20 May 2021
EMA/CHMP/127692/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Ryeqo

International non-proprietary name: relugolix / estradiol / norethisterone acetate

Procedure No. EMEA/H/C/005267/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Ryeqo
Applicant:	Gedeon Richter Plc. Gyomroi ut 19-21 1103 Budapest HUNGARY
Active substance:	ESTRADIOL HEMIHYDRATE / NORETHISTERONE ACETATE / RELUGOLIX
International Non-proprietary Name/Common Name:	relugolix / estradiol / norethisterone acetate
Pharmaco-therapeutic group (ATC Code):	hypothalamic hormones, (H01C)
Therapeutic indication(s):	Treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	40 mg / 1 mg / 0.5 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	28 film coated tablets

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List of abbreviations

ADME	absorption, distribution, metabolism, and excretion
AUC	area under the concentration versus time curve
AUC0-24	area under the concentration versus time curve from time 0 to the end of the dosing interval at 24 hours postdose
AUC0-48	area under the concentration versus time curve from time zero to 48 hours postdose
AUC0-∞	area under the concentration versus time curve from time zero to infinity
AGP	α1-acid glycoprotein, human
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice per day
BMD	bone mineral density
BSEP	bile salt export pump
Caco-2	colorectal adenocarcinoma cells
CEP	Certificate of suitability of the European Pharmacopoeia
CHO	Chinese hamster ovary
CI	confidence interval
CL	plasma clearance
Cmax	maximum plasma concentration
CNS	central nervous system
CPP	critical process parameters
CQA	Critical quality attribute
CYP	cytochrome P450
di-22:6-BMP	di-docosahexaenoyl (22:6)-bis(monoacylglycerol) phosphate
DEPT	Distortionless enhancement by polarization transfer
DMFA	N,N-dimethylformamide
DNA	deoxyribonucleic acid
DOE	design of experiment
DQF-COSY	Double-quantum filtered correlation spectroscopy
E1	estrone
E2	estradiol
FDC	fixed dose combination
FMEA	failure mode effect analysis
FSH	follicle-stimulating hormone
GC	Gas chromatography
GD	Gestation Day
GLP	Good Laboratory Practice
GMR	geometric mean ratio
GnRH	gonadotropin-releasing hormone
HDPE	high-density polyethylene
hERG	human ether-à-go-go-related gene
HPG	hypothalamic-pituitary-gonadal
HPLC	high performance liquid chromatography
HPLC RT	high performance liquid chromatography retention time
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
HSA	human serum albumin
IC50	50% inhibitory concentration
IC90	90% inhibitory concentration
ICH	International Conference on Harmonisation

IND	Investigational New Drug Applications
IV	intravenous
KF	Karl Fisher titration
LC-MS	liquid chromatography–mass spectrometry
LDPE	low-density polyethylene
LH	luteinizing hormone
MATE	multidrug and toxin extrusion transporters
MC	methylcellulose
MTD	maximum tolerated dose
MO	Major objection
Myovant	Myovant Sciences GmbH
NADPH	nicotinamide adenine dinucleotide phosphate
NATP	6-(4-aminophenyl)-1-(2,6-difluorobenzyl)-5-((dimethylamino)methyl)-3-(6-methoxypyridazin-3-yl)thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione
NDMA	N-Nitrosodimethylamine
NET	norethisterone
NETA	norethisterone acetate
NMR	nuclear magnetic resonance spectroscopy
NMT	Not more than
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRU	neutral red uptake
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PEG	polyethylene glycol
P-gp	P-glycoprotein
PK	pharmacokinetic
PLD	phospholipidosis
PR B	progesterone receptor
PVC	portal vein cannulated
PXRD	Powder X-ray diffraction
QbD	Quality by Design
QD	once daily
QTPP	quality target product profile
rCYP	recombinant human CYP
REL	relugolix
SCU	stratified content uniformity
SULT	sulfotransferase
t1/2	terminal phase half-life
TK	toxicokinetics(s)
tmax	time to maximum plasma concentration
UGT	uridine diphosphate glucuronsyltransferase
USP	United States Pharmacopoeia
UV	Ultra violet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gedeon Richter Plc. submitted on 6 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Ryeqo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 December 2018.

The applicant applied for the following indication:

> "[TRADE NAME] is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
>
> [TRADE NAME] maintains bone mineral density and protects the uterus from endometrial hyperplasia in women who choose to use [TRADE NAME] for uterine fibroid treatment."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0108/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance relugolix contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 October 2008	EMEA/H/SA/1164/2/2008/II	Minne Casteels, Cristina Sampaio
24 June 2010	EMEA/H/SA/1164/3/2010/I	Markku Pasanen, Beatriz Silva Lima
26 April 2019	EMEA/H/SA/4098/1/2019/III	Peter Mol, Minne Casteels

The Scientific advice pertained to the following non-clinical, and clinical aspects:

- Strategy for the evaluation of Clinical Efficacy in the proposed phase 2/3 development program:

  Relugolix monotherapy

  Advice was sought on the phase 2 program to support development of relugolix monotherapy for short-term preoperative management of heavy menstrual bleeding. The proposed primary endpoint of a change in MBL volume as measured by the pictorial blood loss assessment chart (PBAC) was supported, and indicated that an assessment of fibroid and uterine volume would be important.

  Relugolix combination therapy

  The clinical program needed to support longer duration of use (> 6 months) for relugolix combination therapy in the EU was discussed in a series of National Scientific Advice procedures. In general, it was agreed that the current clinical program may be sufficient to support a longer duration of use for uterine fibroids depending on the outcome. Usually only 12 to 24 weeks of efficacy data are needed for long-term efficacy claims, while the 1-year data was considered useful for safety, especially to assess BMD. It was also advised that the potential for selection bias in the population of patients enrolled into the extension study should be addressed in interpretation of the results. Assessment of endometrial safety for 1 year was recommended, given that this is a general EU requirement for E2-containing products. It was also recommended that that the known risks associated with hormone replacement therapy be addressed in the application or in the risk management plan.

- Characterization of the genotoxicity profile and definition of appropriate safety margin of a degradant of relugolix.
- Strategy for environmental risk assessment testing for relugolix and the design of the proposed FLC test in the view of the proposed use of relugolix in a fixed-dose combination product containing also estradiol and norethisterone acetate.
- Proposed non-clinical programme, including toxiciology studies, in view of the proposed use of relugolix in a fixed-dose combination product containing also estradiol and norethisterone acetate.
- Proposed Clinical pharmacology programme and the assessment of potential drug interactions for relugolix, as well as the proposed design, study endpoints and sample size for the pivotal Bioequivalence Study MVT-601-042.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Jean-Michel Race

The application was received by the EMA on	6 March 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	16 June 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	26 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 July 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	08 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 January 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	28 January 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 March 2021
The CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and at a potential Oral Explanation to be sent to the applicant on	25 March 2021
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	20 April 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	06 May 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ryeqo on	20 May 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Indication

The claimed therapeutic indication for relugolix-E2/NETA is:

> *[TRADE NAME] is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.*
>
> *[TRADE NAME] maintains bone mineral density and protects the uterus from endometrial hyperplasia in women who choose to use [TRADE NAME] for uterine fibroid treatment.*

The first part of the indication refers to the relugolix-component, which is a GnRH antagonist, to be used in the treatment of symptoms of uterine fibroids. Its mechanism of action is based on binding to the GnRH-receptor in the pituitary gland, thereby blocking release of LH and FSH which subsequently leads to a decrease of estradiol and progesterone concentrations to postmenopausal levels. However, suppression of estradiol leads to decrease in bone mineral density (BMD) which would limit the duration of use. In order to mitigate adverse effects of estrogen deprivation, it is combined with add back therapy, i.e. the combination of estradiol/norethisterone, see second part of the applied indication below.

The second part of the initially applied indication refers to the estradiol/norethisterone (E2/NETA), a combined hormone replacement therapy (HRT) approved in Europe (Activelle), which is added to relugolix to counteract the risk of estrogen loss, which is bone mineral density loss leading to osteoporosis. This add-back therapy provides the possibility for long-term use of the GnRH antagonist.

Disease

Uterine fibroids (also called uterine myomas and leiomyoma) are benign, monoclonal, hormone-sensitive, smooth muscle tumors of the uterus. The hormonal sensitivity of uterine fibroids is indicated on the same clinical observations as observed with endometriosis: development during the reproductive (hormonally active) years and regression after menopause. While estrogen is virtually always required for myomas to develop and grow, it is also clear that growth is regulated by a number of other mediators such as progesterone and local growth factors. It is the most common tumor of the female reproductive tract in pre-menopausal women.

2.1.2. Epidemiology and risk factors

A systemic review of publications published in between January 1995 and April 2015 showed that the incidence of uterine fibroids ranges between 217 to 3,745 cases per 100,000 women-years depending on study populations and diagnostic methods (Stewart, Cookson, Gandolfo, & Schulze-Rath, 2017) and a prevalence ranging between 4.5 to 68.6% depending on study populations and diagnostic methods (Stewart et al., 2017). The prevalence of uterine fibroids increases as women age and is greatest in the 50–54 age group. Prevalence of a reported diagnosis of uterine fibroids in women who had not had a hysterectomy was 0.9%, 3.7%, 6.2%, 9.0%, and 11.1% in the 18–29, 30–34, 35–39, 40–44, and 50–54 age groups, respectively (Fuldeore & Soliman, 2017). Uterine fibroids are estimated to be

clinically apparent in 25% of women of reproductive age and in 25% of women with uterine fibroids, symptoms are severe enough to require treatment.

The incidence of uterine fibroids among Hispanic, Asian and White women is similar, but the incidence in Black women is approximately three times higher than in the other populations (Stewart et al., 2017). Marshall et al. reported age-standardized rates of ultrasound- or hysterectomy-confirmed diagnoses per 1000 woman-years were 8.9 among White women and 30.6 among Black women (Marshall et al., 1997). Additional risk factors are older age, family history of uterine fibroids, smoking, longer time since last birth, premenopausal state and hypertension are all risk factors for the development of uterine fibroids (Stewart et al., 2017).

2.1.3. Clinical presentation, diagnosis

Many women who have uterine fibroids do not have symptoms and the condition may not be diagnosed. Among women who experience symptoms, typical uterine fibroid symptoms include heavy menstrual bleeding, spotting/bleeding between periods, constipation/bloating/diarrhea, passage of clots, and pelvic pressure (Fuldeore & Soliman, 2017). After heavy menstrual bleeding, pain is the second most burdensome symptom for women with uterine fibroids (David, Pitz, Mihaylova, & Siedentopf, 2016; Foth et al., 2017; Monleon et al., 2018). Almost half of women with uterine fibroids report significant dysmenorrhea that can begin earlier in the menstrual cycle and last longer than common menstrual cramps (Monleon et al., 2018; Zimmermann, Bernuit, Gerlinger, Schaefers, & Geppert, 2012). Increasing fibroid burden results in characteristic symptoms depending on the location of the fibroids within the uterine corpus, that is, whether the fibroid is submucosal, intramural, or subserosal. Uterine fibroids distorting the uterine cavity (submucosal and intramural) often produce abnormal uterine bleeding, heavy menstrual bleeding, and/or intermenstrual bleeding in the presence or absence of dysmenorrhea. These cavity-distorting fibroids are often implicated in iron-deficiency anemia (secondary to bleeding) and infertility. If a patient is able to achieve pregnancy with a fibroid impacting the uterine cavity, they also are more likely to experience adverse pregnancy outcomes including recurrent pregnancy loss, abnormal placentation (i.e., placenta previa), foetal malpresentation, preterm delivery, cesarean section, and postpartum haemorrhage. Fibroids in other locations, namely, intramural (well separated from the uterine cavity) and subserosal subtypes, are more often associated with pelvic pressure, pelvic pain, dyspareunia, dyschezia, chronic constipation, and urinary incontinence (Lewis et al., 2018).

Rupture of uterine fibroids causing life-threatening haemorrhage is extremely rare with only around 10 cases reported in the last half decade (Schwartz & Powell, 2017).

2.1.4. Management

Surgery

The mainstay of symptomatic myoma treatment is surgery. The most common procedure is hysterectomy, but less invasive procedures have been developed especially when the patient wishes to preserve fertility and/or her uterus. Less invasive procedures include myomectomy and uterine artery embolization. Endometrial ablation can also be used if the dominant symptom is bleeding, the uterus size relatively small, and fertility is not an issue.

Approved medicinal treatments

Currently, only two approved medicinal options are available for women with symptoms associated with uterine fibroids.

Ulipristal acetate (Esmya) for long-term intermittent treatment

Ulipristal acetate (Esmya), a selective progesterone receptor modulator, is available in the EU and many other countries for short-term presurgical treatment of uterine fibroids and for long-term, intermittent treatment of moderate to severe symptoms of uterine fibroids in patients who are not eligible for surgery. Although very effective in reducing heavy menstrual bleeding and uterine fibroid volume, the PRAC recently recommended the suspension of Esmya (PRAC recommendation March 2020) because of concerns of serious liver injury.

GnRH agonists for short-term pre-operative treatment

The only other pharmaceutical treatment currently registered in Europe for the preoperative treatment of symptomatic fibroids are gonadotropin releasing hormone (GnRH) agonists, i.e. goserelin, leuprorelin, nafarelin and triptorelin.

GnRH agonists suppress estrogen to castration levels resulting in symptoms of menopause such as hot flushes. Their use is restricted to 3-6 months as they lead to loss of bone mineral density, an effect which is partially reversible after discontinuation. In clinical practice HRT are used in combination with GnRH-agonists to reduce effects on BMD and postmenopausal symptoms are used (e.g., combined estrogen and progestins, medroxyprogesterone acetate, tibolone, etc.), in order to allow a longer duration of treatment with GnRH agonists (Pérez-López et al. 2014)).

GnRH antagonists

Relugolix monotherapy (40 mg oral tablet, trade name Relumina) has been approved in Japan since Jan 2019 and is indicated for the improvement of symptoms associated with uterine myoma (hypermenorrhea, lower abdominal pain, lower back pain and anemia). Another oral GnRH antagonist (elagolix monotherapy) has been approved in the US for endometriosis pain since July 2018. A 150 mg dose once daily for up to 24 months or 200 mg twice daily for up to 6 months has been approved. Earlier GnRH antagonists (cetrorelix [1999], ganirelix [2000]) need to be administered parenterally and are only approved in assisted fertility treatment, to inhibit the LH-surge during ovarian stimulation.

<u>Unapproved medicinal treatments</u>

Contraceptives and progestins used as medical treatment for uterine fibroid symptoms (Yao et al. 2017), however few trials have shown efficacy.

Other medical treatments, including tranexamic acid used for heavy bleeding, levonorgestrel IUD, aromatase inhibitors, nonsteroidal anti-inflammatory medications, and danazol, are used but studies suggest limited clinical effectiveness.

NICE Guideline

The current guideline for medicinal treatment of heavy uterine bleeding due to uterine fibroids in the reproductive age is:

1. Non-hormonal: Nonsteroidal anti-inflammatory drugs (NSAIDs like diclofenac, ibuprofen, naproxen) for decrease in pain including dysmenorrhea (not approved), often to be combined with tranexamic acid, an antifibrinolytic (not approved)
2. Combined oral contraceptives (not approved), progestin-only preparations: Mirena IUD, Implanon implant, oral tablets (not approved)
3. Hysterectomy/myomectomy, if necessary, pretreatment with GnRH analogues to decrease the size

4. Ulipristal acetate (Esmya) when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.

Unmet medical need

Long-term treatment of uterine fibroids

Only one medicinal product is approved for long-term treatment of moderate to severe fibroids, i.e. Esmya. However, its use has been restricted to treatment of women when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.

GnRH agonists are only approved for short-term preoperative use (3-6 months) because of the adverse effects on BMD. A medicinal treatment for long-term use of symptoms of uterine fibroids that can safely be given for a longer period without adverse effects on BMD fulfills an unmet medical need in women of childbearing age who still want to have children and are therefore reluctant to have surgery.

Further, unlike GnRH agonists which are administered as a 1-month depot by a subcutaneously administered implant, this product can be given orally once daily.

About the product

The product under review consists of three active ingredients, the GnRH antagonist relugolix 40 mg, estradiol 1 mg (E2) and norethisterone acetate (NETA, also known as norethindrone acetate) 0.5 mg. Relugolix is a new active substance. Relugolix can be taken orally by which it differs from GnRH agonists which are administered as monthly depot by a subcutaneous implant. E2 and NETA are well known and well used active substances, either alone or in combination (Activelle) for hormone replacement therapy i.e. treatment of postmenopausal symptoms of estrogen deficiency. Estradiol and norethisterone are also used in combined contraceptives, but not in this particular combination.

Mode of action

Relugolix:

GnRH binds to specific receptors in the anterior pituitary gland and regulates the release of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Relugolix is an oral nonpeptide GnRH receptor antagonist that results in a competitive and reversible blockade of GnRH receptors on the cell membrane of the gonadotrophic cells in the anterior pituitary. Relugolix leads to a rapid decline in LH and FSH release which subsequent results in a reduction in estrogen, progesterone and testosterone concentrations to castrate levels.

Estradiol:

E2 is similar to the endogenous estradiol.

Norethisterone:

NETA is a synthetic progestagen with anabolic, estrogenic, and androgenic activities similar to those of endogenous progesterone, a natural female sex hormone. NETA binds to and activates nuclear progesterone receptors in target tissues.

Rationale for relugolix + E2/NETA

Similar as for the currently used GnRH agonists, the GnRH antagonist relugolix leads to suppression of estrogen levels which induces symptoms of menopause such as hot flushes and loss of bone mineral density loss. 'Add-back' therapy of combined estrogen and progestins is combined with relugolix in order to reduce these symptoms and to make longer use possible. Although in clinical practice

estrogen+progestin are being used in combination with a GnRH-agonist, which has similar mechanism of action as the GnRH-antagonist, none are approved for combination use in the European Union (EU).

The applicant has studied and developed a combination of a GnRH antagonist with a combined estrogen and progestin HRT (estradiol + norethisterone, approved under the trade name Activelle) with the following rationale:

- The dose of 40 relugolix is effective in reduction of symptoms of uterine fibroids (main symptom heavy menstrual bleeding) by lowering estrogen and progesterone levels to postmenopausal state.
- The added dose of 1 mg estradiol is sufficient to mitigate postmenopausal symptoms (most important safety issue bone mineral density loss, but also symptoms as hot flushes) while not or hardly reducing the effects of relugolix on the symptoms of uterine fibroids.
- The progestin norethisterone 0.5 mg is added to oppose the proliferative effects of estrogens on the endometrium that can lead to endometrial hyperplasia.

Pharmacological classification

ATC code H01C, Group Other hypothalamic Hormones (ATC Code: H01CC54 combination of relugolix, estradiol and progesterone)

Claimed indication

[TRADE NAME] is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

[TRADE NAME] maintains bone mineral density and protects the uterus from endometrial hyperplasia in women who choose to use [TRADE NAME] for uterine fibroid treatment.

Claimed posology

One tablet of [TRADE NAME] is to be taken orally once daily without break, preferably at approximately the same time each day, and at least 1 hour prior to or 2 hours after consumption of a meal (see section 5.2).

It is recommended that the administration of [TRADE NAME] be initiated within five days of the onset of menstrual bleeding. If [TRADE NAME] is initiated on another day of the menstrual cycle, irregular and/or heavy bleeding may initially occur.

As [TRADE NAME] maintains estradiol and progestogen concentrations in a range that maintains bone mineral density and endometrial health, it can ***be used for as long as is required without interruption***.

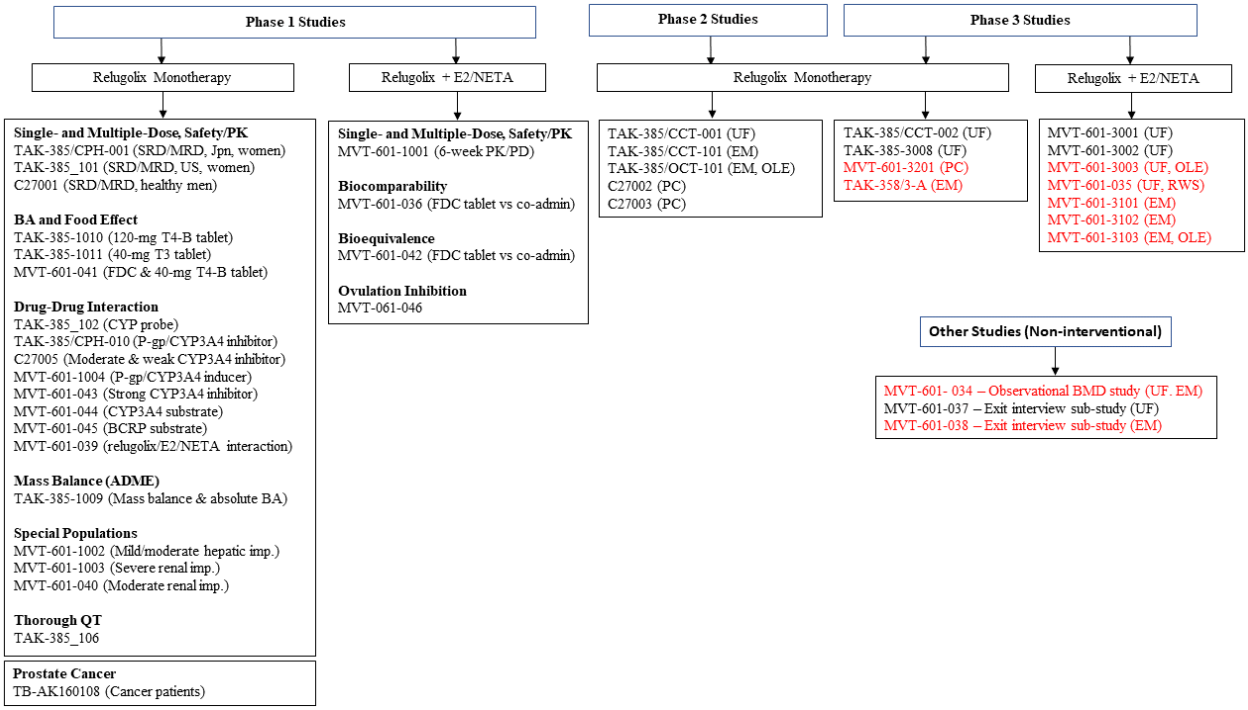
Any hormonal contraception needs to be stopped prior to initiation of [TRADE NAME] (see section 4.3). Nonhormonal methods of contraception should be used for at least one month after initiation of treatment.

Aspects on development

The initial aim of the clinical development program was to develop relugolix as monotherapy in women, for the short-term treatment of symptoms associated with uterine fibroids and pain associated with endometriosis. For this purpose, single- and multiple-ascending dose studies were conducted with relugolix monotherapy.

Relugolix for the treatment for symptoms associated with uterine fibroids will induce a postmenopausal state with adverse effects on bone mineral density and high frequency of hot flushes. Relugolix is therefore combined with E2 1 mg and NETA 0.5 mg with the claim to maintain E2 concentrations within a therapeutic range (20 to 60 pg/mL) and progesterone/progestin concentrations low, in order to maintain BMD and reduce vasomotor symptoms associated with a hypoestrogenic state.

Table : Overview of Relugolix Clinical Development Program



Abbreviations: ADME = absorption, distribution, metabolism and elimination; BA = bioavailability; BCRP = breast cancer resistance protein; co-admin = co-administration; BMD = bone mineral density; CYP = cytochrome P450; E2 = estradiol; EM = endometriosis; FDC = fixed-dose combination; imp. = impairment; Jpn = Japan; MRD = multiple-rising dose; NETA = norethindrone acetate; OLE = open-label extension; PC = prostate cancer; P-gp = P-glycoprotein; PK = pharmacokinetics; QT = QT interval; RWS = randomized withdrawal study; SRD = single-rising dose; UF = uterine fibroid.

Notes:

- Except for TB-AK160108, all phase 1 studies were conducted in healthy participants.
- Phase 3 studies MVT-601-037 (substudy to MVT-601-3001 and MVT-601-3002 in women with uterine fibroids) and study MVT-601-038 (substudy to MVT-601-3101 and MVT-601-3102 in women with endometriosis) are qualitative exit interview studies conducted to provide patient's perspective on the patient-reported outcomes used in the pivotal studies.
- Study MVT-601-034 is an observational (natural history) study evaluating BMD in women with uterine fibroids or endometriosis.
- Red text denotes ongoing studies, but it is noted that a 'Top-line data summary' of study MVT-601-035, which was completed in February 2021, has been submitted during the initial MA procedure.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 40 mg of relugolix, 1 mg of estradiol (as hemihydrate) and 0.5 mg of norethisterone acetate.

Other ingredients are: lactose monohydrate, mannitol (E421), sodium starch glycolate, hydroxypropyl cellulose (E463), magnesium stearate (E572), hypromellose type 2910 (E464), titanium dioxide (E171), triacetin (E1518) and iron oxide yellow (E172).

The product is available in high-density polyethylene (HDPE) bottles with desiccant, closed with an induction-sealed child-resistant polypropylene cap, as described in section 6.5 of the SmPC.

2.2.2. Active Substance: relugolix

General information

The chemical name of relugolix is *N*-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethyl-amino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-6-yl}phenyl)-*N*'-methoxyurea corresponding to the molecular formula $C_{29}H_{27}F_2N_7O_5S$. It has a relative molecular mass of 623.63 g/mol and the following structure, shown in Figure 1:

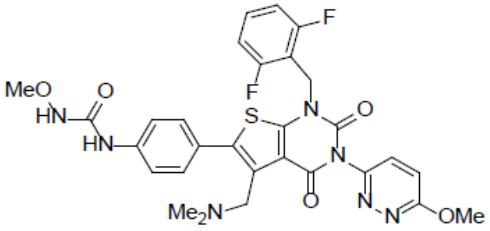


Figure 1: relugolix structure

The chemical structure of relugolix was elucidated by a combination of infra-red spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) including 1D (^{1}H-NMR, ^{13}C-NMR and DEPT-135) analysis and 2D (HMQC, DQF-COSY and HMBC) analysis, mass spectrometry, X-ray powder and single crystal diffractometry, as well as UV/Vis spectroscopy.

The active substance is a white to off-white to slightly yellow solid; the solubility of relugolix decreases with an increase of pH and it is considered a BCS IV Class compound.

Relugolix exhibits polymorphism. The results of polymorph screening study showed that relugolix has several solid forms. The form selected for development and commercial use, is thermodynamically the most stable form under the conditions of manufacture and storageThe polymorphic forms of relugolix can be distinguished by XRPD and the proposed manufacturing process is capable of consistently producing the desired polymorph of relugolix. Relugolix is achiral.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided and it was considered satisfactory.

The manufacturing process consists of several synthetic steps and a purification by crystallisation step.

The proposed sites manufacturing the active substance use identical routes of synthesis. The starting materials are acceptable and are controlled by suitable specifications. The intermediates are sufficiently controlled. In addition, acceptable specifications for reagents, solvents and other materials used in the synthesis have been provided, including a limit for a named impurity as part of the control strategy for nitrosamines, as described under product specification of the finished product.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The information presented regarding potential impurities/degradation products controlled in the active substance is adequate. Overall the defined control strategy is satisfactory.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment and design of experiment (DOE) studies. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and critical process parameters (CPPs) that may have an influence on the active substance quality attributes. The risk identification was based on the process knowledge and sound scientific judgement. No design space has been claimed. The CPPs have been adequately identified and the critical steps of the process were identified and are controlled by justified and appropriate in-process controls.

Relugolix is packed in two sealed, low-density polyethylene (LDPE) bags; desiccant may be placed outside the primary packaging. Then, the double-LDPE bagged material is placed in either an aluminum-laminated bag before packaging in a secondary container or an aluminum-lined fibre drum or equivalent secondary container. The primary packing material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC, UV), particle size (laser light diffraction), assay (HPLC), impurities (HPLC), residue on ignition (Ph. Eur.), residual solvents (GC) and water content (Ph. Eur.).

The specification limits for impurities/degradation products and residual solvents, are in accordance with the requirements of ICH guidelines Q3A and Q3C. All solvents used throughout the entire synthetic process, including those employed prior to the starting material, are routinely controlled in the specification and specified at levels in-line with the ICH Q3C thresholds.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from three registration batches, ten process validation batches, a pilot-scale, a GMP, and an engineering batch are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three primary batches of active substance from the proposed manufacturers stored for up to 36 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, crystal form (PXRD), identification by IR, identification by UV, related substance, water and assay. Storage at the accelerated stability condition, up to 6 months, showed no change for the same stability-indicating and quality parameters. Slight increases in two specified impurities were observed but the results remain conform. The total related substances values remained below the specification limit and all tested parameters were within the specifications.
In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. During exposure, the active substance becomes yellowish white. There is also an increase in unspecified related substances and total related substances. These changes are not observed during long-term or accelerated stability conditions. Based on the results, the active substance is packaged in an aluminum-laminated bag or aluminum-lined fiber drums that prevents exposure to light.

In addition, stressed stability studies were conducted for related substances on samples of relugolix active substance from one manufacture exposed to 50°C, 60°C, and 25°C/93% RH storage conditions and durations for up to 3 months, 2 months, and 3 months, respectively. The related substances method was shown to be stability indicating. There was no degradation observed in relugolix active substance.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months stored in the proposed packaging without storage restriction.

2.2.3. Active substance: estradiol hemihydrate

General information

The chemical name of estradiol hemihydrate is estra-1,3,5(10)-triene-3,17β-diol hemihydrate corresponding to the molecular formula $C_{18}H_{24}O_2$ $1/2H_2O$. It has a relative molecular mass of 281.4 g/mol and the following structure, shown in Figure 1:

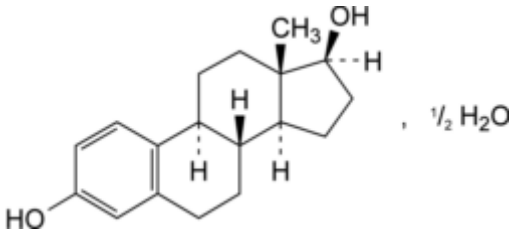


Figure 2: Estradiol hemihydrate propionate structure

The active substance is white or almost white, crystalline powder or colourless crystals, practically insoluble in water with a low solubility over the physiological pH range.

As there is a monograph of estradiol hemihydrate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for estradiol hemihydrate which has been provided within the current Marketing Authorisation Application.

The chirality of estradiol hemihydrate is controlled in the specifications by specific optical rotation, as per Ph. Eur. monograph. The CEP covers three grades of estradiol hemihydrate (micronised, micronised fine and non-micronised). However, estradiol hemihydrate is dissolved during the finished product manufacturing process. Hence, control of particle size distribution and polymorphic form is not relevant for this active substance.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. Only one site is involved in the manufacture of the final active substance.
Material of animal origin (pig skin) is used in the manufacture of estradiol hemihydrate. In the CEP it is stated that "the holder of the certificate has declared the use of material of human or animal origin in the manufacture of the substance and there is no risk of viral contamination"; this is accepted.

The active substance is packaged in double a polyethylene bags placed in a fibre drum. The polyethylene bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

Estradiol is tested in accordance with the analytical procedures, and in conformance to the acceptance criteria, contained in the current European Pharmacopoeia.

The specification of the finished product manufacturer is fully in line with the specification of the active substance manufacturer. The finished product manufacturer has adopted the additional analytical methods for residual solvents used by the CEP holder. All other analytical methods are as per Ph. Eur. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from the finished product manufacturer from two commercial scale batches and batch analysis data from the active substance manufacturer from three commercial scale batches are provided. The results are within the specifications and consistent from batch to batch.

Stability

As no re-test period is proposed in the CEP, stability data from one commercial scale batch at long-term conditions and 3 commercial scale batched at accelerated conditions of micronised active substance (fine grade) from the proposed manufacturer stored in the container stated in the CEP for up to 60 months under long term conditions (25 °C ± 2 °C, 60% ± 5% RH) and for up to 6 months under accelerated conditions (40 °C ± 2 °C, 75% ± 5% RH) according to the ICH guidelines were provided. The tested parameters were within the specifications. Additional batches have been added to the stability study under long-term storage conditions. The tested parameters were within the specifications except for particle size distribution for estradiol hemihydrate micronised fine grade (EHM). For EHM, each batch is impacted by an out-of-specification (OOS) result on Dv50 or on Dv90 at different time-points of the study. For Dv50, the out-of-specification is a result of the variability of the method combined with a Dv50 value which is just at the specification at release. For Dv90, the out-of-specification could come from the difficulty of homogenisation of the stability sample, as retest performed on retained samples (samples bigger than stability samples) meet the specification. The particle size of estradiol is not considered a key parameter for the relugolix/estradiol/norethisterone acetate fixed-dose combination (FDC) tablet as the estradiol is dissolved in the granulation process.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the retest period of 60 months (for micronized fine grade and non-micronized grade) under standard storage conditions of a temperature of maximum 25 ºC when stored in the packaging stated in the CEP as proposed by the active substance manufacturer.

2.2.4. Active substance: norethisterone acetate

General information

The chemical name of norethisterone acetate is 3-Oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate corresponding to the molecular formula C22H28O3. It has a relative molecular mass of 340.5 g/mol and the following structure in Figure 2:

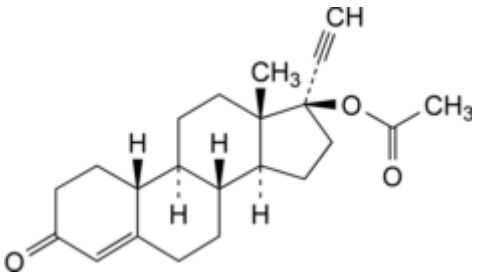


Figure 3: norethisterone acetate structure

The active substance is a white or yellowish-white, crystalline powder and is practically insoluble in water.

As there is a monograph of norethisterone acetate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for norethisterone acetate which has been provided within the current Marketing Authorisation Application.

The chirality of norethisterone acetate is controlled in the specifications by specific optical rotation, as per the Ph. Eur. monograph. Norethisterone acetate is dissolved during the finished product manufacturing process. Hence, control of polymorphic form is not relevant for this active substance.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. Only one site is involved in the manufacture of the final active substance. No grade is specified in the CEP. The active substance is packaged in a double polyethylene bag placed in a fibre drum. The polyethylene bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

Norethisterone acetate is tested in accordance with the analytical procedures and in conformance to the acceptance criteria contained in the current European Pharmacopoeia. In addition to the monograph of the European Pharmacopoeia, the active substance specification includes tests for related substances (GC).

The specification of the finished product manufacturer is fully in line with the specification of the active substance manufacturer. The finished product manufacturer has adopted the additional analytical method for related substances used by the CEP holder. All other analytical methods are as per Ph. Eur. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from three production scale batches are provided. The results are within the specifications and consistent from batch to batch.

Stability

The re-test period of norethisterone acetate is 60 months when stored in the container closure system as stated on the CEP, as stated in the CEP.

2.2.5. Finished Medicinal Product

Description of the product and Pharmaceutical development

Relugolix/estradiol/norethisterone acetate (40/1/0.5 mg) is a light yellow to yellow, round film-coated tablet of 8 mm with "415" on one side and plain-faced on the other side.

The composition of relugolix/estradiol/norethisterone acetate (40/1/0.5 mg) FDC tablets (REL/E2/NETA FDC), is given.

All excipients are well known pharmaceutical ingredients and their quality is compliant with compendial standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

REL/E2/NETA FDC tablets are an immediate release (IR) product designed to disintegrate and dissolve rapidly under the physiological conditions in the stomach.

The quality target product profile (QTPP) was defined based on formulation developed for clinical studies, manufacturing process considerations and the properties of the active substances. The critical quality attributes (CQAs) were selected based on prior information and knowledge gained from pharmaceutical development studies of the same or similar types of formulations.

During the procedure, it has been satisfactorily demonstrated that the polymorphic form of the three active substances is unchanged during the manufacture and storage of the FDC.

The formulation development of the proposed commercial formulation is based on the formulations used in the Phase 3 studies, where relugolix 40 mg single agent tablets (REL T4B SA) were co-administered with commercially available E2/NETA tablets (1mg/0.5mg), namely European brands (Activelle, Kliovance) or the equivalent US brand (Activella), over-encapsulated for blinding purposes, and provided in a co-packaged configuration as the investigational medicinal product. All excipients included in the REL/E2/NETA FDC are present in either the REL 40 mg SA tablets or commercially available Activella. The excipients selected for the FDC are commonly included in immediate-release tablets. As explained under the clinical aspects, the use of the three E2/NETA combination tablets (USA Activella and EU Activelle and Kliovance) in the clinical studies is accepted as Activella's composition is identical to the one of Activelle and Kliovance; additionally, it has been confirmed that the EU and US reference products were manufactured by Novo Nordisk at the same facility using the same manufacturing process and equipment. Therefore, the only difference among these E2/NETA combination tablets was their trade names. A bioequivalence study (study MVT-601-042) was

performed showing bioequivalence between the clinical formulation and the proposed commercial formulation. Bioequivalence was demonstrated based on statistical analysis of all pre-specified primary and secondary endpoints, as explained in detail in the clinical section.

The dissolution method development focused on delivering a robust methodology suitable for commercial product release. The discriminatory power of the dissolution QC method has been demonstrated.

The primary packaging is a high-density polyethylene (HDPE) bottles with desiccant and closed with an induction sealed child resistant polypropylene cap. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process has been described.

Based on the low drug load with respect to estradiol and norethisterone acetate, the process is considered to be a non-standard manufacturing process.

To address a major objection (MO) on process validation, data from three consecutive commercial scale batches have been provided during the procedure. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria demonstrating that the process is robust and capable of reproducibly manufacturing uniform REL/E2/NETA film-coated tablets.

The proposed in-process controls are adequate for this type of manufacturing process.

Holding times have been defined and are supported by data.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (HPLC-UV and HPLC retention time), assay (HPLC), related substances (HPLC), dissolution (Ph. Eur.), content uniformity (Ph. Eur.), water content (KF – Ph. Eur.), microbial examination (Ph. Eur.), residual solvents (GC), NDMA content (LC-MS). The specification includes all the expected tests for this type of pharmaceutical form.

The impurity thresholds for each active substance are set in-line with ICH Q3B. The proposed limits for total impurities of the three active substances are in line with batch data, including upon stability, and reflect the actual process capabilities; the proposed limits are considered acceptable.

As demonstrated during pharmaceutical development, the proposed dissolution limit for E2 and NETA is acceptable.

The dissolution limit proposed for REL is also considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with option 2b of the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

In response to a MO, a risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the

"Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

N-Nitrosodimethylamine (NDMA) is the only nitrosamine detected above the respective LoQ in the FDC tablets, as well as Relugolix single agent tablets. The levels of NDMA are consistently below 10% of the acceptable limit. In order to ensure that the levels of NDMA in the finished product are below the acceptable intake, over the life-cycle of the product, a limit for NDMA has been included in the finished product specification both at release and at shelf-life.

Based on the information provided it is accepted that the risk of possible presence of nitrosamine impurities in the active substance and the related finished product is adequately controlled.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches of the FDC confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 65% RH) for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the FDC tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Different batches of the active substances, manufactured by the proposed REL manufacturers, have been used in the manufacture of the stability batches.

Samples were tested for appearance, assay, related substances, water content, dissolution and microbial quality.

The finished product is generally very stable in the proposed container packaging system and no general trends or signs of degradation are observable. No change in dissolution, water content and assay is noticed for the time-frame covered so far under all storage conditions.

An in-use stability study under ambient conditions was performed. The samples were tested before and after 28 days. No difference in any of the tested quality attributes is observable.

Stress studies were conducted by storing samples of the FDC tablets for two weeks at 50°C, one month at -20°C, and three 48-hour freeze/thaw cycles of 40°C/75% RH and -20°C. These studies support potential excursions to the storage condition and further demonstrate the stability of the product.

FDC tablets were exposed to the forced degradation conditions under acid, base, oxidative, light plus moisture and heat plus moisture. The results confirmed the suitability of the assay and purity methods. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The FDC tablets are stable to light.

Based on available stability data, the proposed shelf-life of 24 months, with no special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.6. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The MOs raised during the procedure on process validation data for the finished product and on the control of nitrosamines have been adequately addressed.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product.

2.2.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.8. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends a point for investigation.:

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamic studies

Relugolix

In vitro – GnRH receptor binding

Relugolix showed a high affinity for human and for the monkey GnRH receptor with IC50 value of 0.12 nmol/L and 0.15 nmol/L, respectively. The binding affinity of relugolix for rat GnRH receptor was much lower, with IC_{50} values of 2,900 nmol/L.

