (0.6)	0	1 (0.2)
Anaemia	0	0	**2 (1.2)***	2 (0.4)
Road traffic accident	0	0	**2 (1.2)***	2 (0.4)
Atrial fibrillation	0	0	**1 (0.6)**	1 (0.2)
Blood pressure increased	0	0	**1 (0.6)**	1 (0.2)
Intervertebral disc protrusion	0	0	**1 (0.6)**	1 (0.2)
Metrorrhagia	0	0	**1 (0.6)**	1 (0.2)
Nephrolithiasis	0	0	**1 (0.6)**	1 (0.2)
Ovarian cyst ruptured	0	0	**1 (0.6)**	1 (0.2)
Pneumonia	0	0	1 (0.6)	1 (0.2)
Radius fracture	0	0	1 (0.6)	1 (0.2)
Syncope	0	0	1 (0.6)	1 (0.2)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as any adverse event that occurred after administration of the first dose of study treatment. SAEs that occurred during the 28-week OLE are bolded.
Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event.
*The SAE was reported to have occurred for 1 of the 2 participants during the OLE.

New SAEs were reported for 5 (3.4%) of participants in the R+delE2/NETA arm and 1 participant (0.6%) in the R+E2/NETA arm, as compared to 11 (6.7%) of participants in the PBO arm. In the pivotal trials combined, the corresponding proportions of the safety population experiencing at least one SAE were 1.9%, 3.1% and 2.3%, for the R+delE2/NETA, R+E2/NETA, and PBO arms, respectively. While an increase in the proportion of participants in the PBO arm who experienced SAEs during treatment with R+E2/NETA is notable, several PTs (i.e., appendicitis, road traffic accident, intervertebral disc protrusion, and nephrolithiasis) are not likely to be related to R+E2/NETA. Narratives for the remaining SAEs are discussed below. Two participants in the R+delE2/NETA arm experienced 3 fractures, which are considered AESIs, and are reviewed in Section 7.4.4 above.

Narrative Reports for SAEs assessed as possibly/probably related:

The events of cholecystitis and cholelithiasis for participants (b) (6) occurred in association with elevations in ALT and/or AST ≥ 3X ULN and are summarized in Table X (see Appendix).

Subject (b) (6): 46 yo BF randomized to R+delE2/NETA in study MVT-601-3001, who began open-label R+E2/NETA on Day 189 and experienced the Grade 3 SAE of Cholecystitis on Day 367. On Day 367 she had stomach pain after eating that progressed to include nausea, constipation and diarrhea. On Day 369 she was evaluated in the ER with multiple tests including hepatobiliary iminodiacetic acid (HIDA) scan that demonstrated gallbladder dysfunction, ultrasound that showed sludge and slight thickening of the gallbladder wall and diffuse fatty liver. On Day 371, the patient underwent a laparoscopic cholecystectomy with intraoperative cholangiogram. At the time of the surgery, the gallbladder was slightly chronically inflamed and distended. The cholangiogram findings were normal. Study drug was interrupted and resumed on Day 372. She completed the study on Day 395. The Investigator assessed the event as possibly related to R+E2/NETA, while the Sponsor's causality assessment was not related to relugolix and possibly related to E2/NETA. This reviewer concurs that the event is possibly related to treatment with E2.

Reviewer Comment: An additional participant (Participant (b) (6) who was originally randomized to PBO experienced the nonserious AE of cholelithiasis (Source: ISS Table 4.26.2.14; MVT-601-3003 CSR Listing 16.3.1.1). Studies among estrogen users suggest a small increased relative risk of developing gallbladder disease. In addition, women who are overweight or obese, similar to the study population and many women with uterine fibroids, are at increased risk for gallbladder disease. Overall, the results of the OLE trial support the inclusion of a warning in labeling regarding the risk of gallbladder disease.

Subject (b) (6): 47 yo WF who was randomized to PBO in Study MVT 601-3001 experienced Grade 3 Menorrhagia that led to study withdrawal. On Day 190 she began open-label R+E2/NETA. Hgb was 9.1 g/dL (reference range 11.6-16.4) and Hct was 31% (reference range 34-48%). On Day 253 Hgb was 6.3 g/dL and Hct 22 % she was treated with IV iron with increase in Hgb to 11.2 g/dL and Hct to 39%. On Day 331 she had grade 3 menorrhagia and was evaluated in the ER on Day 335, at which time she reported changing sanitary pads every 30-60 minutes. Hgb 10.1 g/dL and Hct 30.8%, which deteriorated after transfusion. She underwent emergency hysteroscopy with dilation and curettage and an attempted Novasure ablation followed by total abdominal hysterectomy with left salpingectomy (left ovary intact). Examination of endometrial curettings revealed features of polyps, mixed pattern endometrium (inactive and secretory) and no atypia; uterus had a fibroid distending the endometrial cavity and showed white whorled and slightly erythematous cut surfaces, without necrosis or discrete lesions; the endometrium was approximately 0.2 cm thick; left fallopian tube had an average diameter of 0.8 cm, no discrete lesions, and a pinpoint lumen on sectioning. Study drug was withdrawn on the same day. The Investigator and the Sponsor assessed the event as not related to relugolix and not related to E2/NETA. This reviewer disagrees and assesses the event as possibly related to study drug.

Subject (b) (6): 48 yo WF randomized to PBO in study MVT-601-3001, who began open-label R+E2/NETA on Day 191 and experienced Grade 3 Metrorrhagia on Day 194 (Day 14 of her menstrual cycle) accompanied by weaknesss. Three days later she was hospitalized for profuse vaginal bleeding with clots and Grade 3 Anaemia with Hgb 7.9 g/dL. Study drug was discontinued, and she underwent endocervical and uterine curettage, with ablation of endometrium. Histologic findings from the curettings showed benign metaplastic changes. She was withdrawn from the study on Day 239. On Day 242 she underwent abdominal hysterectomy and bilateral salpingo-oopherectomy. Pathology report was not provided. The investigator assessed the events as not related to study drug. The Sponsor assessed Metrorrhagia as possibly related to R+E2/NETA and assessed Anaemia as not related to study drug. This reviewer cannot rule out that both events are possibly related to R+E2/NETA. The lack of a pathology report hinders full assessment of the etiology of the profuse bleeding.

Subject (b) (6): 42 yo WF randomized to R+E2/NETA in study MVT-601-3001, who began open-label R+E2/NETA on Day 190, and experienced the SAE of uterine hemorrhage on Day 363. Study drug was permanently withdrawn. She was treated with IV tranexamic acid and oral norethisterone in addition to blood transfusion. On Day 365 she underwent laparoscopic total hysterectomy and bilateral salpingo-oophorectomy. uterine volume was abnormally increased, 18 cm in length, deformed with numerous myomatous nodes of an overall diameter between 3 and 7 cm, endometrial cavity occupied by hemorrhagic material, and the fallopian tubes were unaffected. Diagnoses included atrophic endometrium, leiomyomas, cystic endocervix, and chronic cervicitis. The investigator assessed the event as probably related and the Sponsor assessed the event as possibly related to R+E2/NETA. This reviewer concurs.

Subject (b) (6) 44 yo WF randomized to PBO in study MVT-601-3001, who began open-label R+E2/NETA on Day 170 and experienced the SAE of Menorrhgaia on Day 268 that led to study drug withdrawal. Prior to that event, on Day 173, she had Grade 2 Menorrhagia, Day 245 iron deficiency anemia and Day 264 Grade 3 abdominal pain. On Day 280, after having discontinued study drug she had Grade 3 Menorrhagia and underwent laparoscopic supracervical hysterectomy with supravaginal uterine amputation with fallopian tubes, without ovaries. Pathology report was not provided. The Investigator and the Sponsor assessed the event as possibly related to study drug. This reviewer concurs. Again, the lack of a pathology report hinders assessment of the bleeding etiology.

Subject (b) (6): 36 yo F (race-other) randomized to PBO in study MVT-601-3001, who began open-label R+E2/NETA on Day 175 and experienced the SAE of Grade 3 Blood pressure increased on Day 259. During the parent study, on Day 85 she experienced hypertensive crisis with BP 160/105. She was treated with diazepam. On Day 175 the BP was found to be 140/100. ECG and stress test showed no significant abnormalities. Echocardiogram was normal. BP elevations fluctuated. On Day 259, BP was 150/110. She was treated with diazepam and amlodipine in the emergency room (ER) but was not prescribed an antihypertensive medication. She was then lost to follow-up. Both the Investigator and the Sponsor assessed the event as not related to relugolix and possibly related to E2/NETA. This reviewer concurs.

Subject (b) (6): 42 yo WF randomized to R+delE2/NETA in study MVT-601-3002, who began open-label R+E2/NETA on Day 172 and experienced the SAE of uterine leiomyoma (verbatim: worsening of uterine fibroma) on Day 374 (Week 52 visit). At the visit she reported irregular HMB, had anemia with hgb 103 g/L (reference range 116-164 g/L) and Grade 2 uterine leiomyoma. The Investigator "decided to conduct surgery …to resolve the issue". On Day 395 she underwent a laparoscopy-assisted vaginal hysterectomy. The pathology report revealed the left ovary had follicular cysts and one inclusion cyst. No atypical ovarian lesions were detected. In the uterus the cervix was slightly inflamed change. and showed no atypical or dysplastic lesions. The endometrium was proliferative in type. There was also an isthmic endometrial polyp without atypia. The myometrium had several areas of superficial endometriosis and a large leiomyoma, measuring 9 cm. Histologic evaluation of the leiomyoma showed no atypia, no tumor necrosis or significant mitotic activity. Bilateral samples of fallopian tubes appeared normal. There was a benign paratubal cyst measuring 1 cm at widest point. The worsening of the uterine leiomyoma was assessed as not related to study drug by the Investigator and the Sponsor. This reviewer concurs.

Subject (b) (6): 39 yo BF WF randomized to R+E2/NETA in study MVT-601-3002, who began open-label R+E2/NETA on Day 170 and experienced the SAE of menorrhagia. In the parent study, on Day 125, she experienced Grade 3 Menorrhagia and Grade 2 Uterine myoma expulsion. On Day 170 she reported Grade 3 Menorrhagia. On day 312, study drug was permanently discontinued due to menorrhagia and the decision made to proceed with a a hysterectomy. On Day 316 she underwent hysterectomy. The pathology was not reported. The Investigator and the Sponsor assessed the event as possibly related to R+E2/NETA. This reviewer concurs.

Dropouts and/or Discontinuations Due to Adverse Events, Trial MVT-601-3003
Adverse events leading to discontinuation for participants of 3003 are shown in Table 37.

Table 38: Adverse Events Leading to Discontinuation, Safety Population – Study 3003

Preferred Term	Relugolix (52W) + Delayed E2/NETA (40W) N=149 n (%)	Relugolix + E2/NETA (52W) N=163 n (%)	Placebo (24W) & Relugolix+ E2/NETA (28W) N=164 n (%)	Total Participants (52W) N=476 n (%)
Any AE leading to discontinuation	5 (3.4)	5 (3.1)	9 (5.5)	19 (4.0)
Menorrhagia	2 (1.3)	1 (0.6)	2 (1.2)	5 (1.1)
Alanine aminotransferase increased	1 (0.7)	0	0	1 (0.2)
Bronchitis	1 (0.7)	0	0	1 (0.2)
Cholelithiasis	1 (0.7)	0	0	1 (0.2)
Dysmenorrhoea	1 (0.7)	0	0	1 (0.2)
Menstruation irregular	1 (0.7)	0	0	1 (0.2)
Depression	0	2 (1.2)	0	2 (0.4)
Alopecia	0	1 (0.6)	1 (0.6)	2 (0.4)
Uterine haemorrhage	0	1 (0.6)	0	1 (0.2)
Acne	0	0	1 (0.6)	1 (0.2)
Atrial fibrillation	0	0	1 (0.6)	1 (0.2)
Endometrial hyperplasia	0	0	1 (0.6)	1 (0.2)
Hemangioma of liver	0	0	1 (0.6)	1 (0.2)
Hot flush	0	0	1 (0.6)	1 (0.2)
Hypertension	0	0	1 (0.6)	1 (0.2)
Menometrorrhagia	0	0	1 (0.6)	1 (0.2)
Metrorrhagia	0	0	1 (0.6)	1 (0.2)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as any adverse event that occurred after administration of the first dose of study treatment.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of

in treatment arm; n, number of participants with adverse event

In the R+E2/NETA arm, two of the events (Depression and Uterine hemorrhage) were first reported in the OLE. The other events were first reported during the parent study. In the R+delE2/NETA, all but one case of menorrhagia was first reported in the OLE. In the PBO arm, all events that led to discontinuation of study drug were first reported in the OLE, suggesting an association between the AE and study drug. Narratives for these events are discussed below.

AEs leading to study drug discontinuation were also analyzed by FMQ (Table 38).

Table 39: Adverse Events Leading to Discontinuation by FDA Medical Query (Narrow), Safety Population, Trial MVT-601-3003

FDA Medical Query (Narrow)	Relugolix (52W) + Delayed E2/NETA (40W) N=149 n (%)		Relugolix + E2/NETA (52W) N=163 n (%)	Placebo (24W) & Relugolix+ E2/NETA (28W) N=164 n (%)	Total Participants (52W) N=476 n (%)
Abnormal uterine bleeding (narrow FMQ)	3 (2.0)		2 (1.2)	4 (2.4)	9 (1.9)
Haemorrhage (narrow FMQ)	2 (1.3)		1 (0.6)	4 (2.4)	7 (1.5)
Excessive menstrual bleeding (narrow FMQ)	2 (1.3)		1 (0.6)	3 (1.8)	6 (1.3)
Hepatic injury (narrow FMQ)	1 (0.7)		0	0	1 (0.2)
Depression (narrow FMQ)	0		2 (1.2)	0	2 (0.4)
Alopecia (narrow FMQ)	0		1 (0.6)	1 (0.6)	2 (0.4)
Arrhythmia (narrow FMQ)	0		0	1 (0.6)	1 (0.2)
Systemic hypertension (narrow FMQ)	0		0	1 (0.6)	1 (0.2)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as any adverse event that occurred after administration of the first dose of study treatment.
For specific preferred terms under each FMQ, see the table "Adverse Events Leading to Discontinuation by FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of participants in treatment arm; n, number of participants with adverse event

Abnormal uterine bleeding led to discontinuation in approximately 2% of the safety population in the OLE as compared to 1.2%, 0% and 1.6% of participants in the R+E2/NETA, PBO and R+delE2/NETA arms during the placebo-controlled trials indicating that bleeding events may occur with ongoing treatment. Two participants discontinued due to depression and one each discontinued due to alopecia and hypertension. These AEs were identified as safety issues in the placebo-controlled trials and will be included in labeling.

Narrative reports for AEs leading to study drug discontinuation:

Subject (b) (6): 45 yo BF randomized to PBO in study MVT-601-3001, who began open-label R+E2/NETA on Day 183 and experienced the non-serious AE of Grade 2 menometrorrhagia on Day 211. On Day 247 study drug was discontinued. The Investigator assessed the event as possibly related to R+E2/NETA. This reviewer concurs. The Sponsor did not provide a causality assessment.

Subject (b) (6): 48 yo BF randomized to R+delE2/NETA in study MVT-601-3001, who began open-label R+E2/NETA on Day 190 and experienced the non-serious AE of Grade 2 irregular menses on Day 190. Hct 33%, Hbg 10.7 g/dL. On Day 308 study drug was permanently discontinued due to irregular menses. The Investigator assessed the event as possibly related to R+E2/NETA. This reviewer concurs. The Sponsor did not provide a causality assessment.

Subject (b) (6): 31 yo BF randomized to PBO in study MVT-601-3001, who began open-label R+E2/NETA on Day 186 and experienced the AE of complex endometrial hyperplasia without atypia on Day 199. Study drug was permanently discontinued and she was treated with

medroxyprogesterone. She had follow-up with her private physician and information regarding repeat biopsy was not available. Reportedly, she underwent myomectomy. The investigator assessed the event as not related to R+E2/NETA. Given the timing of initiation of R+E2/NETA and the AE, this reviewer concurs.

Subject (b) (6): 48 yo WF randomized to R+E2/NETA in study MVT-601-3001, who began open-label R+E2/NETA on Day 184 and experienced the non-serious AE of Grade 2 depression. During the parent study, on Day 50 she had Grade 1 depression and Grade 1 irritability that resolved after 4 days without treatment. On Day 252 she had Grade 2 depression. She was treated with Escitalopram and on Day 266, study drug was permanently discontinued due to depression. The Investigator assessed the event as possibly related to R+E2/NETA. This reviewer concurs.

Subject (b) (6): 47 yo BF randomized to PBO in study MVT-601-3002, who began open-label R+E2/NETA on Day 175 and experienced the AE of Grade 2 hypertension on Day 200. No BP measurements were reported on that day. On Day 175 the BP was 118/82. On Day 203, study drug was permanently discontinued. The Investigator assessed the event as possibly related to relugolix and not related to E2/NETA. If the participant was actually hypertensive then the reviewer disagrees with the causality because estrogen/progestins have been reported to be associated with increases in BP.

Subject (b) (6): 40 yo WF randomized to R+E2/NETA in study MVT-601-3002, who began open-label R+E2/NETA on Day 187 and experienced the non-serious AE of Grade 2 depression. During the parent study, on Day 22 she reported Grade 1 irritability that resolved on Day 119. On Day 211, the patient was reported to have an AE of Grade 2 depression and study drugs were permanently discontinued due to this AE. No treatment was reported the depression. This reviewer assessed the event as possibly related to R+E2/NETA.

Subject (b) (6): 45 yo WF randomized to R+E2/NETA in study MVT-601-3002, who began open-label R+E2/NETA on Day 179 and experienced the non-serious AE of Grade 2 alopecia. On Day 148 she had Grade 1 alopecia. She was not given treatment and no action was taken with study drug. On Day 225 Grade 2 alopecia was reported to resolve. On Day 260 she reported Grade 2 alopecia. On Day 291, study drug was permanently discontinued. The event resolved on Day 306. The event was assessed as possibly related to R+E2/NETA. This reviewer concurs, although rapid resolution and recurrence described in this case is unusual.

Subject (b) (6): 38 yo BF randomized to R+del E2/NETA in study MVT-601-3002, who began open-label R+E2/NETA on Day 184 and experienced the non-serious AE of Grade 3 dysmenorrhea and menorrhgia on Day 228. She was treated with tramadol for the dysmenorrhea. On Day 231, study drug was permanently discontinued due to both AEs of dysmenorrhea and menorrhagia. The event of menorrhagia resolved on Day 233. The Investigator assessed both events as possibly related to R+E2/NETA. This reviewer concurs.

Subject (b) (6): 46 yo WF WF randomized to R+delE2/NETA in study MVT-601-3002, who began open-label R+E2/NETA on Day 172 and experienced the non-serious AE of Grade 2

menorrhagia. On Day 164, the patient was reported to have an adverse event of grade 2 menorrhagia, which was ongoing on Day 172 when she began open-label R+E2/NETA. On Day 199, study drugs were permanently discontinued due to the adverse event. She completed the study on Day 228 and the event was reported as ongoing. The Investigator assessed the event as not related to R+E2/NETA. This reviewer disagrees. A causal relationship cannot be ruled out.

Subject (b) (6): 32 yo BF randomized to PBO in study MVT-601-3002, who began open-label R+E2/NETA on Day 183 and experienced the AEs of Grade 1 acne, alopecia and hot flush, all leading to withdrawal. On Day 210, the patient was reported to have the AE of grade 1 alopecia. On Day 241, the patient was reported to have the AE of grade 1 acne. Both events were ongoing when, on Day 277, the patient was reported to have the AE of grade 1 hot flush. On Day 279, the patient began treatment with doxycycline for the treatment of acne; no treatment was reported for the events of alopecia or hot flush. On Day 281, study drugs were permanently discontinued due to the three adverse events. The event of hot flush resolved on Day 292, and the events of acne and alopecia resolved on Day 302. Treatment with doxycycline was discontinued on Day 302. The Investigator assessed the events as probably related to R+E2/NETA. This reviewer concurs.

Treatment-Emergent Adverse Events, Trial MVT-601-3003
For the participants of Study 3003, TEAEs assessed as related to study drug by the investigator that were reported during the placebo-controlled trials or during the OLE are shown in Tables 40 and 41, respectively.

Table 40: Treatment-Related Adverse Events Prior to the OLE Period (First 24 Weeks) and Occurring in at Least 2% of Participants in Any Treatment Groups, Safety Population – Study 3003

Preferred Term	R+Delayed E2/NETA N=149 n (%)	R+E2/NETA N=163 n (%)	Placebo N=164 n (%)	Total N=476 n (%)
Any treatment-related AE	84 (56.4)	56 (34.4)	42 (25.6)	182 (38.2)
Hot flush	55 (36.9)	14 (8.6)	10 (6.1)	79 (16.6)
Headache	18 (12.1)	12 (7.4)	10 (6.1)	40 (8.4)
Fatigue	6 (4.0)	2 (1.2)	3 (1.8)	11 (2.3)
Alopecia	5 (3.4)	6 (3.7)	1 (0.6)	12 (2.5)
Night sweats	5 (3.4)	3 (1.8)	0	8 (1.7)
Libido decreased	4 (2.7)	3 (1.8)	0	7 (1.5)
Abdominal pain	3 (2.0)	5 (3.1)	1 (0.6)	9 (1.9)
Arthralgia	3 (2.0)	3 (1.8)	3 (1.8)	9 (1.9)
Breast pain	3 (2.0)	3 (1.8)	0	6 (1.3)
Decreased appetite	3 (2.0)	0	1 (0.6)	4 (0.8)
Hyperhidrosis	3 (2.0)	4 (2.5)	0	7 (1.5)
Metrorrhagia	3 (2.0)	0	0	3 (0.6)
Vulvovaginal dryness	3 (2.0)	1 (0.6)	0	4 (0.8)
Nausea	2 (1.3)	3 (1.8)	5 (3.0)	10 (2.1)
Hypertension	1 (0.7)	4 (2.5)	2 (1.2)	7 (1.5)
Menorrhagia	0	4 (2.5)	0	4 (0.8)

Source: adae.xpt; Software: SAS.
Treatment-related AEs were assessed by investigator as related to any of the study drugs (relugolix and/or E2/NEATA).
Adverse events prior to the OLE period: If adverse event onset date was prior to the first dose date in the open-label extension study period.

Table 41: Treatment-Related Adverse Events During the OLE Period and Occurring in at Least 2% of Participants in Any Treatment Groups, Safety Population – Study 3003

Preferred Term	R+Delayed E2/NETA N=149 n (%)	R+E2/NETA N=163 n (%)	Placebo N=164 n (%)	Total N=476 n (%)
Any treatment-related AE	36 (24.2)	43 (26.4)	51 (31.1)	130 (27.3)
Headache	4 (2.7)	6 (3.7)	10 (6.1)	20 (4.2)
Blood creatine phosphokinase increased	3 (2.0)	2 (1.2)	0	5 (1.1)
Gastroesophageal reflux disease	3 (2.0)	1 (0.6)	0	4 (0.8)
Metrorrhagia	3 (2.0)	0	1 (0.6)	4 (0.8)
Hot flush	2 (1.3)	5 (3.1)	12 (7.3)	19 (4.0)
Depression	1 (0.7)	3 (1.8)	4 (2.4)	8 (1.7)
Dizziness	0	5 (3.1)	3 (1.8)	8 (1.7)
Nausea	0	5 (3.1)	1 (0.6)	6 (1.3)

Source: adae.xpt; Software: SAS.
Treatment-related AEs were assessed by investigator as related to any of the study drugs (relugolix and/or E2/NETA).
AEs during the OLE period: If adverse event onset date is on or after the first dose date in open-label extension period.

For participants who switched from PBO in the parent trial to R+E2/NETA during the OLE trial, 4 participants (2.7%) experienced depression and one participant (0.6%) reported metrorrhagia. The incidence of hot flushes and headache were similar during the parent trial and OLE trial. For

the participants treated with R+E2/NETA for up to 52 weeks, during the latter 28 weeks, a smaller proportion of participants reported AEs hot flushes, headache, alopecia, abdominal pain, hypertension and menorrhagia. Depression was reported for three participants (1.8%). Dizziness and nausea were reported in a greater proportion of participants during the OLE (3.1% each) as compared to the parent trial (<2%) for this treatment arm, but is within the range reported for each of these AEs in the pivotal trials.

The Applicant also provided a summary of AEs according to onset relative to first dose of R+E2/NETA combination therapy (Source: ISS Table 127).

In their analysis of the AEs that occurred in at least 2% of the safety population exposed to R+E2/NETA in any of the three Phase 3 trials, the majority occurred within the first 36 weeks of exposure with little increases thereafter.

Adverse Events and Parameters of Special Interest

Endometrial Biopsies

Endometrial biopsies were required at the Week 52/Early Termination visit for patients consented under Amendment 1 whose last dose of study drug was taken after Week 32. On November 30, 2020, along with their response to Information Requests related to the Midcycle Teleconference (meeting minutes dated Novermber 16, 2020), the Applicant submitted a new summary of endometrial biopsy data from Study MVT-601-3003 because in a post-hoc reconciliation analysis, they noted that 42 specimens had not undergone consensus reads prior to submission of the NDA. All 42 samples were from unplanned biopsies. Reasons for the biopsies included the following: site failed to collect the Week 24 biopsy (13 cases), inadequate sample at Week 24 biopsy (28 cases), collected at Week 52 was an error (one case, before the protocol Amendment 1 that required the biopsy).

The updated endometrial biopsy results for samples from Week 52/EOT are shown in Table 42. A similar proportion of participants from each treatment arm had a biopsy at Week 52/EOT. The biopsy at 52 weeks is being taken from participants who have been on at least 28 weeks of R + E2/NETA in the OLE. None had treatment-related hyperplasia or carcinoma. Approximately one-quarter had atrophy/inactive endometrium, and 3.7-9.4% had inadequate specimens which may have been related to atrophic endometrium. Results are consistent with the mechanism of action of relugolix and E2/NETA on the endometrium and no endometrial safety concerns emerged with up to 52 weeks of continuous treatment with R+E2/NETA.

Table 42: Consensus Diagnosis for Endometrial Biopsies at Week 52/Early Termination – Study 3003

	Parental Arm from Pivotal Studies 3001 & 3002		
	R+delE2/NETA (N=149)	**R+E2/NETA (N=163)**	**PBO (N=164)**
Week 52/EOT			
Number (%) with results	73 (49.0%)	77 (47.2%)	75 (45.7%)
Atrophy/Inactive	40 (26.8%)	39 (23.9%)	42 (25.6%)
Proliferative	7 (4.7%)	16 (9.8%)	9 (5.5%)
Mixed/Secretory/Menstrual	8 (5.4%)	11 (6.7%)	17 (10.4%)
Hyperplasia	0	1 (0.6%)	0
Other*	0	1 (0.6%)	0
Polyp	1 (0.7%)	0	0
Inadequate	17 (11.4%)	9 (5.5%)	7 (4.3%)
Week 52 Follow-up Biopsies for Inadequate Sample			
Number (%) with results	12 (8.1%)	6 (3.7%)	7 (4.3%)
Atrophy/Inactive	3 (2.0%)	1 (0.6%)	2 (1.2%)
Proliferative	2 (1.3%)	2 (1.2%)	0
Mixed/Secretory/Menstrual	2 (1.3%)	1 (0.6%)	3 (1.8%)
Hyperplasia	0	0	0
Other*	0	0	0
Polyp	0	1 (0.6%)	0
Inadequate	5 (3.4%)	1 (0.6%)	2 (1.2%)

Source: Table 4 in Response to Information Request submitted on November 30, 2020
*Other diagnoses include reactive/inflammatory changes.

The case of hyperplasia for the participant in the R+E2/NETA treatment arm (Participant (b) (6)) is discussed above. Overall, these results provide additional data to support the conclusion that treatment with R+E2/NETA is not associated with endometrial hyperplasia or carcinoma

Fractures

Fractures that occurred during the OLE study are discussed above with the pivotal trial fracture cases (see Section 7.4.4).

Blood Pressure

At week 52, mean (SD) change from baseline in SBP was 0.2 (11.4), 0.4 (13.30), and 1.2 (12.7) mm Hg for the R+E2/NETA, R+delE2/NETA and PBO arms, respectively. Corresponding mean (SD) changes in DBP were -0.1 (8.6), 1.3 (9.5) and 0.2 (10.1) mm Hg, respectively. The proportion of participants having pre-specified thresholds for increases in BP are shown in Table X.

Table 43: The Proportion of Participants Meeting Thresholds for Increases in Systolic and Diastolic Blood Pressure over 52 weeks, Safety Population – Study 3003

	R+delE2/NETA (N=149)	R+E2/NETA (N=163)	PBO (N=164)
Systolic Blood Pressure			
≥140 mm Hg	53 (35.6%)	64 (39.3%)	60 (36.6%)
≥180 mm Hg	0	1 (0.6%)	0
≥20 mm Hg increase from baseline	39 (26.2%)	54 (33.1%)	40 (24.4%)
Diastolic Blood Pressure			
≥90 mm Hg	68 (45.6%)	61 (37.4%)	71 (43.3%)
≥105 mm Hg	4 (2.7%)	4 (2.5%)	7 (4.3%)
≥15 mm Hg increase from baseline	42 (28.2%)	32 (19.6%)	42 (25.6%)

Adapted from MVT-601-3003 CSR Table 8.3.10.2

The proportion of participants experiencing two consecutive measurements in SBP ≥ 140 mm Hg ranged from 16-19% in the different treatment arms. No participants had 2 consecutive measurements in SBP ≥ 180 mm Hg. The proportion of participants with two consecutive measurements in DBP ≥ 90 mm Hg was lower (13.5% in the R+E2/NETA arm and 20.1% in each of the other two arms). These proportions are slightly higher than that reported for the pivotal trials where approximately 12% of participants in each treatment arm experienced two consecutive increases in SBP above this threshold (ISS Table 7.3.1.)]. As compared to the pivotal trials, a smaller proportion of participants experienced two consecutive increases incremental in SBP ≥20 mm Hg and DBP ≥15 mm Hg (to approximately 9% and 12% , respectively across treatment arms).

New adverse events associated with hypertension were reported fin the OLE or 2 patients (1.2%) in the R + E2/NETA group, 3 patients (2.0%) in the R+del E2/NETA group, and 11 patients (6.7%) in the PBO group. The increase in the proportion of participants with hypertension AEs in the PBO arm after beginning R+E2/NETA provides additional evidence of an association between R+E2/NETA and increases in BP, and support the inclusion of the risk of increases in BP in labeling. A summary of the narratives for participants with the AE of hypertension during Study 3003 is shown in the Appendix (see Table 49).

Resumption of Menses after Drug Discontinuation

Post-treatment menstrual status was reported for 248 participants who either discontinued the trial prematurely or completed the trial and did not enroll in the next available study MVT-601-035 (Source: MVT-601-3003 CSR Table 8.2.9.1). Results were similar to those observed for the placebo-controlled trials.

Of the participants for whom menstruation status was available, 93.8% (61/63), 97.1% (66/68), and 93.4% (57/61) in the R+ E2/NETA, R+del E2/NETA, and PBO groups, respectively, reported having post-treatment menses. The mean time from last dose of study treatment to occurrence of menses was similar for the R+E2/NETA and R+delE2/NETA arms and slightly shorter for the PBO arm (40.5, 40.6, and 36.9 days, respectively). Mean time to occurrence of menses was longer for the 37 participants who reported amenorrhea over the last 35 days of treatment

than for the 24 participants without amenorrhea over the last 35 days of up to 52 weeks of treatment with R+E2/NETA (45.6 vs. 32.6 days, respectively).

Ten participants did not have return of menses post-treatment, seven of whom underwent surgery (two participants in the R+E2/NETA arm, one participant in the R+delE2/NETA arm and four participants in the PBO arm). Of the three remaining participants, one in the R+E2/NETA arm experienced menopause, one in the R+delE2/NETA arm was using levonorgestrel and for one participant in the R+E2/NETA arm, no reason was identified.

Pregnancies
No pregnancies were reported during the OLE trial.

Laboratory Findings, Trial MVT-601-3003

Hematology
No safety signals related to hematology parameters emerged during this study.

Chemistry
No new safety signals related to chemistry parameters emerged during this study.

Laboratory assessments of special interest are discussed below. Overall, changes in these parameters are consistent with those observed during the placeb-controlled trials.

Transaminases
Seven participants had elevations in AST and/or ALT ≥ 3-fold ULN with onset during the OLE trial. Brief arrative summaries for these participants are included in Table X above. Risk factors were identified in all 7 participants and included hepatic steatosis, concomitant medications, and gallstones/cholecystitis. Liver enzyme elevations improved/resolved in all participants whether medication was continued (4/7) or discontinued (1/7), or was detected after last dose of study drug (2/7).

In addition, one participant (b) (6) in the R+E2/NETA arm was reported to have grade 1 nonserious AST 131 U/L and ALT 77 U/L with onset 41 days following last dose of study drug (359 days of treatment) which was reported outside of the safety reporting period and was not captured as an AESI. Confounders included obesity and use of chromium. ALT and AST were improved on retesting 3 days later.

Glucose and Hemoglobin A1c (HgbA1c)
Fasting blood glucose (FBG) and HgbA1c was assessed at baseline (Week 24 of the parent study) and Week 52, although the Applicant indicated in their response to an information request that they could not ensure that participants were fasting.