In the presence of 40% FBS (fetal bovine serum), binding affinity of relugolix for human GnRH receptor was approximately 3-fold lower than that in the absence of FBS with IC50 value of 0.33 nmol/L. In contrast, GnRH, cetrorelix - a peptide GnRH antagonist - and TAP-144 – a peptide GnRH

agonist - showed approximately the same affinities for GnRH receptors in the presence and absence of 40% FBS. But in either case, this affinity was lower than that of relugolix for human and monkey GnRH receptor in the presence of 40% FBS.

These results suggest that binding affinity of relugolix for human and monkey GnRH receptors is highly species-specific and is slightly lower in the presence of serum, which is related to relugolix protein binding.

In vitro – functional effects on GnRH

The antagonistic effects of relugolix and cetrorelix were examined on CHO cells expressing human GnRH receptors. These compounds inhibited GnRH-induced 3H-arachidonic acid release in a dose-dependent manner. IC50 values were 0.32 and 0.67 nmol/L, and IC90 values were 2.6 and 4.6 nmol/L for TAK-385 and cetrorelix respectively. Relugolix being approximately 2-fold more potent than cetrorelix.

The antagonistic effect of these compounds in the presence of 40% human plasma was also determined. IC50 values were 1.6 and 4.5 nmol/L, and IC90 values were 18 and 75 nmol/L for relugolix and cetrorelix and respectively. IC50 values and IC90 values for relugolix were approximately 3-fold and 4-fold more potent with regard to antagonistic activity compared to cetrorelix in the presence of human serum. These data suggest that relugolix might show a potent GnRH antagonistic effect in human.

Relugolix showed an inhibitory effect on GnRH - induced arachidonic acid release from CHO cells expressing monkey GnRH receptors in a dose-dependent manner. Relugolix had a potent GnRH antagonistic effect even in the presence of 40% monkey plasma. These data suggest that relugolix would show a potent antagonistic activity in monkey models *in vivo*, providing further support for the *in vivo* study in monkey.

In vivo – human GnRH knock-in mice

As reluoglix has only low affinity for the mouse GnRH receptor, a human GnRHR knock-in mice was generated, in which mouse GnRHR was replaced by human GnRHR, to evaluate the effect of relugolix on a hypothalamic-pituitary-gonadal axis. To clarify whether relugolix works as an antagonist for human GnRHR *in vivo*, the effect of chronic oral administration of relugolix on estrous cycle, ovary and uterus weights, GnRHR mRNA expression in the pituitary, and bone density in female human GnRHR knock-in mice was examined. Also, the effect of oral administration of relugolix on the weight of reproductive organs and pituitary human GnRH receptor mRNA expression in male human GnRH receptor KI mice was evaluated.

Relugolix (in 0.5% methylcellulose (MC) containing 6 mg/mL citric acid) was administered by oral gavage for 4 weeks at 30, 100, or 200 mg/kg BID in females and at 3, 10, or 30 mg/kg b.i.d. in males. For both females and males, two control groups were included in each study to receive 0.5% MC vehicle alone: intact (non-ovariectomized/non castrated) animals and ovariectomized/castrated animals.

The intact female mice displayed normal estrous cycles, whereas OVX mice showed di-estrous stage throughout the study period. Oral administration of relugolix induced a constant di-estrous phase at the minimum dose of 100 mg/kg, b.i.d. and significantly decreased the ovary and uterus weight suggesting that relugolix suppresses the secretion of LH and estrogens. In addition, relugolix at 100 mg/kg, b.i.d. also induced down-regulation of the GnRHR mRNA expression in the pituitary indicating

that a non-peptide GnRH antagonist (relugolix), as well as a peptide GnRH antagonist (Cetrorelix), is able to down-regulate the expression of pituitary GnRHR mRNA. There were no differences in cancellous and cortical bone density between intact, OVX and each treatment group. These results indicate that relugolix has suppressive effects on the hypothalamic-pituitary-gonadal axis in female human GnRHR knock-in mice and suggest that relugolix could work as an oral antagonist for human GnRHR *in vivo.*

In vivo – castrated monkeys

Castrated monkeys (3 per dose group) were treated with relugolix at a single dose of 0.1, 0.3, 1.0 or 3.0 mg/kg. Plasma was collected pretreatment (0h) and 1, 2, 4, 8, 24 and 48 hours post treatment. Testosterone levels were determined using mouse testicular cells that were incubated with the monkey plasma. The corresponding LH concentrations in the samples were calculated by logistic regression analysis. The LH levels seem quite variable as for instance for one out of the three monkeys in the 0.3 mg/kg dose group deviating from the other two and one animal in the 1 mg/kg group seems to deviate from the other two animals in the same group. However, this is regarded inherent to the assay. The results show that relugolix at doses of 1 and 3 mg/kg suppressed plasma LH levels in castrated cynomolgus monkeys with maximum suppression that continued for 24 and 48 hours after administration, respectively. In contrast, relugolix at doses of 0.1 and 0.3 mg/kg did not show substantial suppression. Thus, this *in vivo* experiment indicates that relugolix is orally active and effective at dose of over 1 mg/kg in castrated cynomolgus monkeys.

Estradiol and Norethindrone acetate

The pharmacology of estradiol and norethindrone acetate is known and is supported by literature. In short; Estradiol (17β-estradiol, E2) is an endogenous estrogen produced in humans with an essential role in female reproduction and involvement in development, maturation, and various metabolic processes. Norethindrone acetate (NETA) is a prodrug with weak progestin activity that is rapidly and extensively hydrolyzed to the potent synthetic progestin norethindrone (NET; also referred to as norethisterone) that interacts with Progestin Receptor form A and B leading to dimerization of the hormone receptor, recruitment of other transcription modulators, and ultimately resulting in transcriptional gene regulation. The pharmacology of estradiol and norethindrone acetate will not be discussed to a further extent here.

Secondary pharmacodynamic studies

Relugolix

Effects of relugolix on 134 MDSPS assays in Enzyme and Radioligand Binding Assays were investigated. Relugolix in primary screen assays was found to inhibit [3H]SR-49868 binding to Tachykinin NK2 receptors with the activity of 55% at 10 µmol/L. Relugolix had high affinity for the human GnRH receptor with an IC_{50} value of 0.12 nmol/L (1), which indicates that affinity of relugolix to human GnRH receptor was 100,000 times higher than that to Tachykinin NK2 receptors. The results show that relugolix has excellent specificity for the human GnRH receptor. And as the steady state C_{max} for relugolix in humans is 18.3 ng/mL, binding to the Tachykinin NK2 receptor is not anticipated to occur in the clinic.

Estradiol and norethindrone acetate

Estradiol (E2) is a potent activator of ERs, particularly ERα and ERβ, and nongenomic cell signaling cascades, but interactions of E2 with off-target receptors or channels are not expected at the

anticipated clinical dose of E2 (1 mg) as part of the proposed combination with relugolix (40 mg) and NETA (0.5 mg). Norethindrone is associated with weak binding to androgenic receptors (relative binding affinity = 15% compared to the positive control metribolone), which is not expected to be significant at low oral doses in humans (i.e., 0.5 mg) and in particular not when combined with a low-dose estrogen.

Safety pharmacology programme

Relugolix

Relugolix inhibited hERG potassium channel current by 3.4%, 20.5% and 78.5% at 0,.3, 3 and 30 µg/mL respectively and with an IC50 of 9.7 µg/mL (15.5 µM). This IC50 is approximately 530-fold higher than the mean total steady state Cmax of 18.3 ng/mL, reached upon administration of 40 mg relugolix once daily. This is regarded a sufficiently large safety margin for hERG inhibition to occur in the clinic.

Relugolix was administered to telemetered male cynomolgus monkeys (n = 4) at single doses of 0, 30, 100, or 300 mg/kg by oral gavage at 7-day intervals in a crossover manner. The no observed effect level (NOEL) for blood pressure and heart rate (changes in the systolic, diastolic, or mean blood pressures; heart rate; PR interval; or QRS duration) was 300 mg/kg and estimated to correlate with a mean Cmax of 10,400 ng/mL being approximately ~570-fold higher than the human Cmax (18.3 ng/mL at a dose of 40mg/kg/day). As QT and QTc prolongation was observed in monkeys upon 100 mg/kg and 300 mg/kg single dose, the NOEL for QT/QTc interval prolongation was 30 mg/kg and estimated to correlate with a mean Cmax of 1740 ng/mL and approximately 95-fold higher than the human Cmax (18.3 ng/mL at a dose of 40mg/kg/day). Relugolix did not prolong the QTQTcF interval in the clinical thorough QTc study at single doses up to 360 mg (mean Cmax 253 ng/mL). Therefore, the no effect level for QT prolongation in humans is at least ~13.8 fold higher than the mean total relugolix Cmax at steady state in humans associated with the anticipated clinical dose of 40 mg once daily (18.3 ng/mL).

Relugolix was administered to male Sprague Dawley rats (n = 6/group) as a single oral dose via gavage (dose volume = 10 mL/kg) at dose levels of 0 (0.5% MC), 200, 600, or 2000 mg/kg. No acute CNS effects in male rats at doses ≤ 2000 mg/kg at any time point up to 24 hours post-dose estimated to correspond with a Cmax of 7544 ng/mL which is approximately 410-fold higher than the human Cmax (18.3 ng/mL at a dose of 40mg/kg/day).

Relugolix was administered to male Sprague Dawley rats (n = 8/group) as a single oral dose via gavage (dose volume = 10 mL/kg) at dose levels of 0 (0.5% MC), 200, 600, or 2000 mg/kg and respiratory function was evaluated using a whole-body plethysmography system measuring respiratory rate, tidal volume, minute volume, enhanced pause [Penh] before and at 1, 2, 4, 8, and 22 hours post-dose. Relugolix had no acute effects on the respiratory system in male rats at doses up to 2000 mg/kg for 22 hours post-dose estimated to correspond with a Cmax = 7544 ng/mL which is approximately 410-fold higher than higher than the human Cmax (18.3 ng/mL at a dose of 40mg/kg/day).

Estradiol and Norethindrone Acetate

The safety pharmacology profiles of estradiol and norethindrone acetate are known and supported by literature data. Due to the anticipated lack of effects in animal models based on anticipated exposures of E2 and NETA associated with the proposed combination therapy, nonclinical safety pharmacology

studies with the combination of E2 and NETA with or without relugolix were not conducted. This approach was agreed by the CHMP.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed for relugolix, E2, and/or NETA alone or in combination. Pharmacodynamic interactions are not expected for the three individual components of the FDC at the proposed doses. The absence of pharmacology interaction studies has been sufficiently justified and was agreed by the CHMP.

2.3.2. Pharmacokinetics

Absorption after single dose was investigated in rats and monkeys and after repeated dose in mice, rats, rabbits and monkeys. Tissue distribution was investigated in rats. Placental transfer and distribution to milk were investigated in rats. Metabolism was investigated *in vitro* and *in vivo* in rats and monkeys. Excretion was investigated in mass balance studies in rats (intact and bile-duct cannulated rats) and monkeys.

Methods of analysis

Validated methods were used for the toxicokinetic analyses in plasma of mice, rats, rabbits and monkeys. The validation was adequate regarding calibration, accuracy, precision, LLOQ, dilution integrity, matrix effect and stability. In the toxicokinetic studies, bioanalytical reports were provided. The calibration and QC samples met the criteria of the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev 1 Corr 2). The methods used in the pharmacokinetic analyses were agreed by the CHMP.

Absorption

Relugolix has moderate intrinsic permeability in Caco-2 cells. Relugolix is a substrate for P-gp but it is not a substrate for BCRP.

After oral single dose administration, relugolix was absorbed rapidly in rats and monkeys (Tmax 1-3 h). The exposure increased more than dose-proportionally in rats up to 100 mg/kg and monkeys up to 20 mg/kg (maximally approximately 2-fold more than the increase in dose, based on AUC). In rats, relugolix was absorbed mainly from the small intestine, especially from the duodenum. Relugolix was absorbed via the portal route and not via the lymphatic route in rats. In monkeys, plasma exposure was considerably higher in fasted conditions than in fed conditions (Cmax 5-fold higher and AUC 21-fold higher). Volume of distribution was 16 – 39 L/kg in rats and 20 L/kg in monkeys, which implies a wide distribution beyond the total body water. Absolute oral bioavailability was low in rats, but some variation was visible (ranging 9 – 25% based on relugolix in the single dose pharmacokinetic studies). In the excretion study in bile-duct cannulated rats, 37% of total radioactivity was excreted in bile and 2.6% excreted in urine, indicating a bioavailability of approximately 40%. In monkeys, absolute oral bioavailability compared to IV administration was 6.9% at 1 mg/kg under fasted conditions. Estimated oral bioavailability in humans is 12%. Elimination half-life was 2-6 h in rats and 5-7 h in monkeys and 14-16 h in humans. Clearance was 4.5 – 9.3 L/h/kg in rats and 2.8 L/h/kg in monkeys, which is comparable to, or slightly exceeding hepatic blood flow. Only males were used in the single dose pharmacokinetic studies. In the toxicokinetic studies, both sexes were investigated, and no clear gender difference was observed. Therefore, no relevant gender differences are expected in other aspects of the pharmacokinetics.

After multiple dose administration, relugolix concentrations in plasma increased more than dose-proportionally at lower doses (mouse 10-100 mg/kg/day, rat 10-100 mg/kg/day, monkey 1.5-15 mg/kg/day) and approximately dose-proportionally or less than dose proportionally (mouse) at higher doses. No clear gender effect was observed in mice, rats and monkeys. No significant accumulation was observed in monkeys and in mice, except in monkeys at the lowest dose of 1.5-5 mg/kg/day and in mice at the highest dose of 2000 mg/kg/day. In rats, accumulation was observed at all doses. In general, accumulation in rats was approximately 4-fold, except at the lowest dose (10 mg/kg/day, more than 10-fold).

Distribution

Plasma protein binding of relugolix was moderate in mice (80-83%), rats (74-76%), monkeys (57-59%) and humans (68-71%) in the concentration range 0.05 – 5 µg/mL. Binding to human serum albumin and α1-acid glycoprotein combined was lower (38-44%) than binding in human plasma, showing that other proteins may also be involved. *In vitro*, relugolix had no relevant effect on plasma binding of highly bound compounds warfarin, ibuprofen, digoxin and propranolol.

Blood/plasma ratio in rats was 1.5 and 1.3 in males and females respectively at 4 h after dosing. *In vitro*, relugolix-associated radioactivity distributed into blood cells of rats, monkeys and humans for 45-49%, 57-59% and 46-41% respectively, which is a considerable proportion.

Following single dose oral administration to rats, relugolix-associated radioactivity was widely distributed with the highest concentrations in pituitary (up to 133x and 58x plasma concentration in males and females, respectively) thyroid gland (71x and 54x), liver (294x and 170x), adrenals (55x and 55x), kidney (54x and 63x) and GI tract. Maximum concentrations were found at 4-8 h after dosing, except for the GI tract, where maximum concentrations were found at 1 h after dosing. At 168 h after dosing, concentrations were below the limit of quantitation or at trace levels in most tissues. Relugolix-associated radioactivity was distributed similarly to pigmented and non-pigmented skin. Relugolix distributed to the eye, where it could still be found at 12 weeks after dosing. The potential for phototoxicity has been studied and no evidence of phototoxicity was found in mice. Low concentrations were found in the brain up to 24 h after dosing. Concentrations in brain were lower than or similar to concentrations in plasma. Relugolix-associated radioactivity passed the placenta and was found in foetal plasma and tissue in rats. Cmax in foetal plasma was approximately 10% of maternal Cmax. Relugolix-associated radioactivity distributed into the milk of lactating rats. Concentrations in milk were high compared to plasma (approximately 10-fold at 2 h after dosing, the time of the maximum concentration). At 48 h after dosing, still measurable concentrations could be found. The data show that relugolix and relugolix-associated material (e.g. radioactive relugolix metabolites) has the potential to accumulate in milk. These findings are appropriately reflected in the SmPC.

Metabolism

In vitro, the major compound found in microsomes of mice, rats, dogs, monkeys and humans was the parent compound. In the presence of NADPH, the main human metabolites were Metabolite-A and Metabolite-B. Metabolite A was also formed in monkeys, and to a minor extent also in dogs, mice and rats. Metabolite-B was also formed in mice and rats and only to a very low extent in monkeys and dogs. Other metabolites, T-1400567, T-1525140, UK-A and UK-C, were formed to a low extent. An unidentified metabolite UK-E is also mentioned. No quantitative data are given regarding the formation of this metabolite. However, since it was not formed in a previous study and it was also not mentioned in the *in vivo* studies, it is probably not formed in relevant quantities. In the absence of NADPH, T-1525140 was formed in all species and the other metabolites only to a very low extent. In dog microsomes, relugolix underwent less metabolic turnover than in microsomes from the other species. Metabolite A was formed through O-demethylation by CYP3A4. Metabolite B was formed through

hydroxylation by CYP2C8 and, to a low extent, by CYP2C19. Metabolite C was formed through N-demethoxylation, but not by CYP enzymes. Metabolite-C was found in large amounts only in faeces and it was formed in incubations with human faecal homogenates, but not in autoclaved faecal samples and is therefore most likely formed by gut microflora.

In vivo metabolism was investigated in rats and monkeys and humans. Unchanged relugolix was the most abundant component in the plasma. At the time of the maximal radioactivity concentration (2 h in rats and 4 h in monkeys), mainly unchanged relugolix was present at 99% of radioactivity in rats and at 86% in monkeys. In humans at 72 h, unchanged relugolix in plasma ranged from 42 to 68% of total radioactivity. Metabolite-A was found up to 8.7% in plasma of monkeys, whereas it was not found in plasma of rats. Metabolite-B was not found in plasma of rats or monkeys, but it was found in bile of rats. Metabolite-C was found up to 1.9% in plasma of rats and not in plasma of monkeys. Remaining radioactivity consisted of minor, unidentified components. Even though at later time points (at 6 h in rats and 24 h in monkeys) "other components" comprised up to 40% of radioactivity in plasma in rats and up to 77% in monkeys, in absolute sense this concerns only minor amounts. In humans, all metabolites in plasma, which could amount up to 58%, were separately present at < 5% of total radioactivity. There are therefore no major human metabolites that need to be covered in the non-clinical species. Most of relugolix-related material was excreted as metabolites with unchanged relugolix accounting for ≤ 8.0% in excreta of rats and monkeys. In bile of rats, Metabolite-B was the major compound. Metabolite-C was the major component in faeces of rats (59% of dose), monkeys (45% of dose) and also humans (40% of dose). Since Metabolite-C was not present in plasma or only at very low levels, and it was also not formed in incubations with intestinal microsomes, it was probably formed by gut microflora. This was confirmed by inhibition of Metabolite-C formation by autoclaving human faecal homogenates or by treatment of these homogenates with antibiotics.

Excretion

Recovery in the excretion studies following a single oral dose to rats and monkeys was 93-100% of the dose. The major part of relugolix-related radioactivity was excreted via the faeces (92-96% in intact rats and orally-dosed monkeys). In rats, only a minor part was excreted via the urine (1.4-2.6%). In monkeys, the excretion via urine was more variable (4.9-22% after oral administration). In bile-duct cannulated rats, 37% of the dose was excreted via the bile 24 h after administration of [14C]-relugolix. In monkeys, a large part appears to be excreted via the bile (69% of dose was excreted via faeces after IV administration). Yet, a considerable part was excreted via the urine as well (24% after IV administration). In humans, the same pattern was observed as in rats (83% excreted in faeces and 4.4% in urine).

Estradiol (E2)

Estradiol is orally bioavailable and undergoes rapid absorption upon oral administration. Exogenous administration of E2 undergoes rapid and extensive first pass metabolism in the small intestine and liver resulting in low absolute bioavailability (~5%). Following oral administration of E2, circulating levels remain elevated for up to 12 hours post dose due to interconversion between E2 and its metabolites, notably estrone (E1). Estradiol is extensively bound to plasma proteins, primarily to steroid hormone-binding globulin (SHBG) and albumin. Due to its lipophilicity, E2 distributes rapidly and extensively in tissues. Exogenously administered E2 undergoes rapid and extensive first-pass metabolism in the small intestine and liver to estrone by 17β-hydroxysteroid dehydrogenase and subsequently to sulfate and glucuronide conjugates by SULT or UGT enzymes, respectively. Further, E2 can undergo oxidative metabolism by CYP enzymes, including CYP3A4. Sulfate and glucuronide conjugates of these estrogens can re-enter systemic circulation by enterohepatic recirculation. E1 and E2 undergo elimination in urine primarily as glucuronide or sulfate conjugates.

Norethindrone acetate (NETA)

Following oral administration, NETA is hydrolyzed in the intestine and liver to norethindrone (NET) with a total progestin bioavailability of 40%-80%. Following an oral dose of 0.5 mg NETA, the Tmax for NET is approximately 1 hour with maximum plasma concentrations of approximately 5 ng/mL. Upon repeated daily administration with E2, plasma concentrations are approximately 7 ng/mL with a t½ of approximately 7 to 9 hours. Norethindrone acetate, converted to NET *in vivo*, binds extensively to human plasma proteins, namely SHBG (36%) and albumin (61%), with approximately 3.7% unbound in plasma. Binding to plasma proteins is weak and NET is available for distribution into tissues and subsequent metabolism. Following hydrolyzation of NETA to NET in the intestine and liver, NET is metabolized by steroid reductases (e.g., 5α-, β-) to other biologically active metabolites in addition to biotransformation by sulfonation, glucuronidation, and oxidation by SULT, UGT, and CYP enzymes, including CYP3A4. Conjugates of NET and its reduced metabolites can undergo enterohepatic recirculation. NET is primarily eliminated via urine as various polar metabolites.

2.3.3. Toxicology

Single dose toxicity

Table: Single dose toxicity studies with relugolix

Study ID	**Species/ Sex/Number/ Group**	**Dose (mg/kg) /Route**	**Approx. lethal dose / observed max non-lethal dose (mg/kg)**	**Major findings**
TAK-385/00006	Mouse (CD1) 2M	200, 600, 2000 Oral gavage	>2000/2000	No unscheduled mortalities and no treatment-related clinical signs.
TAK-385/00010	Rat (Sprague Dawley) 5M/5F	0, 200, 600, 2000 Oral gavage	>2000/2000	**2000**: Decreased feces in both sexes on day 1. Cloudy urine in both sexes on days 0 to 1 (not considered toxicologically relevant).
TAK-385/00053	Rat (Sprague Dawley) 2M/2F	0, 9, 30, 90 IV	90/30	**90**: Prone position, decrease in locomotor activity, tonic and clonic convulsions, bradypnea, and dyspnea immediately after dosing and all died within 5 minutes. **30**: Prone position and decreased locomotor activity in all animals, with bradypnea also in 2 males immediately. These findings resolved within 5 minutes.
TAK-385/00108	Rat (Sprague Dawley) 5M/5F	0, 9, 30, 90 IV	90/30	**90**: All males and 4 females exhibited prone position, decrease in locomotor activity, bradypnea, or tonic/clonic convulsions, and died within 5 minutes. Dark red discoloration of the lung in some of these animals. Prone position, decrease in locomotor activity, clonic convulsions, and/or bradypnea in 1 surviving female. Body weight gain was lower in the surviving female. **30**: Prone position, decrease in locomotor activity, and tremors (females) in all animals immediately (adverse clinical signs resolved within 5 minutes). One female died due to torsion of the ileum on day 5 (not considered treatment related). No abnormalities at necropsy in surviving animals.
04-015/ac	Monkey (cynomolgus) 2M/2F	0, 100, 300 Oral gavage	>300/300	**300**: Vomiting by 1 female. ≥ **100**: No abnormalities in body weight, food consumption, or clinical chemistry.

Study ID	Species/ Sex/Number/ Group	Dose (mg/kg) /Route	Approx. lethal dose / observed max non-lethal dose (mg/kg)	Major findings
TAK-385/00101	Monkey (cynomolgus) 2M/2F	0, 60, 200, 600, 2000 (escalating dose) Oral gavage	>2000/2000	**2000**: Vomiting in all animals starting at 4 hours post dose until 24 hours post dose. Body weights decreased slightly in all animals. Increased NEUT and decreased LYMPH in 1 male and all females (changes were reversible). **600**: Vomiting in 1 male and 1 female. Increased NEUT and decreased LYMPH in 1 male (changes were reversible). ≥ **600**. Increased AST, total bilirubin, urea nitrogen, and creatinine values and decreased potassium and chloride values. Changes were reversible by 14 days after the last dose (2000 mg/kg). ≥ **200**: Increased ALT and CK.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; DMFA = N, N-dimethylformamide; F = female; IV = intravenous; LYMPH = lymphocyte; M = male; MC = methylcellulose; NEUT = neutrophil; PEG400 = polyethylene glycol 400.

In rats, a single IV dose of 90 mg/kg relugolix was lethal for all animals. The maximum tolerated single oral dose of relugolix in mice, rats and monkeys is at least 2000 mg/kg.

Repeat dose toxicity

Table: Repeat-dose toxicity studies with relugolix

Study ID	Species/Sex/ Number/ Group	Dose (mg/kg) /Route	Duration	NOEL/ NOAEL (mg/kg /day)	Major findings
Mouse					
TAK-385/00073 Nonpivital	Mouse (B6C3F1) Main: 4M/4F TK: 15M/15F	0, 60, 200, 600, 2000 Oral gavage	4 Weeks	600	**2000**: Treatment-related necrosis of the renal tubules (2 males, 3 females) and increased incidence of tubular basophilia in both sexes.
TAK-385/00119 GLP	Mouse (B6C3F1) Main: 10M/10F TK: 23M/23F	0, 200, 600, 2000 Oral gavage	13 Weeks	600	**2000**: histopathology findings in kidneys, spleen, colon, cecum, and femur and sternum bone marrow and corresponding effects on kidney and spleen weights, as well as effects on RBC parameters.
Rat					
TAK-385/00011 Non-GLP	Rat (Sprague Dawley) Main: 4M/4F TK: 3M/3F	0, 30, 100, 300 Oral gavage	2 weeks	M: 30 F: 300	Foamy cell infiltration in the testis was noted in 2 males at 100 mg/kg/day and in all males at 300 mg/kg/day, findings associated with PLD.
TAK-385/00107 GLP	Rat (Sprague Dawley) Main: 10M/10F TK: 3M/3F	0, 10, 30, 300, 2000 Oral gavage	4 weeks	30	**2000**: Mortality, in various tissues cytoplasmic vacuolization, foamy cell infiltration, increased tingible body macrophages. Necrosis due to PLD. **300**: PLD-related histopathology: foamy cell infiltration in lung and testis, vacuolization of tubular epithelial cells in kidney, increased tingible body macrophages in mesenteric lymph nodes.
TAK-385/00120 GLP	Rat (Sprague Dawley) Main: 10M/10F TK: 4M/4F	0, 30, 100, 300, 1000 Oral gavage	13 weeks	M: 30 F: 300	**1000**: 1M dead. Necrosis due to PLD. ≥ **300 (F) and** ≥ **100 (M)**: PLD (cytoplasmic vacuolization and foamy cell infiltration in various tissues, increased tingible body macrophages in lymphoid tissues and bone marrow).

Study ID	Species/Sex/ Number/ Group	Dose (mg/kg) /Route	Duration	NOEL/ NOAEL (mg/kg /day)	Major findings
TAK-385/00145 GLP	Rat (Sprague Dawley) Main: 15M/15F TK: 5M/5F	0, 10, 30, 100, 300 Oral gavage	26 weeks	M: 30 F: 100	**300**: Cloudy urine. ≥ **100** M: PLD in testis.
Monkey					
TAK-385/00012 Non-GLP	Monkey (cynomolgus) 2M/2F	0, 20, 40, 100 Oral gavage	2 weeks	M: 20 F: 40	**100**: ↑ALT, leucyl aminopeptidases, and glutamate dehydrogenase in 2M and 1F, and in AST in 2M. Dark discoloration of liver in 2M and 1F. Bile plugs; pigmentation of hepatocytes and sinusoidal cells and single cell necrosis of hepatocytes in liver; foamy cell infiltration in lungs, spleen, mesenteric lymph nodes, jejunum (F), ileum (F), colon (M), rectum (M), sublingual gland (M), and trachea (M). ≥ **40** mg/kg/day: foamy cell infiltration in duodenum (M at 40 mg/kg and F at 100 mg/kg) and cecum M at 40 mg/kg and both sexes at 100 mg/kg, and vacuolization of parietal cells in M at 40 mg/kg and F at 100 mg/kg.
05-190/su Non-GLP	Monkey (cynomolgus) 2M/2F	0, 5, 10, 15 Oral gavage	2 weeks	15	≥ **5**: No relugolix-related mortalities occurred, and no relugolix-related changes in clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weight, gross pathology, or histopathology were noted.
TAK-385/00102 GLP	Monkey (cynomolgus) 3M/3F	0, 5, 10, 20, 100 Oral gavage	4 weeks	5	**100**: ↑ALT/AST. Histopathology findings in the liver. ≥ **10**: PLD (foamy cell infiltration in submandibular and mesenteric lymph nodes, increased tingible body macrophages in several tissues).
TAK-385/00144 GLP	Monkey (cynomolgus) 4M/4F Recovery: 4M/4F:0, 50	0, 1.5, 5, 15, 50 Oral gavage	39 weeks	1.5	**50**: Liver effects, partly reversible. Reversible changes in F sex organ weight. ≥ **5**: PLD (foam cell infiltration in submandibular lymph node, increased tingible body macrophages, vacuolization in parietal cells of stomach), partly reversible.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; F = female; M = male; MC = methylcellulose; NOAEL = no observed adverse effect level; PLD = Phospholipidosis; RBC = red blood cell; TK = toxicokinetic.

Although relugolix demonstrates a very low affinity for rodent GnRH receptors, mice and rats are appropriate models to evaluate potential chemical-based or off-target toxicologic effects of relugolix. Oral treatment of mice during 4 weeks with 2000 mg/kg/day resulted in necrosis of the renal tubules and increased incidence of tubular basophilia in both sexes. After 13 weeks, at 2000 mg/kg/day in mice, similar histopathology findings were found in kidneys, spleen, colon, cecum, and femur and sternum bone marrow and corresponding effects on kidney and spleen weights, as well as effects on red blood cell (RBC) parameters. In the spleen, minimal to mild increased extramedullary hematopoiesis was observed. The NOAEL based on these effects was 600 mg/kg/day which is more than 1000-fold higher than the intended human dose, based on AUC.

In rats after an oral treatment of 2 weeks, foamy cell infiltration in the testis was observed in 2 males at 100 mg/kg/day and in all males at 300 mg/kg, findings associated with phospholipidosis (PLD). After a 4-week treatment in rats, at 2000 mg/kg relugolix some animals died, the liver enzymes ALT and AST increased, the urine was cloudy, and in various tissues cytoplasmic vacuolization, foamy cell infiltration, increased tingible body macrophages and necrosis due to PLD were shown. At 300 mg/kg, PLD-related histopathology was shown already, like foamy cell infiltration in lung and testis, vacuolization of tubular epithelial cells in kidney, and increased tingible body macrophages in the

mesenteric lymph nodes. After 13 weeks of treatment, in rats at 1000 mg/kg one male died. Urine was cloudy and necrosis in several tissues due to PLD was seen. At ≥300 mg/kg (females) and ≥100 mg/kg (males) signs of PLD were observed (cytoplasmic vacuolization and foamy cell infiltration in various tissues, increased tingible body macrophages in lymphoid tissues and bone marrow). After 26 weeks of treatment at 300 mg/kg, cloudy urine was observed sporadically in a few male and female rats. At ≥ 100 mg/kg males showed signs of PLD in testis. The prolongation of the dosing period of relugolix from 4 or 13 weeks to 26 weeks did not intensify PLD in rats to at least the dosage level of 300 mg/kg. Further, necrosis was not observed in these organs or tissues at this dose-level.

Based on the PLD findings of the 26 week study in rats, the NOAEL is 30 mg/kg for males and 100 mg/kg for females, which is 15 times, respectively 57 times the intended human exposure. However, organ toxicity, adverse clinical signs, and mortality were not observed at the highest dose of 300 mg/kg. The NOAEL for organ toxicity was therefore considered 300 mg/kg in both sexes and around 283 times higher than the intended human exposure. In conclusion, rodent studies do not indicate off-target toxic effects at intended human exposures.

The cynomolgus monkey was selected as the non-rodent species because of the high sequence homology with the human GnRH receptor (97.5% compared to 92.1% in dog) and the similar affinity and potency at the GnRH receptor relative to dogs. When relugolix was administered by oral gavage to cynomolgus monkeys for 2 weeks, dark discoloration of the liver which corresponded histologically to bile plugs, pigmentation of the hepatocytes and sinusoidal cells, and single cell necrosis of the hepatocytes were noted at 100 mg/kg. Histopathology findings in the gastrointestinal tract (foamy cell infiltration in the duodenum and cecum, vacuolization of the parietal cells in the stomach) were noted in males at ≥ 40 mg/kg and females at 100 mg/kg. A supplementary 2-week study in cynomolgus monkeys was followed with three doses up to 15 mg/kg/day to investigate dosage levels not associated with PLD-related observations. However, in the first study no PLD-related observations were made at 20 mg/kg/day, so unfortunately, this second study was unnecessary and indeed, no relugolix-related effects were seen.

In a 4-week oral gavage study in monkeys, increases in ALT/AST and histopathology findings in the liver were noted at 100 mg/kg/day. Findings of PLD (foamy cell infiltration in the submandibular and mesenteric lymph nodes and increased tingible body macrophages in several tissues) were observed at ≥ 10 mg/kg/day. In a 39-week study, relugolix (1.5, 5, 15, or 50 mg/kg/day) was administered by oral gavage to cynomolgus monkeys followed by a 13-week recovery period. The major toxicologic finding was observed in the liver(primarily changes in clinical chemistry) at 50 mg/kg. At the end of the recovery period, there was an overall decrease in the incidence and/or severity of liver findings, indicating ongoing recovery, and full reversibility was observed for the changes of transaminase levels. Reversible changes in female sex organ weight were observed at 50 mg/kg; this finding was attributed to the mechanism of action (GnRH antagonism). PLD was observed in various organs, and the number of affected organs increased with dose, but no marked adverse toxicities were associated with PLD. Histopathology findings indicative of PLD (foam cell infiltration in the submandibular lymph node, increased tingible body macrophages, and vacuolization in parietal cells of the stomach) were observed in males and/or females at ≥ 5 mg/kg. The PLD-related findings showed evidence of recovery. The NOAEL based on PLD is 1.5 mg/kg/day in both sexes, which is 2.1-fold higher than the intended human exposure. The NOAEL for organ toxicity was 15 mg/kg in both sexes based on liver toxicity, which is 48-fold higher than the human intended dose. In conclusion, no serious toxic effects are shown in monkeys at clinical exposures of relugolix.

Genotoxicity

Table: Overview of genotoxicity studies of relugolix

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/ equivocal**
Gene mutations in bacteria TAK-385/00093 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA	39 - 5000 µg/plate +/- S9	Negative
Chromosome aberrations in mammalian cells TAK-385/00068 GLP	Chinese hamster lung (CHL/IU) cells	26 – 400 µg/ml +/- S9	Negative
Chromosomal aberrations in vivo TAK-385/00094 GLP	Rat, induction of micronuclei in bone marrow	0, 500, 1000, 2000 mg/kg/day	Negative

Relugolix was negative in a bacterial reverse mutation (Ames) assay, an *in vitro* chromosomal aberration assay, and in a rat *in vivo* micronucleus assay, indicating that relugolix does not present a genotoxic risk.

Carcinogenicity

Table: Carcinogenicity studies with relugolix

Study ID /GLP	**Dose/Route mg/kg/day**	**Exposure (AUC)**	**Species/No. of animals**	**Major findings**
TAK-385/10217 GLP	0, 10, 30, 100 Oral gavage 2 years	100 mg/kg: 28,117 ng.h/ml	B6C3F1 mice 55/sex/group	Relugolix did not induce any neoplastic changes
TAK-385/10218 GLP	0, 10, 30, 200, 600 Oral gavage 2 years	600 mg/kg: 83,766 ng.h/ml	Sprague Dawley rats 60/sex/group	Relugolix did not induce any neoplastic changes

There was no evidence of treatment-related effects on the incidence of any tumors or in the number of tumour bearing animals in mice administered relugolix up to 100 mg/kg and in rats administered relugolix up to 600 mg/kg for 2 years. Exposure margins are both more than 100 times the intended human exposure based on AUC.

Reproduction Toxicity

Table: Reproductive and developmental toxicity studies with relugolix

Study type/ Study ID / GLP	**Species; Number Female/ group**	**Route & dose (mg/kg/day)**	**Dosing period**	**Major findings**	**NOAEL (mg/kg)**
Female fertility TAK-385/00008 Non-GLP	Rat (Sprague Dawley) 10F	Oral gavage 0, 40, 200, 1000	14 days	**1000**: salivation (transient; likely related to potential irritation of test article) and transient suppression of body weight gain (day 3 to 7). No	1000

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose (mg/kg/day)	Dosing period	Major findings	NOAEL (mg/kg)
				adverse effects on the estrous cycle.	
Male and female fertility TAK-385/00113 GLP	Rat (Sprague Dawley) 20F/M	Oral gavage 0, 40, 200, 1000	M: 2 weeks prior to mating until necropsy at D53 F: 2 weeks prior to mating until GD 6.	**1000**: Food consumption (M/F) and body weight (M)↓	1000
Embryo-fetal development TAK-385/00007 Non-GLP	Rat (Sprague Dawley) 6F	Oral gavage 0, 40, 200, 1000	GD 6 to 17	**1000**: body weight ↓ on GD 6 to 8, food consumption ↓ on GD 6, 8, and 10.	F0: 200 F1: 1000
Embryo-fetal development TAK-385/00110 GLP	Rat (Sprague Dawley) 20F	Oral gavage 0, 40, 200, 1000	GD 6 to 17	**1000**: body weight and food consumption ↓	F0: 200 F1: 1000
Embryo-fetal development TAK-385/00009 Non-GLP	Rabbit (Kbl:JW) 6F	Oral gavage 0, 8, 40, 200, 1000	GD 6 to 18	**1000**: 6/6 F died on GD 12 to 15. Amount of fecal pellets ↓ (all F), emaciation (1 F), locomotor activity ↓ in 2 F on day before death. ≥ **40**: No implants could be confirmed for all F, judged not pregnant (pharmacological effect). **8**: implants could not be confirmed for 2 F, judged not pregnant. 2F lost entire litters (total resorptions) during early phase of dosing period, considered pharmacological effects. Post-implantation loss rate tended to be high (4.3-fold), and number of live fetuses tended to be low (0.56-fold). Frequency of skeletal variations ↑; specifically, the frequencies of full (2.3-fold) and short (1.2-fold) supernumerary ribs.	F0: 200 F1: < 8
Embryo-fetal development TAK-385/00115 GLP	Rabbit (Kbl:JW) 17-20 F	Oral gavage 0, 0.3, 1, 3, 9	GD 6 to 18	**9**: Total litter loss in 7 of 20 animals. High postimplantation loss rate, live foetuses ↓, low fetal viability rate.	F0: 9 F1: 3
Peri & postnatal TAK-385/300136 GLP	Rat (Sprague Dawley) 18-19 F	Oral gavage 0, 20, 100, 1000	GD 6 to 20	**1000**: F0: Body weight, body weight gain, and food consumption ↓	F0: 100 F1: 1000

Relugolix was administered to male and female rats at doses up to 1000 mg/kg/day in a fertility and early embryonic development study. Relugolix had no adverse effects on the estrous cycle in female rats up to 1000 mg/kg, and no adverse effects were noted on reproduction or early embryonic

development. Only minor effects on food consumption and body weight were noted at the highest dose. However, given the low binding affinity of relugolix for rat GnRH receptors, the results provide an assessment of off-target effects of relugolix only.