A trend toward an increase in FBG was observed with increasing duration of treatment with R+E2/NETA, with mean (SD) change from baseline of -2.39 (26.1), 5.2 (30.9), and 7.22 (18.5) in

the PBO, R+delE2/NETA and R+E2/NETA arms, respectively. Of the 161 participants with normal FBG at baseline, 9.3% (15/161) had an increase to Grade 1 (>100 mg/dL, no medical intervention) and 1.9% (3/161) had an increase to Grade 2 (>100 mg/dL, medication required) at Week 52 (Source: CSR MVT-601-3003 Table 8.3.9.5). At Week 52, mean (SD) change from baseline in HgbA1c was minimal and comparable across treatment arms [0.18 (0.6), 0.22 (0.5), and (0.21 (0.4) for the PBO, R+delE2/NETA, and R+E2NETA treatment arms, respectively. The limitations of relying on HgbA1c to assess glucose status in the setting of anemia are discussed above.

Lipids

Fasting lipids were assessed at baseline (Week 24 of the parent study) and Week 52, although the Applicant indicated that they could not ensure that participants were fasting.
At Week 52, mean (SD) change from baseline in lipids are shown in Table X. Mean changes in lipids were small and changes did not appear to be related to duration of exposure to R+E2/NETA.

Table 44: Mean (SD) Change From Baseline in Lipids at Week 52 – Study 3003

	R+delE2/NETA	R+E2/NETA	PBO
Total cholesterol (mg/dL)	1.552 (19.5108)	-2.128 (27.3136)	-4.602 (22.6396)
LDL (mmol/L)	0.087 (0.4357)	0.013 (0.6548)	-0.067 (0.5166)
HDL (mmol/L)	-0.055 (0.1950)	-0.061 (0.2505)	-0.075 (0.2211)
Triglycerides (mmol/L)	0.024 (0.4401)	0.031 (0.8179)	0.073 (0.5527)

Source: Modified from ISS Table 112
Abbreviations: E2 = estradiol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Max = maximum; Min = minimum; N = number of patients in the treatment group; n = number of patients included in summary statistics; NETA = norethindrone acetate; SD = standard deviation.
Baseline value is defined as the last measurement on or before the first administration (date and time) of study drug.

The Applicant assessed grade shifts in worst post-baseline total cholesterol and triglycerides (Source: CSR for Study 3003 Table 8.3.9.5). Of the 156 participants in the R+E2/NETA arm with normal total cholesterol at baseline, 1.9% (3/156) shifted to Grade 1 (>200-300 mg/dL) and 1.3% (2/156) shifted to Grade 2 (>300-400 mg/dL). No participants in this treatment arm with Grade 1 total cholesterol at baseline shifted to higher grades. No participants in any treatment arm had a shift to Grade 3 or 4.

Of the 119 participants in the R+E2/NETA arm with normal triglycerides at baseline (< 150 mg/dL), 18.5% (22/119) had a shift to Grade 1 (150-300 mg/dL), and none in this treatment arm shifted to higher grades. Of the 38 participants with Grade 1 triglycerides at baseline, 7.9% (3/38) shifted to Grade 2 (>300 to 500 mg/dL) and 5.3% (2/38) shifted to Grade 3 (>500 to 1000 mg/dL). One of 24 participants in the R+delE2/NETA arm (4.2%) had a shift in triglycerides from Grade 1 to Grade 4 (>1000 mg/dL). No others participants had Grade 4 triglyceride elevations. No cases of pancreatitis were reported. Marked hypertriglyceridemia is a known risk of oral estrogen and will be included in the Warnings and Precautions section of the label, consistent with class labeling.

During the OLE trial, AEs related to adverse carbohydrate and lipid metabolic effects were reported for an additional two, three and four participants in the PBO, R+delE2/NETA and R+E2/NETA treatment arms. All of these participants had BMI > 30 kg/m^2. In the PBO arm, events were coded to the PTs Insulin resistance and Type 2 diabetes mellitus (T2DM). The participant with T2DM had HgbA1c in the range of T2DM at baseline. In the R+delE2/NETA arm, events were coded to the PTs diabetes mellitus (verbatim: worsening DM), Type 2 diabetes mellitus (verbatim: worsening T2DM), and hypercholesterolaemia. The participants with the events of diabetes/worsening diabetes had elevated FBS in the range of diabetes at baseline and the participant with the AE of hypercholesterolemia had elevated total cholesterol at baseline. In the R+E2/NETA arm, two events were coded to the PTs glycosylated haemoglobin increased, and one to each glucose tolerance impaired and Type 2 diabetes mellitus. Three of these four participants had elevated HgbA1c at baseline.

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

Breast and liver tumors were AESIs.

No breast or liver tumors were reported for females with uterine fibroids that participated in Phase 2 and Phase 3 studies of relugolix monotherapy.

No breast tumors were reported during Studies 3001, 3002, or 3003.

The AE of Hepatic hemangioma was reported for two participants. In Study 3001, one participant (b) (6) in the R+delE2/NETA arm had the AE of hepatic hemangioma that was discovered as part of an evaluation for elevated GGT during the first 12 weeks of the study while she was on relugolix monotherapy. The hemangioma was assessed as not related to study drug. Similarly, in Study 3003, one participant (b) (6) treated with PBO during Study 3002 had the AE of liver hemangioma incidentally identified on ultrasound imaging during evaluation of hepatic transaminase elevations and was assessed by the investigator as not related to study drug.

7.8.2. Human Reproduction and Pregnancy

Pregnancy was reported for one participant in the PBO arm in both Study 3001 and Study 3002, one of whom had an elective abortion and one who was lost to follow-up. In the 120-Day Safety Report, the Applicant submitted an updated report of pregnancies that have occurred in the relugolix clinical development programs through July 7, 2020 (see Appendix, Table 51). Overall, 27 pregnancies were reported, including 11 women who became pregnant while on relugolix monotherapy or R+E2/NETA combination therapy. Of these 11 pregnancies, four resulted in live birth (three full term, one premature), one resulted in missed abortion, three remained ongoing at the time of the report, and three were of unknown status/lost to follow-

up. Of the four live births, three were reported to have healthy infants. One infant had congenital hip dysplasia and a heart murmur with a normal echocardiogram. Possible confounders in this case included nicotine and methamphetamine use during pregnancy. The one pregnancy with conception prior to initiation of treatment resulted in a live birth of a healthy infant at full term. Of the four pregnancies in women who became pregnant after completing treatment with relugolix, two resulted in live birth (one full term, one premature), one resulted in missed abortion, and one remains ongoing. The one pregnancy that occurred in the blinded withdrawal study MVT-601-035 is ongoing.

This drug is not intended for use in pregnant or lactating females, (b) (4) Additionally, because this product is intended for use in premenopausal women, the Agency will require a pregnancy registry and a PMR to better characterize fetal, neonatal and maternal risks associated with exposure to R+E2/NETA during pregnancy. In addition, the recommendation for nonhormonal contraception will be included in Section 8 of the label and in the PPI.

7.8.3. Pediatrics and Assessment of Effects on Growth

Uterine fibroids are extremely rare in adolescent females, and therefore, HMB related to uterine fibroids is not seen in this population. In addition, this condition does not occur in premenarchal females or in males. Because no females < 18 years of age were enrolled in the clinical program, the effect of R+E2/NETA on growth was not assessed.

The Applicant seeks a full waiver from the requirements to obtain pediatric data under the Pediatric Research Equity Act (PREA). The Applicant submitted an initial pediatric study plan (iPSP) on December 5, 2016, and a final Pediatric Study Plan (PSP) on March 27, 2017, requesting a full waiver to conduct pediatric studies in females <17 years and all pediatric males <17 years. Reasons provided by the Applicant to justify a full waiver include:

1. Premenarcheal females are not at risk for fibroids.
2. Studies are impossible or highly impractical in postmenarcheal female adolescents.
3. The prevalence of uterine fibroids in these postmenarcheal adolescents is exceedingly low, especially with the additional requirement of HMB, and is geographically dispersed, making it impossible or highly impractical to conduct clinical studies.
4. Because uterine fibroids are a disease specific to women, pediatric males are not affected by this condition.

On April 7, 2017, FDA issued an Agreed iPSP. Uterine fibroids are so rare in the adolescent female population such that clinical studies in this population would not be feasible. In addition, this condition does not occur in premenarchal females or males. For these reasons, HMB associated with uterine fibroids is included in the list of conditions that qualifies for a full waiver under PREA. Further, we would not recommend studying this product in the adolescent female population because adolescence is a critical time of bone mass accrual; the potential adverse effects on achieving peak bone mass, increasing fracture risk, and developing

osteoporosis later in life are major concerns that alter the benefit/risk for this population. The Pediatric Review Committee (PeRC) reviewed the Applicant's request and agrees with granting a full waiver of studies in pediatric patients because studies are impossible or highly impracticable.

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

In clinical studies, overdose was defined as two or more doses of relugolix monotherapy (i.e., ≥ 80 mg) or R+E2/NETA within a 24 hour period. The following four unintentional overdoses were reported in Phase 3 trials in the uterine fibroid program:

- Participant (b) (6) (Study 3001)-50 y/o white female accidentally took 13-14 extra doses over 25 days while caring for her hospitalized son and mistakenly thought she had not taken her dose.
- Participant (b) (6) (Study 3002)-38 y/o black female found to have 3 missing pill doses; she reported dropping one pill and no explanation was provided for the others. The event was reported as accidental overdose.
- Participant (b) (6) (Study 3003)-32 y/o white female who was randomized to PBO in Study 3001, found to have been taking R+E2/NETA one tablet twice daily over 14 consecutive days (Days 323-337).
- Participant (b) (6) (Study 3003)-50 y/o white female randomized to R+E2/NETA in Study 3002, took R+E2/NETA one tablet twice daily over 4 consecutive days (Days 362-365) because she could not remember having taken the initial daily dose.

Participants were asymptomatic in all cases and no AEs were reported in association with these overdose events.

Abuse Potential

Relugolix is a substrate for the P-gp efflux transporter. Nonclinical studies have demonstrated that it does not cross the blood-brain barrier. Furthermore, relugolix was not associated with off-target activity based on in vitro pharmacology studies with a battery of receptors, enzymes, transporters and ionic channels [see NDA 214621 Office Director Review (Paul Kluetz, MD, Deputy Director for Oncology Center of Excellence and Rashida E. Redd, RPM) dated 12/18/2020 for detailed summary]. Additionally, there is no evidence of abuse potential for E2/NETA (Activella). Withdrawal effect of R+E2/NETA in females with uterine fibroids is being assessed in Study MVT-601-035 (Randomized Withdrawal Study). The Controlled Substance Staff (CSS) at FDA was not consulted to review this NDA because there is no concern for abuse potential with this drug class. Section 9 (Drug Abuse and Dependence) will be omitted from the Prescribing Information.

7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

Relugolix 40 mg monotherapy is marketed in Japan as Relumina ® for the treatment of HMB associated with uterine fibroids. The Applicant included a summary of postmarketing safety reports for Relumina in the 120-Day Safety Update that included the following events that are of potential concern for the R+E2/NETA combination product [PT (number of cases)]: uterine myoma expulsion (3), uterine leiomyoma (degeneration) (1), genital haemorrhage (8), uterine haemorrhage (4), metrorrhagia (1), pulmonary embolism (1), anaphylactic reaction (2), drug eruption (1), hypertension (1), and hepatitis (1). These events or related adverse events are addressed in the safety review of R+E2/NETA.

7.9.2. Expectations on Safety in the Postmarket Setting

- Off-label use of R+E2/NETA for longer than the recommended 2 years could be associated with greater bone loss and increased risk for fracture.
- It is possible that R+E2/NETA could be used off-label to treat endometriosis in females or to treat male to female transgender persons. The safety in either population has not been established, although the drug is being developed by the Applicant for the treatment of endometriosis.
- It is not anticipated that R+E2/NETA will be used in postmenopausal females.

7.9.3. Additional Safety Issues From Other Disciplines

7.10. Integrated Assessment of Safety – Safety Summaries

A total of 634 unique participants have been exposed to R+E2/NETA in Phase 2/3 trials in the uterine fibroid program. In Phase 3 placebo-controlled clinical trials for the uterine fibroid indication (Studies 3001, 3002 and 3003), a total of 451 participants were exposed to R+E2/NETA for six months. Among the 163 participants who received R+E2/NETA in Studies 3001 and 3002 and entered Study 3003, 130 were exposed for 12 months. An additional 11 participants were exposed for 48 to < 52 weeks.

In the placebo-controlled trials, the most common AEs occurring in ≥ 3% of participants treated with R+E2/NETA and at least 1% greater than placebo were hot flush/hyperhidrosis/night sweats (10.6% vs. 6.6%), abnormal uterine bleeding [including menorrhagia, metrorrhagia, vaginal hemorrhage, polymenorrhea, and menstruation irregular); 6.3% vs. 1.2%], alopecia (3.5% vs. 0.8%) and libido decreased/loss of libido (3.1% vs. 0.4%). In Study 3001, more women experienced new or worsening hypertension with R+E2/NETA treatment compared to placebo (7.0% vs. 0.8%). Less common adverse reactions reported in at least 2% and less than 3% of

women in the R+E2/NETA group and greater incidence than placebo included irritability, dyspepsia, and breast cyst.

Venous and Arterial Thromboembolic Events
Approved labeling for estrogen and progestin combinations [in combined hormonal contraceptive products intended for women of reproductive potential and in hormone therapies intended for postmenopausal women, including E2 1 mg /NETA 0.5 mg (Activella)] includes a Box Warning regarding thromboembolic disorders. In the clinical program, no thromboembolic events occurred. However, one event of deep vein thrombosis and pulmonary embolism was reported for a participant treated with R+E2/NETA in the endometriosis clinical development program, and one case of Pulmonary embolism was reported postmarketing for a woman taking relugolix 40 mg monotherapy (Relumina) for uterine fibroids. Because MYFEMBREE is a fixed-dose combination containing E2/NETA, a Box Warning, Contraindications and Warnings and Precautions related to venous and arterial thromboembolic events are included in product labeling. (b) (4)

Bone Loss
The adverse effect of GnRH antagonists on bone is well-known and was demonstrated in the R+delE2/NETA arm in placebo-controlled trials during 12 weeks of relugolix monotherapy. The addition of E2/NETA to relugolix attenuated bone loss, but did not completely prevent it. After 52 weeks of treatment with R+E2/NETA, bone loss of at least 2% at the lumbar spine was observed for 36.4% of participants. In comparison 25.8% of participants from the uterine fibroid cohort of the observational study experienced ≥2% bone loss over 52 weeks of observation. A small number of participants with bone loss had follow-up DXA scans to assess for recovery. Whether full recovery will occur posttreatment is uncertain. Additionally, whether a decline in BMD in younger premenopausal women who have not yet attained peak bone mass, or in older premenopausal women who are at risk for accelerated bone loss at the time of menopause increases fracture risk later in life is uncertain.

Because trabecular-rich skeletal sites, such as the lumbar spine tend to be the most sensitive to reductions in estrogen levels, changes in BMD at this site will be included in product labeling. The Applicant submitted clinic data for only 12 months of use. Given that bone loss occurs in a subset of women with 12 months of treatment and information on recovery is inadequate, considering the benefit-risk, we will require a Limitations of Use of 2 years in the label. (b) (4) the Applicant proposed (b) (4) We disagree with this approach because (b) (4) The recommendation for BMD at baseline and periodically thereafter and a contraindication for use in women with known osteoporosis will also be included in product labeling. In addition, a postmarketing requirement to characterize bone loss with greater duration of treatment (4 years) and to characterize recovery of bone loss will be requested.

Hormone Sensitive Malignancies
In postmenopausal women, the use of estrogen alone and estrogen/progestin combinations may be associated with an increased risk for hormonally-sensitive malignancies, including breast cancer. This association has not been conclusively established in premenopausal women. In the uterine fibroid program, no cases of breast cancer were reported. Nonetheless, given the potential risk of this serious event, labeling for E2/NETA will be applied and use of MYFEMBREE will be contraindicated in women with a current or past history of, or at high risk for hormonally-sensitive malignancies.

Depression, Mood Disorders and Suicidal Ideation
Mood disorders, including suicidal ideation have been described for another GnRH antagonist. In placebo-controlled trials, as compared to placebo, participants treated with R+E2/NETA had a higher incidence of depression (2.4% vs. 0.8%), irritability (2.4% vs. 0%), and anxiety (1.2% vs. 0.8%). No cases of suicidal ideation/behavior occurred in the uterine fibroid program, but cases were reported for women treated with R+E2/NETA in placebo-controlled trials in the endometriosis program. This safety concern will be included in the Warnings and Precautions section of the label.

Elevated Blood Pressure
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogen. In one of the two placebo-controlled trials (Study 3001), a greater proportion of women treated with R+E2/NETA as compared to placebo experienced the AE of hypertension (7.0% vs. 0.8%). Use of MYFEBMREE will be contraindicated in women with uncontrolled hypertension.

Change in Menstrual Bleeding and Reduced Ability to Recognize Pregnancy
In placebo-controlled trials of 6-month duration, amenorrhea was observed during the last 35 days of treatment in 50% of women treated with R+E2/NETA as compared to 4.5% of women treated with placebo. No pregnancies occurred in women taking R+E2/NETA during Phase 3 clinical trials in the uterine fibroid program. Ten pregnancies were reported in women randomized to R+E2/NETA treatment in placebo-controlled trials or who took open label drug in Phase 3 studies in the endometriosis clinical development program. The concern regarding reduced ability to recognize a pregnancy will be included in the Warnings and Precautions section of the label. Additional reproductive concerns, including a potential increase in bleeding/spotting with initiation of treatment and the recommendation for women of reproductive potential to use non-hormonal contraception will be included. A postmarketing requirement to develop a Pregnancy Exposure Registry and to assess pregnancy and neonatal outcomes will be requested.

Uterine Fibroid Prolapse or Expulsion
One case of each uterine fibroid prolapse (0.8%) and uterine fibroid expulsion (0.8%) was described for women with submucosal fibroid who treated with R+E2/NETA in clinical trials. Prescribers will be instructed to informed patients of this risk and the signs and symptoms they

should report to their physician. The risk of these infrequent but serious events will be included in the Warnings and Precautions section of the label.

Alopecia
Hair loss and hair thinning can occur with changes in estrogen levels, and has been described for another GnRH antagonist/E2/NETA combination product. In Studies 3001 and 3002, a greater proportion of participants treated with R+E2/NETA reported hair loss/thinning compared to placebo (3.5% vs. 0.8%). Based on the safety database, the pattern of hair loss or reversibility could not be determined. Alopecia will be included in the Warning and Precautions section of the label because this adverse effect may be important to women contemplating initiating or continuing treatment with MYFEMBREE. In addition, a postmarketing requirement to conduct a prospective observational study will be requires to evaluate the incidence, pattern and reversibility of alopecia in women being treated with MYFEMBREE.

Effects on Lipids
Estrogen therapy in women with pre-existing hypertriglyceridemia may be associated with marked elevations in triglycerides levels leading to pancreatitis. In placebo-controlled trials, an imbalance in triglyceride elevations was not observed. However, in the open-label extension trial, 2 participants were reported to have Grade 3 (>500 to 1000 mg/dL) elevations and one participant was reported to have Grade 4 (>1000 mg/dL) elevation in triglycerides. Pancreatitis was not reported. In addition, in placebo-controlled trials, a greater proportion of women with normal total cholesterol (<200 mg/dL) had a shift to the range of borderline elevation (200 to <240 mg/dL) or high (≥ 240 mg/dL) with R+E2/NETA treatment as compared to placebo (15.4%. vs. 8.3%). Similarly, a greater proportion of women with normal LDL at baseline had shifts to higher categories with R+E2/NETA treatment compared to placebo (11.3% vs. 7.0%). The risk of adverse effects on lipids will be included in the Warnings and Precautions section of the label.

Conclusions and Recommendations
All of the safety concerns identified during this review can be adequately mitigated through labeling, evaluated through enhanced Pharmacovigilance Program, or evaluated via postmarketing requirements. Availability of this product will provide another longer-term treatment option to women desiring non-invasive treatment of HMB associated with uterine fibroids. From a safety perspective, the benefit-risk profile of MYFEMBREE is favorable and the product should be approved.

8. Advisory Committee Meeting and Other External Consultations

Not applicable. An Advisory Committee meeting was not held because no unexpected significant safety or efficacy issues were identified, and no controversial or challenging issues arose that would benefit from advisory committee discussion.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

Significant changes to the Prescribing Information (PI) initially submitted by the Applicant that pertain to safety and efficacy are summarized in Table 45.

Table 45. Recommended Major Labeling Changes Pertaining to Safety and Efficacy

Section	Recommended Labeling Changes
Highlights	• Added a Boxed Warning for thromboembolic disorders and vascular events • Multiple additions based on edits in the Full Prescribing Information
Section 1	• Added Limitation of Use to limit duration of use to 24 months due to risk of bone loss that may not be reversible
Section 2	• Added Limitation of Use to limit duration of use to 24 months • Revised and added clarifying edits for dosing instructions
Section 4	• Revised to clarify high risk of arterial, venous thrombotic or thromboembolic disorders • Revise specified liver diseases to more general hepatic impairment or disease • Added known osteoporosis and undiagnosed abnormal uterine bleeding • Added anaphylactic reactions
Section 5	Significantly revised the following sections and added clinical trial data when available: • 5.1 Thromboembolic Disorders and Vascular events • 5.2 Added Bone Loss • 5.3 Added Hormonally-Sensitive Malignancies to align with class labeling • 5.4 Added suicidal ideation and clinical trial data on mood disorders • 5.5. Revised Liver Disease to include Hepatic Impairment and Transaminase Elevations: revised contraindications, risk mitigation strategies and added clinical trial data • 5.6 Added Gallbladder Disease or History of Cholestatic Jaundice to align with class labeling • 5.7 Elevated Blood Pressure: added section and clinical trial data • 5.8 Revised information on change in menstrual pattern, reduced ability to recognize pregnancy and recommendation for non-hormonal contraception • 5.9 Added risk of early pregnancy loss • 5.11 Added alopecia

	• 5.12 Added effects on Carbohydrate and Lipid Metabolism to align with class labeling • 5.12 Added Effect on Other Laboratory Results to align with class labeling • 5.14 Added Hypersensitivity Reactions based on post-marketing reports for Relumina (relugolix monotherapy)
Section 6	• Added Serious Adverse Reactions • Revised Common Adverse Reactions, to include Libido decreased and exclude Abdominal/pelvic pain • (b) (4) Bone Loss (b) (4) Section 6.1 and significantly revised presentation of clinical trial results • Added clinical trial data on Depression, Mood Disorders and Suicidal Ideation; Resumption of Menses after Discontinuation; and Increases in Lipids (total cholesterol and LDL) • Added 6.2 Postmarketing Experience for relugolix monotherapy
Section 14	• Revised analysis results for primary and secondary efficacy endpoints (b) (4) • Removed (b) (4) • Removed (b) (4) • (b) (4) presentation of clinical trial results significantly revised • Revised language to delete promotional statements
Section 17	• Significantly revised based on changes in Sections 5 and 6

9.2. Nonprescription Drug Labeling

This section is not applicable as the drug will be approved as a prescription drug.

10. Risk Evaluation and Mitigation Strategies (REMS)

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

11. Postmarketing Requirements and Commitments

Our safety review of data submitted to this NDA demonstrated an imbalance for the AE of alopecia, including hair loss and thinning with R+E2/NETA treatment (3.5%) as compared to placebo (0.8%). No specific pattern was discernable and in most of these women, hair loss was continuing at the end of the trial. Data on recovery of hair loss post-treatment are lacking.

Bone loss was also observed with 52 weeks of R+E2/NETA treatment. Percent change from baseline in lumbar spine BMD at week 52 was -0.8%. A clear plateau was not demonstrated. Data on recovery of bone loss post-treatment were insufficient due to small numbers of participants who had a DXA scan post-treatment.

In addition, to these safety findings, it is expected that pregnancies will occur in women who use MYFEMBREE, given the drug's indication (management of heavy menstrual bleeding associated with uterine fibroids) and the target population (premenopausal women). The preapproval safety database was too limited to draw any conclusion about the effect of MYFEMBREE on obstetrical, neonatal, maternal and fetal/neonatal outcomes.

Based on these safety concerns, we have proposed the following PMRs for MYFEMBREE (see Labeling PMR/PMC Discussion Comments dated February 8, 2021 and General Advice Letter dated March 17, 2021):

1. Conduct a prospective observational study in premenopausal women to assess the incidence rate, time to onset, pattern, severity, and reversibility of alopecia. Physician/observer-reported outcome and/or patient survey should be developed and included in the PMR study to capture timing, pattern, severity, and reversibility of alopecia cases. The study should evaluate a minimum of 50 cases of alopecia.

2. Conduct a cohort study to compare the incidence rate of alopecia in premenopausal women who experience heavy menstrual bleeding from uterine fibroids who initiate your product and an appropriate comparator population of women with heavy menstrual bleeding from uterine fibroids who are not treated with your product. Power the study to detect a clinically important minimum increase in the risk of alopecia with use of your product. Propose sensitivity analyses that will show that the analysis is

robust to changes in key assumptions. If an electronic healthcare database is selected for the study, conduct a validation study in the selected database to develop and validate an algorithm with an adequate positive predictive value (PPV) to identify alopecia, prior to initiating the comparative safety study. If an adequate PPV cannot be obtained, conduct a prospective cohort study with primary data collection together with independent case adjudication.

For the alopecia PMRs, we propose the following milestones:

For the Prospective, observational study:
Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022
Interim Study Report: 08/2025
Study Completion: 08/2027
Final Report Submission: 08/2028

For the Cohort study:
Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022
Validation/Feasibility Report: 08/2024
Interim Study Report: 08/2026
Study Completion: 08/2027
Final Report Submission: 08/2028

3. Conduct a prospective cohort study in premenopausal women with heavy menstrual bleeding from uterine fibroids to characterize changes in bone mineral density (BMD) as assessed by dual-energy X-ray absorptiometry (DXA) with long-term use of your product. Obtain BMD measurements every 6 months over a 48-month treatment period. Determine mean percent change from baseline in BMD (with 95% confidence intervals) at the lumbar spine, total hip, and femoral neck for each timepoint. Include a categorical analysis of change from baseline in BMD, reporting the percentage of patients with various degrees of bone loss/gains. Additionally, measure BMD every 6 months for at least 12 months post-treatment to characterize recovery of bone loss post-treatment. In addition to reporting mean change from baseline in BMD and the categorical analysis of change from baseline in BMD, calculate percent recovery of bone loss for each anatomic site. Include power calculations with your statistical analysis plan. Capture fractures as an adverse event of special interest as a secondary endpoint. Adjudicate fractures and provide narrative reports for participants that fracture that includes the bone(s) that fractured, a description of how the fracture occurred (trauma, fall, etc.), concomitant medications, and other risk factors for fracture.

For the BMD study, we propose the following milestones:

Draft Protocol Submission: 02/2022

Final Protocol Submission: 08/2022
Interim Study Report: 08/2026
Study Completion: 08/2028
Final Report Submission: 08/2029

4. Conduct a Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study, that compares the maternal, fetal, and infant outcomes of women exposed to relugolix plus E2/NETA during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

5. Conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to relugolix plus E2/NETA during pregnancy compared to an unexposed control population.

   For the pregnancy PMRs, we propose the following milestones:

   For the Pregnancy Registry:
   Draft Protocol: November 2021
   Final Protocol: May 2022
   Interim Reports: May 2023, May 2025, May 2027, May 2029
   Study Completion: May 2031
   Final Study Report: May 2032

   For the Additional Pregnancy Study:
   Draft Protocol: November 2021
   Final Protocol: May 2022
   Interim Report: May 2025
   Study Completion: May 2026
   Final Study Report: May 2027

The Applicant agreed to the following postmarketing commitments under NDA 214621:

6. Conduct a pharmacokinetic study to evaluate the effect of P-gp inhibitors when administered after relugolix to further inform dosing strategy. Submit the datasets with the final study report. The study results may inform product labeling.

The timetable the Applicant submitted on December 10, 2020, states that they will conduct this study according to the following schedule:

Draft Protocol Submission: 03/2021
Final Protocol Submission: 06/2021
Study Completion: 01/2022
Final Report Submission: 04/2022

7. Submit test report for the currently ongoing study titled "The Zebrafish Extended One Generation Reproduction Test" to support of the environmental risk assessment for relugolix.

   The response the Applicant submitted on November 20, 2020, states that they will conduct this study according to the following schedule:

   Final Report Submission: 08/2021

12. Appendices

12.1. References

See footnotes in body of text

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): MVT-601-3001

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 104		
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): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S 0 Sponsor of covered study: 0		
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)

Covered Clinical Study (Name and/or Number): MVT-601-3002

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 124		
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): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0		

Significant equity interest held by investigator in S 0 Sponsor of covered study: 0		
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)

Covered Clinical Study (Name and/or Number): MVT-601-3003

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 145		
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): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S 0 Sponsor of covered study: 0		
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)

12.3. Supplemental Safety Information

TEAEs

TEAEs organized by System Organ Class and PT that occurred in at least 2% of participants in any treatment arm is shown in Table 46.

Table 46: APPENDIX Adverse Events by System Organ Class and Preferred Term Occurring in at Least 2% of Participants in Any Treatment Arms, Safety Population, Studies 3001 and 3002

System Organ Class Preferred Term	3001 R+del E2/NETA N=132 n (%)	3001 R+ E2/NETA N=128 n (%)	3001 Placebo N=127 n (%)	3002 R+del E2/NETA N=126 n (%)	3002 R+ E2/NETA N=126 n (%)	3002 Placebo N=129 n (%)	Pooled R+del E2/NETA N=258 n (%)	Pooled R+ E2/NETA N=254 n (%)	Pooled Placebo N=256 n (%)	Risk Difference (95% CI)
Skin and subcutaneous tissue disorders (SOC)	12 (9.1)	12 (9.4)	5 (3.9)	13 (10.3)	12 (9.5)	5 (3.9)	25 (9.7)	24 (9.4)	10 (3.9)	5.5 (1.2, 9.8)
Alopecia	4 (3.0)	4 (3.1)	2 (1.6)	5 (4.0)	5 (4.0)	0	9 (3.5)	9 (3.5)	2 (0.8)	2.7 (0.2, 5.2)
Hyperhidrosis	3 (2.3)	3 (2.3)	2 (1.6)	2 (1.6)	2 (1.6)	0	5 (1.9)	5 (2.0)	2 (0.8)	1.2 (-0.8, 3.2)
Night sweats	4 (3.0)	3 (2.3)	0	3 (2.4)	0	0	7 (2.7)	3 (1.2)	0	1.2 (-0.1, 2.5)
Vascular disorders (SOC)	50 (37.9)	21 (16.4)	11 (8.7)	48 (38.1)	12 (9.5)	9 (7.0)	98 (38.0)	33 (13.0)	20 (7.8)	5.2 (-0.1, 10.5)
Hypertension	3 (2.3)	7 (5.5)	0	7 (5.6)	5 (4.0)	4 (3.1)	10 (3.9)	12 (4.7)	4 (1.6)	3.1 (0.1, 6.1)
Hot flush	47 (35.6)	14 (10.9)	10 (7.9)	44 (34.9)	7 (5.6)	5 (3.9)	91 (35.3)	21 (8.3)	15 (5.9)	2.4 (-2.0, 6.8)
Reproductive system and breast disorders (SOC)	12 (9.1)	18 (14.1)	9 (7.1)	21 (16.7)	17 (13.5)	14 (10.9)	33 (12.8)	35 (13.8)	23 (9.0)	4.8 (-0.7, 10.3)
Menorrhagia	2 (1.5)	3 (2.3)	0	4 (3.2)	4 (3.2)	1 (0.8)	6 (2.3)	7 (2.8)	1 (0.4)	2.4 (0.2, 4.6)
Breast cyst	0	2 (1.6)	0	0	3 (2.4)	0	0	5 (2.0)	0	2.0 (0.3, 3.7)
Metrorrhagia	1 (0.8)	3 (2.3)	0	5 (4.0)	2 (1.6)	1 (0.8)	6 (2.3)	5 (2.0)	1 (0.4)	1.6 (-0.3, 3.5)
Menstruation irregular	0	0	0	1 (0.8)	3 (2.4)	1 (0.8)	1 (0.4)	3 (1.2)	1 (0.4)	0.8 (-0.7, 2.3)
Breast pain	1 (0.8)	2 (1.6)	0	3 (2.4)	0	0	4 (1.6)	2 (0.8)	0	0.8 (-0.3, 1.9)
Pelvic pain	2 (1.5)	4 (3.1)	1 (0.8)	1 (0.8)	1 (0.8)	5 (3.9)	3 (1.2)	5 (2.0)	6 (2.3)	-0.3 (-2.8, 2.2)
Vaginal discharge	0	0	1 (0.8)	4 (3.2)	0	1 (0.8)	4 (1.6)	0	2 (0.8)	-0.8 (-1.9, 0.3)
Dysmenorrhoea	0	1 (0.8)	0	1 (0.8)	0	5 (3.9)	1 (0.4)	1 (0.4)	5 (2.0)	-1.6 (-3.5, 0.3)
Vulvovaginal pruritus	0	0	3 (2.4)	1 (0.8)	0	1 (0.8)	1 (0.4)	0	4 (1.6)	-1.6 (-3.1, -0.1)
Psychiatric disorders (SOC)	9 (6.8)	11 (8.6)	9 (7.1)	13 (10.3)	10 (7.9)	1 (0.8)	22 (8.5)	21 (8.3)	10 (3.9)	4.4 (0.3, 8.5)
L bido decreased	2 (1.5)	3 (2.3)	1 (0.8)	3 (2.4)	4 (3.2)	0	5 (1.9)	7 (2.8)	1 (0.4)	2.4 (0.2, 4.6)
Irritability	0	5 (3.9)	0	1 (0.8)	1 (0.8)	0	1 (0.4)	6 (2.4)	0	2.4 (0.5, 4.3)
Anxiety	2 (1.5)	1 (0.8)	2 (1.6)	5 (4.0)	2 (1.6)	0	7 (2.7)	3 (1.2)	2 (0.8)	0.4 (-1.3, 2.1)
Insomnia	1 (0.8)	3 (2.3)	4 (3.1)	2 (1.6)	2 (1.6)	1 (0.8)	3 (1.2)	5 (2.0)	5 (2.0)	0.0 (-2.4, 2.4)
Injury, poisoning and procedural complications (SOC)	6 (4.5)	8 (6.2)	4 (3.1)	4 (3.2)	10 (7.9)	6 (4.7)	10 (3.9)	18 (7.1)	10 (3.9)	3.2 (-0.7, 7.1)
Investigations (SOC)	8 (6.1)	11 (8.6)	7 (5.5)	11 (8.7)	5 (4.0)	4 (3.1)	19 (7.4)	16 (6.3)	11 (4.3)	2.0 (-1.9, 5.9)
Blood creatine phosphokinase increased	1 (0.8)	3 (2.3)	2 (1.6)	2 (1.6)	1 (0.8)	0	3 (1.2)	4 (1.6)	2 (0.8)	0.8 (-1.1, 2.7)
Weight increased	0	3 (2.3)	0	3 (2.4)	0	1 (0.8)	3 (1.2)	3 (1.2)	1 (0.4)	0.8 (-0.7, 2.3)
Bone density decreased	3 (2.3)	0	0	1 (0.8)	0	0	4 (1.6)	0	0	0.0 (0.0, 0.0)