Based on literature (Nakata et al. 2014), the Applicant showed that in female human GnRH receptor knock-in mice, the suppressive effects of relugolix on the hypothalamic-pituitary-gonadal axis at doses of ≥ 100 mg/kg twice daily, induced a constant diestrous phase, and caused decreases in both ovarian and uterine weights. Withdrawal of relugolix after 28 days resulted in recovery of female reproductive function from a completely suppressed state in approximately 5 days, followed by continuous estrous phases for several days. Subsequently, the estrous cycles and the weight of hormone-dependent organs almost recovered to normal within 14 days after drug withdrawal. In monkeys (repeat-dose study TAK-385/00144), decreases in the frequency in menses were observed at 50 mg/kg for up to 39 weeks where all females at 50 mg/kg did not have menses after Day 13, probably related to the pharmacologic effects of relugolix. Additionally, menses in female monkeys demonstrated a recovery tendency within 13 weeks after last treatment. In male human GnRH receptor knock-in mice, relugolix decreased ventral prostate and seminal vesicle weights in a dose-dependent manner from 3 to 10 mg/kg BID. The suppressive effects on ventral prostate weight and serum testosterone concentrations were reversible as there was a return to predose levels within 14 days following cessation of treatment; however, testis weight (~30 % to 40 % decrease) did not fully recover after 28 days. This lack of recovery may be due to incomplete recovery in cell number of the spermatogenic epithelium, which occupies a large component of testicular weight, during this period (Nakata et al. 2014). In conclusion, relugolix has inhibitory effects on the male (at low doses) and female (at high doses) reproductive system, based on its pharmacodynamic action, which is only partly reversible.

In an embryofetal development study in rats, relugolix was administered to pregnant animals on GDs 6 to 17 at doses up to 1000 mg/kg/day. Treatment-related lower body weight, suppression of body weight gain, and decreased food consumption were observed at various intervals of the administration period at 1000 mg/kg, giving a NOAEL for maternal toxicity of 200 mg/kg. There were no relugolix-related changes in pregnancy status or fetal endpoints. The NOAEL for embryofetal developmental toxicity was 1000 mg/kg (exposure is more than 700 times as in the intended human dose) in this pharmaceutically unresponsive model.

In an embryofetal development dose range-finding study in rabbits, relugolix up to 1000 mg/kg was administered on GDs 6 to 18. Relugolix appeared very toxic for rabbits and on GD 12 to 15, all females at 1000 mg/kg died, and from 40 mg/kg on, there were no implants. Some females at 8 mg/kg lost entire litters (total resorptions) during the early phase of the dosing period. These changes are considered related to the pharmacological effects of relugolix. The frequency of skeletal variations at 8 mg/kg was high. In the pivotal study, rabbits were dosed much lower with 0.3 to 9 mg/kg. At 9 mg/kg, total litter loss was observed in 7 of 20 animals and high post-implantation loss rate, a significant decrease in live fetuses, and low fetal viability rate were noted. There were no abnormalities or variations in external, visceral, or skeletal observations. The NOAEL for embryofetal developmental toxicity was 3 mg/kg, which is about 77% lower than relugolix exposures at the proposed clinical dose based on AUC.

In a prenatal and postnatal development study in the pharmacologically unresponsive rat model, relugolix had no effect on maternal function in F0 dams, development in F1 pups/animals, reproductive function in F1 animals, and early embryonic development at exposures up to 1000 mg/kg.

Toxicokinetic data

No measurable amounts of relugolix were found in control samples from the 26-week study in rats, the 39-week study in monkeys, the carcinogenicity studies and the rabbit embryo-foetal development study. In the other repeated dose studies, analyses in control samples were not conducted. Although it would have been preferred to have results from control samples of all the studies, the fact that no relugolix was found in control samples in the most pivotal studies, indicates that no overt abnormalities were induced.

In general, relugolix concentrations in plasma increased more than dose-proportionally at lower doses (mouse 10-100 mg/kg/day, rat 10-100 mg/kg/day, monkey 1.5-15 mg/kg/day) and approximately dose-proportionally or less than dose proportionally (mouse) at higher doses. In pregnant rabbit, plasma concentrations increased approximately dose-proportionally at all doses.

No clear gender effect was observed in mice, rats and monkeys.

No significant accumulation was observed in monkeys and in mice, except in monkeys at the lowest dose of 1.5-5 mg/kg/day and in mice at the highest dose of 2000 mg/kg. In rats, accumulation was observed at all doses. In general, accumulation in rats was approximately 4-fold, except at the lowest dose (more than 10-fold). In pregnant rabbits, plasma concentrations accumulated approximately 2-fold between gestation days 6 and 18.

The exposure was sufficient in all species, except for the pregnant rabbit, where AUC was similar to the human AUC at most.

In pregnant rats, Cmax was 276 ng equiv/mL after a single dose of 30 mg/kg (see section 3.3). Although this represents total radioactivity, the majority can be considered to consist of parent compound (99% in plasma of male rats). This Cmax is higher than Cmax in non-pregnant rats (94 ng/mL after single dose of 30 mg/kg in females at most). No data are available regarding AUC in pregnant rats.

Local Tolerance

For clinical use, the intended route of administration for relugolix is the oral route. No abnormalities suggestive of local irritation were noted in the gastrointestinal tract after administration by oral gavage in repeat-dose toxicity studies except at extremely high dose levels in nonclinical oral toxicity species including mice, rats, rabbits, and monkeys.

Other toxicity studies

The phototoxic potential of relugolix was evaluated in an in vitro phototoxicity neutral red uptake (NRU) assay using BALB/3T3 clone A31 cells, and relugolix elicited a phototoxic response. However, according to the ICH Guidance S10 on Photosafety Evaluation of Pharmaceuticals, a positive result in this test should not be regarded as indicative of a likely clinical phototoxic risk, but rather a flag for follow-up assessment. Hereafter, the Applicant performed an in vivo phototoxicity study (GLP) in hairless mice, and skin reactions indicative of phototoxicity were not observed in any of the mice at doses up to 2000 mg/kg followed by exposure of UV-radiation. Therefore, relugolix is considered not phototoxic, which is agreed.

In a phospholipidosis biomarker study in rats, 0, 30 and 1000 mg/kg/day was orally dosed for 28 days. The study evaluated the sensitivity of di-22:6-BMP as a biomarker for PLD following relugolix exposure. The biomarker di-22:6-BMP was measured in urine, serum, lungs, and testes. At 1000 mg/kg, light

microscopy (mild foamy cell infiltrates in the lungs/lymph nodes), TEM (prominent multilamellar cytoplasmic bodies in lymphocytes), and di-22:6-BMP biomarker analysis (2- to 3-fold increase in urine, lungs, and testes) demonstrated relugolix-related changes indicative of PLD. At 30 mg/kg, no such effects were seen. Thus possibly, urinary di-22:6-BMP can serve as a potential biomarker for detection of PLD in rats exposed to relugolix. A clinical study with up to 120 mg relugolix QD for up to at least 24-weeks did not show meaningful alterations in di-22:6-BMP. This indicates that PLD is not likely to occur in patients at intended doses.

Estradiol

The general toxicity associated with E2 in nonclinical species is associated with its pharmacology and extended pharmacological effects in reproductive tissues and organs of both male and female animals. Repeated administration of E2 resulting in supra-pharmacological exposures in animals is associated with changes in female reproductive organs such as ovaries, uterus and vagina and liver. In general, E2 is not mutagenic but has been associated with increases of chromosome aberrations in *in vitro* and *ex vivo* studies. Evidence of chromosomal aberrations occurs at E2 concentrations that exceed physiological or pharmacological concentrations in humans. Estrogens, including E2, are associated with an increased incidence in tumor formation and promotion in endocrine-responsive tissues in female rodents (mice and rats) including formation of mammary tumors, uterine tumors, and cervical/vaginal tumors, pituitary adenomas, and hepatocellular adenomas. Administration of E2 in nonclinical species at supraphysiological exposures causes embryolethality with limited teratogenic potential. Additionally, estrogens (i.e., ethinyl estradiol) in combination with a progestin (NETA), have been shown to be embryolethal but does not affect surviving offspring in monkeys administered the hormone combination at various stages of pregnancy.

Norethindrone Acetate

Similar to E2, the general toxicity associated with NETA in nonclinical species is associated with its pharmacology and extended pharmacological effects in reproductive tissues and organs of both male and female animals. Repeated administration of NETA resulting in supra-pharmacological exposures in animals is associated with changes in female reproductive organs such as ovaries, uterus and vagina and liver. The genotoxicity potential of NETA is similar to E2. NETA is not mutagenic but has been associated with increases of chromosome aberrations in in vitro and ex vivo studies. Evidence of chromosomal aberrations occurs at NETA concentrations that exceed physiological or pharmacological concentrations in humans. NETA is associated with an increased incidence in tumor formation and promotion in endocrine-responsive tissues in female rodents (mice and rats) including formation of mammary tumors, pituitary adenomas, and hepatocellular adenomas. The effects of chronic NETA treatment, a progestin, potentially mitigate some estrogen-induced (EE) tumors in animals. NETA administration to nonclinical species at supraphysiological exposures (≥ 100 times the human dose of 2.5 mg) is associated with embryolethality but not teratogenicity. Additionally, NETA in combination with an estrogen (ethinyl estradiol), has been shown to be embryolethal but does not affect surviving offspring or cause non-genital teratogenicity in monkeys administered the hormone combination at various stages of pregnancy.

2.3.4. Ecotoxicity/environmental risk assessment

The available data of the ERA do not allow to conclude definitively on the potential risk of relugolix, 17β-estradiol and norethindrone to the environment. A number of studies have to be provided, and the applicant has committed to submit these study reports post-approval as post-authorisation measures (PAMs).

Table: Relugolix - Summary of main study results

Substance (INN/Invented Name): relugolix					
CAS-number (if available): 737789-87-6					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} -0.57, 0.85 and 2.7 at pH 5, 7 and 9			Potential PBT: N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log D_{ow}	-0.57 at pH 5.1-5.2 0.85 at pH 7.1 2.7 at pH 9.1			not B
Persistence	ready biodegradability	not ready			
	DegT50 parent	$DT_{50, water}$ = 3.2/11 d (l/l) $DT_{50, sediment}$ = 72/176 d (l/l) $DT_{50, system}$ = 70/148 d (l/l)			l=lake. DT_{50} values corrected to 12°C. Conclusion: P
	DegT50 metabolites	TP1: $DT_{50, system}$ = 17 d (l) TP5: $DT_{50, system}$ = 129d (l)			Conclusion: not P Conclusion: P
Toxicity	EC10 algae NOEC crustacea NOEC fish	2.1 mg/L ⩾2.5 mg/L test pending			potentially T (vertebrate test pending)
	CMR	not investigated			potentially T
PBT-statement:	relugolix is considered to be not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water\ (refined)}$	2.66	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	potential reproductive effects on vertebrates and/or lower animals. Action limit does not apply.				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ 353, 233 L/kg $K_{oc\ soil}$ 8781, 28346, 289871 L/kg			
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 1.5/5.3 d (l/l) $DT_{50, sediment}$ = 34/83 d (l/l) $DT_{50, system}$ = 33/70 d (l/l) % shifting to sediment = 9% and 26%			l=lake; DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*R. subcapitata*	OECD 201	EC10	2.1	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	⩾2.5	mg/L	reproduction, growth, mortality
Fish, Early Life Stage Toxicity Test/	performance of an FFLC test is planned		N.A.		
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC10	⩾1000 >1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	1253	mg/kg dw	development; normalised to 10% o.c.

N.A. = not available. Questions were asked on fish toxicity.

Conclusions on studies for Relugolix

Relugolix may cause reproductive effects in vertebrates and/or lower animals. The action limit of 0.01 µg/L does not apply, a Phase II assessment is triggered based on the mode of action.

Relugolix is not PBT, nor vPvB.

The ERA cannot be finalized for the surface water compartment.

A risk assessment for the terrestrial compartment is not triggered.

In view of the mode of action of relugolix, performance of a fish, full life cycle study is proposed by the applicant. The dossier is incomplete as it currently contains a test proposal rather than the outcome of the test and a full risk assessment.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of relugolix to the environment.

The applicant commits to perform the following studies as post-authorisation commitments:

- A fish, full life cycle test conducted as per the adapted test protocol.

Table: 17*β*-estradiol - Summary of main study results

Substance (INN/Invented Name): 17*β*-estradiol					
CAS-number (if available): N.A.					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.73			Potential PBT: No
PBT-statement :	17*β*-estradiol is not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, refined F_{pen}	**	µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)	Hormone				Phase II assessment is required
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Soil: 871, 365, 638, 3063 L/kg Sludge: 3993 L/kg			The worst-case Koc should be used in the risk assessment
Ready Biodegradability Test	OECD 301	not required			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	58.3, 42.5, 32.3, 52.3 days			geometric mean: 45.2 days
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/	OECD 201	NOEC	N.A.		not required
Daphnia sp. Reproduction Test	OECD 211	NOEC	N.A.	µg/L	
Fish, Early Life Stage Toxicity Test/	OECD 210	NOEC	N.A.	µg/L	
Fish, full life cycle study		NOEC	2.86	ng/L	F0 fertility
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	N.A.		
Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	N.A.	L/kg	
Sediment dwelling organism		NOEC	N.A.	mg/kg	

N.A. = not available.

** PEC_{sw} is not agreed upon, a question on F_{pen} refinement is asked.

Conclusions on studies for 17β-estradiol

17*β*-Estradiol may cause reproductive effects in vertebrates and/or lower animals. The action limit of 0.01 µg/L does not apply, a Phase II assessment is triggered based on the mode of action.

17β-Estradiol is not PBT nor vPvB.

The applicant is requested to include this indication in the ERA for estradiol and to update the ERA accordingly.

The ERA is incomplete, and the applicant commits to perform the following studies as post-authorisation commitments:

• A bioconcentration study (OECD 305):

• Adsorption-desorption using a batch equilibrium method (OECD 106) for at least 1 type of sewage sludge;

• *Daphnia* sp. reproduction test (OECD 211, use version 2012);

• Activated sludge, respiration inhibition test (OECD 209, use version 2010).

The CHMP agrees that the algal toxicity test can be waived (OECD 201).

Table: norethindrone acetate - Summary of main study results

Substance (INN/Invented Name): norethindrone acetate					
CAS-number (if available): N.A.					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.66 for norethindrone acetate 2.52 for norethindrone			Potential PBT: No because lower than 3 for the active metabolite norethindrone
PBT-statement:	Norethindrone is considered not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, refined F_{pen}	**	µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)	hormone				Phase II assessment is required
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Soil: N.A. Sludge: N.A.			
Ready Biodegradability Test	OECD 301	N.A.			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	N.A.			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	N.A.	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	N.A.	µg/L	
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	N.A.	µg/L	
Fish, full life cycle study					
Activated Sludge, Respiration	OECD 209	NOEC	N.A.	µg/L	

Inhibition Test					
Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	N.A.	L/kg	
Sediment dwelling organism		NOEC	N.A.	mg/ kg	

N.A. = not available.
** PEC_{sw} is not agreed upon, a question on F_{pen} refinement is asked.

Conclusions on studies for norethindrone acetate

Norethindrone acetate (NETA) may cause reproductive effects in vertebrates and/or lower animals. The action limit of 0.01 µg/L does not apply, a Phase II assessment is triggered based on the mode of action.

Norethindrone (NET) is the molecule relevant for the ERA.

NET is not PBT nor vPvB.

The ERA is incomplete, and the applicant commits to submit the following studies as post-authorisation measures:

• Adsorption-desorption using a batch equilibrium method (OECD 106) using 3 soil types and 2 types of sewage sludge;

• Ready biodegradability test (OECD 301);

• Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308);

• *Daphnia* sp. reproduction test (OECD 211, use version 2012);

• A fish, full life cycle study: either a Medaka extended one generation reproduction test (OECD 240), or a Zebrafish extended one generation reproduction test (ZEOGRT);

• Activated sludge, respiration inhibition test (OECD 209, use version 2010).

It is agreed that the algal toxicity test can be waived (OECD 201).

2.3.5. Discussion on non-clinical aspects

Pharmacology

In vitro, Relugolix binds to the GnRH receptor with IC_{50} value of 0.12 nmol/L and in the presence of serum with IC_{50} value of 0.33 nmol/L (in the which is approximately 3-fold lower compared the binding affinity in the absence of FBS with IC50 value of 0.33 nmol/L. The antagonistic effects of relugolix and cetrorelix on CHO cells expressing human GnRH receptors was examined by measuring the GnRH-induced 3H-arachidonic acid release in a dose-dependent manner. The IC_{50} value was 0.32 nmol/L (1.6 nmol/L in the presence of serum) and IC_{90} value was 2.6 nmol/L (18 nmol/L in the presence of serum) for relugolix.

In female hGnRH KI mice relugolix act as an orally active GnRH antagonist and suppresses the hypothalamic-pituitary-gonadal axis, suggesting that relugolix could therefore potentially be efficacious for treatment of reproductive disorders such as endometriosis and uterine leiomyoma. In male hGnRH KI mice, relugolix suppressed the weight of ventral prostates and seminal vesicles, and pituitary human GnRH receptor mRNA in male human GnRH receptor KI mice, suggesting that relugolix could have the potential to be efficacious for treatment of androgen dependent disorders such as prostate cancer by suppressing a hypothalamus-pituitary-gonadal axis. It is remarkable that an efficacious dose

in male hGnRH knock-in mice is approximately ten times lower than an efficacious dose in female hGnRH knock-in mice. Unexpectedly, one the primary effects of antagonism of the GnRH receptor, decreases in LH and FSH were not addressed in these studies.

In addition, orally administered relugolix at doses of 1 and 3 mg/kg suppressed plasma LH levels in castrated cynomolgus monkeys with maximum suppression that continued for 24 and 48 hours after administration, respectively. In contrast, relugolix at doses of 0.1 and 0.3 mg/kg did not show substantial suppression. Thus, this *in vivo* experiment indicates that relugolix is orally active and effective at dose of over 1 mg/kg in castrated cynomolgus monkeys.

No secondary pharmacology or safety pharmacology effects are noted *in vitro* or *in vivo* in animals that would indicate risks on clinical use of relugolix.

Pharmacokinetics

The non-clinical pharmacokinetics have been studied adequately.

Toxicology

Relugolix is not toxic in rodents like mice and rats up to very high doses, and the toxic effects shown at those very high doses are also off-target toxic effects, because relugolix has a very low affinity for rodent GnRH receptors. Relugolix in the cynomolgus monkey has a high affinity for the human GnRH receptor, and also shows effects at lesser doses than in rodents, like on the liver, still with a large margin of exposure related to humans. The only effect seen in monkeys at relatively low doses is phospholipidosis (PLD) in various organs with only a safety margin of about 2. But PLD is not considered a serious toxic effect, and also by use of a PLD-biomarker in humans with three times the normally intended doses of relugolix, no signs of PLD were shown.

Relugolix has been found to have no genotoxic or carcinogenic potential, however, the relevance of the rat and mouse carcinogenicity studies for human carcinogenic risk assessment is limited given the very low binding affinity of relugolix for rat and mouse GnRH receptors. The studies are only directed at off target effects.

In the rabbit, relugolix caused embryo fetal death, but did not cause malformations. In rats, relugolix had no effect on fertility and early embryonic development and was not teratogenic. The toxicology of E2 and NETA are well characterized in the literature and is well known. The Applicant provided sufficient information on the toxicity of E2 and NETA, based on a review of published nonclinical literature. Synergistic or additive toxicity is not expected upon administration of relugolix in combination with E2 and NETA at the proposed clinical doses. Combination toxicity studies of relugolix with E2 and/or NETA would provide no additional human-relevant safety information and available nonclinical pharmacology, pharmacokinetic, and toxicology data support the combination use for the treatment of heavy menstrual bleeding associated with uterine fibroids. The nonclinical toxicity profiles associated with relugolix, E2, or NETA generally do not overlap and reflect the expected pharmacologic effect of each intended target.

2.3.6. Conclusion on the non-clinical aspects

There are no non-clinical objections that would prevent a marketing authorization.

As requested by the CHMP in order to complete the ERA, the applicant has committed to submit a number of studies as post-authorisation measures.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The table below summarises the clinical studies submitted to support the requested indication (treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age.)
Overview of Clinical Studies Providing Efficacy Data for Relugolix Combination Therapy (uterine fibroids indication):

Table: Overview of Clinical Studies Providing Efficacy Data for Relugolix Combination Therapy (uterine fibroids indication)

Protocol No.	# Sites/ Locations	Study Design	Population	Objectives	Drug, Dose, Duration	# Patients (Completed)	Primary Endpoint
PIVOTAL STUDIES **Phase 3: Relugolix Combination Therapy, Uterine Fibroids**							
MVT-601-3001 LIBERTY 1	80 sites/US 32 sites/Rest of World (EU, UK, South America, and Africa)	Randomized, double-blind, placebo-controlled efficacy and safety study.	Premenopausal women between 18 and 50 years of age with a confirmed diagnosis of uterine fibroids and heavy menstrual bleeding associated with uterine fibroids.	Efficacy and Safety	Group A Relugolix 40 mg QD for 24 weeks plus E2/NETA (1 mg/0.5 mg) QD for 24 weeks Group B Relugolix 40 mg QD for 12 weeks plus placebo, followed by relugolix 40 mg QD plus E2/NETA (1 mg/0.5 mg) QD for 12 weeks Group C Placebo QD for 24 weeks	Group A 128 (100) Group B 132 (103) Group C 128 (105)	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.
MVT-601-3002 LIBERTY 2	92 sites/US 38 sites/Rest of World (South America, EU, UK, South America, and Africa)	Randomized, double-blind, placebo-controlled efficacy and safety study.	Premenopausal women between 18 and 50 years of age with a confirmed diagnosis of uterine fibroids and heavy menstrual bleeding associated with uterine fibroids.	Efficacy and Safety	Group A Relugolix 40 mg QD for 24 weeks plus E2/NETA (1 mg/0.5 mg) QD for 24 weeks Group B Relugolix 40 mg QD for 12 weeks then relugolix 40 mg plus E2/NETA (1 mg/0.5 mg) QD for 12 weeks Group C Placebo QD for 24 weeks	Group A 126 (102) Group B 127 (98) Group C 129 (102)	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.
KEY SUPPORTING STUDIES **Phase 3 Patient-Reported Outcome Substudy to MVT-601-3001 and MVT-601-3002**							

Protocol No.	# Sites/ Locations	Study Design	Population	Objectives	Drug, Dose, Duration	# Patients (Completed)	Primary Endpoint
MVT-601-037 (Substudy)	15 sites/ US	Interviews of English-speaking patients as they complete their end of study visit of either MVT-601-3001 or MVT-601-3002.	Patients who completed MVT-601-3001 or MVT-601-3002 and had at least a 1-point improvement from baseline in PGA.	To obtain patient input (via qualitative interviews) on what constitutes a meaningful or relevant improve-ment on several patient-reported outcomes.	NA	31 (30)	NA
Phase 3 Studies: Relugolix Monotherapy, Uterine Fibroids							
TAK-385/CCT-002	34 sites/ Japan	Multicenter, randomized, double-blind, parallel-group, non-inferiority study.	Premenopausal Japanese women aged 20 years or older with a confirmed diagnosis of uterine fibroids.	Efficacy and Safety	Relugolix Placebo QD during run-in then relugolix 40 mg QD for 24 weeks and leuprorelin placebo injection Q4W Leuprorelin Placebo QD during run-in then leuprorelin 1.88 mg or 3.75 mg and relugolix placebo Q4W for 24 weeks	Relugolix 139 (122) Leuprorelin 142 (131)	Proportion of patients with total PBAC score of < 10 from Week 6 to Week 12.
TAK-385-3008	15 sites/ Japan	Multicenter, randomized, double-blind, parallel-group study.	Premenopausal women older than 20 years of age with a confirmed diagnosis of uterine fibroids.	Efficacy and Safety	Relugolix Placebo QD during run-in then relugolix 40 mg QD for 12 weeks Placebo Placebo QD during run-in then placebo QD for 12 weeks	Total: 65 (63) Relugolix 33 (32) Placebo 32 (31)	Proportion of patients with a maximum NRS (an 11-point scale for patient self-reporting of pain symptoms) score of 1 or less during the 28 days before the final dose of study drug.
Studies Relevant to Dose Selection **Phase 2 Dose-Finding Study: Relugolix Monotherapy, Uterine Fibroids**							
TAK-385/ CCT-001	36 sites/ Japan	Multicenter, randomized, double-blind, parallel-group study.	Premenopausal women aged 20 years or older with a confirmed diagnosis of uterine fibroids.	Efficacy and Safety	Relugolix 10, 20, 40 mg or placebo QD for 12 weeks	Total: 216 (211) 10 mg 48 (47) 20 mg 56 (54) 40 mg 55 (55) Placebo 57 (55)	Decrease in MBL volume, as measured by the proportion of patients with a total PBAC score of < 10 from Week 6 to Week 12.
Clinical Pharmacology Studies: Relugolix Monotherapy, Healthy Participants							

Protocol No.	# Sites/ Locations	Study Design	Population	Objectives	Drug, Dose, Duration	# Patients (Completed)	Primary Endpoint
TAK-385_101	1 site/ US	Double-blind, randomized, placebo-controlled, sequential -panel, single and multiple rising-dose study.	Healthy premenopausal women 18 to 49 years of age (Cohorts 1 to 7) or 18 to 45 years of age (Cohorts 8 to 10).	Safety and tolerability, PK, PD and food effect	Cohort 1 to 6 (Single-Dose Phase) Single 1.0, 5.0, 10, 20, 40, or 80 mg doses Cohort 7 (Food Effect) Single 40 mg dose fed and fasted. Cohort 8 to 10 (Multiple-Dose Phase) 10, 20, 40 mg doses QD for 14 days	SRD 72 (71) Food Effects 12 (11) MRD 36 (36)	Safety, tolerability and pharmacokinetics in healthy premenopausal women following single and multiple ascending doses of relugolix.
Clinical Pharmacology Studies: Relugolix Combination Therapy, Healthy Premenopausal Women							
MVT-601-1001	4 sites/ US	Open-label, randomized, parallel group study.	Healthy premenopausal women 18 to 48 years of age.	PK, PD, safety and tolerability	Treatment A Relugolix 40 mg alone QD for 6 weeks Treatment B Co-administration of relugolix 40 mg and E2/NETA (1 mg/0.5 mg) QD for 6 weeks	Treatment A 25 (25) Treatment B 23 (21)	Steady-state PK parameters for relugolix, E2, E1, EE, NETA at Week 3 and Week 6.
MVT-601-046	1 site/ Germany	Open-label, single cohort study.	Healthy premenopausal women between 18 and 35 years of age with no significant ovarian abnormalities.	To assess the effect of relugolix combination therapy on ovarian activity	Relugolix 40 mg plus E2/NETA (1 mg/0.5 mg) QD for 84 days	71 (67)	The proportion (%) of women who demonstrate inhibition of ovulation as indicated by a Hoogland-Skouby score of < 5 during the entire 84-day treatment period: Size of dominant follicle (two-dimensional measurement). Serum E2 and progesterone concentrations.

Abbreviations: λ_z = lambda z; ACTH = adrenocorticotropic hormone; AE = adverse event; AUC_{0-24} = area under the concentration-time curve from time 0 to 24 hours; AUC_{0-last} = area under the concentration-time curve from time 0 to the last quantifiable concentration; AUC_{0-tau} = area under the concentration-time curve from time 0 to tau; AUC_{∞} = area under the concentration-time curve from time 0 extrapolated to infinite time; C_{avg} = average observed concentration; CL/F = apparent systemic clearance after extravascular administration; CL_R = renal clearance; C_{max} = maximum observed concentration; C_{min} = minimum observed concentration; C_{trough} = pre-repeat dose (trough) concentration at the end of the dosing interval; E1 = estrone; E2 = estradiol; ECG = electrocardiogram; EE = ethinyl estradiol; EU = European Union; f_e = fraction of drug excreted in urine; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; MBL = menstrual blood loss; MRD = multiple-rising doses; NA = not applicable; NETA = norethindrone acetate; No. = number; NRS = Numerical Rating Scale; PBAC = Pictorial Blood Loss Assessment Chart; PD = pharmacodynamic; PGA = Patient Global Assessment; PK = pharmacokinetic; PRL = prolactin; Q4W = every four weeks; QD = once daily; SRD = single-rising dose; $t_{½}$ = elimination half-life; t_{max} = time to maximum observed concentration (C_{max}); UK = United Kingdom; US = United States; V_z/F = apparent volume of distribution after extravascular administration associated with the terminal phase.

Studies finalized during the application procedure

Two studies were finalized during the evaluation procedure, the open-label efficacy and safety extension study (MVT-601-3003) and the observational study of BMD (MVT-601-034) evaluating BMD in women with uterine fibroids or endometriosis.

It concerns the following studies:

Table: Finalised studies of which the full CSR was provided during the response to questions

Study Status (CSR Date) No. Sites/Locations	**Short Title**	**Study Type**	**Monotherapy or Combination Therapy**	**Study Design and Objectives**	**Population**
MVT-601-3003 (International) Completed 149 sites/US and Rest of World: EU, South America, and Africa	LIBERTY EXTENSION: Open-Label Extension to Pivotal Phase 3 Studies MVT-601-3001 and MVT-601-3002 in Women with Uterine Fibroids	Open-label extension	Combination	Open-label, single-arm, long-term efficacy and safety extension study enrolling eligible patients who have completed participation in study MVT-601-3001 or MVT-601-3002	Premenopausal women 18 to 50 years of age with a confirmed diagnosis of uterine fibroids and heavy menstrual bleeding associated with uterine fibroids. Had completed MVT-601-3001 or MVT-601-3002.
MVT-601-034 Completed	A prospective observational study of bone mineral density in women with uterine fibroids or endometriosis	Observational (natural history)	NA	A prospective observational study to characterize longitudinal BMD of premenopausal women with uterine fibroids or endometriosis over a 52-week observational period	Women 18 to 50 years of age diagnosed with uterine fibroids or endometriosis

An additional ongoing study, MVT-601-035, a 52-week randomized withdrawal study including patients who completed MVT-601-3003, was finalised during the procedure, and is listed below (Table X). It was agreed that the applicant could submit a summary of the results obtained in this study for support of their claim of treatment beyond 52 weeks. The full data of this study will be submitted within an upcoming Type 2 variation post-authorisation.

Table: Outline of study MVT-601-035

Study Status (CSR Date) No. Sites/Locations	Short Title	Study Type	Monotherapy or Combination Therapy	Study Design and Objectives	Population
MVT-601-035 (International) Ongoing	Randomized Withdrawal Study in Women with Uterine Fibroids	Randomized withdrawal study	Combination	Double-blind, placebo-controlled, randomized withdrawal study to evaluate long-term efficacy and safety of oral relugolix 40 mg QD co-administered with E2/NETA (1 mg/0.5 mg) or placebo for up to 52 weeks in patients with uterine fibroids. This study enrolled eligible patients who had also completed MVT-601-3003 and met the definition of a treatment response to relugolix with E2/NETA.	Premenopausal women 18 to 51 years of age with uterine fibroids who complete the open-label extension study MVT-601-3003 and who met the definition of responder

2.4.2. Pharmacokinetics

The clinical pharmacology program was designed to support the women's health programs in uterine fibroids and endometriosis with relugolix combination therapy with relugolix as monotherapy (120-mg dose). To support the MAA for uterine fibroids with relugolix combination therapy, this section provides a characterization of the pharmacokinetic and pharmacodynamic profile of relugolix, the new molecular entity, and, where appropriate, includes relevant information regarding E2 and NETA (or norethindrone [NET], the active metabolite of NETA), either from individual studies (MVT-601-039, MVT-601-046, MVT-601-1001), the literature or from the prescribing information for Activelle (EU brand) or Activella (US brand) when information was not available in the literature.

The clinical pharmacology program for relugolix consisted of 23 dedicated studies. Briefly, the clinical pharmacology program included three single- and multiple-ascending dose studies to characterize the safety and tolerability, pharmacokinetics and pharmacodynamics of relugolix, two of which were conducted in healthy adult premenopausal women (TAK-385_101 and TAK-385/CPH-001) and 1 study conducted in healthy adult men (C27001) eight drug interaction studies (TAK-385_102, TAK-385/CPH-010, C27005, MVT-601-1004, MVT-601-039, MVT-601-043, MVT-601-044, MVT-601-045); a human ADME and oral bioavailability study (TAK-385-1009); special population studies including a study to assess the effect of mild and moderate hepatic impairment (MVT-601-1002) and 2 separate studies to assess the effect of moderate or severe renal impairment (MVT-601-040, MVT-601-1003); a thorough QT/QTc study (TAK-385_106); a 6-week pharmacokinetics and pharmacodynamics study with the combination of relugolix, E2, and NETA (MVT-601-1001); and a study to assess the effect of the combination of relugolix, E2, and NETA on ovarian function (MVT-601-046).

A population pharmacokinetic (PopPK) model, using relugolix concentration data from clinical pharmacology (phase 1), phase 2, and phase 3 studies, was developed to further characterize the

effect of demographic parameters (age, race, body weight, and BMI) and renal function on the pharmacokinetics of relugolix. Additional demographic parameters, including race (from similarly designed studies), sex, and menopausal status, were evaluated by cross-study comparisons.

Exposure-response models were developed for relugolix:

- to support the proposed clinical dose of 40 mg of relugolix and to define the therapeutic window of relugolix for interpretation of clinically meaningful decreases/increases in relugolix exposure from dedicated clinical pharmacology studies, and
- to characterize the effects of relugolix combination therapy on bone mineral density (BMD) loss and predict the potential for relugolix combination therapy to maintain BMD at physiologic levels with long-term treatment (see further PK/PD analyses).

Table: Clinical Pharmacology Program for Relugolix

Protocol	Short Title
TAK-385_101	Single- and Multiple-Rising Dose Study in Healthy Premenopausal Women
TAK-385/CPH-001	Single- and Multiple-Rising Dose Study in Healthy Japanese Premenopausal Women
C27001	Safety and Tolerability, Pharmacokinetic and Pharmacodynamic Study in Men (Prostate Cancer-Enabling Study)
TAK-385-1009	Human ADME and Absolute Bioavailability Study
MVT-601-1002	Mild and Moderate Hepatic Impairment Study
MVT-601-040	Moderate Renal Impairment Study
MVT-601-1003	Severe Renal Impairment Study
TAK-385/CPH-010	Erythromycin (Strong P-gp and Moderate CYP3A4 Inhibitor) Drug Interaction Study
C27005	Fluconazole and Atorvastatin (Moderate and Weak CYP3A4 Inhibitor) Drug Interaction Study
MVT-601-043	Voriconazole (Strong CYP3A4 Inhibitor) Drug Interaction Study
MVT-601-1004	Rifampin (Strong P-gp and CYP3A4 Inducer) Drug Interaction Study
MVT-601-039	E2/NETA Drug Interaction Study
MVT-601-044	Midazolam (CYP3A4 Substrate) Drug Interaction Study
MVT-601-045	Rosuvastatin (BCRP Substrate) Drug Interaction Study
TAK-385_102	Drug Interaction Study with Indiana Cocktail
Pharmacodynamic Studies	
MVT-601-1001	6-Week PK/PD Study with Relugolix Alone and in Combination with E2/NETA
TAK-385_106	Thorough QT/QTc Study
MVT-601-046	Ovulation Inhibition Study
MYV-PKER-RELUGOLIX-737	Population Pharmacokinetic (PopPK) Analysis (Report 01) Exposure-Response (Efficacy) Analysis (Report 01) Exposure-Bone Mineral Density (BMD) Loss Analysis (Report 02)

The pharmacokinetic parameters of relugolix, estradiol (E2), total estrone (E1), and norethindrone (NET) following oral administration of the FDC tablet of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg to healthy postmenopausal women under fasted conditions are summarized below.

Table: Single dose PK parameters of relugolix, estradiol, total estrone, and norethisterone from 88 healthy postmenopausal women (study MVT-601-042)

	Relugolix	Estradiol (E2)	Total Estrone (E1)	Unconjugated Estrone (E1)	Norethindrone (NET)
$AUC_{0-\infty}$ (ng*hr/mL or pg*hr/mL)	198.1 (111.6)	818.7 (334.4)	181.7 (67.40)	4126 (1650)	17.5 (8.46)
C_{max} (ng/mL or pg/mL)	25.99 (18.21)	27.95 (19.15)	20.82 (6.129)	188.4 (59.09)	3.57 (1.43)
t_{max} (hr)	2.00 (0.25, 5.00)	7.00 (0.25, 24.00)	1.00 (0.27, 4.00)	6.00 (2.00, 12.00)	1.01 (0.50, 4.00)
Half-life $t_{1/2}$ (hr)	61.5 (13.2)	16.6 (7.67)	25.2 (11.1)	15.9 (6.52	10.9 (3.05)

Note: arithmetic means and standard deviations are shown except for t_{max}, where median and range (minimum, maximum) are shown. $AUC_{0-\infty}$ is presented in ng*hr/mL for relugolix, total E1, NET and in pg*hr/mL for E2 and unconjugated E1. C_{max} is presented in ng/mL for relugolix, total E1, NET and in pg/mL for E2 and unconjugated E1.
Abbreviations: $AUC_{0-\infty}$ = area under concentration-time curve from time zero extrapolated to infinity; C_{max} = maximum observed concentration; E1 = estrone; E2 = estradiol; NET = norethindrone; t_{max} =time to the maximum observed concentration

The pharmacokinetic parameters of relugolix, estradiol (E2), total estrone (E1), and norethindrone (NET) following oral administration of the FDC tablet at steady state to the target population of adult premenopausal women after 6 weeks of treatment are summarized in Table.

Table: PK parameters of relugolix, estradiol, estrone, and norethindrone in 48 premenopausal women at steady state after 6 weeks of relugolix combination therapy (study MVT-601-1001)

	Relugolix	Estradiol (E2)	Unconjugated Estrone (E1)	Norethindrone (NET)
$AUC_{0-\tau}$ (ng*hr/mL or pg*hr/mL)	157 (94.7)	784 (262)	4450 (1980)	25.5 (11.4)
C_{max} (ng/mL or pg/mL)	26 (21.4)	46.8 (17.3)	303 (137)	5.21 (1.53)
T_{max} (hr)	3 (0.5, 6)	3 (0.50, 12.00)	4 (1, 8.08)	1 (1, 2)
Effective $t_{1/2}$ (hr)	~25	17.1 (4.03)	13.9 (4.14)	8.28 (1.87)

Abbreviations: $AUC_{0-\tau}$ = area under the concentration-time curve during a dosing interval (τ); C_{max} = maximum observed concentration; E1 = estrone; E2 = oestradiol; NET = norethindrone; t_{max} = time to the maximum observed concentration.
Note: Arithmetic means and standard deviations are shown except for t_{max}, where median and range (minimum, maximum) are shown. $AUC_{0-\tau}$ is presented in ng*hr/mL for relugolix and NET and in pg*hr/mL for unconjugated E2 and unconjugated E1. C_{max} is presented in ng/mL for relugolix and NET and in pg/mL for unconjugated E2 and unconjugated E1. Effective half-life for relugolix is estimated from accumulation ratios based on AUC values after multiple-dose administration of relugolix at 40 mg.

Analytical methods

All bioanalytical methods for relugolix, E1 and E2, and norethindrone were validated as phase-appropriate in accordance with the guideline documents. Validation was successful with respect to linearity, sensitivity, accuracy, precision, dilution, selectivity, hemolyzed plasma, lipemic plasma, recovery, matrix effect, batch size, and carryover. E2 and E1 were determined simultaneously in one assay.

For clinical studies MVT-601-042 (pivotal BE study), and MVT-601-3001 and -3002 (pivotal Phase 3 studies), all clinical study samples were analyzed within the demonstrated stability period following storage at -70°C. Incurred Sample Reanalysis (ISR) results met the acceptance criteria, with more than 67% of samples having repeat and original values within 20.0% of each other. No repeats for pharmacokinetic reasons were done. Twenty percent of chromatograms were included in the bioanalytical study reports. Within-study QC samples met the acceptance criteria (≤ 15%).

Absorption

Relugolix

After administration of the FDC tablet under fasted conditions, mean C_{max} for relugolix of 25.99 ng/mL is reached at a median t_{max} of 2.0 hours (range 0.25 to 5 hours) postdose. After reaching C_{max}, relugolix concentrations decline in a multi-phasic manner, initially with a rapid decrease in concentrations (between approximately 6 and 16 hours postdose), followed by a slower decline (between approximately 12 and 24 hours postdose) and subsequently by a slow terminal elimination phase characterized by a relatively flat slope (beginning at approximately 48 to 72 hours postdose) with a terminal elimination half-life of approximately 61.5 hours (study MVT-601-042). However, the majority of the total exposure to relugolix occurs within the first 24 hours after administration with little contribution to the overall AUC from the terminal portion of the elimination phase.

Relugolix reaches an initial peak by 0.25 hours postdose followed by one or more subsequent absorption peaks up to 12 hours postdose. Because no secondary peaks were observed following intravenous administration of relugolix, it seems unlikely that enterohepatic recirculation of relugolix plays a major role. The absorption of relugolix after oral administration seems to be primarily mediated by P-gp, because the bioavailability of relugolix increased 6-fold when co-administered with erythromycin, which is a strong inhibitor of P-gp and CYP3A4, whereas voriconazole an inhibitor of CYP3A4 increased the exposure only 1.5-fold.

The estimated fraction absorbed is ~40% for a 80 mg dose based on the mass balance data, given that the preclinical data indicate that metabolite C can be formed in the intestinal flora (see below under Metabolism). As the absolute bioavailability at this dose was 11.6% (TAK-385-1009), there is a considerable first-pass effect.

After oral administration, local relugolix concentrations may be high enough to saturate P-gp efflux, resulting in the greater than proportional increases that become more pronounced at relugolix doses greater than 20 mg (see below under Dose proportionality). However, in vitro data do not suggest that relugolix is an inhibitor of P-gp at clinically relevant concentrations. As the absorption of relugolix is characterised by multiple peaks or a prolonged absorption phase, it might be argued that the observed prolonged absorption phase of relugolix is suggestive of iterative cycles of efflux and re-absorption along the human gastrointestinal tract. In case of saturation of P-gp, these iterative cycles would be less prominent and hence at higher doses the absorption curve would be more steep, while at lower relugolix doses a prolonged absorption phase would be expected. Comparing (dose normalised) relugolix plasma exposures at 20 mg with 40 and 120 mg, the absorption at the higher doses showed the more prolonged absorption phase. So this is not entirely consistent with the hypothesis of P-gp saturation and others factors are likely to contribute.

Formulation development for relugolix

Four single-agent oral tablet formulations of relugolix, designated as T1, T2, T3, and T4B, in multiple tablet strengths, were used in the clinical development program for relugolix. The T1 and T2 formulations (in tablet strengths of 1 to 20 mg and 10 to 80 mg, respectively) were used in the initial clinical pharmacology and biopharmaceutics (phase 1) studies and in the phase 2 study (TAK-385/CCT-

001). The 40-mg T3 formulation was used in later phase 1 studies and in the phase 3 safety and efficacy studies of relugolix monotherapy for the treatment of symptoms associated uterine fibroids; it is the formulation currently approved for commercial use in Japan. The 40-mg T4B formulation was used in several more recently conducted clinical pharmacology and biopharmaceutics studies, as well as in the pivotal phase 3 studies of relugolix combination therapy in women with heavy menstrual bleeding associated with uterine fibroids.

The pharmacokinetic performance of the four 40-mg single-agent tablet formulations, in terms of the total exposure (AUC), C_{max}, and time to C_{max} (t_{max}), were relatively comparable and associated with a similar degree of variability. Slightly higher mean AUC and C_{max} values were shown in some studies for the T3 and T4B tablet formulations, which are not considered to be a true difference in formulation performance in the context of the high variability associated with these parameters (CV%: approximately 40% to 70% for AUC; 53% to 86% for C_{max}). Otherwise, it needs to be noted that most of the above studies were using within-study comparisons, and results of these studies can be reasonably generalized to the final FDC formulation.

Estradiol and norethindrone

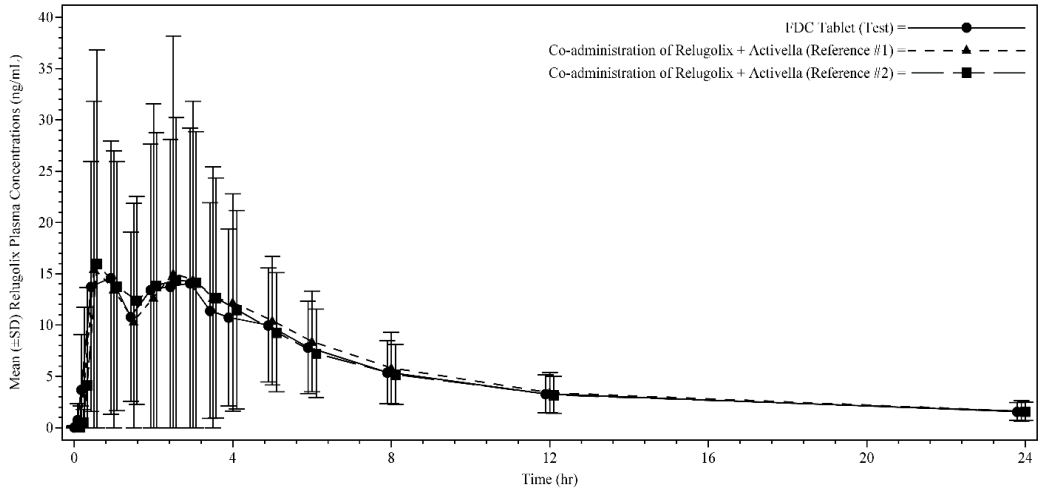
After oral administration (fasted state), unconjugated E2 concentrations increased slowly, with mean concentrations reaching peak concentrations at 8 hours postdose (MVT-601-042). Norethindrone acetate, rapidly undergoing biotransformation to its active form, NET (Back et al. 1978; Stadberg et al. 1999; Zdravkovic et al. 2001) and after oral administration (fasted state), is rapidly absorbed with initial quantifiable concentrations at 0.5 hours postdose, increasing thereafter with mean concentrations reaching peak concentrations at 1 hour postdose (MVT-601-042).

Bioequivalence of the FDC formulation

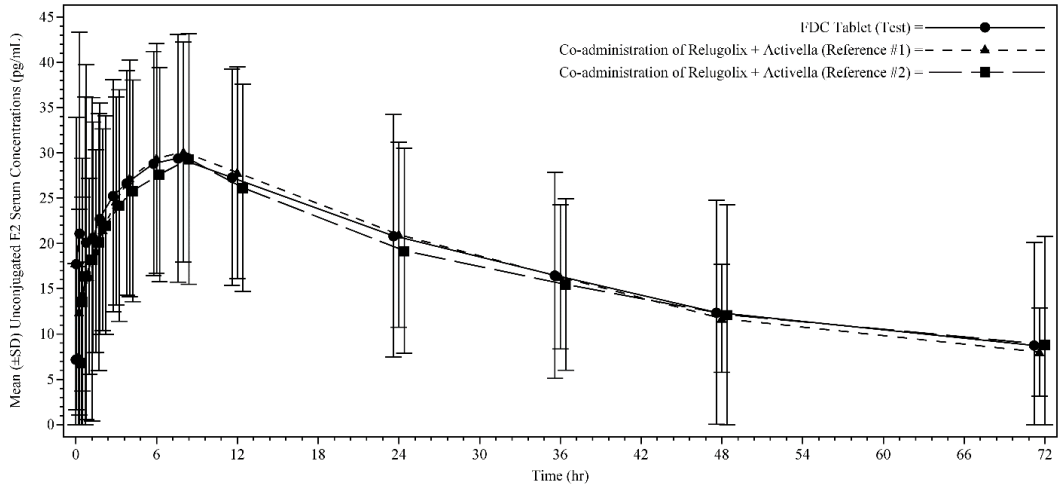
An FDC tablet formulation consisting of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg has been developed and is the intended commercial formulation. A bioequivalence study (MVT-601-042) was conducted to bridge safety and efficacy data from the pivotal phase 3 studies, where a relugolix 40-mg T4B tablet and an over-encapsulated commercially available E2/NETA (1 mg/0.5 mg) tablet (known by the brand names Activelle and Kliovance in Europe and Activella in the US) were co-administered, to the FDC tablet, the intended market formulation. The bioequivalence study was also intended to support bridging from nonclinical and clinical data generated during development of relugolix and information about E2 and NETA known from the literature, the Activella prescribing information, or the summary of product characteristics from a corresponding European brand (Activelle or Kliovance).

Table: Mean (±SD) PK Profiles of (a) Relugolix, (b) E2, and (c) NET After Administration of FDC Tablet or Co-administration of Relugolix 40 mg and Activella (MVT-601-042)

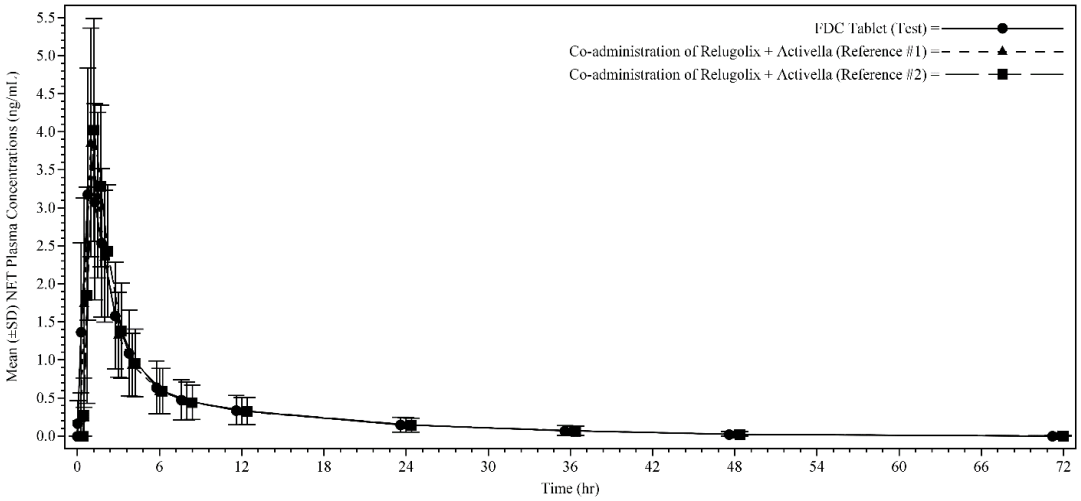
(a) Relugolix



(b) Unconjugated E2



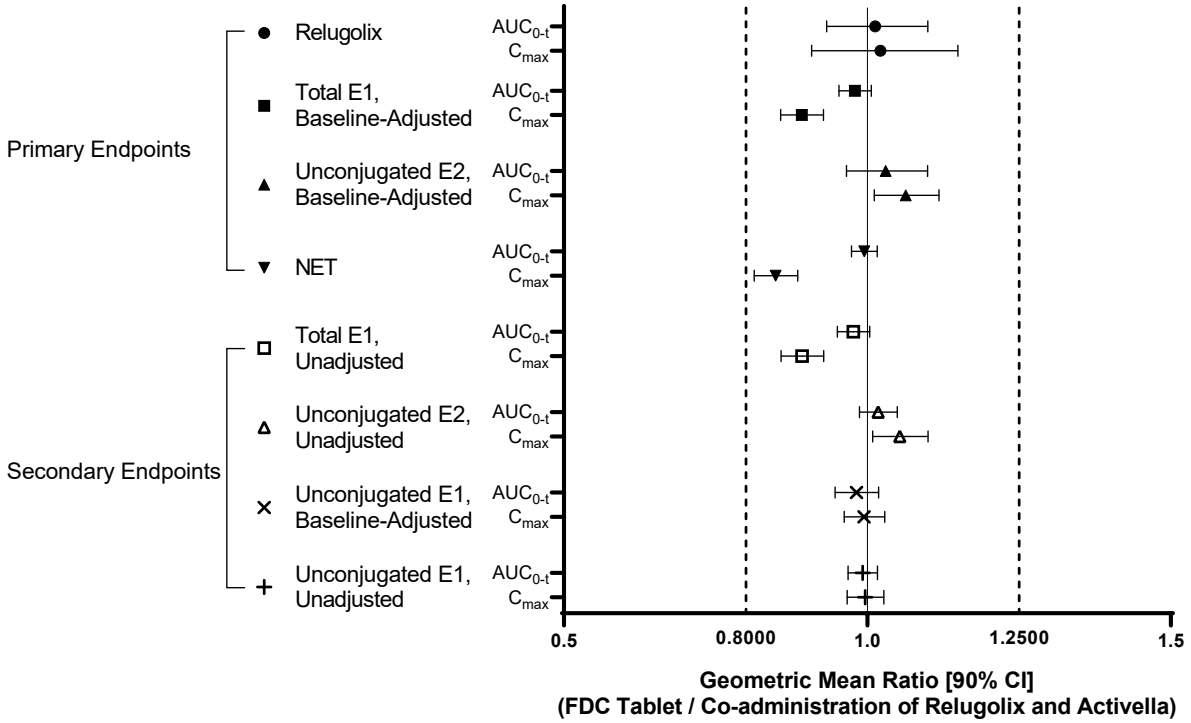
(c) NET



Note: values of mean-SD that are less than 0 are presented at 0.

Prior to the bioequivalence study, a biocomparability study (MVT-601-036) was conducted to confirm the variability estimates for pharmacokinetic endpoints, and therefore to inform the design and sample-size estimate with sufficient statistical power for the subsequent bioequivalence study. The mean pharmacokinetic profiles after administration of the FDC tablet and co-administration of relugolix 40 mg and Activella were nearly superimposable. Based on prespecified primary and secondary endpoints, bioequivalence between the to-be-marketed FDC tablet and co-administration of relugolix 40 mg and E2/NETA (1 mg/0.5 mg; Activella) was established. The 90% confidence intervals for the geometric mean ratios of FDC formulation over combined products were all contained within the usual acceptance range of 80-125% for all the relevant PK parameters for relugolix, E2 and NET, even for relugolix C_{max} (for which widening of the acceptance range was justified).

Table: GMR and the Associated 90% CI for the Primary and Secondary Endpoints for the Bioequivalence Assessment Between the FDC Tablet and Co-Administration of a 40-mg Relugolix T4B Tablet and Activella (1-mg E2/0.5-mg NETA) in Healthy Postmenopausal Women Under Fasted Conditions (MVT-601-042)



Note: C_{max} of relugolix was assessed by the reference-scaled ABE approach recommended by the EMA Guideline on the Investigation of Bioequivalence, with the limit of (0.8000, 1.2500) for the GMR and with the adjusted limit of (0.6984, 1.4319) for the associated 90% CI as the acceptance criteria. The limit (0.6984, 1.4319) for the 90% CI was applied based on the within-subject CV% for the relugolix Cmax (CV%=59.2%).

Three commercially available E2/NETA combination tablets (Activella, Activelle, and Kliovance) were used to deliver the E2/NETA components in the clinical studies with relugolix combination therapy. The three E2/NETA combination tablets used in the clinical studies were manufactured by Novo Nordisk with identical composition and formulation and were manufactured at the same facility using the same manufacturing process and equipment. Therefore, the only difference among these E2/NETA combination tablets was their trade names.

In conclusion, bioequivalence between the intended FDC commercial formulation and the formulations used in the pivotal clinical studies has been demonstrated; safety and efficacy data from the pivotal phase 3 studies can be bridged to the FDC commercial formulation.

Food effects

In the food effects study (MVT-601-041), after administration of the to-be-marketed relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet with a high-fat, high-calorie meal, the $AUC_{0-\infty}$ and C_{max} of relugolix were decreased by 38% and 55%, respectively. Small numerical differences for the baseline-adjusted $AUC_{0-\infty}$ and C_{max} of unconjugated E2, baseline-adjusted $AUC_{0-\infty}$ of total E1, and the C_{max} of NET were observed, whereas the baseline-adjusted C_{max} for total E1 was decreased by 40% and the $AUC_{0-\infty}$ of NET was increased by 1.3-fold. The effect of food for the FDC tablet with respect to the unconjugated E2 and NET components were comparable to that reported for Activella (no effect on the bioavailability of E2 and a 19% increase in the AUC_{0-72h} for NET), which is recommended to be taken without regard to food (Activella Prescribing Information 2017).

However, considering the effect of food on the relugolix component and that in the pivotal phase 3 studies with relugolix combination therapy, participants were instructed to take study drug once daily in the morning at approximately the same time each day, 1 hour prior to or 2 hours after a meal, it is acceptable that the FDC tablet can be taken without regard to food.

Distribution

Relugolix

Relugolix is 68.2% to 70.8% bound to plasma proteins, primarily to albumin and to a lesser extent to α_1-acid glycoprotein, in addition to other plasma proteins. The exposure of total radioactivity in whole blood is lower compared with that in plasma, indicating limited distribution into red blood cells (mean whole blood-to-plasma ratio of 0.78). The value for apparent volume of distribution (Vz) of 19 x 10^3 L derived from the absolute bioavailability study after intravenous administration indicates relugolix distributes widely into tissues.

Estradiol and norethindrone

Estradiol extensively binds to plasma proteins, primarily to steroid hormone-binding globulin (SHBG, 37%) and albumin (61%), with approximately 1%-2% of circulating concentrations as unbound drug (Activelle SmPC, 2016). Due to its lipophilicity, E2 distributes rapidly and extensively in tissues (Kuhl 2005; Levin et al. 2013). Norethindrone extensively binds to human plasma proteins, primarily SHBG (36%) and albumin (61%), with approximately 3.7% unbound in plasma (Activelle SmPC, 2016). Binding to plasma proteins is weak and NET is available for distribution into tissues and subsequent metabolism (Kuhl 2005; Levin et al. 2013; Stanczyk et al. 2013).

Elimination

Relugolix

Based on study TAK-385-109, in which a single 80-mg dose of [^{14}C]-relugolix was administered, total radioactivity in plasma was associated with a similar concentration-time profile with rapid absorption followed thereafter by a multi-phasic decline. The mean $t_{1/2}$ associated with the terminal elimination phase based on radioactivity was estimated to be 226 hours as a result of the very slow (flat) elimination of total radioactivity, particularly after 72 hours postdose. The slower elimination of radioactivity might be due to slow release of relugolix from tissues, but also might be caused by metabolites with slow elimination. The effective elimination half-life of relugolix is estimated to be ~25 hours.

The mean clearance after intravenous administration of an 80-µg dose of [^{14}C]relugolix was 29.4 L/hour (from absolute bioavailability study TAK-385-1009). Mean terminal elimination half-life based on plasma concentrations for relugolix is approximately 60 hours.

Estradiol and norethindrone

Mean terminal elimination half-lives for estradiol and norethindrone are approximately 17 and 11 hours, respectively.

Metabolism

Relugolix

In vitro studies with human liver microsomes fortified with NADPH (nicotinamide adenine dinucleotide phosphate) indicate that Metabolite-A and Metabolite-B are the main metabolites formed in the liver. Other metabolites were formed to a low extent (TAK385/00040). Up to 63% of total radioactivity in plasma was attributed to multiple minor unidentified metabolites.

In vitro CYP reaction phenotyping results indicated that the primary CYP enzymes contributing to the overall hepatic oxidative metabolism of relugolix were CYP3A4/5 (45%) > CYP2C8 (37%) > CYP2C19 (< 1%). Metabolite-A was formed through O-demethylation by CYP3A4. Metabolite-B was formed through hydroxylation by CYP2C8 and, to a low extent, by CYP2C19. Metabolite C was formed through N-demethoxylation, but not by CYP enzymes, i.e. it is likely formed from unabsorbed drug by intestinal microflora.

Metabolite-C was identified as the major metabolite in human feces, representing approximately 40% of the total radioactive dose. Metabolite-C was detected only at low levels in human plasma, likely from absorption of trace amounts after formation in the intestine.

Because Metabolite-A and Metabolite-B (combined) represent approximately 2.2% and 3.8% of total radioactivity in plasma in the 72-hour post-dose period after oral administration of a single 80-mg dose of [^{14}C]-relugolix in the human ADME study (TAK-385-1009), CYP3A4/5 and CYP2C8-mediated metabolism of relugolix are thought to be relatively minor pathways of systemic clearance in vivo.

The metabolic fate of relugolix is not entire clear. Approximately half of the radioactivity in plasma, urine and faeces has not been identified, as 53% of radioactivity in plasma during first 72 hours after administration has been identified, 53% of radioactivity in urine and 56% of radioactivity in faeces, which is considerably lower than the 80% recommended in the guideline. However, multiple minor metabolites were detected in plasma, urine and faeces indicating that relugolix is extensively metabolised by various pathways.

Based on the fraction absorbed of ~40% and an absolute bioavailability of 11.6%, there is a considerable first-pass effect. Of the fraction escaping the first-pass metabolism, 19% is eliminated as unchanged relugolix in the urine; hence, pre-systemic and systemic metabolism contribution of approximately 70-80% of an absorbed dose. Given the effects of the drug-drug interaction study with voriconazole (see below under Extrinsic factors/Drug interactions), with a 50% increase in relugolix exposure at the 40 mg relugolix dose, CYP3A4 is estimated to contribute 34% of the elimination of relugolix. Based on in vitro data, CYP2C8 is likely to be involved, but to lesser extent than CYP3A4 and is estimated to contribute for 20%, based on in vitro data.
Based on the many minor peaks observed in the radio-chromatograms multiple other enzymes are likely to be involved, although not identified. Based on hydrophilic metabolites excreted in bile in rats, and hydrophilic metabolite observed in excreta in humans, UGT involvement cannot be excluded and this might be in line with the reasonably high first-pass metabolism and potential elimination via bile.

As these unknown pathways contribute less than CYP3A4, for which inhibition led to a 50% increase in relugolix exposure, potential inhibition of these pathways are unlikely to result in clinically relevant increase of relugolix exposures and therefore no further identification is considered needed.

Estradiol and norethindrone

As with endogenous estrogens, exogenously administered estradiol undergoes rapid and extensive first pass metabolism in the small intestine and liver to estrone by 17β-hydroxysteroid dehydrogenase or subsequently to sulfate and glucuronide conjugates by sulfotransferase (SULT) or uridine diphosphate glucuronosyltransferase (UGT) enzymes, respectively (Kuhl 2005). Estradiol also undergoes oxidative metabolism by CYP enzymes, including CYP3A4 (Tsuchiya et al. 2005).

After oral administration, NETA is hydrolyzed in the intestine and liver to NET with a total progestin bioavailability of 40-80% (Kuhl 2005). Norethindrone is metabolized by steroid reductases (e.g., 5α-,β-) to other biologically active metabolites (e.g., this isomers 5αdihydro-norethindrone and tetrahydro-norethindrone, which are primarily excreted in the urine as sulfate or glucuronide conjugates) in addition to biotransformation by sulfonation, glucuronidation, and oxidation by SULT, UGT, and CYP enzymes, including CYP3A4 (Kuhl 2005; Korhonen et al. 2008).

Excretion

Relugolix

Recovery of radioactivity in the mass balance study was 87.1%, hence the collection period of 12 days is considered acceptable. The majority (82.7%) of radioactivity was recovered in faeces, with approximately 4.4% recovered in urine.

Approximately 2.2% of the total radioactive dose of relugolix is excreted unchanged in the urine and, based on an absolute bioavailability of 11.6%, an estimated 19% of an absorbed dose (i.e. following pre-systemic clearance) is excreted unchanged in the urine and 80% is eliminated through metabolism by multiple minor metabolic pathways and/or biliary secretion of unchanged drug. Approximately 38% of the administered dose is excreted as metabolites (other than Metabolite-C) in the feces and urine. Metabolite-C, which is formed by intestinal microflora, is the primary metabolite in feces (50.6%) and further reflects non-absorbed drug. However, the continuous excretion of radioactivity in the feces beyond 72 hours after administration indicates that a substantial part (at least 40%) of relugolix is being absorbed and suggests a reasonably high first-pass effect, because the absolute bioavailability was only 11.6%.

These metabolism pathways and/or elimination processes are likely to be consistent after administration of a 40-mg dose and therefore the 80-mg dose selected for the human ADME and absolute bioavailability study provided a reasonable dose to support the MAA for relugolix combination therapy for the treatment of symptoms associated with uterine fibroids.

Estradiol and norethindrone

Estradiol, estrone (E1), and estriol (E3) are primarily excreted in urine as glucuronide or sulfate conjugates, with glucuronide conjugates also excreted into bile and subsequently extensively hydrolyzed in the colon by bacterial enzymes. The unconjugated moieties are then re-absorbed with this enterohepatic re-circulation providing considerable contribution to systemic concentrations of E2 and E1 (Kuhl 2005; Levin et al. 2013).

Norethindrone is primarily excreted in urine as various polar metabolites (Levin et al. 2013).

Drug transporters

Relugolix has moderate intrinsic permeability in Caco-2 cells compared to the low and high permeability controls used. Relugolix is a substrate for P-gp. The expression of BCRP in the Caco-2 cells in the Applicant's study is not entirely clear and it cannot be concluded with certainty that relugolix is not a substrate for BCRP. Nevertheless, it is clear from the in vitro and in vivo studies that the absorption of relugolix is mainly affected by P-gp.

Results of in vitro transporter studies in OATP-expressing cells indicated that relugolix is not a substrate for the OATP1B1 or OATP1B3 hepatic uptake transporters. It seems unlikely that OCT1 plays a major role in the uptake of relugolix in the liver based on the moderate passive permeability of relugolix, the high molecular weight, and wide tissue distribution observed in pre-clinical species including high tissue distribution in pituitary, which does not rely on OCT1. Although it cannot be excluded that relugolix might be a substrate for OCT1, the clinical relevance seems limited.

Dose proportionality and time dependency

Dose proportionality

Relugolix is associated with greater than proportional increases with respect to dose, which become most pronounced at doses greater than 20 mg of relugolix and appear to plateau at a dose of 80 mg and higher. Thus. around the selected dose of 40 mg relugolix greater than proportional increases in exposure are most pronounced. This conclusion is supported by the results of the PopPK analysis, which showed that the dose effect on relative bioavailability (F1) indicated a more than dose-proportional increase in relugolix exposure in the dose range of 10 to 40 mg with an exponent of 0.463 on Dose. There remains uncertainty what the underlying reason is for the dose dependent pharmacokinetics of relugolix, saturation of CYP3A4 or saturation of P-gp, since there are no data on metabolite formation and no interaction study with relugolix as inhibitor of P-gp has been conducted yet (see also Interactions).

Accumulation ratio

Upon multiple-dose administration of relugolix to premenopausal women, the degree of accumulation of relugolix is approximately 2-fold; i.e. the mean accumulation ratios for $AUC_{0-\tau}$ and C_{max} [Day 14/Day 1] were 2.07 and 1.72, respectively). This means that the exposure to relugolix (in terms of AUC and C_{max}) at steady state with once-daily administration is approximately 2-fold of the relugolix exposure after administration of the first dose.

The mean effective half-life ($t_{1/2,\ eff}$) was estimated to be 24.8 hours, indicating that the systemic exposure (in terms of AUC) to relugolix is reduced by half in approximately 24 hours and thereby supporting once daily administration.

The accumulation for E2 and NET upon once daily administration is reported to be 33% to 47%. When co-administered with relugolix, a weak inducer of intestinal (pre- systemic) CYP3A-mediated metabolism, the accumulation for E2 is expected to be similar or slightly lower.

Attainment of steady state

Steady state is reached after 12 to 13 days of once daily administration of relugolix. This conclusion is slightly dependent on the availability of pre-dose samples, which were not taken earlier than on Day 11/12 after statrt of once daily dosing. Taking into account a terminal half-life of approximately 60 hours for relugolix, it is expected that steady state for relugolix is reached after 12.5 days (5 times 60 hours), which is in line with this finding.

Given the shorter half-lives for E2 and NET as compared to relugolix, it is reasonable to assume that by 12 days also steady state for E2 and NET will have been reached.

Time dependency

Results from the population pharmacokinetic (popPK) analysis indicated that the pharmacokinetics of relugolix is time-independent. Moreover, consecutive trough concentrations of relugolix on Days 11 to 14 during once-daily administration of 40-mg doses of relugolix in several drug interaction studies were used to determine steady state. Results showed that steady state was achieved by Day 12 to Day 13 of the multiple-dose administration (i.e., no change with statistical significance in trough concentrations of relugolix after Day 13), also consistent with time-independent pharmacokinetics of relugolix upon once-daily administration of 40-mg dose observed in the phase 3 studies.

Intra- and inter-individual variability

Relugolix is a highly variable ([CV_{WR}] > 30%) compound with an intra-individual (within-subject) coefficient of variation of 38% for AUC and 59% for C_{max}, as determined from the replicate design study MVT-601-042 (N=85).

The (total) inter-individual coefficient of variation (CV_{total}%) is on average around 55% for AUC and around 70% for C_{max} of relugolix.

The inter-individual variation on C_{trough} values in the Phase 1 studies ranged from 35 to 52%, which is substantially lower than the variation in the trough concentrations in the Phase 3 studies with CV values being greater than 100% in general. This shows that the high variability in the trough concentrations in the Phase 3 is probably more a reflection of less study design control in those studies (see below).

Variability in E2 and NET PK parameters appears to be somewhat lower than that in relugolix PK parameters. As an example, reported intra-individual variability in study MVT-601-042 was 37% for E2 AUC and 9% for NET AUC. Also inter-individual variability on E2 and NET was lower with CV_{total}% values of 41% for E2 AUC and 48% for NET AUC, based on study MVT-601-042.

Pharmacokinetics in target population

The pharmacokinetics in the target population are best described by the results from the 6-week PK/PD Study with relugolix alone and in combination with E2/NETA (MVT-601-1001) and the results from both pivotal Phase 3 studies MVT-601-3001 and -3002.

6-week PK/PD study (MVT-601-1001)

The 6-week PK/PD study (MVT-601-1001) was a randomized, open-label, parallel-group study to assess a.o. the pharmacokinetics and pharmacodynamics after administration of multiple 40-mg doses of relugolix alone or in combination with E2/NETA (1 mg/0.5 mg) once daily for 6 weeks in 48 healthy adult premenopausal women.

After coadministration of relugolix 40 mg and E2/NETA (1 mg/0.5 mg) once daily for 6 weeks, the exposure to relugolix (AUC_{0-24} and C_{max}) was similar to that after administration of relugolix alone. The GMR (coadministration [relugolix + E2/NETA]/relugolix alone) and 90% CI for the AUC_{0-24} and C_{max} of relugolix were 1.10 (0.84, 1.44) and 1.07 (0.76, 1.51), respectively, showing that coadministration of relugolix with E2/NETA did not alter the exposure to relugolix. Both for Treatment A (relugolix 40 mg) and Treatment B (relugolix 40 mg and E2/NETA [1 mg/0.5 mg]) the relugolix exposure parameters at Week 3 and Week 6 are generally similar.

Plasma NET PK parameters were only measured in Treatment B (relugolix 40 mg and E2/NETA [1 mg/0.5 mg]). Following multiple doses of Treatment B, the mean NET PK parameters are generally similar for Weeks 3 and 6.

Following multiple doses of Treatment A (relogolix 40 mg) or Treatment B (relugolix 40 mg and E2/NETA [1 mg/0.5 mg]), 3.3-fold higher E2 concentrations are observed for Treatment B, as expected. Slightly lower E2 concentrations at Week 6 compared to Week 3 are seen with both treatments (probably due to some outliers for reasons of non-compliance to treatment). Mean E2 PK parameters for Treatment B were generally greater than for Treatment A and E2 parameters for Week 3 were generally greater than for Week 6 for both Treatments A and B.

Trough concentrations Phase 3 studies

In the Phase 3 studies MVT-601-3001 and -3002 only trough concentrations of relugolix, E2 and NET were determined. In general, the trough concentrations were consistent between both pivotal Phase III clinical studies and, as noted above, the variation in the trough concentrations was very high for relugolix, E2 and NET with CV values being greater than 100% in general. The big variation in the trough concentrations is probably more a reflection of less study design control in Phase 3 studies, leading to big variation in sampling times after previous drug intake, less control on food conditions, less accurate recording of sampling times and drug intake.

For both clinical studies, after administration of relugolix + E2/NETA, trough plasma concentrations of relugolix at Week 4 and Week 12 were similar and were also similar to those after administration of relugolix alone, suggesting that the overall exposure to relugolix was similar between the treatment groups through Week 12. At Week 24, there was a slight trend towards lower exposures in both groups compared with Week 12 values.

At Week 24, NET plasma concentrations for the relugolix + E2/NETA group were similar to NET plasma concentrations at Week 24 for the relugolix + delayed E2/NETA group. However, over Weeks 4, 12, and 24, NET plasma concentrations for the relugolix + E2/NETA group tended to decrease.

Apparent decreasing trend in mean relugolix and NET predose concentrations over time in the phase 3 studies appeared to be a result of outliers included in the dataset. Achievement of steady state upon multiple-dose administration of relugolix by Day 12 was demonstrated in several other more controlled clinical studies.

At Week 4 and Week 12, after administration of relugolix alone (prior to delayed E2/NETA administration), median estradiol concentration was 5-fold lower compared with the relugolix + E2/NETA group. At Week 24, mean estradiol concentrations were similar between the treatment groups.

Special populations (Intrinsic Factors)

No studies with E2 and/or NETA in special populations were conducted, including patients with renal or hepatic impairment. The use of commercial products containing the combination of E2 and NETA (e.g., Activella, Activelle) is contraindicated in patients with liver dysfunction or disease (Activella Prescribing Information 2017, Activelle Summary of Product Characteristics 2018) based on established knowledge of the metabolism and excretions of sex steroid hormones. Additionally, because E2 and NET are primarily metabolized in the liver, no studies have been conducted in patients with renal impairment based on the available information for commercially available products. Therefore, the information provided in this section is based on assessments of relugolix only.

The potential effects of intrinsic factors on exposure to relugolix, including demographic parameters (age, race, sex, body weight, menopausal status, renal impairment) were evaluated either in dedicated studies, by cross-study comparisons, or with the population pharmacokinetic analysis.

PopPK analysis

The PK of relugolix following PO administration was sufficiently characterized based on data from premonopausal women. Relugolix pharmacokinetics were described by a two-compartment structural model with first order absorption and elimination, inter-individual variability on absorption rate constant (Ka), apparent systemic clearance after oral administration (CL/F), and relative bioavailability (F1), and residual variability described by a proportional error model. All parameters could be estimated with adequate precision, as measured by RSE < 30% for fixed effects (with the largest RSE of 27% for the covariate effect of body weight on CL/F) and RSE < 10% for random effects.

Body weight was implemented in the model as a covariate effect on CL/F, and its exponent was estimated to be 0.27 (95% CI: 0.13-0.42), significantly lower than the more common allometric exponent of 0.75. Body weight as a significant covariate on CL/F with the allometric exponent value of 0.27 was determined based on covariate evaluations for the pharmacokinetics of the analysis population, and was able to characterize the observed trend in CL with body weight within the dataset. Fixing the allometric exponent to a value of 0.75 would have introduced a bias for estimation of clearance in patients with a relatively high body weight. This estimate of the allometric exponent value seems to indicate some deficiency for the model or the used dataset. However, the primary purpose of the covariate analysis was to characterize the pharmacokinetics within the analysis population, not for purposes of extrapolation to lower or higher body weights, in which case a fixed exponent might have been considered.

Despite the limitations of the PopPK model mentioned above, the PopPK model can be used to predict effects within the studied population of premenopausal women but will not allow extrapolation beyond this population.

Using the final PopPK model simulations were done to predict the effects of covariates race and body weight on exposure to relugolix (in terms of model-predicted total exposure or trough concentrations at steady state [AUC_{ss}; $C_{trough,ss}$]. Overall, the predicted collective effects of covariates race and body weight were relatively modest and well within the comparability bounds of (0.50 to 2.00) for clinically meaningful changes in exposure (AUC and $C_{trough,ss}$) associated with the established safety and efficacy profile for relugolix (see PK/PD analyses).

Age / elderly /children

Of the 1103 study participants with available relugolix pharmacokinetic data in clinical pharmacology studies, a total of 27 (2.4%) were older than 65 years of age. Of these 27 study participants, 24 (2.2% of the total 1103 participants) were 65-74 years of age, 3 (0.3% of the total 1103 participants) were 75-84 years of age, and 0 (0.0% of the total 1103 participants) were > 85 years of age. There are only few data in elderly, which is acceptable given the indication.

Age was not found as a significant covariate in the compartmental PK model for relugolix, which is not surprising as the age range was limited: only premenopausal women were included in the studies on which the PopPK analysis was performed.

No children (< 18 yrs of age) have been dosed with relugolix so far.

Race

Overall, based on cross-study analysis and the PopPK analysis no clinically meaningful effect of race or ethnicity on relugolix exposure could be identified, indicating that pharmacokinetics of Japanese and non-Japanese subjects are similar. This implies that pharmacodynamic, safety and efficacy assessments made across studies with non-Japanese and Japanese populations in the relugolix clinical development program can be compared assuming underlying pharmacokinetics are the same.

Sex / gender

After single or multiple-dose administration of relugolix to healthy women (premenopausal or postmenopausal) and healthy men, no obvious difference in the exposure to relugolix was identified based on direct comparison of AUC and C_{max} at corresponding doses or dose-normalized AUC and C_{max} in various studies. Therefore, the conclusions from the clinical pharmacology studies performed in men only or in men and women also apply to the population of premenopausal women for this MAA.

Body weight

Although body weight was identified as a significant covariate on clearance, simulations using the PopPK model indicated the effect of body weight to be limited ($C_{trough,ss}$ ratio of 0.96 for body weight > 63.2 kg vs. body weight ≤ 63.2 kg) and to fall well within the overall variability of relugolix exposure across the population.

A simulation for a high-weight subject of 107 kg predicted a 21% lower $C_{trough,ss}$ and a 13.5% lower AUC_{ss} as compared to a subject with median body weight of 63.2 kg, which appears to be acceptable.

Menopausal status

Several biopharmaceutics and clinical pharmacology studies were conducted in postmenopausal women to facilitate study assessments, because postmenopausal women have lower and less variable endogenous production of estradiol, despite the target population being premenopausal women with uterine fibroids. A comparison of PK data from one clinical study (MVT-601-041), which included both postmenopausal (Part 1) and premenopausal (Part 2) women within the same study demonstrated that overall exposure ($AUC_{0-\infty}$) and peak concentration (C_{max}) of relugolix in premenopausal and postmenopausal women were similar.

Renal impairment

Results from a PopPK analysis indicate that mild renal impairment does not appear to affect the pharmacokinetics of relugolix. The potential effect of moderate and severe renal impairment on the exposure to relugolix was evaluated in two clinical pharmacology studies (MVT-601-1003; MVT-601-041). After administration of a single 40-mg dose in patients with moderate or severe renal impairment, the total exposure ($AUC_{0-\infty}$) to relugolix was increased by 1.5-fold. However, based on AUC_{0-t} the total exposure to relugolix in patients with several renal impairment was increased 2.0-fold with an upper 90% confidence limit of 3.7. The exclusion of one subject in the reference group may have evened out the comparison of $AUC_{0-\infty}$ for several renal impairment versus healthy controls.

The increase in relugolix exposure in subjects with impaired renal function is likely to be attributed to the increase in absorption in this population. The underlying mechanism of this increase is unclear which enforces the uncertainty on possible long-term safety issue (i.e. BMD loss). Therefore, a "Special warning and precautions for use" statement in Section 4.4 of the SmPC has been included regarding the use of relugolix in patients with moderate or severe renal impairment, also given the defined upper comparability safety bound of 2.00 by the Applicant.

According to the Activella SmPC, "The effect of renal impairment on the pharmacokinetics of Activella has not been studied". Data from the literature regarding the effects of renal impairment on the pharmacokinetics of E2 or NETA also is limited. However, renal impairment is not mentioned in Sections 4.3 and 4.4 of the Activella SmPC.

The effect of end-stage renal disease requiring haemodialysis on the PK of relugolix, E2 and NET has not been studied and the amount of relugolix, E2 or NET removed by haemodialysis is unknown.

Hepatic impairment

After administration of a single 40-mg dose of relugolix to patients with mild or moderate hepatic impairment, no clinically meaningful effects on the rate or extent of absorption of relugolix were observed, although small numerical differences in the exposure-related pharmacokinetic parameters were noted. In patients with mild hepatic impairment total exposure to relugolix was decreased by 31% and in patients with moderate hepatic impairment exposure was decreased by 5%, compared with healthy participants with normal hepatic function.

The terminal elimination $t_{1/2}$ estimates were nearly the same (52, 51, 49 hours) in patients with mild or moderate hepatic impairment and healthy participants with normal hepatic function, respectively. Based on these results, no dose adjustment in mild or moderate hepatic impairment for the relugolix component of the FDC tablet would be required.

Administration of E2/NETA in patients with severe hepatic disease is contraindicated, and as such administration of the FDC tablet to patients with presence or history of severe hepatic disease also is contraindicated, as long as liver function values have not returned to normal. It is understood that relugolix has not been studied in patients with severe hepatic impairment, as E2/NETA is already contraindicated in patients with severe hepatic impairment. The Activelle label actually mentions the contraindication as "Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal". The effects of mild and moderate hepatic impairment on E2 and NETA appear to be limited.