System Organ Class Preferred Term	3001 R+del E2/NETA N=132 n (%)	3001 R+ E2/NETA N=128 n (%)	3001 Placebo N=127 n (%)	3002 R+del E2/NETA N=126 n (%)	3002 R+ E2/NETA N=126 n (%)	3002 Placebo N=129 n (%)	Pooled R+del E2/NETA N=258 n (%)	Pooled R+ E2/NETA N=254 n (%)	Pooled Placebo N=256 n (%)	Risk Difference (95% CI)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	2 (1.5)	4 (3.1)	1 (0.8)	0	1 (0.8)	0	2 (0.8)	5 (2.0)	1 (0.4)	1.6 (-0.3, 3.5)
Gastrointestinal disorders (SOC)	17 (12.9)	23 (18.0)	18 (14.2)	20 (15.9)	21 (16.7)	23 (17.8)	37 (14.3)	44 (17.3)	41 (16.0)	1.3 (-5.2, 7.8)
Abdominal pain	1 (0.8)	4 (3.1)	3 (2.4)	4 (3.2)	5 (4.0)	1 (0.8)	5 (1.9)	9 (3.5)	4 (1.6)	1.9 (-0.8, 4.6)
Dyspepsia	2 (1.5)	2 (1.6)	0	0	3 (2.4)	1 (0.8)	2 (0.8)	5 (2.0)	1 (0.4)	1.6 (-0.3, 3.5)
Abdominal pain upper	4 (3.0)	2 (1.6)	2 (1.6)	2 (1.6)	2 (1.6)	1 (0.8)	6 (2.3)	4 (1.6)	3 (1.2)	0.4 (-1.6, 2.4)
Vomiting	1 (0.8)	2 (1.6)	3 (2.4)	3 (2.4)	2 (1.6)	1 (0.8)	4 (1.6)	4 (1.6)	4 (1.6)	0.0 (-2.2, 2.2)
Constipation	0	2 (1.6)	1 (0.8)	2 (1.6)	1 (0.8)	3 (2.3)	2 (0.8)	3 (1.2)	4 (1.6)	-0.4 (-2.4, 1.6)
Nausea	5 (3.8)	4 (3.1)	6 (4.7)	4 (3.2)	6 (4.8)	10 (7.8)	9 (3.5)	10 (3.9)	16 (6.2)	-2.3 (-6.1, 1.5)
Metabolism and nutrition disorders (SOC)	11 (8.3)	0	3 (2.4)	9 (7.1)	8 (6.3)	2 (1.6)	20 (7.8)	8 (3.1)	5 (2.0)	1.1 (-1.6, 3.8)
Decreased appetite	4 (3.0)	0	1 (0.8)	1 (0.8)	1 (0.8)	0	5 (1.9)	1 (0.4)	1 (0.4)	0.0 (-1.1, 1.1)
Renal and urinary disorders (SOC)	4 (3.0)	4 (3.1)	2 (1.6)	2 (1.6)	1 (0.8)	1 (0.8)	6 (2.3)	5 (2.0)	3 (1.2)	0.8 (-1.4, 3.0)
Endocrine disorders (SOC)	2 (1.5)	1 (0.8)	1 (0.8)	0	2 (1.6)	0	2 (0.8)	3 (1.2)	1 (0.4)	0.8 (-0.7, 2.3)
Hepatobiliary disorders (SOC)	0	1 (0.8)	0	2 (1.6)	1 (0.8)	0	2 (0.8)	2 (0.8)	0	0.8 (-0.3, 1.9)
Cardiac disorders (SOC)	2 (1.5)	1 (0.8)	1 (0.8)	3 (2.4)	1 (0.8)	0	5 (1.9)	2 (0.8)	1 (0.4)	0.4 (-0.9, 1.7)
Ear and labyrinth disorders (SOC)	0	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.6)	1 (0.4)	2 (0.8)	3 (1.2)	-0.4 (-2.1, 1.3)
Surgical and medical procedures (SOC)	0	0	0	0	0	1 (0.8)	0	0	1 (0.4)	-0.4 (-1.2, 0.4)
Musculoskeletal and connective tissue disorders (SOC)	18 (13.6)	13 (10.2)	14 (11.0)	23 (18.3)	13 (10.3)	14 (10.9)	41 (15.9)	26 (10.2)	28 (10.9)	-0.7 (-6.0, 4.6)
Muscle spasms	2 (1.5)	1 (0.8)	1 (0.8)	0	2 (1.6)	3 (2.3)	2 (0.8)	3 (1.2)	4 (1.6)	-0.4 (-2.4, 1.6)
Pain in extremity	5 (3.8)	1 (0.8)	0	4 (3.2)	0	2 (1.6)	9 (3.5)	1 (0.4)	2 (0.8)	-0.4 (-1.7, 0.9)
Back pain	5 (3.8)	2 (1.6)	5 (3.9)	5 (4.0)	5 (4.0)	4 (3.1)	10 (3.9)	7 (2.8)	9 (3.5)	-0.7 (-3.7, 2.3)
Arthralgia	7 (5.3)	4 (3.1)	4 (3.1)	8 (6.3)	1 (0.8)	4 (3.1)	15 (5.8)	5 (2.0)	8 (3.1)	-1.1 (-3.8, 1.6)
Musculoskeletal pain	1 (0.8)	0	1 (0.8)	4 (3.2)	0	3 (2.3)	5 (1.9)	0	4 (1.6)	-1.6 (-3.1, -0.1)
Eye disorders (SOC)	7 (5.3)	1 (0.8)	3 (2.4)	3 (2.4)	2 (1.6)	2 (1.6)	10 (3.9)	3 (1.2)	5 (2.0)	-0.8 (-3.0, 1.4)
Vision blurred	4 (3.0)	0	1 (0.8)	0	0	0	4 (1.6)	0	1 (0.4)	-0.4 (-1.2, 0.4)
General disorders and administration site conditions (SOC)	11 (8.3)	11 (8.6)	10 (7.9)	19 (15.1)	1 (0.8)	5 (3.9)	30 (11.6)	12 (4.7)	15 (5.9)	-1.2 (-5.1, 2.7)
Fatigue	6 (4.5)	4 (3.1)	5 (3.9)	7 (5.6)	1 (0.8)	2 (1.6)	13 (5.0)	5 (2.0)	7 (2.7)	-0.7 (-3.3, 1.9)
Oedema peripheral	0	0	1 (0.8)	4 (3.2)	0	1 (0.8)	4 (1.6)	0	2 (0.8)	-0.8 (-1.9, 0.3)
Immune system disorders (SOC)	0	0	3 (2.4)	1 (0.8)	0	1 (0.8)	1 (0.4)	0	4 (1.6)	-1.6 (-3.1, -0.1)
Infections and infestations (SOC)	35 (26.5)	17 (13.3)	29 (22.8)	26 (20.6)	30 (23.8)	28 (21.7)	61 (23.6)	47 (18.5)	57 (22.3)	-3.8 (-10.8, 3.2)
Bronchitis	0	1 (0.8)	2 (1.6)	0	5 (4.0)	2 (1.6)	0	6 (2.4)	4 (1.6)	0.8 (-1.6, 3.2)
Sinusitis	3 (2.3)	3 (2.3)	4 (3.1)	2 (1.6)	1 (0.8)	1 (0.8)	5 (1.9)	4 (1.6)	5 (2.0)	-0.4 (-2.7, 1.9)
Upper respiratory tract infection	7 (5.3)	1 (0.8)	3 (2.4)	3 (2.4)	6 (4.8)	7 (5.4)	10 (3.9)	7 (2.8)	10 (3.9)	-1.1 (-4.2, 2.0)
Influenza	4 (3.0)	1 (0.8)	3 (2.4)	1 (0.8)	1 (0.8)	3 (2.3)	5 (1.9)	2 (0.8)	6 (2.3)	-1.5 (-3.6, 0.6)
Nasopharyngitis	2 (1.5)	2 (1.6)	5 (3.9)	3 (2.4)	4 (3.2)	6 (4.7)	5 (1.9)	6 (2.4)	11 (4.3)	-1.9 (-5.0, 1.2)
Urinary tract infection	5 (3.8)	1 (0.8)	5 (3.9)	5 (4.0)	2 (1.6)	3 (2.3)	10 (3.9)	3 (1.2)	8 (3.1)	-1.9 (-4.4, 0.6)
Bacterial vaginosis	1 (0.8)	1 (0.8)	2 (1.6)	0	0	6 (4.7)	1 (0.4)	1 (0.4)	8 (3.1)	-2.7 (-5.0, -0.4)
Blood and lymphatic system disorders (SOC)	0	4 (3.1)	7 (5.5)	3 (2.4)	4 (3.2)	11 (8.5)	3 (1.2)	8 (3.1)	18 (7.0)	-3.9 (-7.7, -0.1)
Anaemia	0	4 (3.1)	6 (4.7)	2 (1.6)	2 (1.6)	8 (6.2)	2 (0.8)	6 (2.4)	14 (5.5)	-3.1 (-6.5, 0.3)
Respiratory, thoracic and mediastinal disorders (SOC)	8 (6.1)	3 (2.3)	12 (9.4)	5 (4.0)	2 (1.6)	8 (6.2)	13 (5.0)	5 (2.0)	20 (7.8)	-5.8 (-9.5, -2.1)

System Organ Class Preferred Term	3001 R+del E2/NETA N=132 n (%)	3001 R+ E2/NETA N=128 n (%)	3001 Placebo N=127 n (%)	3002 R+del E2/NETA N=126 n (%)	3002 R+ E2/NETA N=126 n (%)	3002 Placebo N=129 n (%)	Pooled R+del E2/NETA N=258 n (%)	Pooled R+ E2/NETA N=254 n (%)	Pooled Placebo N=256 n (%)	Risk Difference (95% CI)
Nasal congestion	4 (3.0)	0	0	0	0	1 (0.8)	4 (1.6)	0	1 (0.4)	-0.4 (-1.2, 0.4)
Cough	0	1 (0.8)	7 (5.5)	1 (0.8)	0	4 (3.1)	1 (0.4)	1 (0.4)	11 (4.3)	-3.9 (-6.5, -1.3)
Nervous system disorders (SOC)	23 (17.4)	17 (13.3)	25 (19.7)	34 (27.0)	12 (9.5)	25 (19.4)	57 (22.1)	29 (11.4)	50 (19.5)	-8.1 (-14.3, -1.9)
Migraine	2 (1.5)	0	0	4 (3.2)	0	1 (0.8)	6 (2.3)	0	1 (0.4)	-0.4 (-1.2, 0.4)
Dizziness	4 (3.0)	0	3 (2.4)	5 (4.0)	1 (0.8)	5 (3.9)	9 (3.5)	1 (0.4)	8 (3.1)	-2.7 (-5.0, -0.4)
Headache	14 (10.6)	14 (10.9)	19 (15.0)	28 (22.2)	11 (8.7)	15 (11.6)	42 (16.3)	25 (9.8)	34 (13.3)	-3.5 (-9.0, 2.0)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as any adverse event that occurred after administration of the first dose of study treatment
Risk difference is estimated using the pooled relugolix+E2/NETA minus pooled placebo (with 95% confidence interval).
Abbreviations: N, number of participants in treatment arm; n, number of participants with adverse event; SOC, system organ class

Hypertension Narratives

A summary of narratives for participants with the AE of hypertension for Phase 3 trials provided by the Applicant are shown in the tables 47, 48 and 49 below. All but two participants (Participant (b) (6) randomized to R+E2/NETA in Study 3002 and Participant (b) (6) randomized to PBO who reported hypertension in Study MVT-601-3003) had BMI in the range of overweight or obese. Additionally, two of the four participants in the R+E2/NETA arm in Study MVT-601-3001 and one of the two participants in Study MVT-601-3002 without a medical history of hypertension had BP in the range of hypertension (defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg) at screening/baseline. In Study MVT-601-3001, the imbalance in the AE of blood pressure increase/hypertension was seen for both participants with and without a history of hypertension at baseline for R+E2/NETA vs. PBO.

Table 47: APPENDIX Summary of Participants with the Adverse Event of Hypertension Reported During Study MVT-601-3001

Patient	Age BMI	Race	Baseline BP (mmHg)	Pertinent Medical History	Start/Stop Day Grade Preferred Term	Event BP (mmHg)	Treatment Action Taken Status
Relugolix + E2/NETA							
(b) (6)	42 47.7	Black or African American	135/80	Obesity	117/- 1 Essential hypertension	130/72-76[a]	None None Ongoing
	43 28.36	Black or African American	137/78	None	113/- 2 Hypertension	156/99	Antihypertensive None Ongoing
	38 34.61	Black or African American	133/82 (screening 160/90)	None	36/- 2 Hypertension	120-151/ 75-92[a]	None None Ongoing
	35 24.35	White	139/70	Hypertension	55/55 2 Hypertension	155/95	Antihypertensive None Resolved
	42 40.16	American Indian or Alaska Native	131/91	Hypertension[b], overweight, cardiometabolic syndrome	24/- 1 Hypertension	152/84	Antihypertensive None Ongoing
	44 33.06	White	132/92	None	115/- 2 Hypertension	154/102 139-148/ 93-96[c]	None None Ongoing
	47 34.05	Black or African American	131/88	Hypertension, hyperlipidemia, glucose tolerance impaired, hypothyroidism	~ 30/- 2 Hypertension	135/82[d]	Antihypertensive None Ongoing
	42 25.51	White	110/70	Hypertension	69/117 2 Hypertension	140-150/ 65-95[a]	Antihypertensive, Diuretic None Resolved
	34 30.12	Black or African American	118/72	Mild cardiomegaly	142/143 2 Blood pressure increased	106-128/ 73-89[a]	None None Resolved

Relugolix + Delayed E2/NETA							
(b) (6)	41 44.26	Black or African American	120/90	Hypertension, obesity	98/132 2 Hypertension	160/102	Re-education on anti-hypertensive compliance Study drugs withdrawn (Day 132) Resolved
	47 33.26	White	141/74	None	8/- 2 Hypertension	NR 139/75 on Day 29	Captopril, Antihypertensive, Analgesics, Muscle relaxant Study drugs withdrawn (Day 29) Ongoing
	43 32.66	White	130/80	Autoimmune thyroiditis	~ 30/~ 60 2 Hypertension	128-145/ 71-72[a]	Antihypertensive and Diuretic None Resolved
	33 37.27	Black or African American	130/87	None	29/48 1 Blood pressure increased	159/91	None None Resolved
	36 28.17	Other: brown skinned	130/80	None	85/- 3 Hypertensive crisis	160/105 140-150/ 90-100[a]	Anxiolytic None Ongoing

Abbreviations: - = unknown; BMI = body mass index; BP = blood pressure; E2 = estradiol; NETA = norethindrone acetate; NR = not reported.