Extrinsic Factors / Drug Interactions

A total of eight clinical drug-drug interaction studies with relugolix were conducted, four studies with relugolix as a victim of the interaction that included five potential perpetrators and four studies with relugolix as the perpetrator of the interaction, including a study to assess the potential effect of relugolix on the pharmacokinetics of E2 (and other related moieties) and NET. The potential effect of E2 and NETA on the pharmacokinetics of relugolix was assessed in the 6-week PK/PD study in healthy premenopausal women (MVT-601-1001).

DDI potential for E2/NETA

Drug-drug interactions for E2 and NETA were not evaluated in dedicated (clinical) studies. The information regarding drug-drug interaction potential for E2 and NET in Section 4.5 of the SmPC is the same as that in the label for the E2/NETA combination product Activella. The DDI information with respect to strong CYP3A4 and P-gp inducers on relugolix and E2/NETA has been aligned in Section 4.5 of the SmPC (see further below).

In vitro: Effect of Other Drugs on Relugolix (Victim Interactions)

As noted previously, relugolix is a substrate for the P-gp efflux transporter responsible for the limited oral bioavailability (11.6%) and the absorption-related drug interactions due to P-gp inhibition or induction. Although a minor pathway in vivo, in vitro data showed that CYP3A4 is responsible for 45% of CYP-mediated metabolism, and therefore the potential effects of P-gp and/or CYP3A4 inhibitors or

inducers on the pharmacokinetics of relugolix were clinically studied (see next section on In vivo: Effect of Other Drugs on Relugolix (Victim Interactions)).

In vitro: Effect of Relugolix on Other Drugs (Perpetrator Interactions)

In pooled human liver microsomes, relugolix was not a direct inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, nor was there a time-dependent inhibition of any CYP enzyme, including CYP3A4/5. However, based on in vitro studies, relugolix has the potential for CYP3A4/5-mediated drug interactions due to induction (relugolix induced CYP3A4 mRNA expression in human hepatocytes in a concentration-dependent manner at concentrations ≥ 1 µM) or direct inhibition (relugolix inhibited midazolam 1'-hydroxylase activity with an IC_{50} value of 16 µM).

Based on the exposure associated with the proposed clinical dose of 40 mg once daily, results from the in vitro studies indicate that relugolix has the potential to interact with intestinal CYP3A, and therefore a drug interaction study with midazolam, a sensitive CYP3A4 substrate, was conducted (MVT-601-044).

For CYP2B6, the lowest concentration of relugolix that resulted in a positive in vitro CYP2B6 mRNA induction signal was observed at ≥ 3 µM relugolix, which is at least 319-fold higher than the unbound C_{max} for relugolix based on oral doses of 40 mg QD ($C_{max,u,ss}$ = 9.4 nM). Taken together with the weak clinical induction of CYP3A by relugolix at 40 mg QD, the potential for clinically meaningful induction of CYP2B6 is unlikely, which is agreed.

In vitro studies demonstrated that relugolix was not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP at the concentrations tested, but relugolix inhibited transport by P-gp, BCRP, MATE1, and MATE2-K. However, based on in vitro inhibitory potencies and estimated relugolix exposures associated with administration of 40-mg or 120-mg doses of relugolix once daily, there is potential for relugolix to inhibit intestinal BCRP based on thresholds defined in the agency guidelines for drug interactions (for a 40-mg dose, the I_{gut}/IC_{50} value was 10.3, marginally exceeding the recommended threshold of 10, indicating potential for a clinically meaningful drug interaction with intestinal BCRP. Therefore, for BCRP a clinical drug-drug interaction study with rosuvastatin, a substrate for the BCRP efflux transporter, was conducted (MVT-601-045).

Although the projected I_{gut} concentration based on a 40 mg dose of relugolix (256.6 µM) results in an I_{gut}/IC_{50} value of < 10, suggesting that a clinically-relevant interaction with P-gp substrates is unlikely. However, the Applicant suggests that the more than dose proportional increase in relugolix exposure is due to saturation of P-gp. Therefore, a clinical DDI study with a P-gp substrate such as dabigatran etexilate or fexofenadine is required for the 40 mg dose of relugolix, which will be a post-approval commitment. Until that study has been completed, co-medication with sensitive P-gp substrates is not recommended.

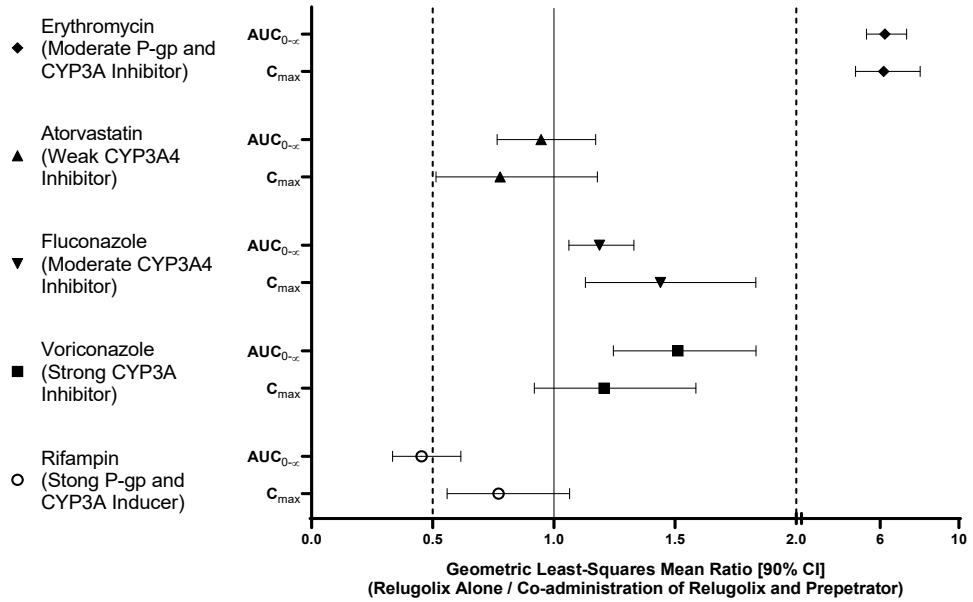
In vivo: Effect of Other Drugs on Relugolix (Victim Interactions)

The potential effects of P-gp and/or CYP3A inhibitors or inducers on the pharmacokinetics of relugolix were assessed in four dedicated clinical pharmacology studies. The selection of specific inhibitors and inducers facilitated a better understanding of the relative contribution from P-gp and CYP3A mediated effects.

In general, the designs of the clinical DDI studies were considered acceptable. It should be noted that the daily erythromycin dose of 1200 mg lower is than the therapeutic dose and doses typically seen in erythromycin DDI studies (often 3 times 500 mg). Therefore, the real effect (i.e. effect with higher dose) might be slightly higher.

A summary of the results from these studies is presented below:

Table: Geometric Mean Ratios and 90% CI for the AUC and C_{max} of Relugolix Upon Coadministration with P-gp and/or 3A Inhibitors and Inducers



Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum observed concentration; P-gp = P-glycoprotein.

Results from these studies that evaluated the effects of other drugs on the pharmacokinetics of relugolix (victim interactions) showed that upon:

- co-administration of a single dose of 20 mg relugolix with multiple doses of erythromycin, a strong P-gp and moderate CYP3A inhibitor (300 mg dose four times a day, study TAK-385/CPH-010), resulted in a 6.2-fold increase in relugolix exposure ($AUC_{0-\infty}$) as compared to administration of relugolix alone (90% CI 5.3 - 7.3);
- co-administration of a single dose of 40 mg relugolix with voriconazole, a strong CYP3A inhibitor devoid of P-gp inhibition (200 mg every 12 hours, study MVT-601-043), resulted in a 1.5-fold increase in relugolix exposure ($AUC_{0-\infty}$) as compared to administration of relugolix alone (90% CI 1.2 - 1.8), which is not considered clinically meaningful. At the higher relugolix dose (120 mg), co-administration of voriconazole did not increase the exposure to relugolix as compared to relugolix alone (point estimate 1.1, 90% CI for $AUC_{0-\infty}$ 0.7-1.8), which may suggests that relugolix inhibited intestinal CYP3A4 at higher doses, thereby decreasing the effect of voriconazole. It also emphasizes the relatively low fraction metabolized by CYP3A4 in the whole metabolism of relugolix;
- co-administration of a single dose of 40 mg relugolix with fluconazole, a moderate CYP3A4 inhibitor (200 mg once daily), or atorvastatin, a weak CYP3A4 inhibitor (80 mg once daily, study C27005) resulted in a 1.2-fold (90% CI 1.1 – 1.3) increase and no change (90% CI 0.8 – 1.2) in relugolix exposure ($AUC_{0-\infty}$), respectively as compared to administration of relugolix alone, which effects are not considered clinically meaningful;
- co-administration of a single dose of 40 mg relugolix with rifampin, a strong P-gp and CYP3A4 inducer (7 days of 600 mg once daily induction, study MVT-601-1004), resulted in a 2.2-fold decrease in relugolix exposure ($AUC_{0-\infty}$) as compared to administration of relugolix alone (90% CI 1.6 - 3.0).

Effects of erythromycin on the pharmacokinetics of relugolix could be multifactorial such as inhibition of intestinal and hepatic transporters and enzymes but also affecting the intestinal flora and thereby reducing the formation of metabolite C. It was shown that the formation of metabolite C could be inhibited by erythromycin but the effect of erythromycin on relugolix exposure was very fast, while formation of metabolite C is likely to occur later, further down the intestinal tract. Thus, the effect of erythromycin is probably related to a first-pass effect on the oral bioavailability of relugolix.

These results indicate that the increase in exposure associated with co-administration of erythromycin was primarily a P-gp-mediated effect and likely to result from an increase in oral bioavailability due to inhibition of intestinal P-gp efflux. B

Classification of weak, moderate and strong inhibitors of transporters is difficult to achieve, because of lack of sensitive and selective substrates. Many drugs are substrates for multiple transporters or there is an interplay between metabolising enzymes and transporters. Digoxin and dabigatran are reasonable selective substrates for P-gp, but the increase in their exposure is < 5-fold and these drugs cannot be classified as sensitive substrates. Therefore, P-gp inhibitors cannot be classified as weak, moderate or strong inhibitors at this moment. Further, the effects of intestinal P-gp inhibition are likely to be reduced when the P-gp inhibitor and relugolix are not administered at the same time but several hours apart. Therefore, when use is unavoidable, a dose separation strategy is allowed for orally administered P-gp inhibitors with a once or twice daily dosing regimen, where relugolix is administered first and at least 6 hours prior to the P-gp inhibitor.

It is agreed that the effects of mild, moderate or strong CYP3A inhibitors devoid of P-gp inhibition will remain below the upper limit of the proposed acceptability (comparability) bounds of 0.50-2.00 for concluding no clinically relevant effect.

Based on in vitro data, dedicated clinical pharmacology studies to assess the potential effect of relugolix on midazolam, a sensitive CYP3A4 substrate (MVT-601-044) and rosuvastatin, a BCRP substrate (MVT-601-045) were considered necessary. In the two studies, the potential effects of both a 40- and 120-mg dose of relugolix were evaluated in Part 1 and Part 2 of each study, respectively, considering that potential inhibition and/or inductive effects are dose (concentration)-dependent. Although the 120-mg dose was included to support the prostate cancer indication, the data generated at the 120-mg provide additional scientific insight into the nature of the interactions. In general, the designs of the clinical DDI studies were considered acceptable.

Results from the midazolam interaction study (MVT-601-044), in which a single 5-mg dose of midazolam was co-administered with a 40-mg (Part 1) or a 120-mg (Part 2) dose of relugolix following once daily administration of respective doses of relugolix for 14 days, showed that the potential inductive and/or inhibitory effects of relugolix on CYP3A4-mediated metabolism of midazolam, a sensitive CYP3A4 substrate, are slight and do not appear to be dose dependent:

- After co-administration of midazolam and relugolix, following administration of 40-mg doses of relugolix once daily for 14 days, the $AUC_{0-\infty}$ and C_{max} of midazolam were decreased by 18% (90% CI 3%-30%) and 26% (90% CI 9%-39%), respectively, as compared to administration of midazolam alone;
- After co-administration of midazolam and relugolix, following administration of 120-mg doses of relugolix once daily for 14 days, the $AUC_{0-\infty}$ and C_{max} of midazolam were decreased by approximately 22% (90% CI 15%-29%), and 14% (90% CI 2%-28%), respectively, as compared to administration of midazolam alone.

Based on results from the midazolam interaction study, relugolix is considered to be a weak inducer of CYP3A4. Because the relatively small decreases in exposure to midazolam observed upon co-

administration with relugolix, a clinically meaningful decrease in exposure for other CYP3A4 substrates is unlikely. However, individual variability in induction was high with relugolix being a moderate inducer in some individuals.

Results from the rosuvastatin interaction study (MVT-601-045), in which a single 10-mg dose of rosuvastatin was co-administered with a 40-mg (Part 1) or a 120-mg (Part 2) dose of relugolix following once daily administration of respective doses of relugolix for 14 days, showed a small decrease in exposure to rosuvastatin, a BCRP efflux transporter, that appeared to have a dose-related effect:

- After co-administration of rosuvastatin and relugolix, following administration of a 40-mg dose once daily for 14 days, the $AUC_{0-\infty}$ and C_{max} of rosuvastatin were decreased by 13% (90% CI -2%-26%), and 23% (90% CI 10%-35%), respectively, as compared to administration of rosuvastatin alone;
- After co-administration of rosuvastatin and relugolix, following administration of a 120-mg dose once daily for 14 days, the $AUC_{0-\infty}$ and C_{max} of rosuvastatin were decreased by 27% (90% CI 15%-37%), and 34% (90% CI 24%-42%), respectively, as compared to administration of rosuvastatin alone.

Overall, upon co-administration with relugolix, the total exposure ($AUC_{0-\infty}$) to rosuvastatin decreased with a trend toward a dose-related effect (13% reduction for 40 mg dose and 27% reduction for 120-mg dose of relugolix). The decreases in exposure to rosuvastatin upon co-administration with relugolix were unexpected considering that inhibition of the BCRP efflux transporter would be expected to result in an increase, rather than a decrease, in exposure. One might speculate that relugolix induces expression of either BCRP or OATP1B1, for which rosuvastatin is a substrate. Although the effect is not well understood, specifically the effect of the 40-mg dose is considered small and not clinically relevant. Relugolix does not appear to be an inhibitor of BCRP in vivo.

Results from a drug-drug interaction study with the Indiana Cocktail (TAK-385-102) showed that administration of 20-mg doses of relugolix once daily for 7 days did not have a clinically meaningful effect on the pharmacokinetics of substrates for select CYP enzymes, including caffeine (CYP1A2), tolbutamide (CYP2C9), dextromethorphan (CYP2D6), and midazolam (CYP3A4), when administered concomitantly as a drug cocktail. Doses of relugolix administered in this study were lower than the therapeutic dose for relugolix, but results are in line with in vitro data that indicate that relugolix does not have the potential to inhibit or induce CYP enzymes other than the weak induction of CYP3A4 with a 40-mg dose of relugolix, which was evaluated in the midazolam interaction study (MVT-601-044).

Potential Drug Interactions Among the Components of the Relugolix/E2/NETA FDC Tablet

The potential effect of coadministration of E2 and NETA on the pharmacokinetics of relugolix was assessed in the 6-week PK/PD study in premenopausal women (MVT-601-1001). Comparing the pharmacokinetics of relugolix after 6 weeks of administration of relugolix alone or coadministration with E2/NETA showed coadministration of E2 and NETA had a negligible effect on the PK of relugolix.

Upon coadministration of a single dose of E2/NETA at steady state for relugolix in study MVT-601-039 in postmenopausal women, some small decreases up to 20% in exposure to the estrogens were observed. The observed decreases in exposure to the estrogens are consistent with the weak inductive effect of relugolix on midazolam, a sensitive CYP3A substrate. However, in the context of the clinical development program for relugolix and at the selected doses of relugolix, E2 and NETA, the consequences are limited, as the relevant studies for PD, efficacy and safety have been done with coadministration of all components. There was no effect on PK of norethindrone.

Based on available information, coadministration of estradiol with norethindrone acetate did not elicit any apparent influence on the pharmacokinetics of norethindrone. Similarly, no relevant interaction of norethindrone on the pharmacokinetics of estradiol was found within the NETA dose range investigated in a single dose study (Activella Prescribing Information 2017).

Drug Interaction Potential for Drugs Effecting Gastric pH

It is agreed with the Applicant that despite pH sensitivity of relugolix dissolution, relugolix is expected to be fully dissolved at all potential physiological conditions, and coadministration of medications that raise gastric pH (such as PPIs and H2-receptor antagonists) with relugolix is not expected to affect the oral bioavailability of relugolix and therefore, dedicated studies were not conducted.

2.4.3. Pharmacodynamics

The clinical pharmacology program included three single- and multiple-ascending dose studies to characterize the safety and tolerability, pharmacokinetics and pharmacodynamics of relugolix, two of which were conducted in healthy adult premenopausal women (TAK-385_101 and TAK-385/CPH-001, similarly designed and conducted in the US and Japan, respectively) and 1 study conducted in healthy adult men (C27001):

The following studies including pharmacodynamics have been assessed:

Table: Studies including pharmacodynamics

Protocol Number	Short Title
Single and Multiple Rising-Dose Studies - monotherapy	
TAK-385_101	Single- and Multiple-Rising Dose Study in Healthy US Premenopausal Women
TAK-385/CPH-001	Single- and Multiple-Rising Dose Study in Healthy Japanese Premenopausal Women
C27001	Safety and Tolerability, Pharmacokinetic and Pharmacodynamic Study in Men (Prostate Cancer-Enabling Study)
Pharmacodynamic Studies – combination therapy	
MVT-601-1001	6-Week PK/PD Study with Relugolix Alone and in Combination with E2/NETA
TAK-385_106	Thorough QT/QTc Study
MVT-601-046	Ovulation Inhibition Study
Pharmacokinetic and Pharmacodynamic Modeling	
MYV-PKER-RELUGOLIX-737 Report 01	Population Pharmacokinetic (PopPK) Analysis Exposure-Response (Efficacy) Analysis
MYV-PKER-RELUGOLIX-737 Report 02	Exposure-Bone Mineral Density (BMD) Loss Analysis

Relugolix monotherapy

TAK-385_101 (Single- and Multiple-Rising Dose Study in Healthy Premenopausal Women, US)

This single- and multiple-rising dose study was a double-blind, randomized, placebo-controlled study to assess the safety and tolerability, pharmacokinetics, and pharmacodynamics of relugolix in healthy adult premenopausal women.

Overall, a total of 120 female participants were enrolled and 118 participants completed the study across single rising dose, food effect, and multiple-rising dose phases. This study was conducted in the United States.

In the *single-rising dose phase*, participants were randomized to receive a single 1-, 5-, 10-, 20-, 40-, or 80-mg dose of relugolix or placebo (5:1 ratio).

In the *multiple-rising* dose phase, participants were randomized to receive multiple 10-, 20-, or 40-mg doses once daily for 14 days of relugolix or placebo (3:1 ratio) (beginning within 2 to 7 days after the onset of their menstrual cycle). Study drug was administered daily approximately 35 minutes before the start of a standard breakfast.

Estradiol – single dose

After administration of single 1- to 80-mg doses of relugolix, mean E2 concentrations decreased in a dose-dependent manner with maximum reductions in E2 concentrations occurring at later postdose time points and with a longer duration of suppression for higher doses of relugolix, such that mean E2 concentrations remained lower than baseline values at 48 hours postdose for doses ≥ 20 mg.

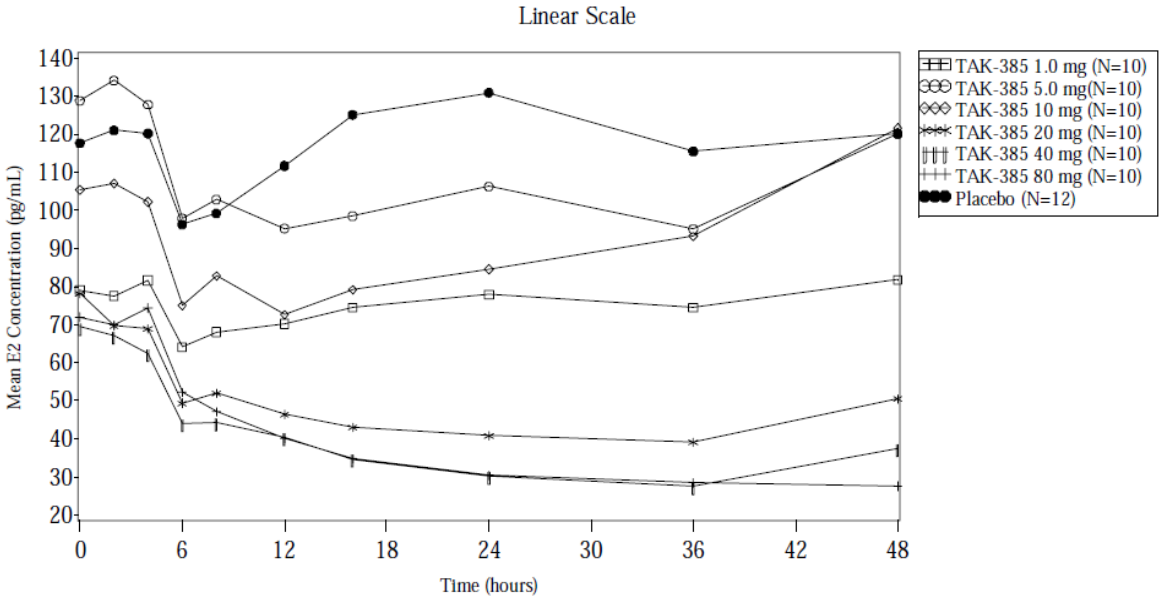
Initial reductions in the mean change from baseline in E2 concentrations occurred as early as 2 hours postdose for the 20- to 80-mg doses and, across all doses, near maximum reductions in the mean change from baseline values achieved by 6 hours postdose, with greater decreases compared with placebo observed for 5- to 40-mg doses (mean change from baseline of -25.4 pg/mL to -30.9 pg/mL, respectively vs. -21.4 pg/mL for placebo).

By 8 hours postdose, the decreases in the mean change from baseline E2 concentrations were greater than placebo for 5- to 80-mg doses (e.g., -25.2 pg/mL for the 40-mg dose vs. -13.7 pg/mL for placebo), which were sustained through at least 36 hours postdose. For the 20- to 80-mg doses, beginning at 16 hours postdose, mean E2 concentrations continued to decrease, with maximum decreases observed by 36 hours postdose (e.g., -41.9 pg/mL for the 40-mg dose vs. -2.2 pg/mL for placebo).

At 48 hours postdose, E2 concentrations continued to be decreased, with a trend towards recovery for the 20- and 40-mg doses whereas the 80-mg dose was still associated with maximum reductions in serum concentrations.

Importantly, at 24 hours postdose, mean E2 concentrations for the 40- and 80-mg doses of relugolix were similar (30.2 pg/mL and 30.3 pg/mL, respectively), suggesting that doses higher than 40 mg are unlikely to provide further suppression of E2 concentrations with once daily administration.

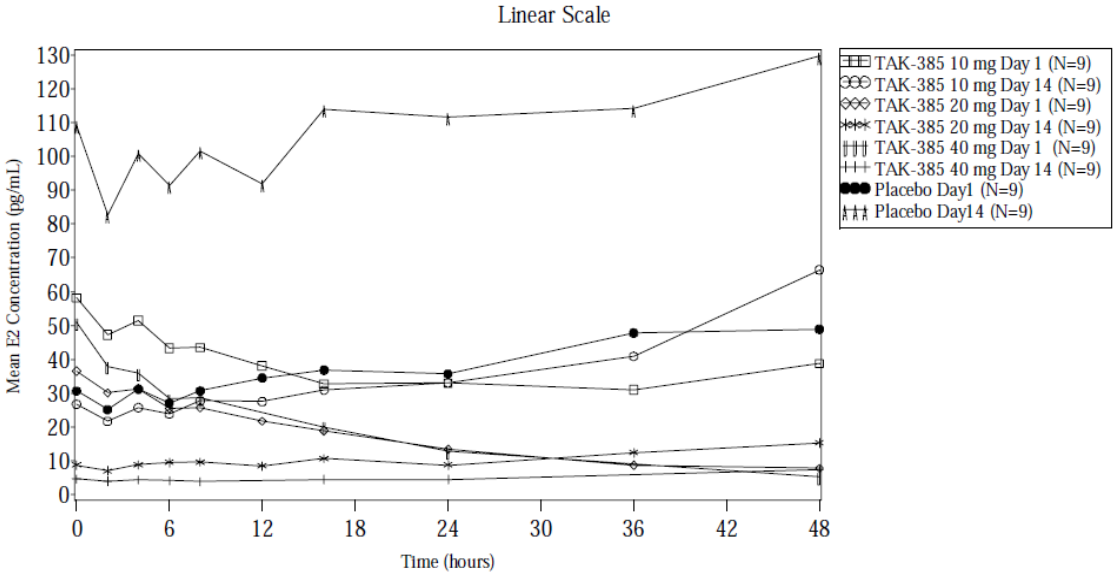
Figure: Mean Concentration Profiles for Serum Estradiol (E2) After Administration of Single Doses of Relugolix and Placebo in Healthy Adult Premenopausal Women (TAK 385_101)



Based on the results obtained in the single dose part, the applicant documented the rationale for the dose selection for 40 mg relugolix, as 80 mg did not result in any further suppression. At 24 hours the mean E2 concentration is not lower but similar for the 80-mg dose than for the 40-mg dose. As the product will be taken once daily, and as no extra lowering is expected from a higher dose, the results support that 40 mg will be sufficient. The multiple dose phase of this study has therefore been performed with 40 mg as maximum dose.

Mean concentration levels of 10, 20, and 40 mg relugolix and placebo over 14 days are shown in the figure below:

Figure: Mean Concentration Profiles for Serum Estradiol (E2) After Administration of Multiple Doses of Relugolix and Placebo in Healthy Adult Premenopausal Women (Day 1 and Day 14)



After 14 daily doses, the E2 serum concentration in the 40 mg group remains low at 4.6 pg/mL at 24 hours, which is in the postmenopausal range (≤20 pg/mL).

LH, FSH, progesterone

After administration of 10- 20- and 40-mg doses of relugolix for 14 days, dose-dependent reductions in mean LH, FSH, and progesterone concentrations also were observed, as can be seen in the following figures:

Figure: Mean Concentration Profiles for Serum Luteinizing Hormone (LH) After Administration of Multiple Doses of Relugolix and Placebo in Healthy Adult Premenopausal Women (Day 1 and Day 14)

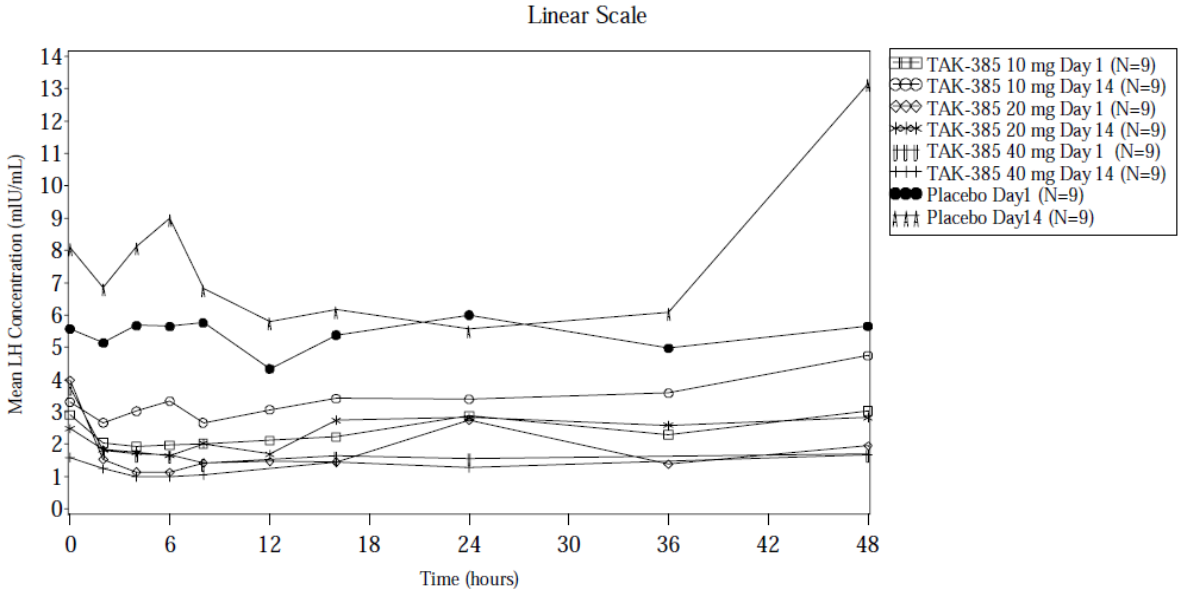


Figure: Mean Concentration Profiles for Serum Follicle Stimulating Hormone (FSH) After Administration of Multiple Doses of Relugolix and Placebo in Healthy Adult Premenopausal Women (Day 1 and Day 14)

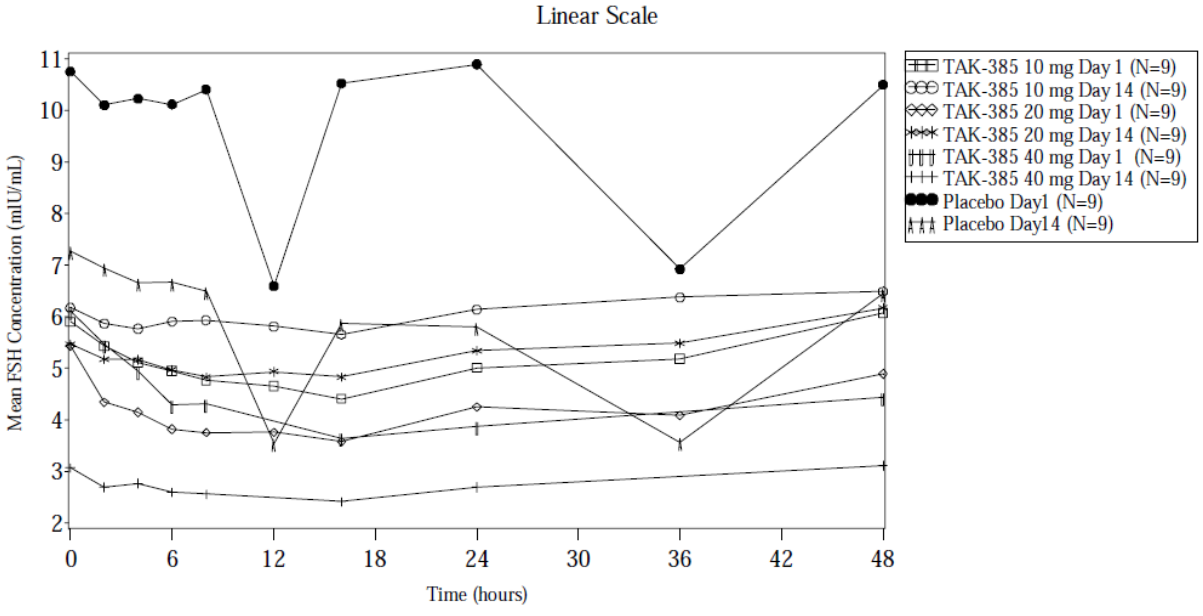
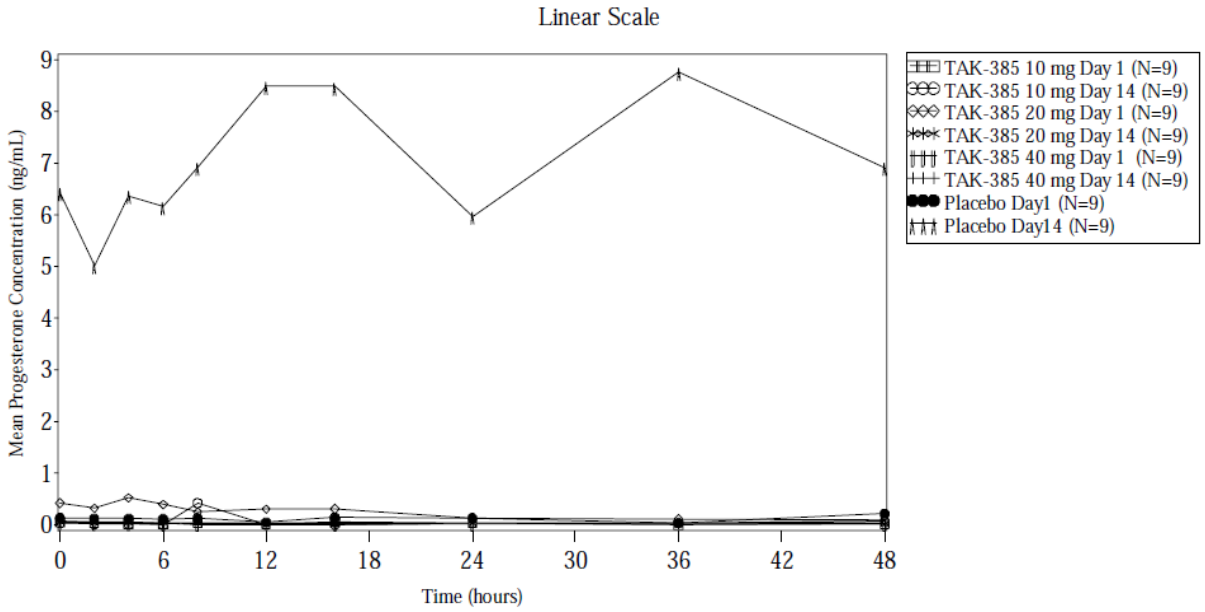


Figure: Mean Concentration Profiles for Serum Progesterone After Administration of Multiple Doses of Relugolix and Placebo in Healthy Adult Premenopausal Women (Day 1 and Day 14)



Growth hormone (GH), Prolactin (PRL), thyrotropin, or Adrenocorticotropic hormone (ACTH)

No changes in endogenous growth hormone, prolactin, thyrotropin (thyroid-stimulating hormone), and adrenocorticotropin hormone concentrations were observed with 14 days of 10-, 20-, or 40-mg daily dose of relugolix, demonstrating that relugolix does not disrupt the regulation of other hypothalamic neuroendocrine hormones that stimulate or inhibit the release of pituitary hormones other than GnRH.

Safety

In this study, single 1- to 80-mg doses and 10-, 20-, and 40-mg doses of relugolix once daily for 14 days were generally safe and well tolerated. No unexpected safety signals have been observed.

Summary

Study TAK-385_101 was a PK/PD single and multiple dose study. After administration of single 1- to 80-mg doses of relugolix, dose-dependent reductions in mean LH, FSH, and E2 serum concentrations with respect to both degree and duration were observed, consistent with the mechanism of action of relugolix as a GnRH receptor antagonist.

In the single dose part, the rationale for the dose selection for 40 mg relugolix was shown. At 24 hours the mean E2 concentration with the 40 mg dose was not lower but similar for the 80-mg dose. As the product will be taken once daily and no extra lowering is expected from a higher dose, 40 mg will be sufficient. The multiple dose phase has been performed with 40 mg as maximum dose.

Just like after administration of a single dose, after administration of 10- 20- and 40-mg doses of relugolix once daily for 14 days, dose-dependent reductions in mean E2, LH, FSH, and progesterone concentrations were observed, which remained for at least 24 hours.

No changes in endogenous growth hormone, prolactin, thyrotropin (thyroid-stimulating hormone), and adrenocorticotropin hormone concentrations were observed.

TAK-385/CPH-001 (Single- and Multiple-Rising Dose Study in Healthy Japanese Premenopausal Women, Japan)

The single- and multiple-rising dose study (TAK-385/CPH-001) was a double-blind, randomized, placebo-controlled, sequential-panel study to assess the safety and tolerability, pharmacokinetics, and pharmacodynamics of relugolix in healthy adult Japanese premenopausal women, having single 1- to 80-mg doses and 10-, 20, and 40-mg doses of relugolix once daily for 14 days. Overall, a total of 169 female participants, 20 to 45 years of age, inclusive, were enrolled and 143 participants completed the study across single-rising dose, food effect, and multiple-rising dose phases. Seventy-two female participants were enrolled and completed the single-rising dose phase, 24 female participants were enrolled and completed the food effect phase, and 48 female participants were enrolled and 47 completed the multiple-rising dose phase.

Pharmacodynamic results

Dose-dependent reductions in LH, FSH, and E2 concentrations were observed after both single- and multiple-dose administration of relugolix. Progesterone concentrations after multiple-dose administration also were markedly decreased, i.e. mean progesterone concentrations were consistently maintained between 1 and 1.3 nmol/L. The pharmacodynamic results from this Japanese study are in line with the results from the similar study TAK-385_101 (Single- and Multiple-Rising Dose Study in Healthy Premenopausal Women), conducted in the US.

Safety

Single 1- to 80-mg dose and 10-, 20-, or 40-mg doses of relugolix once daily for 14 days were generally safe and well tolerated in the healthy adult Japanese premenopausal women.

Summary

The pharmacodynamic results from the single- and multiple-rising dose study (**TAK-385/CPH-001**) showed that serum LH, E2, FSH, and progesterone concentrations were reduced in Japanese women, in accordance with the principal mechanism of action of GnRH antagonists.

The pharmacodynamic results in US women and Japanese women were similar.

C27001 (Safety and Tolerability, Pharmacokinetic and Pharmacodynamic Study in Men (Prostate Cancer-Enabling Study, UK)

The single- and multiple-rising dose study (C27001) was a double-blind, randomized, placebo controlled, 4-part study to assess the safety and tolerability, pharmacokinetics, and testosterone lowering efficacy of relugolix in healthy adult men. Dosing comprised of single 80-, 120-, 180-, or 360-mg dose of relugolix (Part 1) and multiple 20-, 40-, 80-, or 180 mg doses of relugolix once daily for 14 days (Part 2) or 40-, 60-, 80- or 160-mg doses of relugolix once daily for 28 days (Part 3). Overall, a total of 176 male participants were enrolled and 171 participants completed the study across all study parts.

Pharmacodynamic results

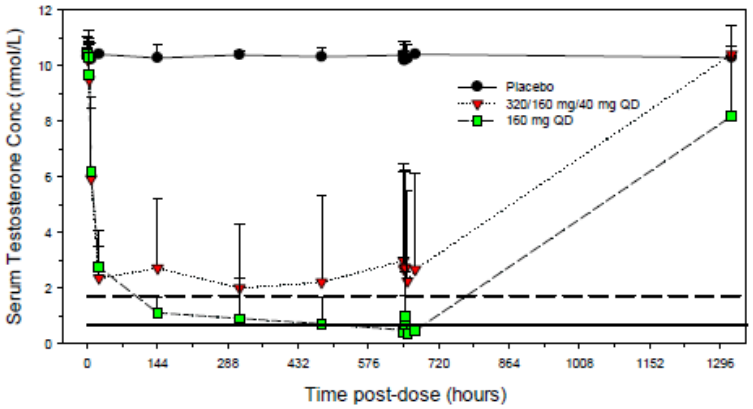
While no changes were observed in the placebo groups, serum LH and testosterone levels were markedly suppressed in all TAK-385 dose groups.

Testosterone

Consistent with the observed dose-dependent suppression of testosterone across the 20 to 180-mg QD studied dose range, the magnitude of the testosterone lowering-response was correlated with individual TAK-385 plasma trough concentrations; the higher the TAK-385 systemic exposure, the

greater the number of subjects achieving and maintaining medical castration throughout the treatment period. Median TAK-385 trough concentrations of > 4 ng/mL, which were associated with maintenance doses of 80 mg or greater, reduced testosterone to below conventional castration levels of 1.73 nmol/L in all subjects with the majority having serum testosterone levels decreased to below the lower castration threshold of 0.69 nmol/L after 28 days of treatment with TAK-385.

Figure: Mean (SD) Time-Course of Serum Testosterone Lowering Following Multiple Oral Dose Administration of TAK-385 for 28 Days, Part 3



Source: Table 14.2.5.4C and Listing 16.2.8.14C.
Abbreviations: QD = once daily; SD = standard deviation.
Dotted and solid lines represent medical castration, testosterone levels < 1.73 nmol/L and < 0.69 nmol/L, respectively.

Safety

The study showed that in accordance with the principal mechanism of action of GnRH antagonists, TAK-385 caused an immediate and effective suppression of gonadotropins (LH, FSH) and testosterone.

Reversible Transaminase elevations (ALT and AST) that reached ≥ 3 × ULN were considered to be an adverse event of clinical interest and would lead to study discontinuation. Elevations were observed in two participants. Additionally, one participant was also discontinued from the study due to reversible transaminase elevations (ALT and AST) that however, did not meet the criteria of an adverse event of clinical interest (i.e., maximum values were < 3 × ULN).

Summary

The single- and multiple-rising dose study (**C27001**) in 171 healthy adult men in the UK, showed that in line with the mechanism of action of GnRH antagonists, TAK-385 caused an effective suppression of gonadotropins (LH, FSH) and testosterone. Overall, a single 80-, 120-, 180-, or 360-mg dose of relugolix and multiple 20-, 40-, 80-, or 180 mg doses of relugolix once daily for 14 days or 40-, 60-, 80- or 160-mg doses of relugolix once daily for 28 days was generally safe and well tolerated in healthy adult men.

Relugolix monotherapy versus relugolix + E2/NETA combination

MVT-601-1001 (6-Week PK/PD Study with Relugolix Alone and in Combination with E2/NETA, United States)

This 6-week pharmacokinetic/pharmacodynamic study was a randomized, open-label, parallel-group study to assess the safety and tolerability, pharmacokinetics, and pharmacodynamics after administration of multiple 40-mg doses of relugolix alone or in combination with E2/NETA (1 mg/0.5 mg) once daily for 6 weeks in healthy adult premenopausal women. A total of 48 female participants, 18 to 48 years of age, inclusive, were enrolled and 46 participants completed the study. This study was

conducted in the United States. The treatment period was 6 weeks to encompass one complete menstrual cycle and characterize the PK/PD of relugolix combined with add-back therapy. Steady state PK and PD (FSH, LH, E2, and P) should have been reached after approximately 2 weeks of dosing.

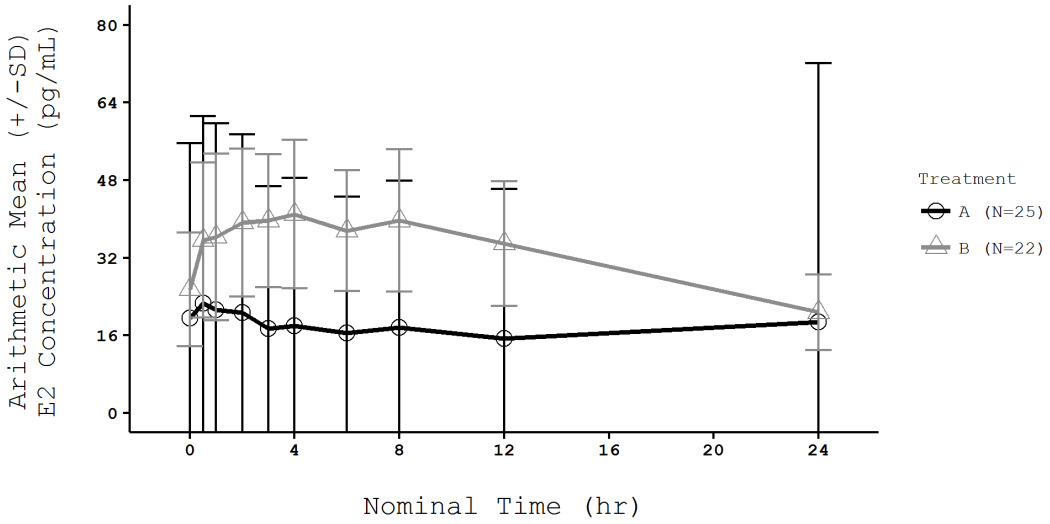
Additionally, bone resorption markers and serial PK/PD assessment were collected at Week 3 and Week 6.

Pharmacodynamic results:

Estradiol (E2)

Concentration-time curve over 24 hours for oestradiol is presented in the figure below:

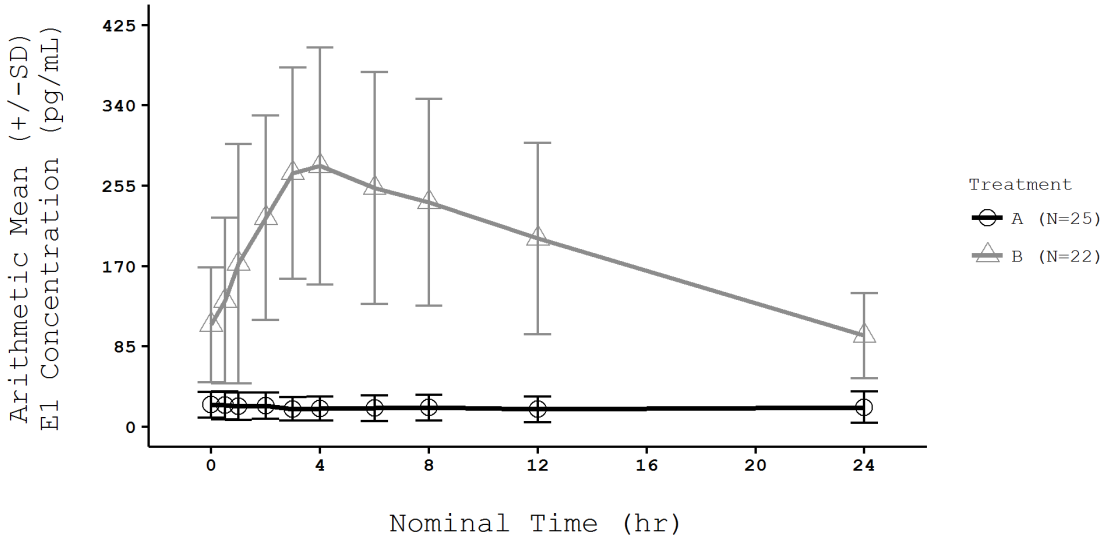
Figure: Concentration-time curve over 24 hours for E2



Estrone (E1)

Concentration-time curve over 24 hours for estrone is presented in the figure below:

Figure: Concentration-time curve over 24 hours for E1



E2 and E1 concentrations over 6 weeks

The effect of treatment B (relugolix 40 mg+E2 1mg/NETA 0.5 mg versus treatment A (relugolix 40 mg) was evaluated by calculating the relative exposure to E2. The results (and estrone (E1)) are presented in the table below and indicated that treatment B resulted in approximately 3-fold higher peak and overall extent of exposure (Cmax and AUC0-24).

Table: Pharmacokinetic Parameters for Serum Estradiol (E2) and Estrone (E1) After Administration of Multiple 40-mg Doses of Relugolix Alone and Coadministration with E2/NETA in Healthy Adult Premenopausal Women (Week 6) (MVT 601 1001)

	E2 (Week 6)		E1 (Week 6)	
Pharmacokinetic Parameters Statistics	**40 mg Relugolix Alone N = 21**	**Coadmin. of 40 mg Relugolix + E2/NETA N = 22**	**40 mg Relugolix Alone N = 25**	**Coadmin. of 40 mg Relugolix + E2/NETA N = 22**
AUC_{0-24} (pg*hr/mL)				
n	19	22	25	22
Mean (SD)	480 (917)	784 (262)	473 (337)	4450 (1980)
Median	148	755	414	4090
Min, Max	69.3, 4080	186, 1210	167, 1830	880, 7880
C_{max} (pg/mL)				
n	21	22	25	22
Mean (SD)	28.5 (55.3)	46.8 (17.3)	25.3 (16.6)	303 (137)
Median	7.22	49.2	23.1	270
Min, Max	2.74, 255	13.0, 78.9	7.98, 93.6	80.8, 621
C_{trough} (pg/mL)				
n	21	22	25	22
Mean (SD)	20.0 (54.3)	20.8 (7.81)	20.9 (16.7)	96.4 (45.0)
Median	5.77	21.4	16.9	98.6
Min, Max	2.50, 255	3.60, 39.0	7.04, 93.6	20.1, 184
C_{avg} (pg/mL)				
n	19	22	25	22
Mean (SD)	20.0 (38.2)	32.6 (10.9)	19.7 (14.1)	186 (82.4)

Median	6.17	31.5	17.2	170
Min, Max	2.89, 170	7.73, 50.2	6.95, 76.3	36.7, 329

Abbreviations: AUC = area under the concentration-time curve; AUC_{0-24} = AUC from time 0 to 24 hours; C_{avg} = average concentration; C_{max} = maximum observed plasma concentration; coadmin = coadministration; CSR = clinical study report; C_{trough} = trough concentration; E1 = estrone; E2 = estradiol; Max = maximum; Min = minimum; NETA = norethisterone acetate; N = number of participants; n = number of participants included in summary statistics; SD = standard deviation.
Note: Noncompartmental pharmacokinetic parameters and summary statistics.

Given some outlier E2 profiles or samples were observed (see PK sections on E2), potentially biasing the mean values, an additional summary of median E2 Cmax and Ctrough is presented below:

Table: Median serum E2 Cmax and Ctrough summary statistics by treatment and week (PK population)

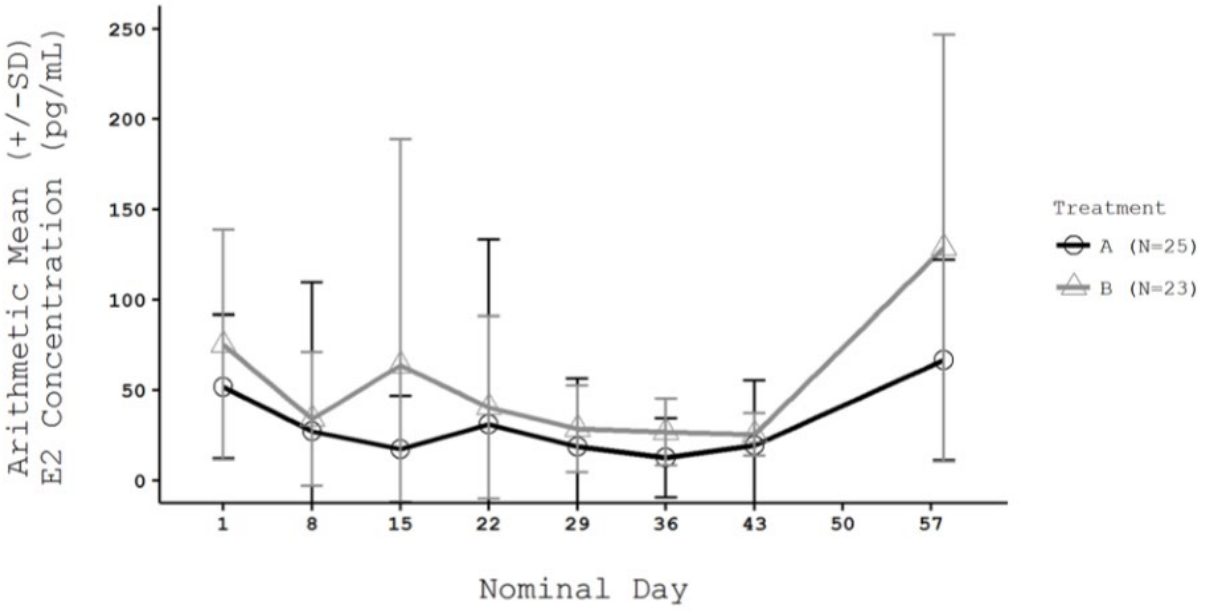
	Treatment A: relugolix 40 mg		Treatment B: relugolix 40 mg and E2/NETA (1 mg/0.5 mg)	
PK parameter	Week 3 (N = 23)	Week 6 (N = 21)	Week 3 (N = 23)	Week 6 (N = 22)
C_{max} (pg/mL)	9.55 (4.55, 606)	7.22 (2.74, 255)	44.7 (12.2, 487)	49.2 (13.0, 78.9)
C_{trough} (pg/mL)	6.40 (2.56, 606)	5.77 (2.50, 255)	22.6 (3.02, 104)	21.4 (3.60, 39.0)

Source: Table 14.2.2.2.1 and Table 14.2.2.2.2.
Abbreviations: hr = hour; N = number of subjects.
Median (minimum, maximum) are shown.

The effect of Treatment B versus Treatment A was evaluated by calculating the relative exposure to E2. The results are presented in the table above and indicate that Treatment B resulted in approximately 3-fold higher peak and overall extent of exposure (Cmax and AUC0-24) (See PK sections).

For both treatment groups, assessment of mean predose E2 concentrations over the 6-week treatment periods showed consistent predose E2 concentrations over time (Figure 9), suggesting that suppression of endogenous E2 production by relugolix was maintained (relugolix alone) and that coadministration of the same daily dose of E2 provided consistent minimum daily exposures, which were relatively higher, on average.

Figure: Mean (SD) Concentration-Time Profiles for Estradiol (E2) at Predose and Follow-up Visit After Administration of Multiple 40-mg QD Doses of Relugolix Alone and Coadministration with E2/NETA in Healthy Adult Premenopausal Women (Pharmacokinetic Analysis Set) (Linear Scale).



However, difference between relugolix and relugolix/E2/NETA can only be observed at time points Day 36 (estimated difference of 22.67 ng/L, p=0.024) and Day 15 (estimated difference of 30.55 ng/L, p=0.197 [not statistically significant]). After discontinuation of study treatment, mean E2 concentrations were similar to daily predose values during study treatment up to at least 48 hours after administration of the last dose (Day 45).

After administration of relugolix 40 mg alone or in combination with E2/NETA (1 mg/0.5 mg) once daily for 6 weeks, there was a greater number of participants with E2 predose concentrations below < 10 pg/mL and < 20 pg/mL after administration of relugolix alone compared with coadministration of relugolix and E2/NETA.

After administration of relugolix 40 mg alone, E2 predose concentrations < 10 pg/mL and < 20 pg/mL were observed in 68% and 72% of participants, respectively, compared with 4.3% and 26.1% of participants, respectively, after coadministration with E2/NETA (1mg/0.5 mg).

Figure: LS means change from baseline in E2 by time and treatment (PD analysis set)

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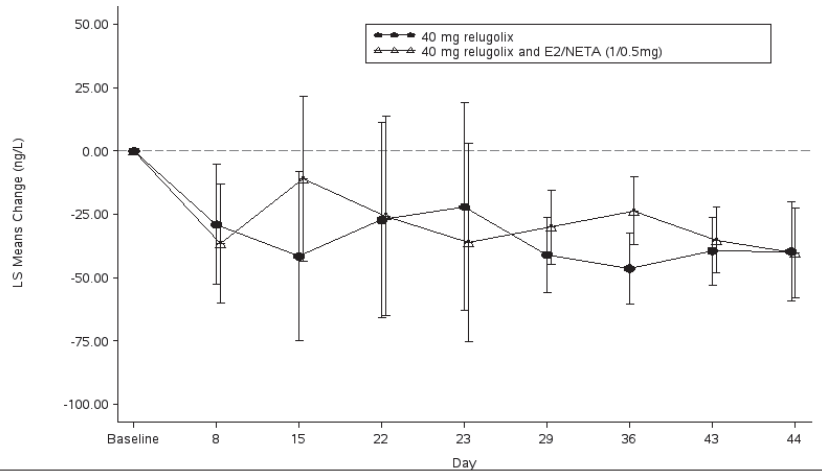
Figure 14.2.3.6 LS Means Change from Baseline in E2 by Time and Treatment (PD Analysis Set)



Only the predose E2 data are presented
Dashed line represent the reference line for change from baseline.
Vertical lines represent the 95% confidence interval around the least squares means from the linear mixed model which includes treatment, time, treatment by time interaction as factors and baseline value as covariate and assuming a compound symmetric covariance structure.

Data Source: ADPD Filename: F_14_2_3_6 Programmer: MI 08MAR2017 04:36 SAS 9.2

The results on E2 plasma levels indicate that with relugolix combination therapy (relugolix+E2/NETA), the average E2 plasma concentrations are 20.0 (38.2) in the relugolix monotherapy arm versus 32.6 (10.9) pg/mL in the relugolix combination arm, indicating an average of 50% increase in E2, in a range between 7.7 to 50 pg/mL. Based on the 24 hour measurements, plasma levels ranged between 20 to 60 pg/mL.

After administration of relugolix 40 mg alone once daily for 6 weeks, E2 predose concentrations below < 10 pg/mL and < 20 pg/mL were observed in 68% and 72% of participants, respectively, compared with 4.3% and 26.1% of participants, respectively, after co-administration with E2/NETA (1 mg/0.5 mg).

The target estradiol level to preserve bone is hypothesized as within 20 to 50/60 pg/mL (Friedman et al 1990). Add back therapy has been recommended for longer use of GnRH-agonists (> 6 months) since two decades in order to compensate for the loss of bone mineral density, and is mostly given in a dose of 1-2 mg estradiol or 0.625 mg conjugated estrogens in combination with a progestogen. Estradiol concentrations less than 20 pg/mL are associated with greater BMD loss over time. Based on modeling of E2 and BMD loss data collected during use of GnRH receptor agonists and antagonists form several published studies, it was postulated that a 90% reduction from baseline values in E2 concentrations to approximately 10 pg/mL results in a significant decrease in the % change from baseline lumbar spine BMD of up to -6% after 12 months of treatment, whereas an 80% decrease from baseline E2 concentrations to approximately 20 pg/mL prevented the decrease in BMD loss to no greater than -2% from baseline values, with the degree of loss beginning to plateau between 6 and 12 months (Riggs et al. 2012).

In conclusion, following multiple doses of Treatment A (relugolix 40 mg) or Treatment B (relugolix 40 mg and E2/NETA [1 mg/0.5 mg]), 3.3-fold higher E2 concentrations are observed for Treatment B, as expected. The results in this PK/PD study indicate that the addition of 1 mg estradiol results in an increase in estradiol concentrations which falls within the level that is assumed to preserve bone

mineral density. However, the DEXA results in the phase 3 extension trials will be decisive in the conclusion whether the 1 mg estradiol dose adequately protects BMD when used in combination with relugolix.

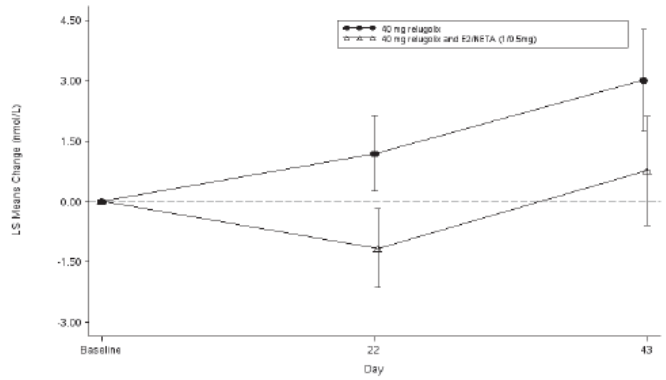
LH, FSH, progesterone

Serum concentrations of LH, FSH, and progesterone were consistent during the 6-week treatment period and with a similar degree of suppression during administration of relugolix alone and upon coadministration of relugolix with E2/NETA, suggesting a similar degree of suppression of the hypothalamic-pituitary-gonadal (HPG) axis.

Biomarkers of bone resorption NTx and CTx

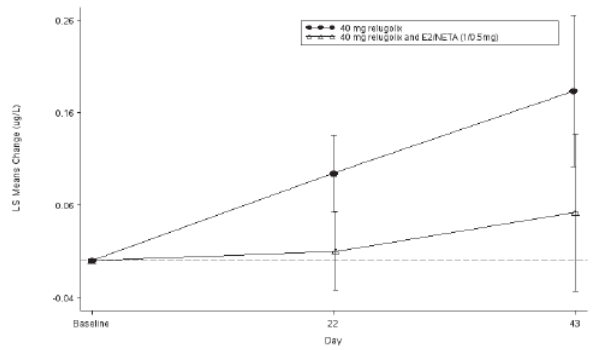
The biomarkers of bone resorption, serum N-telopeptide (NTx) and C-telopeptide (CTx), are normally suppressed in premenopausal E2 concentrations. Bone resorption is the process by which osteoclasts break down the tissue in bones and release the minerals. As expected, treatment with relugolix alone showed an increase of these markers. During coadministration of E2/NETA no significant change from baseline in these biomarkers was observed.

Figure: Least square means change from baseline in bone resorption biomarker N-telopeptide (NTx) by time and treatment



Source: Figure 14.2.3.4.
Abbreviations: hr = hour; N = number of subjects; SD = standard deviation.
Dashed line represents the reference line for change from baseline.
Vertical lines represent the 95% CI around the least squares means from the linear mixed model which includes treatment, time, treatment by time interaction as factors and baseline value as covariate and assuming a compound symmetric covariance structure.

Figure: Least square means change from baseline in bone resorption biomarker C-telopeptide (CTx) by time and treatment



Source: Figure 14.2.3.5.
Abbreviations: hr = hour; N = number of subjects; SD = standard deviation.
Dashed line represents the reference line for change from baseline.
Vertical lines represent the 95% CI around the least squares means from the linear mixed model which includes treatment, time, treatment by time interaction as factors and baseline value as covariate and assuming a compound symmetric covariance structure.

The biomarkers of bone resorption, serum N-telopeptide (NTx) and C-telopeptide (CTx), are normally suppressed in premenopausal E2 concentrations. As expected, treatment with relugolix alone showed an increase of these markers. During coadministration of E2/NETA (hormonal add-back therapy) no significant change from baseline was observed.

Bleeding patterns and incidence of hot flushes

Each of the study treatments (Treatment A [relugolix 40 mg] or Treatment B [relugolix 40 mg and E2/NETA, 1 mg/0.5 mg]) was observed to mitigate the incidence of menstrual bleeding during the study; the proportions of subjects reporting no menstrual bleeding (except spotting) over the last 28 days of treatment were 88.0% and 47.8% after treatment with relugolix alone or relugolix and E2/NETA, respectively. The proportion of subjects reporting hot flushes (any grade) was significantly mitigated by the addition of E2/NETA (17.4%, versus 60.0% for relugolix alone during Week 6). Severe hot flushes were also reduced by the addition of E2/NETA (reported by 2 subjects with a mean of 9 events compared to 5 subjects with a mean of 63.2 events after treatment with relugolix alone).

Safety

Overall, administration of relugolix 40 mg alone or co-administration with E2/NETA (1 mg/0.5 mg) once daily for 6 weeks was generally safe and well tolerated in healthy premenopausal women.

After administration of relugolix 40 mg alone once daily for 6 weeks, the safety profile was consistent with the pharmacological effects associated with suppression of sex steroid hormones, particularly E2, such as hot flushes and reduced or irregular menstrual bleeding.

After co-administration of relugolix 40 mg and E2/NETA (1 mg/0.5 mg) once daily for 6 weeks, the frequency of participants who reported hot flushes and no menstrual bleeding (except spotting) were reduced (17.4% and 47.8%, respectively) compared to administration of relugolix alone (60.0% and 88.0% of participants, respectively).

MVT-601-046 (Ovulation Inhibition Study, Germany)

In an open-label, five-period, single-arm study in healthy premenopausal women consisting of a pre-treatment period to confirm ovulatory status, an 84-day (3x 28-day) treatment period to assess the effects of relugolix combination therapy on ovarian activity, and a post-treatment follow-up period to determine the duration of time of the return to ovulation, ovulation was inhibited (based on the

Hoogland-Skouby scale) in 100% of women during the entire 84-day treatment period. A total of 84 female participants, 18 to 35 years of age, inclusive, were enrolled, 70 ovulatory participants entered the treatment period and 67 participants completed the study.

Primary endpoint results

Ovarian inhibiting activity

Ovarian inhibiting activity, as evidenced by the degree of follicular growth, was markedly suppressed during the 84-day treatment period. The percentage of women achieving a Hoogland-Skouby score of <5 during the 84-day treatment period, consistent with a lack of luteal activity, was 100% (95%CI: 94.6, 100%) in the Completers Population. Thus, 100 % inhibition of ovulation was achieved with relugolix combination therapy (relugolix 40 mg in combination with E2 1 mg and NETA 0.5 mg).

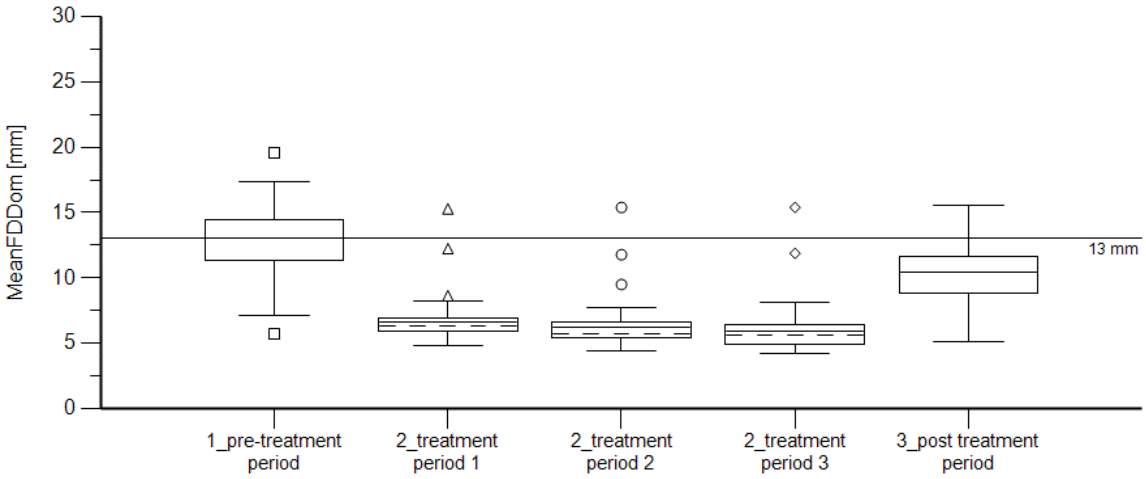
Table: Hoogland-Skouby Score Frequency Analysis by Treatment Period, N = Number of Observations, Evaluable Population

	1 No activity		2 Potential activity		3 Non-active FLS		4 Active FLS		5 LUF		6 Ovulation		
Period	N	[%]	N	[%]	N	[%]	N	[%]	N	[%]	N	[%]	N total
Treatment Period 1	60	85.71	4	5.71	1	1.43	5	7.14	0	0.00	0	0.00	70
Treatment Period 2	65	94.20	1	1.45	1	1.45	2	2.90	0	0.00	0	0.00	69
Treatment Period 3	65	97.01	0	0.00	1	1.49	1	1.49	0	0.00	0	0.00	67
Post-treatment Period	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	66	100.00	66

Follicular growth

Follicular growth was considerably suppressed during relugolix combination therapy, with mean dominant follicle size (diameter) consistently maintained at approximately 6 mm throughout the 84-day treatment period (mean [SD] dominant follicle diameter in Treatment Period 1, Treatment Period 2, and Treatment Period 3 of 6.62 [1.494] mm, 6.19 [1.627] mm, and 5.96 [1.688] mm, respectively). Mean values measured in the Pre- and Post-Treatment Periods were higher due to the normal follicular growth during the untreated study periods (mean [SD] dominant follicle diameter of 13.01 [2.455] and 10.43 [1.840], respectively), as visualized below:

Figure: Box and Whisker Plots of Mean Dominant Follicle Size (mm) in the Pre-Treatment Period, Treatment Periods (1, 2, and 3), and Post-Treatment Period



Pituitary and Ovarian Hormones

Ovarian production of E2 and progesterone (primary) and pituitary secretion of FSH and LH as well as were markedly suppressed with relugolix combination therapy.

In total, mean serum E2 concentrations (mean and median E2 serum concentrations consistently maintained between 0.11 and 0.16 nmol/L [31.00 and 43.66 pg/ml] during the 84-day treatment period). Mean progesterone concentrations were consistently maintained between 1 and 1.3 nmol/L, with individual values all below 5 nmol/L (1 ng/mL), the cut-off value for luteal activity in the Hoogland-Skouby assessment scale, which is consistent with the suppression of ovulation observed across all three treatment periods.

Per period, the mean values for FSH, LH, estradiol (nmol/L and pg/L) and progesterone in the three active treatment periods and in the post-treatment period (T4) are given below:

Table: Mean Values (SD) per Participant per Period of FSH, LH, estradiol and progesterone

Treatment period (TP)	Parameter	Mean value per participant FSH [U/L]	Mean value per participant LH [U/l]	Mean value per participant estradiol [nmol/L]	Mean value per participant estradiol [pg/mL]	Mean value per participant progesterone [nmol/L]
TP 1	N	70	70	70	70	70
	Arithmetic Mean (SD)	2.33 (1.27)	0.50 (0.71)	0.13 (0.042)	35.61 (11.35)	0.94 (0.54)
TP 2	N	70	70	70	70	70
	Arithmetic Mean (SD)	2.32 (1.66)	0.80 (1.08)	0.14 (0.47)	38.65 (12.78)	1.25 (0.49)
TP 3	N	68	68	68	68	68
	Arithmetic Mean	2.34 (1.67)	1.04 (1.38)	0.14 (0.06)	39.10 (15.12)	1.25 (0.50)
TP 4	N	67	67	67	67	67
	Arithmetic Mean (SD)	5.58 (1.14)	7.78 (4.57)	0.27 (0.10)	72.43 (27.90)	8.97 (5.30)

Secondary endpoint results

Return to ovulation

The mean time to ovulation following discontinuation of relugolix combination therapy was 23.5 days, with 97.01% (65 of 67) of women having a confirmed ovulation within 36 days post-treatment, with

one additional participant who ovulated on Day 43 and another participant who missed all post-treatment assessments and began menstruating on Day 39. As a result, 66 out of 67 study participants (100% of evaluable participants) had a return of ovulation and one additional participant had a return of menses after discontinuation of treatment.

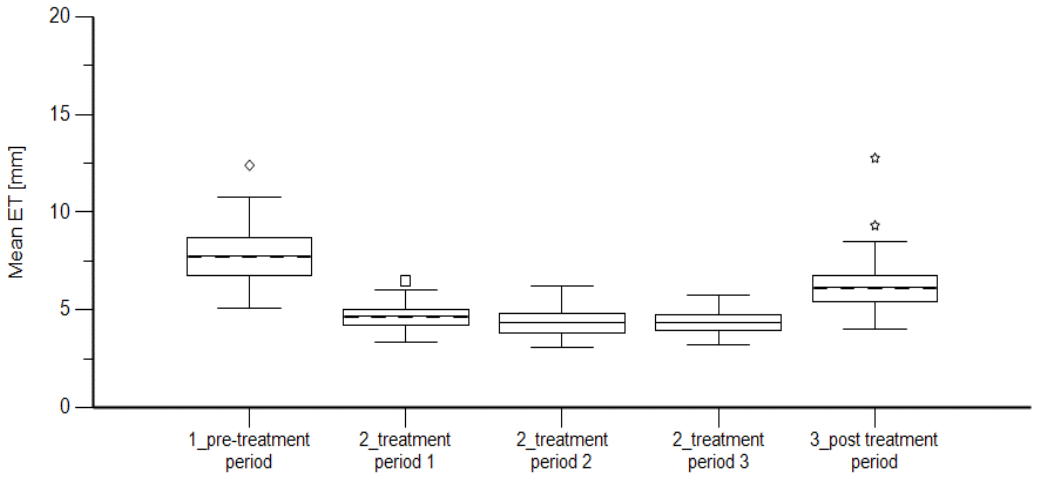
Bleeding pattern

Of the total 5159 evaluable days during the 84-day treatment period, the majority of days were reported as "no bleeding" (88.23%) or as "spotting" (9.52%). Only 2.25% of evaluable days during the 84-day treatment period were reported as "bleeding".

Endometrial proliferation

Endometrial proliferation was suppressed with relugolix combination therapy, with endometrial thickness being consistently maintained between 4 and 5 mm and likely contributing to the reduction in overall bleeding. The following plot shows that suppression of endometrial proliferation during treatment (TP 1, 2, 3) was pronounced:

Figure: Box and Whisker Plots of Endometrial Thickness (mm) in the Pre-Treatment Period, Treatment Periods (1, 2, and 3), and Post-Treatment Period



Note: Median values (dashed line) and arithmetic mean values (solid line) with 25th and 75th percentiles (box), most extreme point within 1.5 interquartile ranges (whiskers) and outliers.

Safety

Co-administration of relugolix 40 mg, E2/NETA (1 mg/ 0.5 mg; Activelle) once daily for 84 days was generally safe and well tolerated in healthy premenopausal women.

TAK-385_106 (Thorough QT/QTc Study, United States)

In a randomized, double-blind (open-label moxifloxacin), placebo- and positive (moxifloxacin)-controlled, parallel-group study conducted to assess the potential effects of a therapeutic (60-mg) dose and a supratherapeutic (360-mg) dose of relugolix on QT interval prolongation in healthy adult men and women (N = 280; n = 70 per treatment group), administration of single 60- or 360-mg doses of relugolix did not prolong the QT/QTc interval (based on the QT interval with Bazett, Fridericia, or individual correction methods). This finding was evidenced by an upper bound of the 95% CI for the time-matched maximum mean baseline- and placebo-adjusted QTc interval of < 10 msec, indicating no QTc interval prolongation of clinical or regulatory concern, in accordance with ICH guidelines.

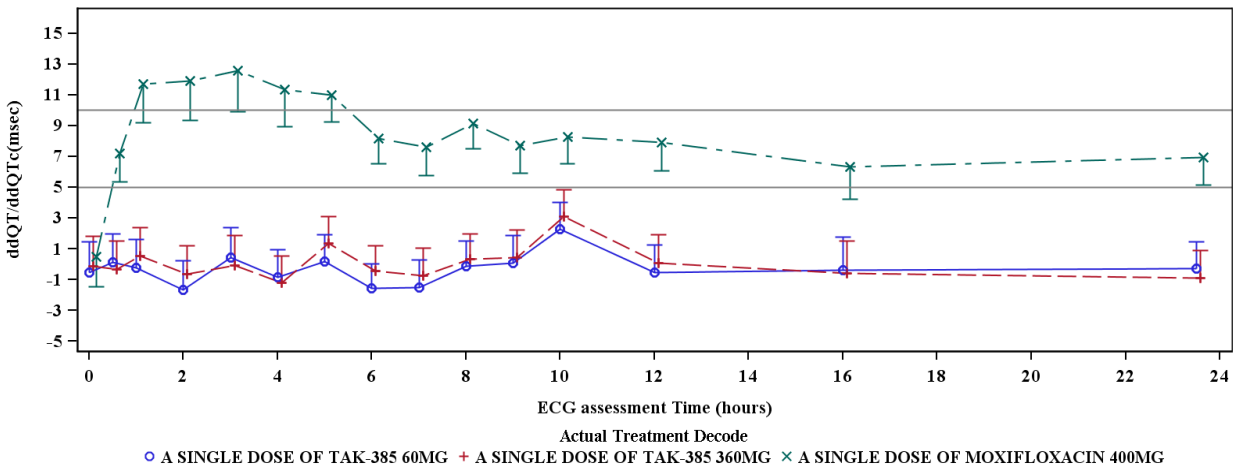
Table: QTcF for a Single 60-mg or 360-mg Dose of Relugolix vs. Placebo in Healthy Adult Men and Women (TAK 38_106)

	60-mg Relugolix vs. Placebo			360-mg Relugolix vs. Placebo		
ECG Parameter	Time at Maximum Upper Bound (hr)[a]	LS Means of Difference (msec)	Upper Bound of 95% 1-Sided CI[b]	Time at Maximum Upper Bound (hr)[a]	LS Means of Difference (msec)	Upper Bound of 95% 1-Sided CI[b]
QTcF	10	2.3051	4.0328	10	3.1059	4.8340

Abbreviations: CI = confidence interval; CSR = clinical study report; ECG = electrocardiogram; LS = least squares; QTcF = QT interval with Fridericia correction method.
Note: A linear mixed-effect model with repeated measures was used. Baseline, gender, treatment, scheduled time point, and interaction between treatment and scheduled time point are fixed factors in the model. Mean QTc on Day 1 was used as Baseline; unstructured was used as the covariance structure.
a. Time at the maximum of the upper bound of the 95% 1-sided CI over all time points.
The 95% 1-sided CI is for the difference from placebo in the LS means of the change from baseline.

Furthermore, a linear mixed-effects analysis of the change from baseline in QTc interval and relugolix plasma concentrations showed no concentration-related effects of relugolix on QTc interval prolongation, with a slope of concentration versus QTc interval using Fridericia's formula (QTcF) of -0.004 msec/ng/mL (90% CI -0.008, 0.001). The positive control moxifloxacin resulted in the expected increase in QTc interval (lower bound of placebo and baseline adjusted change in QTc > 5 msec 1 to 4 hours postdose). The C_{max} of relugolix after administration of a single 360-mg dose was at least 9 times greater than the C_{max} after administration of a 40-mg dose of relugolix once daily.

Figure: Least Squares Means (95% CI) ddQT/ddQTc vs. ECG Assessment Time by Treatment for QTcF in Healthy Adult Men and Women (TAK-385_106)



The study did not suggest for any QT prolonging effect of relugolix with point estimates for the corrected ddQTcF around 5 ms and thus far below the 10 ms for regulatory concern. There appears some hysteresis as the largest effect was observed after 10 hours instead of around tmax (3 hours), however, with no suggestion for QT prolongation this is not considered of such relevance to be further pursued.

QTcF data in other studies (phase 3 clinical program)

During the two phase 3 relugolix 24-week combination therapy studies, ECGs were obtained at baseline, Week 12, and Week 24. No patients in any treatment group had a QTcF excursion > 501 msec at any of the assessed time points with up to 24 weeks of treatment with study drug. A change

from baseline of ≥ 30 msec was reported in comparable number of patients across treatment groups, including 5.9% (15/254) of patients treated with relugolix + E2/NETA, 5.0% (13/258) of patients treated with relugolix + delayed E2/NETA, and 4.3% (11/256) of patients treated with placebo; these changes were not assessed as clinically meaningful.

A change from baseline of ≥ 60 msec was reported for one patient (MVT-601-3001) in the relugolix + delayed E2/NETA group. At baseline, the ECG showed normal sinus rhythm with normal T wave morphology with a heart rate of 68 bpm and QTcF of 383 msec. The patient was reportedly dosed 14 minutes before the baseline ECG, and therefore the screening ECG with QTcF of 367 msec was used as the reference baseline. At Week 12, this woman had a QTcF value of 439 msec, a 72 msec increase from the reference baseline (screening) and a 56 msec increase from the baseline visit. The prolongation relative to the reference baseline persisted; at Week 24 the QTcF interval was 440 msec (73 msec increase from reference baseline and 57 msec from the baseline visit), and at the safety follow-up visit the QTcF was 436 msec (69 msec increase from reference baseline and 53 msec from the baseline visit). No adverse events suggestive of arrhythmia were reported.

In the Uterine Fibroids Long-Term Safety Population (MVT-601-3003 extension study), QTcF results with the addition of up to 28 weeks of exposure are consistent with those in the Uterine Fibroids 24-Week Safety Population, with no clinically significant changes in QTcF identified in this population which received relugolix combination therapy for up to 52 weeks.

Overall, no clinically significant changes in QTcF were identified during these studies.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics of relugolix, E2 and NETA have been investigated and described extensively. No major issues have been identified.

Clinical pharmacodynamics

Mechanism of action

Relugolix

Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to GnRH receptors in the anterior pituitary gland. This binding blocks endogenous GnRH from binding to and subsequent activation of GnRH receptors, preventing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are reduced. Reduction in FSH concentrations will prevent follicular growth and development, thereby limiting the production of estrogen by the developing ovarian follicles and secretion into the systemic circulation. Prevention of an LH surge inhibits ovulation and therefore, the corpus luteum does not develop, which precludes the production and secretion of progesterone into the systemic circulation.

The mechanism of action of relugolix was supported by several studies performed during the clinical development phase. Dose-dependent decreases in LH, FSH and E2 occurred after administration of relugolix, consistent with the mechanism of action of a GnRH receptor antagonist suppressing the hypothalamic–pituitary–adrenal axis (HPA axis), two of which were conducted in healthy adult premenopausal women (**TAK-385_101 and TAK-385/CPH-001**) and 1 study conducted in healthy adult men (**C27001**).

Dose-finding

Near maximal reductions in E2 concentrations were observed with the proposed clinical dose of 40 mg. Upon administration of 40-mg doses of relugolix, low E2, i.e. on average 6 pg/mL which is within the postmenopausal range, and low progesterone concentrations were maintained between 1 and 1.3 nmol/L over time and during a dosing interval. This was shown in the single/multiple dose PK/PD studies conducted in healthy adult premenopausal women (**TAK-385_101** in the US (and **TAK-385/CPH-001** in Japan). A cross-study analysis on the effect of race or ethnicity on relugolix exposure identified no clinically relevant effects, indicating that pharmacokinetic, pharmacodynamic, safety and efficacy assessments made across studies with non-Japanese and Japanese populations in the relugolix clinical development program can be compared (see below **MYV-PKER-RELUGOLIX-737 Report 01**).