[a] Blood pressure recorded near event start date.

[b] Patient stopped taking amlodipine 9 days prior to onset of the event.

[c] Blood pressure taken subsequent to the initiating event.

[d] Patient stopped taking lisinopril and hydrochlorothiazide two months prior to the onset of the event, they were restarted to treat the event. Listed blood pressure was after resuming medication.

[e] Patient had two grade 2 events.

[f] Patient had three grade 2 events.

Source: Demographics = Listing 16.1.2.1; BP = Listing 16.3.1.19; Medical history = Listing 16.1.5.1; Event information = Listing 16.3.1.1.

Source: MVT-601-3001 CSR Table 26

Table 48: APPENDIX Summary of Participants with the Adverse Event of Hypertension Reported During Study MVT-601-3002

Treatment Group and Patient	Age BMI	Race	Baseline BP (mmHg)	Pertinent Medical History	Start/Stop Day Grade Preferred Term	SAE?	BP at time of Event (mmHg)	Treatment Action Taken Event Status
Relugolix + E2/NETA								
(b) (6)	41 35.59	Black or African American	130/96	Type 2 Diabetes	175/- 3 Hypertension	No	132/101	Hydrochlorothiazide Dose not changed Ongoing
	42 31.39	Black or African American	135/91	Hypercholesterolemia	114/172 2 Hypertension	No	150/101	None Dose not changed Resolved
	47 19.96	Black or African American	122/78	None	120/- 2 Hypertension	No	149/95	None Dose not changed Ongoing
	45 32.98	White	143/87	None	170/- 2 Hypertension	No	137/98[a]	Perindopril arginine Dose not changed Ongoing
	37 33.62	Black or African American	126/84	Hypertension	57/- 2 Hypertension	No	156/95	None Dose not changed Ongoing
Relugolix + delayed E2/NETA								
(b) (6)	45 34.78	Black or African American	142/92	Hypertension	29/58 1 Blood pressure increased	No	142/108	Hydrochlorothiazide Dose not changed Resolved
	34 41.32	Black or African American	138/91	None	53/- 2 Hypertension	No	149/94	Chlortalidone Dose not changed Ongoing
	36 25.29	Black or African American	124/84	None	220/- 2 Hypertension	No	142/102	None Dose not changed Ongoing
	39 30.6	Black or African American	144/90	None	36/124 3 Hypertension	No	137/101[b]	None Dose not changed Resolved

Treatment Group and Patient	Age BMI	Race	Baseline BP (mmHg)	Pertinent Medical History	Start/Stop Day Grade Preferred Term	SAE?	BP at time of Event (mmHg)	Treatment Action Taken Event Status
(b) (6)	43 34.92	Black or African American	156/96	Hypertension	78/89 2 Hypertension	No	162/116[b]	None Dose not changed Resolved
	47 27.34	White	139/89	None	57/- 1 Hypertension	No	140/89	Perindopril erbumine Dose not changed Ongoing
	41 30.45	Black or African American	117/89	Hypertension	94/- 1 Hypertension	No	144/100[c]	Hydrochlorothiazide/lisinopril, nifedipine Dose not changed Ongoing
	47 29.14	Black or African American	122/82	Hypertension	87/- 2 Hypertension	No	128/90[b]	Losartan Dose not changed Ongoing
Placebo								
(b) (6)	45 29.01	Black or African American	133/84	None	10/148 3 Blood pressure diastolic increased	No	138/101	None Dose not changed Resolved
	39 39.47	Black or African American	138/86	Obesity	45/- 2 Hypertension	No	140/98[a]	Atenolol Dose not changed Ongoing
	41 34.66	Black or African American	125/88	None	82/137 2 Hypertension	No	157/108	None Dose not changed Resolved
	48 35.72	White	138/85	None	127/- 2 Hypertension	No	158/96[a]	Indapamide Dose not changed Ongoing
	44 26.85	Black or African American	140/89	None	57/58 1 Blood pressure increased	No	160/90	None Dose not changed Resolved
	40 45.13	Black or African American	150/89	Hypertension	60/- 2 Hypertension	No	150/90[a]	Lisinopril Dose not changed Ongoing

Abbreviations: BP = blood pressure; BMI = body mass index; E2 = estradiol; mmHg = millimeters of mercury; NETA = norethindrone acetate; SAE = serious adverse event.

[a] Blood pressure recorded at visit prior to onset of event.

[b] Blood pressure recorded at visit after onset of event.

[c] Patient noncompliant with usual antihypertensive regimen.

Source data: Table 8.3.8.20

Source: Response to Information Request dated December 15, 2020, submitted on January 11, 2021

Table 49: APPENDIX Summary of Participants with the Adverse Event of Hypertension Reported During Study MVT-601-3003

Patient	Age BMI	Race	Baseline BP and Range from Screening to Week 24 (mmHg)	Pertinent Medical History	Start/Stop Day Grade Preferred Term	Event BP (mmHg)	Treatment Action Taken Status
Relugolix + E2/NETA							
(b) (6)	45 34.01	White	121/80 120-148/ 75-87	Hypertension	230/259 1 Hypertension	161/87	None None Resolved
	50 27.85	White	147/89 108-148/ 78-93	None	347/- 2 Hypertension	123/75	Nebivolol and Perindopril None Ongoing
Relugolix + delayed E2/NETA							
(b) (6)	47 31.59	Black or African American	122/88 120-132/ 80-94	None	340/382 2 Hypertension	144/102	Lisinopril started/Referred to PCP None Resolved
	40 36.47	American Indian or Alaska Native	135/81 135-153/ 68-85	None	203/400 2 Hypertension	157/69	Losartan started None Resolved
	40 32.79	Black or African American	151/88 122-151/ 76-88	None	197/NR 2 Hypertension	143/80	Captopril started then enalapril None Ongoing
Placebo							
(b) (6)	43 52.74	Black or African American	130/80 106-140/ 70-98	Hypertension	308/NR 1 Hypertension	173/96	No changes in therapy None Ongoing
	47 23.48	Black or African American	128/84 118-132/ 78-84	None	200/205 2 Hypertension	133/95	Cod liver oil started Drug Withdrawal Resolved
	48 45.88	Black or African American	141/96 110-145/ 71-98	None	216/NR 1 Hypertension	No BP recorded on day 216	Started HCTZ None Ongoing

(b) (6)							
	37 40.9	Black or African American	135/90 127-143/ 85-97	Hypertension; type II diabetes mellitus	208/390 3 Hypertension	154/106	Amlodipine and acetyl salicylic acid added to ongoing therapy None Resolved
	38 32.83	Black or African American	128/82 118-142/ 68-97	None	260/288 2 Hypertension	144/102	None None Resolved
	36 27.58	Other	130/80 120-160/ 80-105	None	259/259 3 Blood Pressure Increased	150/110	Diazepam and amlodipine started None Resolved
	44 32.2	White	125-84 125-143/ 81-95	None	229/422 1 Hypertension	No BP recorded on Day 229	Olmesartan, atenolol, and losartan started None Ongoing
	46 45.77	Black or African American	140/98 124-146/ 84-101	Hypertension; hypercholesterolemia; overweight	352/395 2 Hypertension	No BP recorded on Day 352	Changed to Olmesartan/HCTZ None Resolved
	47 39.52	Black or African American	123/83 114-153/ 63-97	Hypertension; diabetes mellitus inadequate control	271/311 2 Hypertension	169/88	Lisinopril (dose increased) None Resolved
	39 25.01	Black or African American	135/76 110-140/ 69-91	None	294/308 1 Hypertension	No BP recorded on Day 294	Amlodipine started None Resolved
	46 31.64	White	125/70 105-140/ 70-90	None	332/332 2 Hypertension	135/89	Furosemide started None Resolved

Abbreviations: - = unknown; BMI = body mass index; BP = blood pressure; E2 = estradiol; HCTZ = hydrochlorothiazide; NETA = norethindrone acetate; NR = not reported; PCP = primary care physician.

Source: MVT-601-3003 CSR Table 23

Table 50: APPENDIX Summary of Narratives for Participants with Any Postbaseline ALT and/or AST ≥ 3-fold Upper Limit of Normal (ULN) in Studies 3001, 3002, and 3003

Subject ID/ Country	Age (years) /Race	Rx	Onset (Day)	ALT (6-34 U/L)	AST (9-34 U/L)	Other Labs (reference range)	Drug D/C (Day)	Resolution/ Improvement (Day)	Related Inv/App	Comments
(b) (6) US	39/W	R+E2/NETA	D 142	118 (3.5X)	86 (2.5X)	GGT 87 U/L (4-49)	D 156	D 216 ALT: 57/52/ 66 U/L	N/P	Baseline ALT 1.7X/AST 1.6X EtOH Fatty liver HepBcAb positive
(b) (6) US	47/B	R+E2/NETA	D 69	40 (ref: 9-52 U/L)	117 (3.2X) (ref: 14-36 U/L	TSH 69, 79 CK 6534 U/L	D 69-71 only	D 84 resolved with rx of hypothyroidism	N/N	Rhabdomyolysis, hypothyroidism
(b) (6) US	47/W	R+delE2/ NETA	D 85	193 (5.7X)	94 (2.8X)	GGT 185 (4-49 U/L) ALP 285 (31-106 U/L) TBili 5 micromol/L (3-21 micromol/L)	No	D 101	P/P	Began R+E2/NETA on D 85; ALT 45 at baseline, ALP elevated at baseline and throughout study ALP 143 U/L at screening. Maximum ALP 285 U/L on D 85. Hep A Ab +;Con med: acetaminophen
(b) (6) Poland	46/W	R+delE2/ NETA	D 106	68 (2X)	153 (4.5X)	CK 8275 U/L (26-192 U/L) NI ALP, GGT, TBili	1-3 days	D 142	P/P	Began R+E2/NETA on D 78; Etiology of elevated CK unclear. All resolved together
(b) (6) US	46/B	PBO	D 184	88 (2.6X)	109 (3.2X)	Elevated CK 9138 U/L	No; began R+E2/NETA on D 184 in study 3003	D 189	P/P	Had initiated physical therapy, EtOH 1-3/day for 1 week prior to labs; CK elevations persisted through end of study
(b) (6) US	42/B	R+E2/NETA	D 1 (pre-rx)	105 (3.1X)	37 (1.1X)	GGT 149 U/L (4-49 U/L); NI TBili	No	D 10 GGT elevated	N/N	Acetaminophen 1500 mg for 4 days before baseline test. D 148 ALT and AST<3XULN
(b) (6) US	50/W	R+E2/NETA	D 110	91 (2.7X)	146 (4.3X)	NI ALP and TBili	No	D 114 ALT 18, AST 34, CK 621 U/L	N/N	Increase ALT occurred post-op cholecystectomy; T2DM, cholelithiasis, obesity, steatohepatitis (biopsy-proven)
(b) (6) US	41/W	R+delE2/ NETA	D 190 (Post-rx D 16)	120 (3.5X)	100 (2.9X)		N/A	Improved ALT 2X 4 weeks later	P/P	Baseline ALT 1.7X, obesity pre-DM
(b) (6) Chili	37/Lat	R+E2/NETA	D 370	102 (2.9X)	51 (1.5X)	Tbili <0.2 mg/dL	No	D 388	-/N	Numerous con meds; Case noted by Applicant during aggregate data review
(b) (6) US	41/B	R+delE2/ NETA	Post-rx	285 (8.4X)	103 (3.0X)	GGT 172 (4-49 U/L)	N/A	D 396 ALT 22,	N/N	Con meds: Ibuprofen

			D 38			Bili normal		AST 81 U/L		hydrocodone bitartrate/ paracetamol
(b) (6) Poland	47/W	R+delE2/ NETA	D 181	401 (11.8X)	N/A		D 177 For cholelithi-asis and ALT elevation	D 198 ALT 14 U/L	N/N	Cholelithiasis, echogenic liver parenchyma on ultrasound; resolution of elevated ALT after endoscopic treatment of cholelithiasis
(b) (6) US	36/W	PBO	D 231	103 (3.0X)	71 (2.1X)	Nl ALP, GGT, Tbili	No	D 500 ALT 62, AST 43 U/L	P/P	ALT 2X, AST 1.5X during 3002; ultrasound pronounced fatty liver
(b) (6) US	51/B	PBO	D 341	174 (5.1X)	332 (9.8X)	ALP 172; GTT 221 (GGT max 312 on D 285)	D 320 for haemang-ioma of liver	D 351 GGT 18 and ALP 132 U/L- remained elevated	P (GI consulta nt)/ P	D 86 (3002) Grade 2 GGT elevation; GGT 208, AP 125 (nl 35-123 U/L); D 368 Extensive GI eval: liver hemangioma, gallstones, drug-induced changes in liver enzymes
(b) (6) US	47/B	PBO	D 310	508 (14.9X) D 304: 138	1080 (35.8X)		No	D 330 per narrative; D 310 per lab data	N/N	Acute cholecystitis D 312 laparoscopic cholecystectomy
(b) (6) US	44/B	PBO	D 208	87 (2.6X)	306 (9.0X)	CK 18,552 Nl GGT, ALP, TBili	No	D 222	N/N	D 180-began R+E2/NETA; Strenuous physical activity, dehydration Rx-intravenous fluid

Source: Narrative reports for Studies 3001, 3002 and 3003.
Rx=treatment; R+AB=relugolix + E2/NETA; Del=Delayed; PBO=placebo; D=Study Day; ALT=alanine aminotransferase; AST=asparate aminotransferase; US=United States; X=times upper limit of normal; GGT=gamma-glutamyl transpeptidase; ALP=alkaline phosphatase; TBili=total bilirubin; TSH=thyroid stimulating hormone; CK=creatine kinase; B=black; W=white; Lat=Latino; D/C=discontinuation; N/A=not available; Inv=investigator; App=applicant; N=not related; P=poss bly related; con med=concomitant medication(s);T2DM=type 2 diabetes mellitus; EtOH=alcohol; bx=biopsy; Nl=normal; GI=gastroenterologist;Rx=treatment

Table 51: APPENDIX Summary of Pregnancies Reported for Relugolix Clinical Development Programs as of July 7, 2020

Study	Patient ID	Treatment Assignment	Treatment Start/Stop Dates	Estimated Conception Date/Study Day	Contraceptive Method	Missed Diary Entries/Dosing in 28 Days Prior to Conception	Pregnancy Outcome
MVT-601-035	(b) (6)	Blinded		(b) (6)	None		Ongoing.
TAK-385/CCT-001		Relugolix 10 mg			Condoms	Unknown	Live birth at 39 weeks gestation; healthy infant.
MVT-601-3001		Placebo			Condoms and Spermicide	0/0	Unknown - lost to follow-up.
MVT-601-3002		Placebo			Condoms and Spermicide but use was inconsistent	1/1	Elective abortion.
MVT-601-3101		Placebo			Condoms and Spermicide	3/0	Ongoing.
MVT-601-3101		Placebo			Condom and Coitus Interruptus	n/a	Elective abortion.
MVT-601-3101		Placebo			Condoms and Spermicide	3/0	Live birth at 40 weeks by cesarean section due to fetal distress; healthy infant.
MVT-601-3102		Placebo			Condoms	n/a	Unknown - lost to follow-up
MVT-601-3102		Placebo			Condoms but use was inconsistent	5/1	Live birth at 39 weeks gestation by cesarean due to slow labor; healthy infant.
MVT-601-3102		Placebo			Condoms and Spermicide	13/0	Live birth at 40 weeks gestation.

MVT-601-3102	(b) (6)	Placebo	(b) (6)	Condoms and Spermicide but use was inconsistent	13/0	Live birth at 38 weeks gestation.
MVT-601-3102		Placebo		Condoms	4/0	Ongoing.
MVT-601-3101		Relugolix + E2/NETA		Condoms	n/a	Live birth at 39 weeks gestation; healthy infant.
MVT-601-3101		Relugolix + delayed E2/NETA		Condoms and Spermicide	5/1	Live birth at 37 weeks by cesarean following induction at 36 weeks due to oligohydramnios; healthy infant.
MVT-601-3101		Relugolix + delayed E2/NETA		Condoms and Spermicide	9/6	Ongoing.
MVT-601-3102		Relugolix + delayed E2/NETA		Condoms	n/a	Live birth at 39 weeks gestation; healthy infant.
MVT-601-3102		Relugolix + delayed E2/NETA		Condoms (reported 95% compliance with use)	n/a	Live birth (pre-term at 35 4/7 weeks); healthy infant.
MVT-601-3102		Relugolix + E2/NETA		Condoms and Spermicide	1/0	Missed abortion.