Estradiol/norethisterone (E2/NETA)

This combination is a known hormone replacement therapy (HRT, marketed in the EU with the name Activelle). The estradiol is similar to the endogenously produced hormone estradiol. Exogenously administered estradiol will compensate for the strong suppression of endogenous estradiol production during relugolix monotherapy. The slight increase in estradiol plasma levels is claimed to alleviate symptoms associated with a hypoestrogenic state, i.e. vasomotor symptoms and bone mineral density loss.

Norethisterone acetate is a synthetic progestogen. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Relugolix + E2/NETA

The mechanism of action of a GnRH antagonist, bringing the patient to postmenopausal (castrate) hormone levels, is expected to prevent the hormone-dependent proliferative effects on the endometrium, reducing the degree of heavy bleeding associated with uterine fibroids. However, patients reach postmenopausal (castrate) hormone levels, will have consequent postmenopausal symptoms (i.e. vasomotor symptoms) and bone mineral density (BMD) loss. To mitigate the BMD loss and reduce postmenopausal symptoms, estradiol (E2 1 mg) was added. The progestin norethisterone (NETA) 0.5 mg has been added to oppose estrogen-induced endometrial proliferation due to exogenous administration of E2. E2/NETA has been on the market since 1998 as hormone replacement therapy (HRT) under the brand name Activelle. Additionally, estradiol is the estrogen component in two combined oral contraceptives, i.e. estradiol/nomegestrol and estradiol valerate/dienogest. Norethisterone containing COCs are all combined with the estrogen ethinylestradiol (EE).

The doses of E2 and NETA selected by the MAH for combination with relugolix were based on data in the literature, particularly from studies that supported the dose selection and approval of the E2/NETA combination, Activelle (known also as Kliovance some European countries and Activella in the US and EU), for treatment of vasomotor symptoms and prevention of BMD loss associated with menopause, with the addition of NETA 05 mg which is shown to have adequate protection of the endometrium. Effect of estradiol (and other estrogens) on BMD is dose-dependent; estradiol doses of 1 to 2 mg are prescribed. The data available that evaluated lower estradiol doses (0.5 mg) on BMD is limited and effect on reduction in fracture rate is not clear. Data from these studies supported that low E2 doses of 1 mg did provide adequate benefit (Stadberg et al. 1996) and that doses of NETA lower than 0.5 mg would be associated with less predictable bleeding patterns (Archer et al. 1999). They also confirmed that a 0.5 mg dose of NETA was sufficient to protect the endometrium from the proliferative effects of

a 1 mg dose of E2 (Kurman et al. 2000). However, in postmenopause the effect of estradiol on BMD increase is dose-dependent, i.e. 2 mg estradiol has been shown is have greater effect.

Pharmacodynamic effects

Effects on pituitary and ovarian hormones

A 6-week pharmacokinetic (PK) and pharmacodynamic study in healthy premenopausal women (**MVT-601-1001**) was conducted to confirm that relugolix combination therapy, at the selected doses of relugolix, E2, and NETA, would provide systemic E2 concentrations considered sufficient to mitigate vasomotor symptoms and the negative effects of hypoestrogenism on BMD. Data from this study demonstrated that relugolix combination therapy maintained E2 levels within the targeted range of 20 to 50 pg/mL (therapeutically effective range is considered 20-60 pg/ml for estradiol and < 3 ng/ml for progesterone) over 24 hours and for as long as the study drug was taken, with a low incidence of vasomotor symptoms and with minimal changes in markers of bone resorption (carboxy-terminal and amino-terminal cross-linked telopeptide of type 1 collagen), relative to relugolix monotherapy. Coadministration of relugolix with E2/NETA did apparently not influence the suppression of the HPA axis. Higher E2 exposure in the relugolix-E2/NETA group showed more subject-reported menstrual bleeding and reduced frequency and severity of hot flushes.

Ovulatory function

The Ovulation Inhibition Study (MVT-601-046) was performed to assess the effect of co-administration of relugolix/E2/NETA on the potential to suppress ovarian activity in 70 ovulatory participants in Germany, for three 28-day treatment periods. The primary study endpoint was met.

In an open-label, non-randomized (single treatment group) study in healthy premenopausal women, administration of [TRADENAME] once daily for 84 days substantially suppressed follicular growth throughout the 84-day treatment period (mean dominant follicle size of approximately 6 mm) and ovulation was inhibited in 100% of women as assessed by the Hoogland-Skouby score. After discontinuation of [TRADENAME), the mean time to ovulation was 23.5 days, with ovulation demonstrated in all evaluable women (66 of 67) by Day 43. The remaining subject missed all the assessments post-treatment but reported menstruation commencing on Day 39.

Bone resorption

The biomarkers of bone resorption, serum N-telopeptide (NTx) and C-telopeptide (CTx), are normally suppressed in premenopausal E2 concentrations. As expected, treatment with relugolix alone showed an increase of these markers. During coadministration of E2/NETA (hormonal add-back therapy) no significant change from baseline was observed, which is supportive for the possibility of long term use.

An exposure-BMD model was developed to support long-term use of relugolix combination therapy based on the predicted risk for BMD loss over time. Simulations performed with the model show that the plateau in BMD loss observed in the phase 3 studies was maintained for up to 2 years of treatment and the predicted values for relugolix combination therapy were similar to those predicted for placebo (see below for long term BMD modelling **MYV-PKER-RELUGOLIX-737 Report 02**).

Endometrium

In the ovulation inhibition study (MVT-601-046), endometrial thickness assessed by transvaginal ultrasound was markedly reduced during relugolix combination therapy (mean endometrial thickness consistently between 4-5 mm) compared with mean values prior to and after study treatment (7.8 and 6.2 mm, respectively). Endometrial proliferation was suppressed with relugolix combination therapy, with endometrial thickness being consistently maintained between 4 - 5 mm and likely contributing to the reduction in overall bleeding.

QTc interval prolongation

In a randomized, double-blind, placebo- and positive-controlled (open-label moxifloxacin), parallel-group, single-dose thorough QT/QTc study (TAK-385_106), neither a 60-mg dose (therapeutic dose; estimated to have similar exposure as a single dose to those associated with a once daily 40-mg dose) nor a 360-mg dose (supratherapeutic dose) of relugolix resulted in prolongation of the QT interval with Fridericia's correction (QTcF) of clinical or regulatory concern. There appears some hysteresis as the largest effect was observed after 10 hours instead of around tmax (3 hours), however, with no suggestion for QT prolongation this is not considered of such relevance to be further pursued.

QTc interval in other studies

During the two phase 3 relugolix 24-week combination therapy studies (**MVT-601-1001, MVT-601-1002**), ECGs were obtained at baseline, Week 12, and Week 24. No patients in any treatment group had a QTcF excursion > 501 msec at any of the assessed time points with up to 24 weeks of treatment with study drug. A change from baseline of ≥ 30 msec was reported in comparable number of patients across treatment groups, including 5.9% (15/254) of patients treated with relugolix + E2/NETA, 5.0% (13/258) of patients treated with relugolix + delayed E2/NETA, and 4.3% (11/256) of patients treated with placebo; these changes were not assessed as clinically meaningful. In the Uterine Fibroids Long-Term Safety Population (MVT-601-3003, extension study), no patients in any treatment group at Week 52 were observed to have a post-baseline QTcF of ≥ 500 msec. In the relugolix +E2/NETA group three patients had post-baseline findings (QTcF ≥ 480 msec or excursion ≥ 60 msec). Overall, no clinically significant changes in QTcF were identified during these studies.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

In general, pharmacokinetics of relugolix, E2 and NETA have been investigated and described extensively and sufficiently.

Pharmacodynamics

After administration of relugolix monotherapy, decreases in mean concentrations of LH, FSH, E2 and progesterone were expected to be observed, consistent with the mechanism of action for relugolix as a GnRH receptor antagonist.

The decreased concentrations of estradiol (and progesterone) with relugolix are expected to prevent the hormone-dependent proliferative effects on the endometrium, reducing the degree of bleeding associated with menstruation. To minimize the consequent postmenopausal symptoms (i.e. vasomotor symptoms and bone mineral density (BMD) loss), an E2 1 mg is administered within the relugolix combination therapy. The progestin norethisterone 0.5 mg has been added to oppose estrogen-induced endometrial proliferation due to exogenous administration of E2.

Relugolix Monotherapy

Mechanism of action and dose-finding

Study TAK-385_101 was a PK/PD single and multiple dose study in 120 healthy premenopausal women in the US. After administration of single 1- to 80-mg doses of relugolix, dose-dependent reductions in mean LH, FSH, and E2 serum concentrations with respect to both degree and duration were observed, consistent with the mechanism of action of relugolix as a GnRH receptor antagonist. In the single dose part, the rationale for the dose selection for 40 mg relugolix was shown. At 24 hours postdose, mean E2 concentrations for the 40- and 80 mg doses of relugolix were similar (30.2 pg/mL

and 30.3 pg/mL, respectively), suggesting that doses higher than 40 mg are unlikely to provide further suppression of E2 concentrations with once daily administration.

The multiple dose phase has therefore been performed with 40 mg as maximum dose. After administration of 10- 20- and 40-mg doses of relugolix once daily for 14 days, dose-dependent reductions in mean E2, LH, FSH, and progesterone concentrations were observed, which remained for at least 24 hours. For the 40 mg dose group, absolute mean E2 predose concentrations on Day 4, 6, 8, 10, 12, and 14 were consistently low, ranging from 4.7 to 6.7 pg/mL compared with 59.5 to 109.1 pg/mL for placebo.

No changes in endogenous growth hormone, prolactin, thyrotropin (thyroid-stimulating hormone), and adrenocorticotropin hormone concentrations were observed.

Dose-finding in Japanese women

Study **TAK-385/CPH-001** was a single- and multiple-rising dose study in premenopausal Japanese women The pharmacodynamic results showed that serum LH, E2, FSH, and progesterone concentrations were reduced in a comaprable way as seen in US women.

Relugolix 40 mg + E2 1 mg/NETA 0.5 mg combination therapy

In the 6-week pharmacokinetic/pharmacodynamic study (**MVT-601-1001**) in 48 healthy adult premenopausal women in the US, decreases of serum concentrations of LH, FSH, and progesterone were similar degree during the 6-week period during administration of relugolix 40 mg alone and during relugolix 40 mg+E2 1mg/NETA 0.5 mg. Coadministration of relugolix with E2/NETA did apparently not influence the suppression of the HPG axis. The addition of E2 1 mg resulted in approximately 3-fold higher peak and overall extent of exposure. The exogenous E2 exposure in the relugolix-E2/NETA group showed more subject-reported menstrual bleeding and reduced frequency and severity of hot flushes.

The results on E2 plasma levels indicate that with (relugolix+E2/NETA), the average E2 plasma concentrations increase about 3.3 fold as expected. An average of 50% increase in E2, in a range between 7.7 to 50 pg/mL. Based on the 24 hour measurements, plasma levels ranged between 20 to 60 pg/mL. Based on modeling of E2 and BMD loss data collected during use of GnRH receptor agonists and antagonists form several published studies, it was postulated that a 90% reduction from baseline values in E2 concentrations to approximately 10 pg/mL results in a significant decrease in from baseline lumbar spine BMD of up to -6% after 12 months of treatment, whereas an 80% decrease from baseline E2 concentrations to approximately 20 pg/mL prevented the decrease in BMD loss to no greater than -2% from baseline values, with the degree of loss beginning to plateau between 6 and 12 months (Riggs et al. 2012). After administration of relugolix 40 mg alone, E2 predose concentrations < 10 pg/mL and < 20 pg/mL were observed in 68% and 72% of participants, respectively, compared with 4.3% and 26.1% of participants, respectively, after co-administration with E2/NETA (1mg/0.5 mg). The results in this PK/PD study indicate that the addition of 1 mg estradiol results in an increase in estradiol concentrations which falls within the level that is assumed to preserve BMD and that a lower number of subjects have estradiol levels associated with significant % decrease in BMD. However, the DXA results in the phase 3 extension trials will be decisive in the conclusion whether the 1 mg estradiol dose adequately protects BMD when used in combination with relugolix.

The biomarkers of bone resorption, serum N-telopeptide (NTx) and C-telopeptide (CTx), are normally suppressed in premenopausal E2 concentrations. As expected, treatment with relugolix alone showed an increase of these markers. During coadministration of E2/NETA (hormonal add-back therapy) no significant change from baseline was observed.

Ovulation inhibitory properties

The Ovulation Inhibition Study (**MVT-601-046**) was performed to assess the effect of co-administration of relugolix/E2/NETA on the potential to suppress ovarian activity in 70 ovulatory participants in Germany, for three 28-day treatment periods. The primary study endpoint was met. Ovulation was inhibited in 100% of women during the entire 84-day treatment period with relugolix combination therapy, as determined by a Hoogland-Skouby score (HSS) < 5 during the 84 day treatment period. The mean time to ovulation following discontinuation of relugolix combination therapy was 23.5 days.

QT study

A dedicated thorough QT study with parallel design (60 mg, supratherapeutic 360 mg, placebo and positive control (moxifloxacin) did not suggest for any QT prolonging effect of relugolix with point estimates for the corrected ddQTcF around 5 ms and thus far below the 10 ms for regulatory concern. There appears some hysteresis as the largest effect was observed after 10 hours instead of around tmax (3 hours), however, with no suggestion for QT prolongation this is not considered of such relevance to be further pursued.

In conclusion, based on the pharmacodynamic results, it was shown that LH and FSH (and subsequently E2 and progesterone) decreased after oral use of relugolix , consistent with the mechanism of action for relugolix as a GnRH receptor antagonist with suppression of the hypothalamic–pituitary–adrenal axis (HPA axis). Near maximal reductions in E2 concentrations were seen with the proposed dose of 40 mg relugolix. Relugolix-E2/NETA combination therapy increased E2 concentrations to 20 to 50-60 pg/mL which falls within the level that is assumed to preserve BMD and that a lower number of subjects had estradiol levels <10 ng/mL associated with significant % decrease in BMD. Relugolix +E2 1mg/NETA 0.5 mg resulted in 100% ovulation inhibition, which was reversible after an 84-day treatment period, the mean time to ovulation following discontinuation being 23.5 days, with 97.01% of women having ovulation within 36 days post-treatment. The biomarkers of bone resorption, NTx and CTx, remained suppressed during coadministration with E2/NETA (hormonal add-back therapy), despite treatment with a GnRH antagonist. A dedicated thorough QT study indicated no suggestion for QT prolongation.

PK/PD analyses

Exposure-Response (Efficacy, PBAC score) Model for Relugolix

The relationship between relugolix trough (predose) concentrations at steady state ($C_{trough,ss}$; exposure parameter) and the percent change from baseline in total PBAC score from Week 6 to Week 12 (response parameter) from the phase 2 study in women with uterine fibroids (TAK-385/CCT-001), in which participants received 10-, 20- or 40-mg doses of relugolix (n = 48, 53, 54, respectively) or placebo (n = 57) once daily for 12 weeks, was well characterized by an E_{max} model (Hill exponent and EC_{50} with narrow 95% CI and p-values lower than 0.01).

A sensitivity analysis using the model was used to define a clinically meaningful decrease in relugolix exposure ($C_{trough,ss}$) to support the lower comparability bound to facilitate interpretation of treatment-related comparisons or covariates for intrinsic and extrinsic factors (see below). The percent change from baseline in total PBAC score from Week 6 to Week 12 associated with reductions in $C_{trough,ss}$ by 30%, 40% and 50% of the geometric mean $C_{trough,ss}$ value for the 40-mg dose group was estimated, and demonstrated that 50% reduction in relugolix $C_{trough,ss}$ would still achieve a decrease in the percent change from baseline in total PBAC score of 67%, on average, with a minimum percent change from baseline in total PBAC score of 51% (95% CI: -51%, -81%).

Exposure-Response (Efficacy, MBL responder) Model for Relugolix

The relationship between relugolix exposure (C_{trough}) and the MBL responder rate in the phase 3 studies in women with uterine fibroids was sufficiently described by a logistic regression E_{max} model. Responders were defined as patients who achieved the primary endpoint [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]) in the pivotal phase 3 studies (MVT-601-3001, MVT-601-3002). Four hundred seventy-six (476) patients treated with the relugolix combination therapy or placebo were included in this relugolix exposure-MBL analysis and divided in two subgroups (individual C_{trough} < median C_{trough}; individual C_{trough} or ≥ median C_{trough}) in order to enable exploratory evaluations of the impact of relugolix exposure to support the appropriateness of a 40-mg dose of relugolix as the therapeutic dose.

The analysis showed that, based on pooled data from phase 3 studies, patients who received relugolix combination therapy for 24 weeks with low C_{trough} values (range: 0.34 – 1.95 ng/mL) versus high C_{trough} values (range: 1.95 – 16.7 ng/mL) were equally as likely to respond to treatment (approximately 80% rate of response), confirming that a 40-mg dose of relugolix provides sufficient exposure in the majority of women to provide effective treatment. Furthermore, it was shown that a reduction of 50% in $C_{trough,ss}$ relative to the median $C_{trough,ss}$ for relugolix 40-mg was predicted to be associated with a responder rate of 73% (compared to 79% at the median C_{trough}).

Comparability bounds / Acceptance criteria

In order to facilitate interpretation of treatment-related comparisons or covariates for intrinsic and extrinsic factors (see Section 3.3.1), comparability bounds of 0.50 to 2.00 were proposed by the Applicant to define either clinically meaningful decreases or increases in relugolix exposure ($C_{trough,ss}$).

A lower comparability bound of 0.50 is supported by the exposure-response analysis used to defined a clinically meaningful decrease in relugolix exposure ($C_{trough,ss}$) based on the percent change from baseline in total PBAC score. Based on the mechanism-of-action for relugolix, C_{trough} for relugolix is considered to be an appropriate measure of drug exposure as it reflects the minimum concentration above which pharmacologic effects are expected to occur. The PBAC score, the method used to measure MBL volume in the phase 2 study with uterine fibroids is a validated semiquantitative measurement tool for diagnosing heavy menstrual bleeding that generally correlates with qualitative measures of menstrual blood volume. Therefore, the predicted percent decrease in PBAC score from the exposure-response model should represent a corresponding reduction in MBL volume.

The sensitivity analysis mentioned above using the exposure-response (efficacy) E_{max} model for PBAC showed that a 50% reduction in relugolix $C_{trough,ss}$ (i.e. effectively a two-fold lower dose of relugolix) would still achieve a decrease in the percent change from baseline in total PBAC score of 67%, on average, with a minimum percent change from baseline in total PBAC score of 51% (95% CI -51%, -81%). This analysis was supported by the analysis describing the relationship between relugolix trough plasma concentration and MBL responder rate, which showed that a reduction of 50% in $C_{trough,ss}$ relative to the median $C_{trough,ss}$ for relugolix 40-mg was predicted to be associated with a responder rate of 73% (compared to 79% at the median C_{trough}).

An upper comparability bound of 2.00 is based on the safety data from the relugolix development program at doses and exposures higher than the proposed clinical dose of 40 mg, including:

- The safety profile of relugolix after administration of single doses ranging from 1 to 360 mg in healthy premenopausal women and healthy men in three single and multiple rising-dose studies (TAK-385_101, TAK-385/CPH-001, C27001) and healthy women and men in the thorough QT/QTc study (TAK-385-106);

- The safety profile of relugolix after administration of multiple doses ranging from 10 to 180 mg in healthy premenopausal women and healthy men (TAK-385_101, TAK-385/CPH-001, C27001);
- The safety profile of relugolix after administration of up to 120 mg once daily for up to 48 weeks in men with advanced prostate cancer (TAK-385-C27002; TAK-385-C27003).

It is agreed that the data support the use of comparability bounds (acceptance criteria) of 0.50 to 2.00 to interpret clinically meaningful changes in drug exposure to relogolix from e.g. drug-drug interaction studies.

Exposure-BMD model

An exposure-BMD model was developed to support long-term use of relugolix combination therapy based on the predicted risk for BMD loss over time. In the development of the E2 concentration-BMD model, a modified version of a multiscale quantitative systems pharmacology (QSP) model proposed by Riggs et al., which describes BMD loss over time during treatment with GnRH receptor modulators (Riggs et al. 2012), was used to establish the relationship between circulating E2 concentrations and BMD change over time upon treatment with the relugolix combination therapy.

The following assumptions are underlying the E2-BMD model and seem to be supported by the clinical data of relugolix:

- E2 suppression by GnRH receptor agonists or antagonists reaches the maximal effects no later than two months after initiation of treatment and remains stable thereafter.
- As a consequence of E2 suppression by GnRH receptor antagonism, there is a rapid loss in BMD, which reaches physiological steady state no later than 12 months after initiation of treatment and remains stable thereafter.

Using the BMD data from both phase 3 studies it is demonstrated that relugolix monotherapy suppressed E2 levels and the rate of BMD change was well captured by the model. Transition from relugolix monotherapy to relugolix + E2/NETA was associated with stabilisation of BMD loss rather than reversibility of BMD loss. Nevertheless, these data support the dose of E2 in relugolix + E2/NETA to minimize bone loss associated with hypoestrogenism.

Data from the long-term extension (LTE) study (MVT-601-3003), in which women who had participated in the phase 3 studies were treated with relugolix combination therapy for up to 12 months, were used for the validation of the E2-BMD model. The observed LTE data, in which the BMD at lumbar spine following a 9–12-month treatment period were captured, were compared with the corresponding predictions based on the E2-BMD model. The observed median BMD loss in the LTE study seemed to be reasonably captured by the E2-BMD model.

Overall, the model seems to indicate that there is a reduction of the BMD decrease with the addition of E2/NETA as compared to the relugolix monotherapy. However, the clinical study data seem to indicate that the BMD decrease is not stabilized at the specific time point of 12 weeks, as BMD decreased further at month 9 and month 12.

How long the effect on the BMD decrease is maintained according to the model, is primarily dependent on the second assumption, that the changes in bone formation and resorption in the studied population remain at the same physiological steady state level during the treatment. The model included E2 levels as the main driver of rate change in BMD; baseline BMD, age and BMI were no statistically significant covariates in the model. Since in the model steady-state E2 levels are reached within 1 to 2 months after start of relugolix + E2/NETA and remain stable over time, no change in rate of BMD change is to be expected for longer treatment based on the exposure-BMD model. However, small changes in BMD over time were observed in an age-matched cohort of premenopausal women with uterine fibroids. It cannot be excluded that other factors not related to relugolix + E2/NETA treatment, which are not

captured by the model, could contribute to changes in BMD over time (see further discussion under Clinical Efficacy and Safety).

2.5. Clinical efficacy

Introduction

The main clinical studies for relugolix-E2/NETA in the uterine fibroids indication are:

- Two replicate, multi-national, **pivotal phase 3 studies (MVT-601-3001 and MVT-601-3002**) in women with uterine fibroids in which relugolix is combined with E2/NETA.
- **Extension study MVT-601-3003,** an open-label extension study of 28 weeks for all eligible women who completed the 24-week studies MVT-601-3001 and MVT-601-3002.

Supportive studies for the proposed indication were:

- Three Japanese studies conducted by Takeda: a phase 2 study (**TAK-385/CCT-001 [dose finding healthy volunteers**]) and two phase 3 studies (**TAK-385/CCT-002 [monotherapy vs GnRH agonist]**, and **TAK-385-3008 [pain symptoms**, vs placebo], respectively).
- Exit interview substudy (**MVT-601-037**), providing the patient's perspective on the patient-reported outcomes used in the pivotal studies MVT-601-3001 and MVT-601-3002.
- Study **MVT-601-034 (natural history)** observational study evaluating BMD in women with uterine fibroids or endometriosis to characterize longitudinal BMD of premenopausal women aged 18-50 years with uterine fibroids or endometriosis over a 52 week observational period. This natural history study is conducted to support assessment of the long-term effects on BMD with relugolix combination therapy, by enrolling an age-matched concurrent reference group of women with uterine fibroids or endometriosis not receiving GnRH receptor agonists or antagonists, in whom BMD is assessed every 6 months for one year.

Other studies:

- The clinical pharmacology studies that provided safety, efficacy, pharmacokinetic and pharmacodynamic data of relugolix alone and/or in combination with E2 and NETA **(TAK-385_101 [PK/PD healthy volunteers], MVT-601-1001 [mono vs combination therapy], and MVT-601-046 [ovulation inhibition]**) are discussed earlier in this AR.

Study of which a 'Top line data summary has been' submitted during the procedure:

- Study **MVT-601-035 (an extension of extension study MVT-601-3003)** is completed in February 2021, i.e. during the initial MA. This is a double-blind, placebo-controlled, randomized withdrawal study to evaluate long-term (104 week) efficacy and safety of relugolix 40 mg combined with E2/NETA (1 mg/0.5 mg) or placebo for up to 52 weeks in patients with uterine fibroids. This study enrolled eligible patients who had also completed MVT-601-3003 and met the definition of responder to relugolix with E2/NETA.

2.5.1. Dose response study(ies)

Selection of dose

Based on a PK/PD single and multiple dose study **TAK-385-101** in 120 healthy premenopausal women in the US, investigating single doses of 1- to 80-mg of relugolix, dose-dependent reductions in mean LH, FSH, and E2 serum concentrations with respect to both degree and duration were observed,

consistent with the mechanism of action of relugolix as a GnRH receptor antagonist. As at 24 hours postdose, mean E2 concentrations for the 40- and 80 mg doses of relugolix were similar (30.2 pg/mL and 30.3 pg/mL, respectively), doses higher than 40 mg are unlikely to provide further suppression of E2 concentrations with once daily administration. Therefore, the 40 mg dose was selected for further development.

The dose of E2 1mg + NETA 0.5 mg selected for combination with relugolix was based on data in the literature, particularly from published studies that supported the estradiol dose of 1 mg to have efficacy in prevention of bone loss in postmenopausal women. Further, the E2/NETA combination, Activelle, is registered in Europe for treatment of vasomotor symptoms and prevention of osteoporosis in postmenopausal women.

2.5.2. Main study(ies)

Pivotal phase 3 studies (MVT-601-3001 and MVT-601-3002)

As the multi-national, pivotal phase 3 studies (MVT-601-3001 and MVT-601-3002) were replicates, they are described together and differences, if any, are addressed.

Title of Study

MVT-601-3001 (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.

This study was performed at 80 centers, including North America (United States), and Rest of World (Brazil, Italy, Poland, South Africa, and the United Kingdom) between 2017-2019 (database lock was 08 May 2019).

MVT-601-3002 (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.

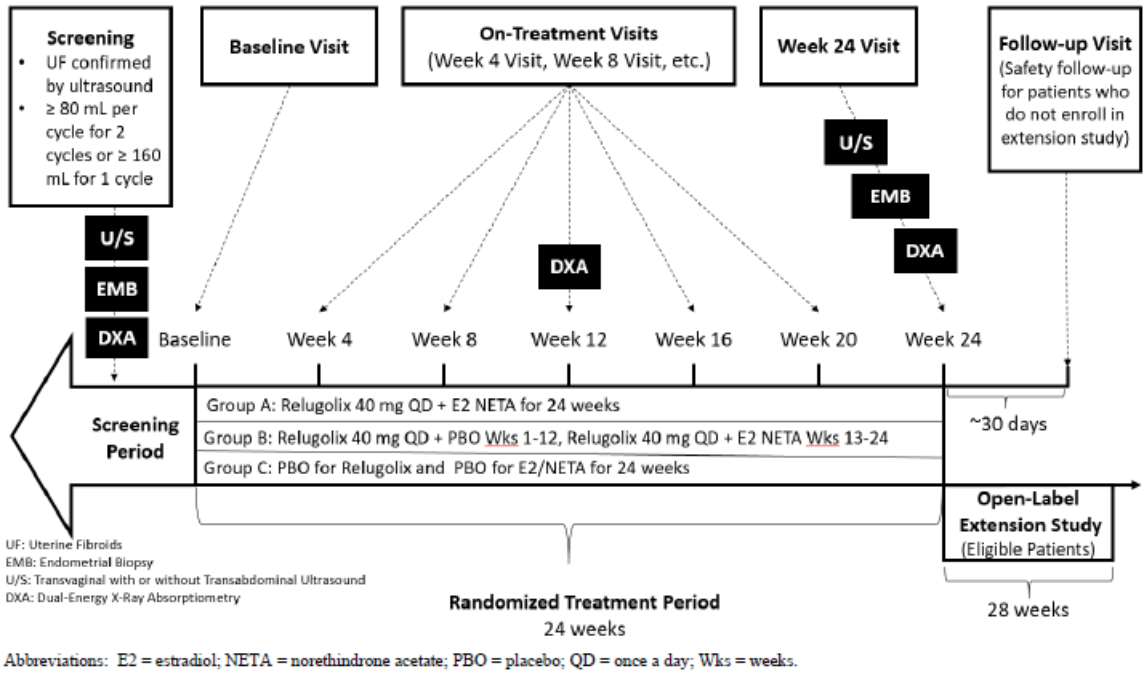
This study was performed at 99 centers globally, including centers in North America (United States), Belgium, Brazil, Chile, Czech Republic, Hungary, Poland, and South Africa between 2017-2019 (database lock was 16 July 2019).

Methods

The studies consisted of a screening period (up to approximately 13 weeks), a randomized treatment period (24 weeks), and a follow-up period (approximately 30 days).

The study design is given in the following figure:

Figure: MVT-601-3001 and MVT-601-3002 Study schedule



Abbreviations: E2 = estradiol; NETA = norethindrone acetate; PBO = placebo; QD = once a day; Wks = weeks.

Study Participants

Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids were planned to be randomized in each study.

The planned study population were premenopausal women 18 to 50 years of age with heavy menstrual bleeding associated with uterine fibroids (≥ 80 mL per cycle for two cycles or ≥ 160 mL for one cycle as measured by the alkaline hematin method) during the screening period. Women with a baseline BMD z-score < -2.0 at spine, total hip, or femoral neck or a history of or currently had osteoporosis or other metabolic bone disease were not allowed in the study.

Use of hormonal contraceptives was excluded and patients had to agree to use non-hormonal contraception throughout the study, including through 30 days following the last dose of study drug.

Impact demographic characteristics

To assess the potential impact of demographic parameters, a cross-study analysis and PopPK analysis (MYV-PKER-RELUGOLIX-737 Report 01) was performed and found no clinically meaningful effect of race or ethnicity on the efficacy of the treatment intervention, relugolix + E2/NETA, on heavy menstrual bleeding or reduction in uterine fibroid-associated pain.

Main inclusion and exclusion criteria

Main inclusion criteria

- Premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
- 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;

- 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 cm3

- 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.

Main Exclusion Criteria:

- Had transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be 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 requiring further evaluation and/or treatment during the study.
- Had known rapidly enlarging uterine fibroids in the opinion of the investigator;
- Had undergone myomectomy, 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;
- Had a weight that exceeded the weight limit of the DXA scanner or 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);
- Had a baseline BMD z-score < -2.0 at spine, total hip, or femoral neck;
- 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.

Removal of subjects

Completion of the Week 24 visit defined completion of the study. Patients may have withdrawn consent to participate in the study and discontinue treatment at any time for any reason. Investigators could remove patients from therapy for reasons of safety and/or lack of compliance. If a patient failed to attend the clinic for the required study visit, the site attempted to contact the patient and only after at least three documented telephone calls and if necessary, a certified letter to the patient's last known mailing address, was the patient withdrawn from the study with a primary reason of "Lost to Follow-up."

Contraception and Pregnancy Avoidance

In these studies, medication and devices containing hormones for contraception were excluded, and patients had to agree to use non-hormonal contraception throughout the study, including through 30 days following the last dose of study drug.

Patients were provided with information on acceptable methods of contraception as part of the informed consent process and confirmed when they signed the ICF that they understood the requirements for the avoidance of pregnancy during the study.

Urine pregnancy tests were performed at monthly intervals during the study (including just prior to receiving the first dose of study drug), and patients received continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who became pregnant during the study were withdrawn from the study and followed for pregnancy outcome.

Treatments

Women meeting all eligibility criteria at the end of the screening period were randomized 1:1:1 to receive blinded therapy once a day with:

- relugolix 40 mg co-administered with E2 1 mg and NETA 0.5 mg for 24 weeks;
- relugolix 40 mg monotherapy once a day for 12 weeks followed by relugolix 40 mg once a day co-administered with E2 1 mg and NETA 0.5 mg for 12 weeks;
- placebo for 24 weeks.

The primary efficacy analysis was the comparison with respect to responder rate of the relugolix + E2/NETA group with the placebo group.

The additional arm of relugolix 40 mg once a day monotherapy for 12 weeks followed by relugolix 40 mg once a day co-administered with E2 1 mg and NETA 0.5 mg for 12 weeks was included to assess the effectiveness of E2/NETA in mitigating the adverse effects of the hypoestrogenic state (BMD loss and vasomotor symptoms) brought on by relugolix monotherapy.

The study subjects had to take the blinded study medication each morning, at least one hour before breakfast (fasted state). This is in line with the proposed posology.

Objectives and Endpoints

Table: Objectives and Endpoints (MVT 601 3001 and MVT 601 3002)

Objectives	**Endpoints**
Primary Efficacy	
To determine the benefit of relugolix 40 mg once a day co-administered with E2 1 mg and NETA 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids	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, as measured by the alkaline hematin method
Key Secondary Efficacy (Alpha-Protected for Hierarchical Hypothesis Testing — relugolix + E2/NETA versus placebo)	
Achievement of amenorrhea	Proportion of women who achieve amenorrhea over the last 35 days of treatment
Heavy menstrual bleeding associated with uterine fibroids	Percent change from baseline to Week 24 in MBL volume
Impact of uterine fibroids on symptoms, activities and health related quality-of-life as measured by	Change from baseline to Week 24 in the UFS-QoL bleeding and pelvic discomfort scale score, a sub-scale of the UFS-QoL

components of the UFS-QoL	Symptom Severity scale
Change in hemoglobin	Proportion of women with a hemoglobin ≤10.5 g/dL at baseline who achieve an increase of > 2 g/dL from baseline at Week 24
Pain associated with uterine fibroids	Proportion of patients with a maximum NRS score ≤ 1 during the 35 days before the last dose of study drug in the subset of women with a maximum NRS score ≥ 4 for pain associated with uterine fibroids during the 35 days prior to randomization
Uterine fibroids volume	Percent change from baseline to Week 24 in uterine fibroids volume
Uterine volume	Percent change from baseline to Week 24 in uterine volume

Randomisation and blinding (masking)

Randomization was stratified by:

- Geographic region: North America versus Rest of World;
- Mean screening MBL volume measured by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study were blinded to treatment. All study subjects were to take one tablet (relugolix or placebo) and one capsule (E2/NETA or placebo) per day. The placebo relugolix tablet and the relugolix tablet, and the placebo capsule and the capsule with E2/NETA active product had matching appearances.

Statistical methods

For the comparison of the relugolix + E2/NETA group with the relugolix + delayed E2/NETA group with respect to the percent change in BMD from Baseline to Week 12 at the lumbar spine (L1–L4), approximately 260 women in the relugolix + E2/NETA group (pooled between the LIBERTY 1 and LIBERTY 2 studies) and 260 women in the relugolix + delayed E2/NETA (pooled) will provide at least 90% power at a 2-sided 0.05 significance level to detect a 1.25% absolute treatment difference, assuming a standard deviation of 4% and up to 15% dropout rate for each treatment group. Power calculations for this BMD comparison are based on a two-sample t-test. For efficacy in the individual studies, this would provide > 99% power to detect a difference of greater than 30 percentage points using a two-sided test at a significance level of 0.05.

Efficacy analyses will be performed using the modified Intent-to-Treat (mITT) population, unless otherwise specified, defined as all randomized patients who have received any amount of study drug and analyses will be performed as randomized. The Per-Protocol population will consist of those members of the mITT population who do not have any of the specified subset of important protocol deviations. The Per-Protocol population will be used for sensitivity analysis of the primary efficacy endpoint. Safety analyses will be performed using the Safety population unless otherwise specified, defined as all randomized patients who have received any amount of study drug and analyzed according to the actual treatment received.

The primary treatment comparison between relugolix + E2/NETA and placebo will be analysed using a Cochran-Mantel-Haenszel test statistic for proportions stratified by the Baseline mean MBL volume using the alkaline hematin method (< 225 mL versus ≥ 225 mL) and geographic region (North America versus Rest of World). The difference in responder rates between the relugolix + E2/NETA and placebo and its two-sided 95% CI will be estimated using stratum-adjusted Mantel-Haenszel proportions.

For the evaluation of primary endpoint, missing data handling rules were implemented for deriving responder status at Week 24/EOT, see the table below:

Table: Derivation of Responder Status at Week 24/End-of-Treatment and Missing Data Handling Rules for Primary Analysis

Treatment Exposure	FP Collection (FPRR)	Observed MBL Volume	Reason for No FP Collection	Responder Status
< 4 weeks	N/A	N/A	N/A	Imputed as non-responder
≥ 4 weeks	100% FP Compliance	N/A	N/A	Based on the observed MBL volume
	<100% FP Compliance	MBL ≥ 80 mL or <50% reduction from baseline	N/A	Imputed as non-responder based on the observed MBL volume
		MBL < 80 mL and ≥ 50% reduction from baseline	N/A	**Based on the imputed MBL volume**
	No FP Collection	N/A	Reported "Amenorrhea"	Imputed as responder
			Reported "Spotting or negligible bleeding" and confirmed by eDiary[a]	Imputed as responder
			Reported "Spotting or negligible bleeding" although not confirmed by eDiary or any other reason, had at least 8 weeks of MBL data	**Based on the imputed MBL volume**
			The entries in the eDiary did not verify "Spotting or negligible bleeding" or any other reason and if had less than 8 weeks of MBL data	Imputed as non-responders

Abbreviations: eDiary = electronic diary; FP = feminine product; FPRR = feminine product return rate; EOT = end-of-treatment; MBL = menstrual blood loss; N/A = not available.

[a] Defined as those patients who meet the following criteria: eDiary entry rate >70% and no more than 3 consecutive days and no more than 5 days of bleeding/spotting and use of feminine product reported on the eDiary over the Week 24/EOT visit window (see Table 5 of the SAP).

To assess the robustness of the primary analysis, sensitivity analyses of the primary endpoint will be conducted at Week 24/EOT. These will assess the potential impact of: unvalidated feminine product use, missing data due to inadequate collection of feminine products, early discontinuation on the primary endpoint and the length and full exposure of the treatment. Furthermore, the primary endpoint will be analyzed on the Per-Protocol population and using the mixed-effects model with multiple imputation for imputing missing MBL volumes.

Key secondary efficacy endpoints that are evaluating proportions will be performed using a stratified Cochran-Mantel-Haenszel test. For key secondary efficacy endpoints evaluating percent change from Baseline in uterine fibroid volume and uterine volume, an analysis of covariance (ANCOVA) model will be used. Key secondary efficacy endpoints evaluating the change from Baseline in MBL volume and UFS-QoL BPD scale, treatment comparisons will be performed using a mixed model repeated measures approach. All analyses take randomization stratification factors and baseline values where appropriate into account.