MVT-601-3101	(b) (6)	Relugolix + E2/NETA	(b) (6)	Condoms and Spermicide	Unknown	Unknown - pregnancy reported after the Week 16 visit but was never confirmed because patient was lost to follow-up.
MVT-601-3102		Relugolix + E2/NETA		Condoms and Spermicide	Unknown	Unknown - pregnancy reported after the Week 4 visit but was never confirmed because patient was lost to follow-up.
MVT-601-3102		Relugolix + E2/NETA		Condoms but reported problems with use on one occasion prior to positive pregnancy test	2/0	Live birth at 34 weeks gestation via cesarean section due to gestational hypertension; healthy infant.
MVT-601-3102		Relugolix + E2/NETA		Condoms and Spermicide	22/0	Live birth at 38 weeks gestation; healthy infant.

MVT-601-3101	(b) (6)	Relugolix + delayed E2/NETA	(b) (6) (Began study drug on day 8 of menstrual cycle)	(b) (6) (b) (6) (during monotherapy)	Condoms and Spermicide	1/0	Live birth via cesarean section due to breech position at 37 weeks. Infant with right congenital hip dysplasia and heart murmur but normal echocardiogram. Nicotine and methamphetamine use were documented during pregnancy.
MVT-601-3103		Relugolix + E2/NETA	(b) (6)		Condoms and Spermicide	25/1	Unknown - lost to follow-up.
MVT-601-3103		Relugolix + E2/NETA			Condoms and Spermicide	7/0	Ongoing.
MVT-601-3103		Relugolix + E2/NETA			Condoms and Spermicide	3/1	Missed abortion.
MVT-601-3103		Relugolix + E2/NETA			None	18/0	Ongoing.

Abbreviations: E2 = estradiol; NETA = norethindrone acetate.

Data cutoff date is (b) (6)

Note: Unless otherwise specified, participants assigned to relugolix + E2/NETA or relugolix + delayed E2/NETA received relugolix 40 mg, with or without (ie, delayed treatment group) E2 1 mg/NETA 0.5 mg.

Source: ISS Listings 65, 66; and 67; CIOMS Reports; and eDiary Data.

Source: 120-Day Safety Update Table 37

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/s/

JENNIFER W LAWRENCE
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05/24/2021 05:02:38 PM

COA Tracking ID: C2020295
NDA Number: 214846 /Referenced IND for NDA: 131161

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA tracking number	C2020295
NDA#/Referenced IND for NDA	NDA 214846/IND 131161
Applicant:	Myovant
Established Name/Trade Name:	MYFEMBREE (relugolix, estradiol and norethindrone acetate) tablets
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. ☐Rare Disease/Orphan Designation ☐Pediatrics
PDUFA Goal Date:	May 27, 2021
Review Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Clinical Reviewer	Jennifer Lawrence
Clinical Team Leader (TL)	Gerald Willett
Regulatory Project Manager:	Maria Wasilik
COA Reviewer:	Parima Ghafoori, PharmD.
COA TL:	Selena Daniels, PharmD, M.S.
COA Deputy Director:	Elektra Papadopoulos, M.D., M.P.H
Instruments reviewed:	1. Uterine Fibroid Symptom and Health Related Quality of Life -Bleeding and Pelvic Discomfort subscale ☒ Patient-reported outcome (PRO) 2. Pain Numeric Rating Scale ☒ Patient-reported outcome (PRO)

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1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of relugolix in combination with estradiol (E2) and norethindrone acetate (NETA) for the treatment of heavy menstrual bleeding associated with uterine fibroids. The sponsor (b) (4)

(b) (4)

From a COA perspective, the UFS-QoL BPD subscale is inadequate (b) (4) due to issues surrounding the instrument's content validity. (b) (4)

2 REVIEW CONCLUSIONS

UFS-QoL BPD subscale

The UFS-QoL BPD subscale was reviewed for content validity and the other measurement properties. Due to issues surrounding the content validity the (b) (4) . The UFS-QoL BPD subscale is inadequate (b) (4) due to following content validity issues:

- **Issue 1:** Distress is not part of the clinical definition for this indication per discussion with Clinical. Per Clinical, assessment of the disease symptoms may be more clinically appropriate (i.e., distress does not reflect actual symptom improvement).

- **Issue 2:** Distress is not a well-defined concept; it is difficult to interpret as it can mean different things across patients as demonstrated in the patient interviews (e.g., worried, aggravated, fearful, bothered, overwhelmed).

[1] In the subset of women with a maximum pain NRS score ≥ 4 during the last 35 days prior to randomization.

Pain NRS

The Pain NRS was reviewed for content validity and the applicant's proposed threshold for meaningful within-patient score change. There is a lack of data regarding the other measurement properties of a Pain NRS within a uterine fibroid population. However, the measurement properties for a Pain-NRS is well-documented in the literature for chronic pain populations. The Pain NRS is adequate (b) (4) in this context of use as the instrument is:

- appropriate for measurement of pain (at its worst) caused by uterine fibroids;
- validly and reliably measures pain (a clinically relevant and important concept to patients);
- (b) (4)

Further, the magnitude of the statistically significant treatment effect appears clinically meaningful to patients. Based on qualitative data from exit interviews (n=20), at least a 3-point improvement in the 11-point Pain NRS appears to be a meaningful improvement to patients.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, it may be helpful to explore including the localization of pain in the question stem of the pain assessment, as well as a pictorial diagram indicating the areas where pain may present to ensure patients understand and interpret the concept of interest appropriately. In addition to the assessment of pain, we recommend using a well-defined and reliable instrument with an appropriate recall period to measure other clinically relevant and important signs and symptoms to patients, as well as other aspects of symptom burden, such as interference with activities of daily living to evaluate the effect of treatment on how a patient functions. Additionally, sponsors should plan to incorporate anchor-based methods for COAs in their protocol and analyses using appropriate anchor scales agreed to by the Agency as anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in COA endpoints.

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

The applicant was informed in a Type C meeting on January 31, 2019 that there is insufficient evidence that the UFS-QoL BPD subscale is fit-for-purpose (b) (4) .

The applicant planned to conduct Study MVT-601-037 (exit interviews from studies 3001 and 3002) to provide patient input on what is clinically meaningful.

Previous COA Reviews:

- C2020056_IND 131161_Daniels dated March 12, 2020 (DARRTS Reference ID: 4570680)
- C2019240_IND 131161_Illoh dated January 24, 2019 (DARRTS Reference ID: 4486724)
- C2019207_IND 131161_Illoh dated January 24, 2019 (DARRTS Reference ID: 4464364)
- C2019082_IND 131161_Illoh dated January 24, 2019 (DARRTS Reference ID: 4416699)

- C2018384_IND 131161_Illoh dated January 24, 2019 (DARRTS Reference ID: 4404033)
- C2018327_IND 131161_Illoh dated February 8, 2019 (DARRTS Reference ID: 4387311)

Disease Background:
Uterine leiomyomas (i.e., uterine fibroids) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus in 20-40% of women of reproductive age.

- Symptoms include heavy bleeding, pain, as well as bulk symptoms, such as pressure in the abdomen and pelvis due to large myoma(s), urinary frequency or urinary tract obstruction, and constipation. Other symptoms associated with uterine fibroids are bulk-type symptoms, which are the result of the mass effect of the enlarged uterus on surrounding organs, leading among others to pain or pressure in the abdomen and pelvis, low back pain, dyspareunia, and dyschezia.
- Typically, in women with uterine fibroids, menstrual periods can last as long as 10 to 14 days, and menstrual blood loss (MBL) volume can be as high as 300 to 500 mL.
- Outside of bleeding, pain is the second most debilitating sign/symptom for women with uterine fibroids. Almost half of women with uterine fibroids report significant dysmenorrhea that can begin early in the menstrual cycle and last longer than common menstrual cramps.

Investigational Product:
Relugolix in combination with estradiol (E2) and norethindrone acetate (NETA) is an orally active, nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist. Relugolix + E2/NETA binds to GnRH receptor and causes decline of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which results in suppression of estradiol and progesterone.

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Studies MVT-601-3001 and -3002 are adult women (18 to 50 years) diagnosed with heavy menstrual bleeding associated with uterine fibroids.

A complete list of the inclusion and exclusion criteria is summarized in section 4 of the clinical study protocol for Studies MVT-601-3001 and -3002.

5.2 Clinical Trial Design

Table 2 describes the clinical trial design of Studies MVT-601-3001 and -3002

Table 2. Clinical Trial Design for Studies MVT-601-3001 and -3002

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled	Approximately 39-41 weeks	Yes

Trial Phase	Trial Design	Trial Duration	Registration Intent
	☐ Active comparator-controlled ☐ Cross-over ☒ Multinational ☐ Non-inferiority		

Refer to section 4 of clinical study protocol for Studies MVT-601-3001 and -3002 for more details on the clinical trial design.

Reviewer's comment(s): *Studies MVT-601-3001 and -3002 are almost identical in design to Study MVT-601-3001. The length of studies differs slightly. Study MVT-601-3001 consists of a screening period (approximately 13 weeks), a randomized treatment period (24 weeks), and a follow-up period (approximately 30 days). Whereas, Study MVT-601-3002 consists of a screening period (~11 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days).*

These studies were designed to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low dose E2/NETA and 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose E2/NETA compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to one of these therapy groups:

- *Relugolix plus low-dose hormonal add-back therapy group; or*
- *Relugolix monotherapy followed by co-administration with low-dose hormonal addback therapy group; or*
  Placebo group

5.3 Endpoint Position, Definition, and Assessment Schedule

Table 3 describes the intended placement of the COAs in the endpoint hierarchy, including the endpoint definition and assessment schedule for Studies MVT-601-3001 and -3002. The COAs listed in Table 3 were used to support the key secondary endpoints.

Table 3. Endpoint Position, Definition, and Assessment Schedule for Studies MVT-601-3001 and -3002:

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Primary	Alkaline hematin method (biomarker)	Proportion of women in the relugolix + E2/NETA group versus the placebo group who achieve an MBL volume of < 80 mL AND at least a 50% reduction from baseline MBL volume over the last 35 days of treatment	Screening; Weeks 4, 8, 12, 16, 20, and 24

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	Uterine Fibroid Symptom and Health Related Quality of Life (UFS-QoL)-Bleeding and Pelvic Discomfort (BPD) subscale (PRO)	Change from baseline to week 24 in the UFS-QoL BPD subscale score	Baseline; Weeks 12 and 24
Secondary ☒ Multiplicity adjusted	Pain Numerical Rating Scale (NRS) (PRO)	Proportion of patients with a maximum pain NRS score ≤ 1 for pain associated with uterine fibroids during the last 35 days of treatment[2]	Daily

PRO= Patient-reported outcome

Reviewer's comment(s): *Patients entered eDiary information on daily basis for their compliance with study treatment starting at Baseline/Day 1, menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the NRS, and use of pain medications starting at screening 3 visit and continued until Week 24 or early termination.*

[2] In the subset of women with a maximum pain NRS score ≥ 4 during the last 35 days prior to randomization.

(b) (4)

[redacted]

Reviewer's comment(s): *The relugolix + E2/NETA study showed statistically significant difference in the primary and COA secondary endpoints Studies MVT-601-3001 and -3002:*

- *Study MVT-601-3001:*
  - *For the endpoint on the UFS-QoL BPD subscale, statistical significance was reached (i.e., p-value: <0.0001); mean change from baseline at week 24 is -45.0 for relugolix + E2/NETA, versus -16.1 for placebo*
  - *For the endpoint on the pain NRS, statistical significance was reached (i.e., p-value: <0.0001); 25 (43.10%) patients met the endpoint responder definition for relugolix + E2/NETA, versus 7 (10.14%) for placebo*
- *Study MVT-601-3002:*
  - *For the endpoint on the UFS-QoL BPD subscale, statistical significance was reached (i.e., p-value: <0.0001); mean change from baseline at week 24 is -51.7 for relugolix + E2/NETA, versus -18.3 for placebo*
  - *For the endpoint on the pain NRS, statistical significance was reached (i.e., p-value: <0.0001); 32 (47.10%) patients met the endpoint responder definition for relugolix + E2/NETA, versus 14 (17.1%) for placebo*

There were additional supportive analyses of pain that take analgesic use into account (summarized below); (b) (4) [redacted]

The reduction in pain medication use coincided with a reduction in mean NRS pain scores, from 7.2, 7.2, and 6.9 at baseline in the relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo groups, respectively, to 1.9, 2.2, and 5.1 at Week 24/EOT. To assess the possible impact of analgesic use on the response rate to treatment, an analysis adjusting for increased pain medication use was performed. When patients with increased use of medications for uterine fibroid pain were considered a non-responder, the proportion of dysmenorrhea evaluable patients who achieved a maximum NRS pain score ≤ 1 remained higher in the relugolix + E2/NETA and relugolix + delayed E2/NETA groups (34 patients [61.82%] and 38 patients [59.38%], respectively) compared with the placebo group (9 patients [13.24%]). The difference in the proportions between the relugolix + E2/NETA group and placebo group was significant (nominal p < 0.001).

(b) (4)

The Pain NRS (b) (4) *as the instrument is appropriate for measurement of pain caused by uterine fibroids; validly and reliably measures pain (a clinically relevant and important concept to patients;* (b) (4) *. For more details, see Sections 5.5.4, 5.5.5, and 5.5.6 of this review.*

5.5 Clinical Outcome Assessment(s)

5.5.1 Clinical Outcome Assessment Description(s)

Uterine Fibroid Symptom and Health Related Quality of Life (UFS-QoL)-Bleeding and Pelvic Discomfort (BPD) Subscale

The UFS-QoL BPD subscale is a 3-item subdomain within the 37-item UFS-QoL PRO instrument. The BPD subscale is designed to assess distress with the following uterine fibroid symptoms: bleeding, passing blood clots, and pressure/tightness in the pelvic area. Each item is rated on a 5-point verbal rating scale ranging from 1 (“Not at all”) to 5 ("A very great deal”). The recall period is over the previous 3 months.

Reviewer’s comment(s): *The three-item subscale was derived from the UFS-QoL Symptom Severity scale of the UFS-QoL.*

Pain Numeric Rating Scale (NRS)

The Pain NRS is a single item PRO instrument designed to assess pain intensity caused by uterine fibroids on an 11-point NRS ranging from 0 (“No pain”) to 10 (“Pain as bad as you can imagine”). The recall period is over the previous 24 hours.

5.5.2 Conceptual Framework(s)

The conceptual frameworks for the UFS-QoL BPD subscale and Pain NRS are shown in Tables 4 and 5.

Table 4. Conceptual Framework for the UFS-QoL BPD subscale

Item	Domain	General Concept
Item 1: Distress with heavy bleeding	Bleeding and Pelvic Discomfort	Distress with uterine fibroid symptoms
Item 2: Distress with passing blood clots		
Item 5: Distress with pelvic pressure/tightness		

Table 5. Conceptual Framework for the Pain NRS

Item	General Concept
Item 1: Worst pain intensity caused by uterine fibroids	Pain Intensity

5.5.3 Scoring Algorithm

UFS-QoL BPD Subscale:
The UFS-QoL BPD subscale generates a summary score that ranges from 3 to 15 (raw score). The raw scores are transformed to a normalized score using the formula below:

$$\text{Transformed Score} = \frac{[(\text{Actual raw score} - \text{lowest possible raw score})}{(\text{Possible raw score range})]} * 100$$

The summary (transformed) score of the three items in the UFS-QoL BPD subscale ranges from 0 to 100, with a higher score indicating a higher level of distress and a lower score a lower level of distress.

Pain NRS
The Pain NRS score ranges from 0 to 10, with a higher score indicating greater pain intensity caused by uterine fibroids.

5.5.4 Content Validity

UFS-QoL-BPD Subscale
The applicant completed an exit interview study (Study MVT-601-037) to evaluate the content validity of the UFS-QoL BPD Subscale. The exit interview study included hybrid concept elicitation and cognitive interviews.

The objectives of Study MVT-601-037 were to ask participants about:

- Their experience related to sign and symptoms of uterine fibroids and associated impacts
- Their interpretation of the term “distress”
- Their comprehension of the UFS-QoL BPD subscale
- The suitability of the 3-month recall period including interpretation of the recall period.

- Their input on meaningful improvement on the UFS-QoL BPD subscale (see section B.8 of this review)

Participants were included in Study MVT-601-037 if they:

- were enrolled in Study MVT-601-3001 or Study MVT-601-3002
- consented to participate in Study MVT-601-037
- were able to read, write and speak English
- completed week 24 of Study MVT-601-3001 or Study MVT-601-3002
- completed the Patient Global Assessment (PGA) for Symptoms scale at baseline and week 12
- reported a one or greater category improvement in the PGA for Symptoms scale from baseline to week 12

A summary of the results is described below:

- Thirty patients were interviewed on meaningful change to ensure they were able to reliably report on its meaning.
- According to the qualitative report, heavy bleeding (100%), pelvic pain (93.3%) and passing blood clots (80%) were commonly reported as signs/symptoms of uterine fibroids.
- A majority of patients (70%) were unable to distinguish the concept of "tightness/pressure" (i.e., item 5 of BPD subscale) in the pelvis from pelvic pain.
- Most patients (67.9%) reported pain (i.e., leg pain, back pain, headache) exclusively in the context of menstruation. However, occurrence of other pain concepts (i.e., tightness/pressure in the pelvic area and leg pain) was reported by several patients (23%) and varied in occurrence, and they were not exclusively reported during menstruation days, during non-menstruation days, or under both conditions. Please refer to the following section (i.e., Review of Content Validity of Pain NRS) for additional information on number of patients reporting on different types of pain (i.e., pelvic pain versus tightness/pressure).
- With regard to the recall period, most patients (24/30) were able to accurately interpret the recall period. Two patients (6.7%) misinterpreted the recall period, four patients (13.3%) did not provide a clear interpretation of the recall period, and one patient (3.3%) responded "It's not difficult".
- All participants conceptualized "distress" in terms of negative connotation. However, interpretation of the term "distress" differed among participants (e.g., patients interpreted as: worried, aggravated, fearful, bothered, overwhelmed, etc.). Most common interpretation of the term distress (i.e., 30%) was "worried or concerned" & "aggravated, annoyed, frustrated, or upset".

Reviewer's comment(s): *While this reviewer agrees that heavy bleeding, pelvic pain, and passing blood clots are clinically relevant signs/symptoms of uterine fibroids, the UFS-QoL BPD subscale does not measure the improvement of these symptoms but rather the "distress" due to these symptoms. (Note the UFS-QoL does not measure "distress" due to pelvic pain but pelvic tightness/pressure; these two concepts were interpreted similarly across patients in the exit interview study. As such, pelvic tightness/pressure may not be the correct concept to measure for this target population.).*

Based on the exit interview study, it is unclear whether "distress" is an important concept to patients. Participants in the interviews were queried about their experience with uterine fibroids in the context of their symptoms and impacts. Negative impacts on emotional wellbeing were reported spontaneously (S) by nearly all patients (n=27, 90.0%); however, the use of the term "distress" did not seem to be utilized. Patients most commonly expressed feeling embarrassed (n=14, 46.7% [S=14, 46.7%]), worried or anxious (n=11, 36.7% [S=11, 36.7%]), sad or depressed (n=11, 36.7% [S=10, 33.3%; Probed=1, 3.3%]), or angry or irritable (n=8, 26.7% [S=8, 26.7%]) about their uterine fibroid signs/symptoms. Among those feeling worried or anxious, patients indicated that they felt this way due to concerns related to their symptoms.

Based on discussion with Clinical, "distress" due to uterine fibroid symptoms is not part of the clinical definition for this indication. Per Clinical, in managing the disease symptoms, the distress caused by them will decrease as a consequence. Therefore, it is management of the disease symptoms that is meaningful from a Clinical perspective. Clinical noted that there may be measures that could be taken to decrease one's distress about a condition, but the patient would still have the condition. Lastly, Clinical noted that "distress" can mean many things (e.g., bleeding issues, cramping from clots, bladder and back discomfort).

Regarding the 3-month recall period, while most patients were able to accurately interpret the recall period, the UFS-QoL BPD subscale remains susceptible to recall error as it requires patients to reflect over 3 menstrual cycles.

Overall, the applicant has provided insufficient evidence to support the content validity of the UFS-QoL BPD subscale.

Pain NRS
The applicant cited literature to support the content relevance of the pain NRS in the target population.

- *Deal LS, Williams VS, Fehnel SE. Development of an electronic daily uterine fibroid symptom diary. The Patient: Patient-Centered Outcomes Research. 2011;4(1):31-44.*

  - Deal et al. (2011) completed qualitative studies involving focus groups (n=8) and individual concept elicitation interviews (n=27) in women diagnosed with uterine fibroids.

  - Based on the focus groups, the most commonly reported symptoms reported were heavy menstrual bleeding, prolonged periods, pain, menstrual cramping, fatigue, and bloating. Other types of pain reported included pain related to the back, abdominal, during intercourse, headache/migraine, tenderness to touch, pelvic, kidney, legs, or during ovulation.

  - Based on individual concept elicitation interviews, the most commonly reported uterine fibroid symptoms were abnormal bleeding (n=27), pain (n=27), and menstrual cramping (n=21). Pain symptoms included back pain, abdominal pain, headache/migraine, leg pain, ovulation pain and pain during intercourse.

- Other studies are summarized in Table 6.

Table 6. Summary of pain descriptions related to uterine fibroids in literature

Pain Described	Study*	Findings
Menstrual pain or cramping during menstrual cycle	David et al, 2016[6]; Fuldeore and Soliman, 2017[4]	78.8% of sample ever experienced[6]; 74.9% of UF sample[4]
Pre-menstrual pain	David et al, 2016[6];	72.6% of UF sample ever experienced[6];
Non-menstrual pelvic pain	Fuldeore and Soliman, 2017[4];	33.2% of UF sample[4]
Pelvic pressure	Fuldeore and Soliman, 2017[4]	22.4% of UF sample[4]
General abdominal pain	Fuldeore and Soliman, 2017[4]	35% of UF sample[4]
Pain during sexual intercourse	Zimmerman et al, 2012[22] Fuldeore and Soliman, 2017[4]	23.5% UF vs 9.1% non-UF ever experienced[22] 29.3% of UF sample[4]
Chronic pain	Zimmerman et al, 2012[22]	On all or most days of the month and at various points of the menstrual cycle more common among women with UF than non-UF[22] (14.5% vs 2.9%)
Lower back pain	Fuldeore and Soliman, 2017[4]	68.4% of UF sample[4]

*David et al, 2016: study was carried out in Berlin, Germany; Zimmerman et al, 2012: study was carried out in Brazil, Canada, France, Germany, Italy, South Korea, the UK, and the US; Fuldeore and Soliman, 2017: study was carried out in the US.

Study MVT-601-037 (exit interview study) also elicited concepts related to the content relevance of the Pain NRS to the target population. Based on the results of this study, pain was a commonly reported symptom. Pelvic pain was most frequently reported (n=28, 93.3%), followed by back pain (n=9, 30%), and tightness/pressure (n=7, 23.3%).

Reviewer's comment(s): *In addition, to the qualitative studies described above, the content validity of the Pain NRS has been well-documented in the literature and previous clinical studies. This reviewer does not have any critical concerns regarding the design of the Pain NRS scale used in the registration trials. The general approach of assessing symptom severity at its worst over the past 24 hours appears reasonable.*

This reviewer acknowledges that the item did not specify the localization of pain. Based on the disease, the location of the fibroid can determine where pain may present. For example, a large fibroid on the back surface of the uterus is more likely to cause back pain than a small fibroid

within the uterine wall. Generally, pain presents in the pelvic area. For future studies, it may be helpful to include the localization of pain in the question stem of the pain assessment, as well as a pictorial diagram indicating the areas where pain may present to ensure patients understand and interpret the concept of interest appropriately.

The Pain NRS was translated and linguistically validated in 14 languages, including English. The applicant indicated that forward and backward translations were conducted and certificates of translations were obtained per recommendations of the ISPOR taskforce.

5.5.5 Other Measurement Properties

UFS-QoL BPD Subscale
The applicant performed an exploratory factor analysis and confirmatory factor analysis to confirm that the UFS-QoL symptom severity scale is multi-factorial. Per the applicant, the BPD subscale (Factor 1) was selected for further assessment in the development program because it captures distress from symptoms experienced by most patients with uterine fibroids.

The applicant evaluated the psychometric properties of the UFS-QoL BPD subscale using pooled, blinded data from the first 1/3 of patients in each of the two Phase 3 studies who completed the PGA for symptoms and the UFS-QoL at baseline and at week 24. A summary of results is provided below:

- For assessment of internal consistency, Cronbach's alpha ranged from 0.77 – 0.88 (Cronbach's alpha = 0.77 at baseline; Cronbach's alpha = 0.88 at week 12).
- The assessment of test-retest reliability and convergent validity were not performed.
- For the assessment of responsiveness, the median score change in the BPD subscale score ranged from -16.67 – -66.67 as anchored to the Patient Global Assessment scores from -1 to -4, respectively.

Reviewer's comment(s):
In general, the results for internal consistency and responsiveness is within acceptable and within reasonable range. There was no data related to the test-retest reliability and convergent validity of the instrument.

In lieu of assessment of known groups validity, the applicant used an item discrimination index to assess the ability of each item to discriminate between high and low severity patients. The applicant provided limited details with regard to how they calculated the item discrimination index; as such, this reviewer cannot comment on the appropriateness of this method.

Although quantitative data (e.g., factor analysis) can help support content validity, it will not replace or rectify the identified problems with content validity.

Pain-NRS
The applicant conducted a literature review to identify studies that summarized psychometric properties of the pain NRS. Per the applicant, the reliability of the pain NRS within a uterine fibroid population has not been explored; however, reliability has been demonstrated in other chronic pain populations (e.g., rheumatoid arthritis, endometriosis).

Reviewer's comment(s):
The other measurement properties for Pain NRS is well-documented. No additional quantitative analyses are needed.

5.5.6 Interpretation of Meaningful Within-Patient Score Changes

UFS-QoL BPD Subscale
The applicant proposed (b) (4) is a meaningful within-patient score change in the UFS-QoL BPD Subscale. However, due to issues surrounding the content validity the applicant's proposed threshold for meaningful within-patient score change was not reviewed.

Reviewer's comment(s): *The interpretability of the anchor-based analyses would be difficult as the anchor scale administered in Studies MVT-601-3001 and MVT-601-3002 had limitations (e.g., the anchor scale did not measure the distress related to uterine fibroid symptoms but rather the severity of uterine fibroid symptoms).*

Pain NRS
The applicant proposed the following responder definition as a key secondary endpoint:

- The proportion of women who achieved a maximum NRS score for pain associated with uterine fibroids ≤1 (minimal to no pain) over the last 35 days of treatment in the subset of women with a maximum pain score of ≥4 (moderate pain) during the period prior to randomization and who completed 80% of the daily eDiary entries (pain evaluable population).

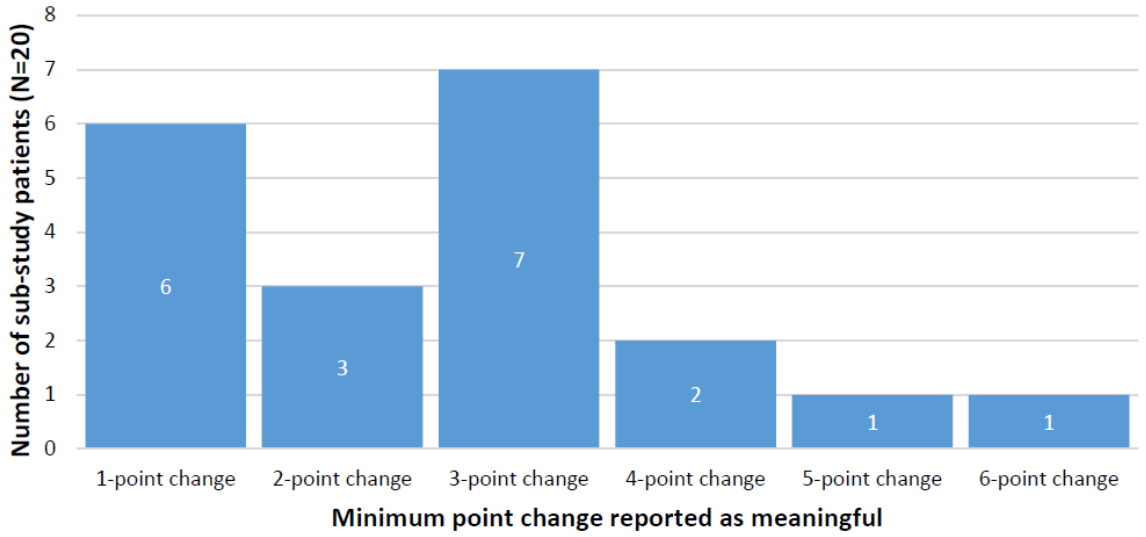
To meet the endpoint criteria, a patient is required to experience at least a 3-point change from baseline in NRS pain score.

The applicant did not conduct anchor-based analyses to support the proposed responder definition as Studies MVT-601-3001 and -3002 did not include relevant anchor scales for the Pain NRS (i.e., anchor scales were related to overall uterine fibroid symptoms, see Appendices C and D). However, the applicant conducted exit interviews (n= 20) to obtain patient input to help inform the improvement threshold. The inclusion criteria for the exit interview study included the following:

- A reported improvement from baseline Day 1 to week 24 on the patient global assessment (PGA) for symptoms, and
- A maximum score on the pain NRS ≥ 4 during the 35 days prior to randomization

The findings from the exit interviews suggested that the median point change that patients considered to be a meaningful improvement was 3 points (range: 1 to 6). Most patients (n=16; 80%) reported a point change between 1 to 3 points to be meaningful; where majority of these participants (n=7, 35%) reported than a 3-point is considered to be a meaningful improvement for them. A distribution of meaningful change reported by patients in the exit interviews is shown in Figure 1

Figure 1. Distribution of meaningful change estimation reported by patients during the pain NRS Exercise (applicant's Figure 12 in PRO Evidence Dossier)



Reviewer's comment(s):
Based on the results of the exit interview study, at least a 3-point improvement in the Pain NRS score appears to be a meaningful improvement to patients, which is in alignment with the pre-specified endpoint for the Pain NRS. For future studies, anchor-based methods should be used to confirm this threshold.

6. APPENDICES

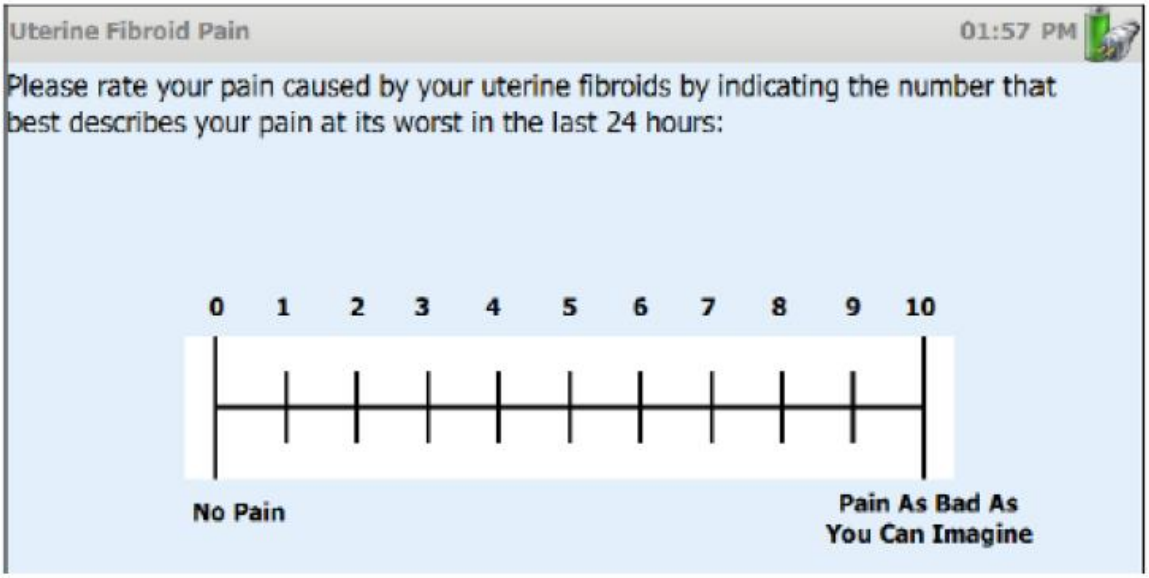
Appendix A: Bleeding and Pelvic Discomfort (BPD) Subscale
Appendix B: Pain Numeric Rating Scale (NRS)
Appendix C: Patient Global Assessment (PGA) for Symptoms
Appendix D: Patient Global Assessment (PGA) for Function

Appendix A: Bleeding and Pelvic Discomfort (BPD) Subscale

Instructions: "Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months. There are no right or wrong answers. Please be sure to answer every question by checking (√) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response."

During the previous 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix B: Pain Numeric Rating Scale (NRS) item in patient eDiary



Appendix C: Patient Global Assessment (PGA) for Symptoms

Patient Global Assessment (for symptoms)

How severe were your uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. Not severe
2. Mildly severe
3. Moderately severe
4. Very severe
5. Extremely severe

Appendix D: Patient Global Assessment (PGA) for Function

Patient Global Assessment (for function)

How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. No limitation at all
2. Mild limitation
3. Moderate limitation
4. Quite a bit of limitation
5. Extreme limitation

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/

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01/28/2021 07:16:52 AM

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