For testing whether relugolix + E2/NETA (Group A) is statistically significantly superior to placebo for the primary efficacy endpoint as well as the seven key secondary endpoints, a gate-keeping mixed sequence testing procedure will be applied to maintain the family-wise type I error rate. The primary

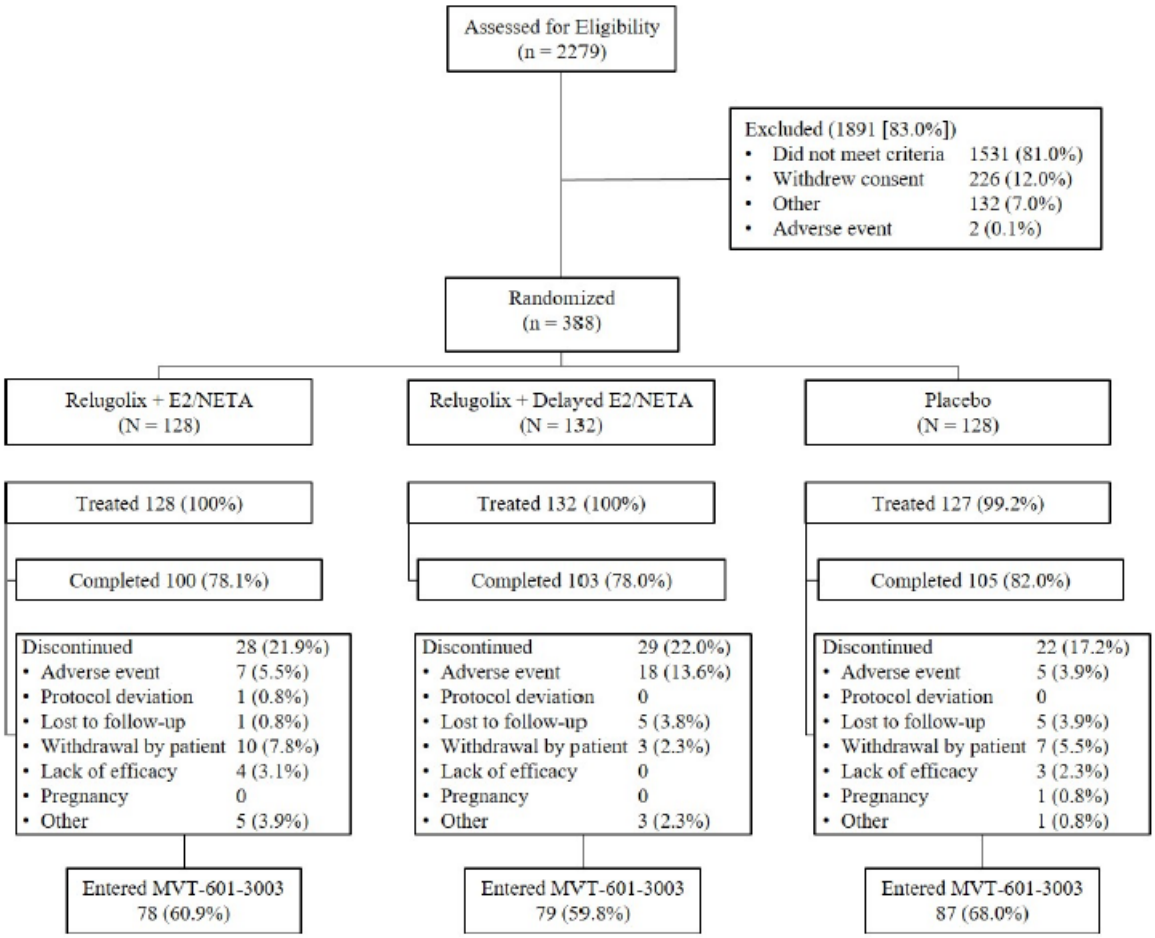
endpoint and first four key secondary endpoints will be tested sequentially at a 2-sided 0.05 significance level. If the two-sided p-value is < 0.05 for the fourth key secondary endpoint, the remaining three endpoints will be tested using the Hochberg step-up procedure.

Analysis methods previously described for primary and secondary efficacy endpoint analyses will be used for the analysis of other secondary endpoints. Kaplan-Meier methods will be used to describe the time to event distributions. A log-rank test stratified by the randomization stratification factors using the proportional hazard model (p-value from score test) will be used to compare relugolix + E2/NETA to placebo.

Results (MVT-601-3001 and MVT-601-3002)

Participant flow

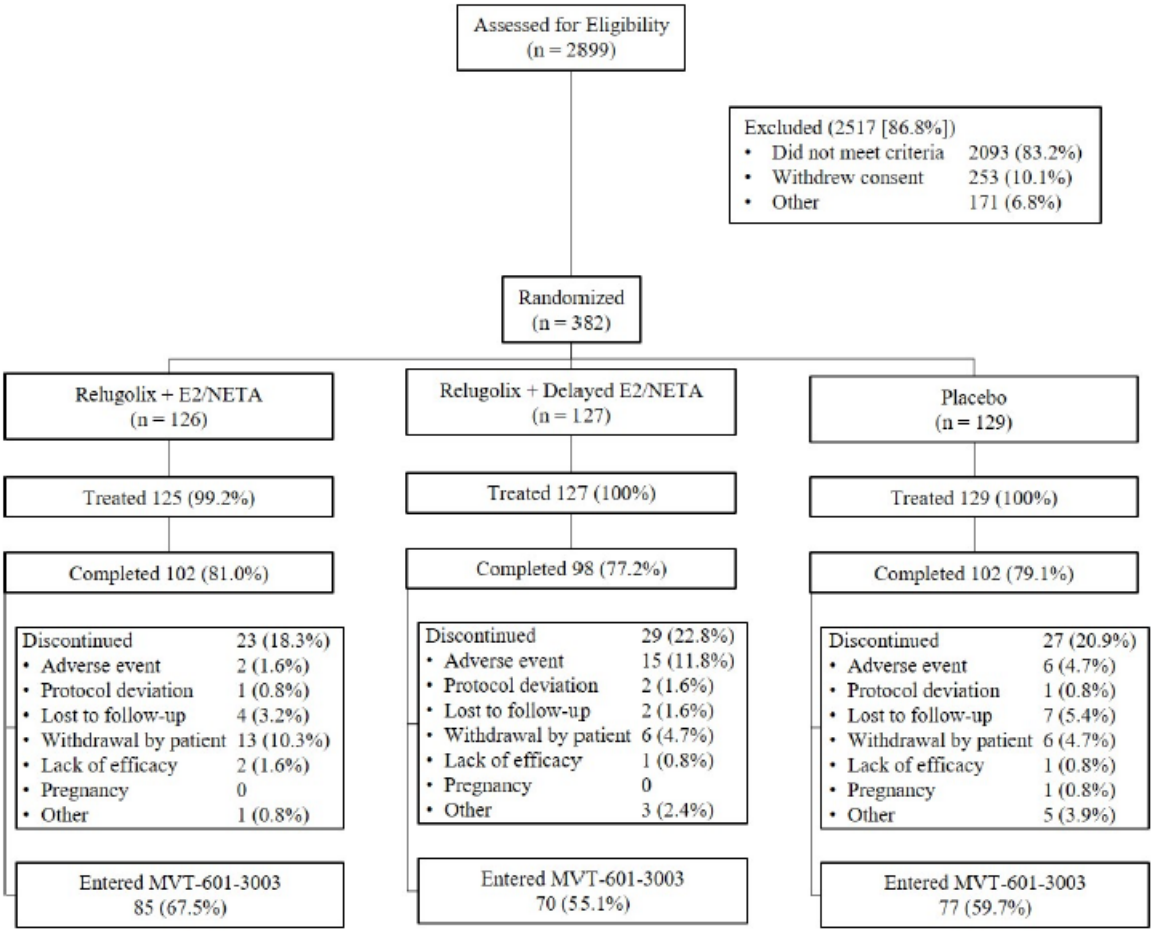
Figure Study Participant flow MVT-601-3001



Abbreviations: E2 = estradiol; ICF = informed consent form; n = number of patients; NETA = norethindrone acetate.

Note: Percentages for eligibility status were based on the total number of patients who signed the ICF and reason for screen failure was based on the total number of patients who failed screening.

Figure: Study Participant flow MVT-601-3002



Abbreviations: E2 = estradiol; ICF = informed consent form; n = number of patients; NETA = norethindrone acetate.
Note: Percentages for eligibility status were based on the total number of patients who signed the ICF and reason for screen failure was based on the total number of patients who failed screening.
Source: Table 7.1.1.3 and Table 7.1.2.1.

For both studies, the proportion of patients completing the study and the proportion of patients who discontinued the study early is similar across treatment groups.

In study MVT-601-3001, one patient in the placebo group was randomized and not treated because a serious adverse event was observed prior to initiation of blinded study drug.

In study MVT-601-3002, one patient in the relugolix + E2/NETA group was randomized but not treated because the patient was randomized in error before eligibility was confirmed.

The primary reasons for early discontinuation in both studies were similar among the treatment groups except for discontinuation due to adverse events, which occurred with greater frequency in the relugolix + delayed E2/NETA group, and withdrawal by patient, which occurred more in the relugolix + E2/NETA group. The adverse events leading to discontinuation in the relugolix + delayed E2/NETA group were generally related to the hypoestrogenic state associated with 12 weeks of relugolix monotherapy.

Baseline data

Baseline characteristics of both phase 3 studies are displayed in the tables below:

Table: Summary of Patient Demographics (mITT/FAS Populations)

	Pivotal Studies	
Study No.	**MVT-601-3001**	**MVT-601-3002**
Study Phase	**3**	**3**
Total N	**387**	**381**
Age (yrs) Mean (SD)	42.0 (5.38)	42.1 (5.29)
Height (cm)	164.3 (7.04)	164.3 (6.85)
Weight (kg)	85.40 (20.89)	84.47 (19.1)
BMI (kg/m^2)	31.69 (7.47)	31.27 (6.69)
Race N (%)		
White	173 (44.7)	157 (41.2)
Black or African American	191 (49.4)	202 (53.0)
Asian	4 (1.0)	4 (1.0)
Ethnicity N (%)		
Hispanic of Latino	90 (23.3)	84 (22.0)
Not Hispanic of Latino	294 (76.0)	292 (76.6)
Geographic Region N (%)		
North America	297 (76.7)	283 (74.3)
Rest of the World	90 (23.3)	98 (25.7)
Smoking Classification N (%)		
Never	312 (80.6)	277 (72.7)
Current	51 (13.2)	64 (16.8)
Former	24 (6.2)	40 (10.5)
History of Prior Pregnancy N (%)		
Yes	151 (78.6)	172 (82.7)
No	41 (21.4)	36 (17.3)

Abbreviations: BMI = body mass index; CSRs = clinical study reports; FAS = full analysis set; mITT = modified intent-to-treat; N = number or participants; NR = not reported; SD = standard deviation; yrs = years.

Notes: mITT (MVT-601-3001 and MVT-601-3002) defined as all patients who were randomized and received at least one dose of study drug.

Table: Summary of Selected Baseline Characteristics (Continued)

	Pivotal Studies	
Study No.	MVT-601-3001	MVT-601-3002
Study Phase	3	3
N	387	381
MBL volume (mL)	229.1 (156.6)	228.5 (152.2)
PBAC score	NR	NR
N	387	381
Hgb concentration (g/dL)	11.25 (1.531)	11.16 (1.556)
N	385	381
Uterine fibroid volume (cm3)[a]	79.32 (132.414)	75.56 (136.224)
N	386	381
Uterine volume (cm3)	416.28 (362.299)	399.52 (372.555)
PGA for symptoms N(%)		
No limitation	32 (8.3)	27 (7.1%)
Mild to extreme limitation	268 (69.3)	300 (78.7)
Missing	87 (22.5)	54 (14.2)
N	385	376
Maximum NRS score	5.4 (3.24)	5.6 (3.07)
N	384	375
UFS-QoL symptom severity score [b]	58.6 (20.87)	60.3 (20.81)
UFS-QoL total score [c,d]	36.5 (21.01)	37.2 (21.82)

Abbreviations: BPD = bleeding and pelvic discomfort; CSRs = clinical study reports; Hgb = hemoglobin; max = maximum; MBL = menstrual blood loss; N = number of participants; NR= not reported; NRS = Numerical Rating Scale; PBAC = Pictorial Blood Loss Assessment Chart; PGA = Patient Global Assessment; SD = standard deviation; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.

Note: Data represent mean (SD) unless otherwise specified.

A Uterine fibroid volume based on the largest fibroid among those measurable at baseline. Note that inclusion criteria for baseline uterine fibroid volumes differed between studies. For studies MVT-601-3001 and MVT-601-3002, the largest index uterine fibroid was required to be ≥ 2 cm in length, confirmed by transvaginal ultrasound, whereas in studies TAK-385/CCT-001, TAK-385/CCT-002, and TAK-385-3008 the largest index uterine fibroid was required to be ≥ 3cm in length.
B Transformed score ranges from 0 to 100. Higher scores are indicative of greater distress and lower scores indicate less distress (ie, low score = good).
C Scores for each individual scale (concern, activities, revised activities, energy/mood, control, self-conscious, and sexual function) were summed and transformed to normalized scores, where higher scores are indicative of better quality of life.
D UFS-QoL total score also known as health-related quality of life total score (transformed scores from 0 to 100, high score = good).

Overall, the demographic characteristics of the patients in the two pivotal phase 3 studies were similar among treatment groups.

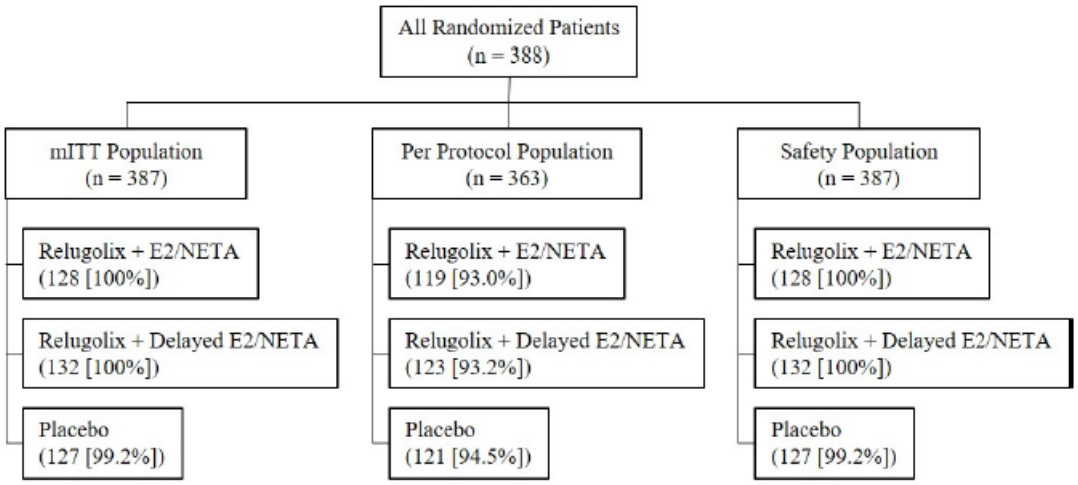
As the pivotal relugolix combination therapy studies were conducted in multiple countries, a broad range of region, race, and ethnic backgrounds are represented. In these two studies most patients (approximately 75%) were from North America (United States) and primarily either Black or African American (approximately 50%) or White (approximately 45%), with other races accounting for approximately 5% of enrolled patients. Furthermore, approximately 20% of women in the relugolix combination therapy studies were of Hispanic or Latino ethnicity.

The relugolix monotherapy studies (see supportive studies) were conducted only in Japanese women. Furthermore, BMI (~ 32 kg/m^2) was higher in the multi-national relugolix combination therapy studies compared with the relugolix monotherapy studies (~ 23 kg/m^2), which were conducted only in Japanese patients. The mean age of patients was similar (approximately 42 years) across all studies.

Numbers analysed

Study MVT-601-3001

Figure: Number of Patients in Each Analysis Population by Treatment Group (All Randomized Patients, Study MVT-601-3001)

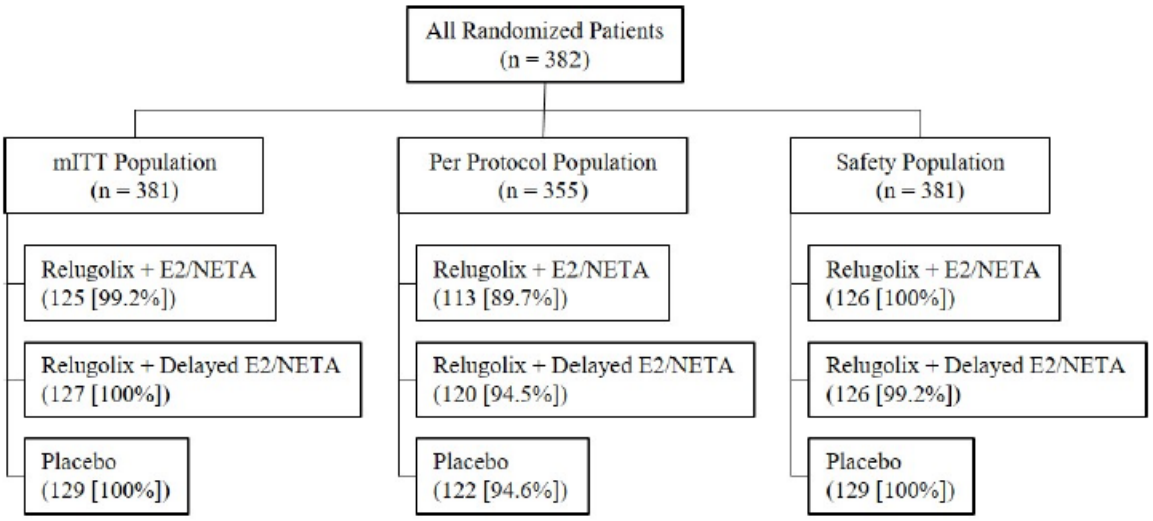


Abbreviations: E2 = estradiol; mITT = modified intent-to-treat; n = number of patients; NETA = norethindrone acetate.
Note: Percentages are based on the total number of patients in each treatment group or total.
Source: Table 7.1.1.1.

Except for the one patient randomized to the placebo group who did not receive study drug, all randomized patients were included in the mITT and safety populations. The proportion of patients included in the per-protocol population was similar across treatment groups, ranging from 93.0% in the relugolix + E2/NETA group to 94.5% in the placebo group.

Study MVT-601-3002

Figure: 4 Number of Patients in Each Analysis Population by Treatment Group (All Randomized Patients, Study MVT-601-3002)



Abbreviations: E2 = estradiol; mITT = modified intent-to-treat; n = number of patients; NETA = norethindrone acetate.
Note: Percentages are based on the total number of patients in each treatment group or total.
Source: Table 7.1.1.1.

In the relugolix + E2/NETA group, one patient was excluded from the mITT population because the patient was randomized in error before eligibility was confirmed and was never dosed with study drug. In the relugolix + delayed E2/NETA group, one patient was excluded from that group's safety population due to receiving the incorrect treatment assignment.

The proportion of patients included in the per-protocol population was slightly lower in the relugolix + E2/NETA group (89.7%) compared with the relugolix + delayed E2/NETA group (94.5%) and the placebo group (94.6%).

The primary efficacy endpoint and safety endpoint was performed in the mITT population.

Outcomes and estimation

Primary Efficacy Analysis (MVT-601-3001 and MVT-601-3002) 24 weeks duration

The primary efficacy endpoint

The primary efficacy endpoint was the proportion of women who achieved an MBL volume of < 80 mL and ≥ 50% reduction from baseline in MBL volume over the last 35 days of treatment (Week 24/EOT), compared to placebo (responder rate).

Primary efficacy analysis

Comparison of the responder rate of the relugolix + E2/NETA group with the placebo group.

A summary of primary efficacy endpoint responder rates in the two individual studies is provided in the following table:

Table: Proportion of Responders at Week 24/EOT (mITT Population)

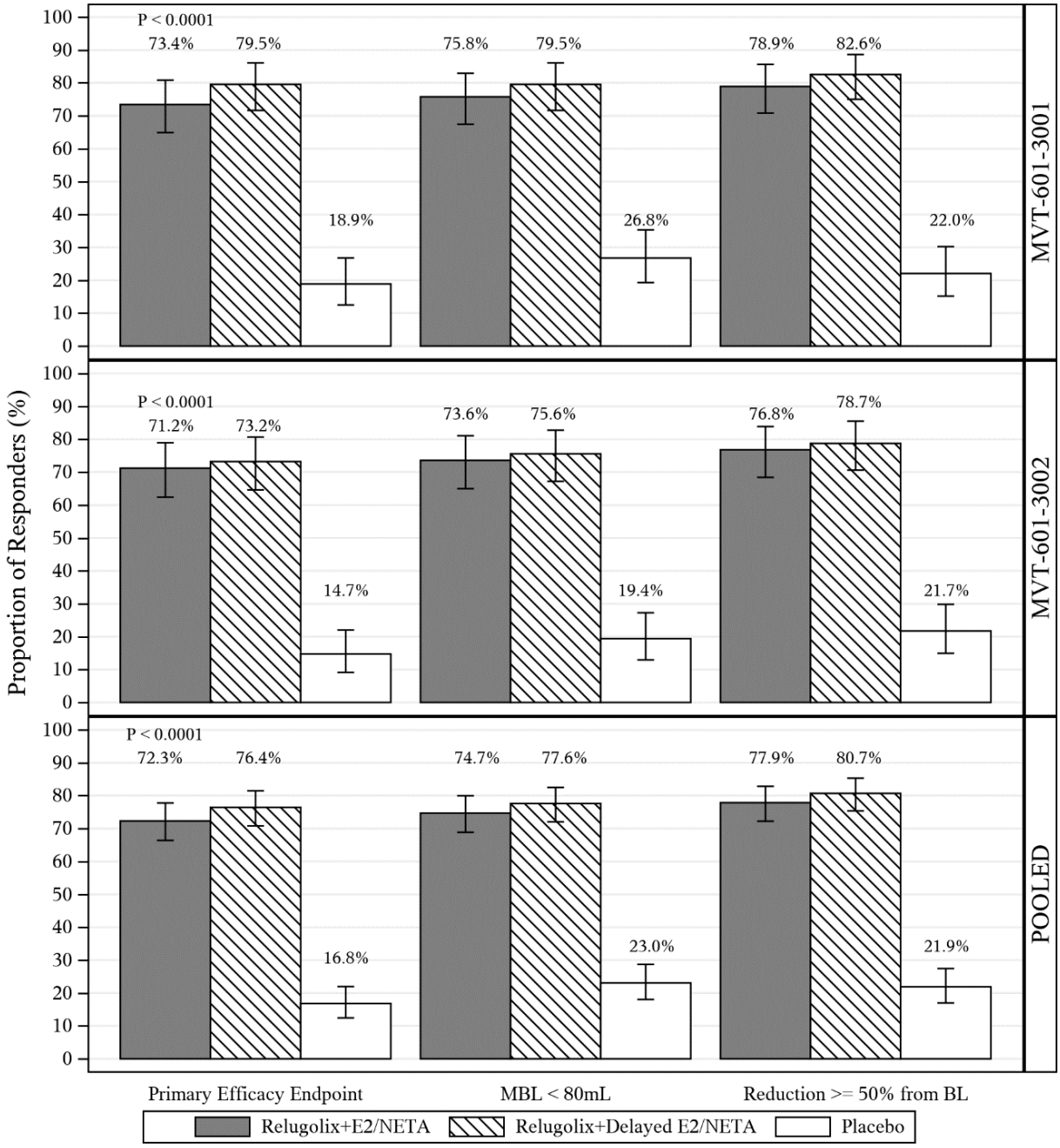
	MVT-601-3001		MVT-601-3002	
	Relugolix + E2/NETA (N = 128)	**Placebo (N = 128)**	**Relugolix + E2/NETA (N = 126)**	**Placebo (N = 129)**
Number (%) of responders	94 (73.44%)	24 (18.90%)	89 (71.20%)	19 (14.73%)
(95% CI) [a]	(64.91%, 80.85%)	(12.50%, 26.80%)	(62.42%, 78.95%)	(9.11%, 22.04%)
Difference from placebo[b]	54.54%		56.47%	
Un-adjusted 95% CI	44.30%, 64.78%		46.45%, 66.49%	
P-value [c]	< 0.0001		< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end of treatment; MBL = menstrual blood loss; mITT = modified intent-to-treat; N = number of patients; NETA = norethindrone acetate.
Note: A responder is defined as a woman achieving an MBL volume of < 80 mL and ≥ 50% reduction from baseline in MBL volume over the last 35 days of treatment. The denominator for percentage is number of patients in the mITT population for each treatment group.
[a] Based on exact binomial 95% CI (Clopper-Pearson).
[b] Difference is relugolix + E2/NETA minus placebo.
[c] P-value is based on Cochran-Mantel-Haenszel test stratified by baseline MBL volume (< 225 mL, ≥ 225 mL) and geographic region (North America, Rest of World).

Both studies MVT-601-3001 and MVT-601-3002 met their primary endpoint, and results were consistent between studies. Relugolix combination therapy was associated with statistically significant greater proportions of responders in the relugolix + E2/NETA groups in MVT-601-3001 and MVT-601-3002 studies (73.44% and 71.20%, respectively) compared to the proportion of responders in the placebo groups (18.90% and 14.73%, respectively).

A similar pattern in responder rate was observed for the individual components of the composite primary endpoint (i.e., MBL volume < 80 mL, or reduction in MBL volume ≥ 50% from baseline), demonstrating that no single component of the composite drove the results for the primary endpoint.

Figure: Proportion of Responders and for Individual Components of the Primary Endpoint (mITT Population)



Secondary efficacy analysis at Week 24

Comparison of the responder rate of the relugolix + delayed E2/NETA group with the placebo group.

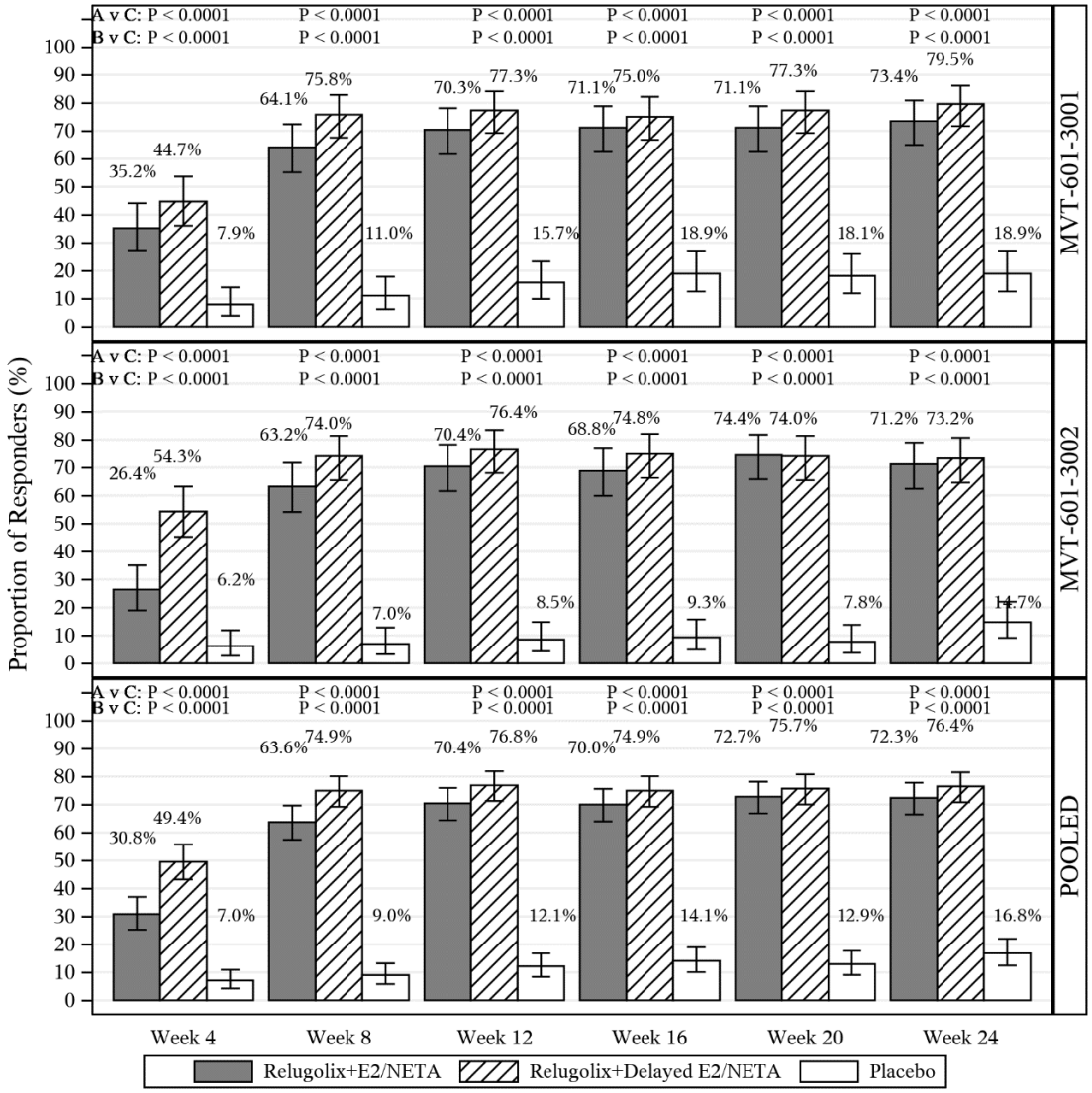
In addition to the primary analysis, a secondary analysis was performed comparing the relugolix + delayed E2/NETA group with the placebo group with respect to the responder rate at week 24. In the MVT-601-3001, the proportion of responders was 79.55% in the relugolix + delayed E2/NETA group compared with to 18.90% in the placebo group. The observed difference between the two groups was 60.65% (95% CI: 50.97% to 70.33%) in favour of the relugolix + delayed E2/NETA

group and was significant (nominal p < 0.0001). In study MVT-601-3002, the proportion of responders 73.23% in the relugolix + delayed E2/NETA group compared with 14.73% in the placebo group. The observed difference between the two groups was 58.50% (95% CI: 48.67% to 68.33%) in favor of the relugolix + delayed E2/NETA group and was statistically significant (nominal p < 0.0001).

Efficacy relugolix monotherapy vs. relugolix + E2/NETA and placebo at Week 12

The relugolix + delayed E2/NETA treatment arm (initial treatment with relugolix monotherapy for 12 weeks followed by 12 weeks relugolix + E2/NETA) was added to be able to evaluate the effect of addition of exogenous estrogen on the efficacy of relugolix and on prevention of bone loss. In the figures below (Weeks 4, 8, and 12) a difference between the percent of responders in the relugolix + E2/NETA group versus percent of responders in relugolix + delayed E2/NETA group is observed. The difference is largest at Week 4 (about 20% difference), but from Week 4 onwards the difference between relugolix and relugolix+ E2/NETA diminishes to about 5% at week 12 (end of relugolix monotherapy). After Week 12 when these patients received relugolix + E2/NETA, this difference remained from Week 12 to Week 24.

Figure: Proportion of Responders by Visit (mITT Population)



Sensitivity analyses

To assess the robustness of the primary efficacy analysis, six sensitivity analyses were conducted. Overall, the results of the sensitivity analyses were consistent with the primary analysis with a higher proportion of patients who received relugolix + E2/NETA meeting the definition for responder than patients who received placebo:

Table: Results of the Sensitivity Analyses of the Primary Endpoint in the Pivotal Phase 3 Studies with Relugolix Combination Therapy (mITT Population)

	MVT-601-3001			MVT-601-3002		
Sensitivity Analysis	**Relugolix + E2/NETA (N = 128)**	**Placebo (N = 127)**	**Difference (95% CI)[a] p-value[b]**	**Relugolix + E2/NETA (N = 125)**	**Placebo (N = 129)**	**Difference (95% CI)[a] p-value[b]**
1. Sensitivity analysis using MBL volume from validated feminine products	93 (72.66%)	24 (18.90%)	53.76% (43.46%, 64.05%) < 0.0001	90 (72.00%)	18 (13.95%)	58.05% (48.16%, 67.93%) < 0.0001
2. Sensitivity analysis using observed MBL volume	97 (75.78%)	27 (21.26%)	54.52% (44.24%, 64.80%) < 0.0001	91 (72.80%)	21 (16.28%)	56.52% (46.45%, 66.59%) < 0.0001
3. Sensitivity analysis treating early discontinuation as non-responders	93 (72.66%)	25 (19.69%)	52.97% (42.61%, 63.34%) < 0.0001	88 (70.40%)	21 (16.28%)	54.12% (43.89%, 64.35%) < 0.0001
4. Sensitivity analysis using 24-week completers	84 (84.00%)	23 (21.90%)	62.10% (51.41%, 72.78%) < 0.0001	82 (80.39%)	18 (17.65%)	62.75% (52.06%, 73.43%) < 0.0001
5. Sensitivity analysis using per protocol population	84 (70.59%)	22 (18.18%)	52.41% (41.72%, 63.10%) < 0.0001	85 (75.22%)	18 (14.75%)	60.47% (50.32%, 70.61%) < 0.0001
6. Sensitivity analysis using multiple imputation for handling missing MBL[c]	71.81%	19.46%	52.35% (41.33%, 63.36%) < 0.0001	70.63%	16.96%	53.67% (42.59%, 64.75%) < 0.0001

Abbreviations: CI = confidence interval; CSR = clinical study report; E2 = estradiol; MBL = menstrual blood loss; mITT = modified intent-to-treat; N = number of patients; NETA = norethindrone acetate.

[a] Difference is relugolix + E2/NETA minus placebo and un-adjusted 95% CIs.

[b] P-value was based on Cochran-Mantel-Haenszel test stratified by baseline MBL volume (< 225 mL or ≥ 225 mL) and geographic region (North America or Rest of World).

[c] Results represent the weighted responder rates over the datasets from the multiple imputations.

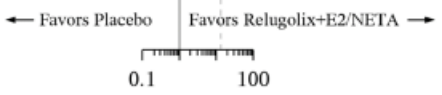
Sensitivity analyses are consistent with the primary analysis, thereby supporting the results of the primary analysis.

Ancillary analyses (subgroup analyses)

In the pivotal studies (MVT-601-3001 and MVT-601-3002), subgroup analyses of the primary efficacy endpoint comparing the relugolix + E2/NETA group versus the placebo group were performed to assess whether treatment effects were consistent across clinically important subgroups. The odds ratio and its 95% CI based on a logistic regression model were displayed in a forest plot for each subgroup.

Table: MVT-601-3001: Summary of Subgroup Analyses for the Primary Endpoint (mITT Population)

Subgroup	Relugolix+ E2/NETA (N=128)	Placebo (N=130)	Odds Ratio (95% CI)[a]
Geographic region			
North America	69 (70.4%)	16 (16.3%)	12.73 (6.33,25.59)
Rest of World	25 (83.3%)	8 (27.6%)	13.11 (3.71,46.33)
MBL Vol at BL (mL)			
< 225 mL	67 (79.8%)	15 (17.6%)	18.75 (8.56,41.06)
>= 225 mL	27 (61.4%)	9 (21.4%)	6.35 (2.36,17.09)
Age (years)			
< 40 years	19 (63.3%)	6 (16.7%)	11.46 (3.14,41.80)
>= 40 years	75 (76.5%)	18 (19.8%)	13.45 (6.67,27.12)
Race			
Black/African American	36 (61.0%)	8 (11.9%)	11.95 (4.73,30.22)
White	55 (85.9%)	16 (28.6%)	15.19 (6.01,38.36)
Uterine Vol at BL (cm3)			
< 300 cm3	59 (79.7%)	11 (17.2%)	20.59 (8.39,50.51)
>= 300 cm3	35 (66.0%)	13 (20.6%)	8.04 (3.42,18.90)
BMI (kg/m2) at BL			
< 30	46 (75.4%)	12 (22.2%)	11.95 (4.82,29.62)
>= 30	48 (71.6%)	12 (16.4%)	13.68 (5.95,31.43)
Max. NRS pain score at BL			
< 4	32 (74.4%)	3 (9.7%)	33.66 (7.93,142.96)
>= 4	61 (72.6%)	21 (22.1%)	10.36 (5.08,21.13)
Overall	94 (73.4%)	24 (18.9%)	12.82 (6.96,23.60)



Abbreviations: BL = baseline; E2 = estradiol; max = maximum; MBL = menstrual blood loss; n = number of patients in subset; NETA = norethindrone acetate.

[a] Odds ratio > 1 favors relugolix + E2/NETA over placebo based on logistic regression with treatment group, baseline MBL volume (< 225 mL or ≥ 225 mL), and geographic region (North America or Rest of World) as covariates.

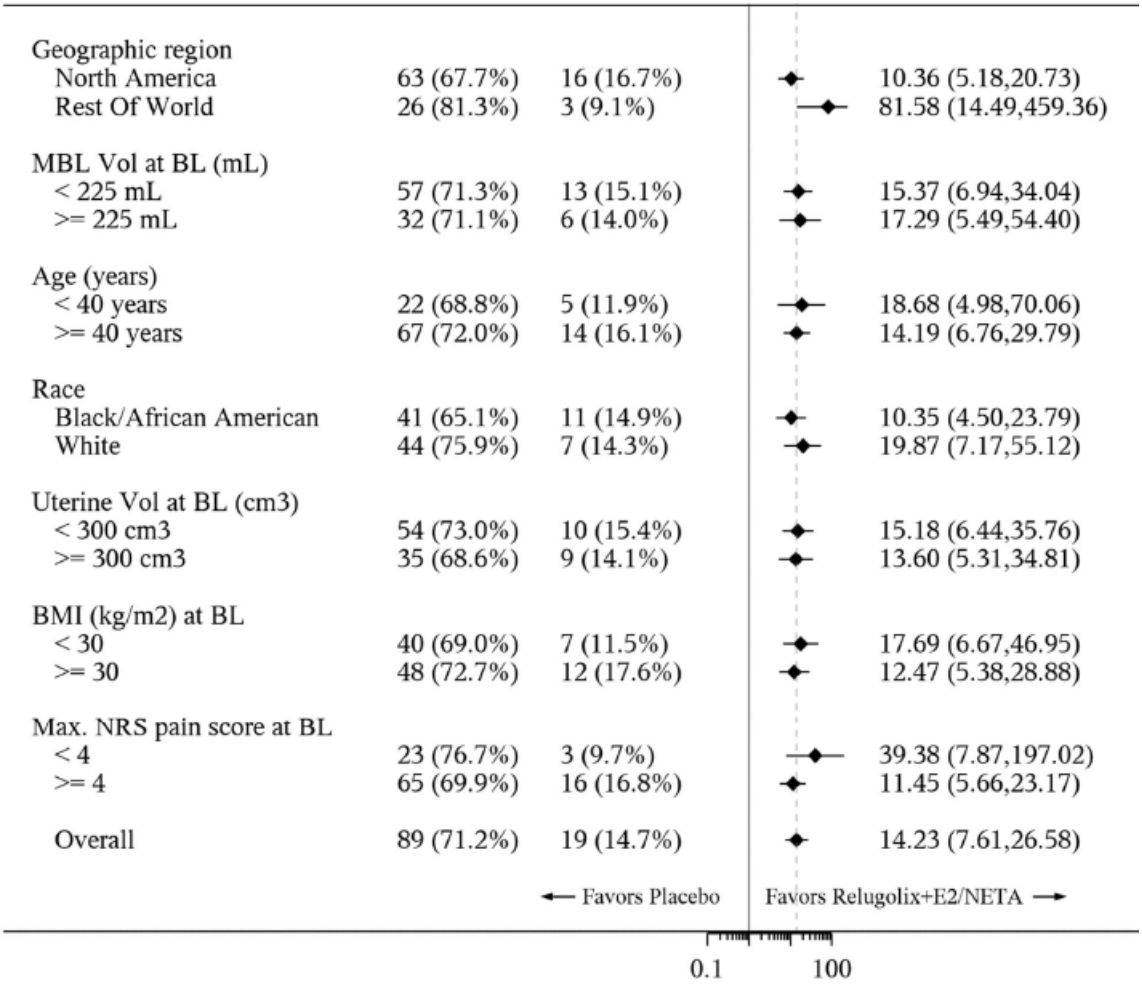
Source: Table 7.2.1.2.

The magnitude of the responses across these subgroups was generally consistent with that observed in the analysis of the primary efficacy endpoint in the overall population, especially in the subgroups with larger sample sizes. Treatment effect was similar in Black/African American and White patients, while small sample sizes in Asian and other racial groups made it difficult to make robust comparisons. Smaller treatment differences were observed in the subgroups of women with larger uterine volumes (≥ 300 cm3) and women with greater MBL volume at baseline (≥ 225 mL)

relative to the rest of the subgroups; however, the odds ratio (95% CI) in these subgroups was still in favor of relugolix + E2/NETA.

Table: MVT-601-3002: Summary of Subgroup Analyses for the Primary Endpoint (mITT Population)

Subgroup	Relugolix+ E2/NETA (N=125)	Placebo (N=129)	Odds Ratio (95% CI)[a]
Geographic region			
North America	63 (67.7%)	16 (16.7%)	10.36 (5.18,20.73)
Rest Of World	26 (81.3%)	3 (9.1%)	81.58 (14.49,459.36)
MBL Vol at BL (mL)			
< 225 mL	57 (71.3%)	13 (15.1%)	15.37 (6.94,34.04)
>= 225 mL	32 (71.1%)	6 (14.0%)	17.29 (5.49,54.40)
Age (years)			
< 40 years	22 (68.8%)	5 (11.9%)	18.68 (4.98,70.06)
>= 40 years	67 (72.0%)	14 (16.1%)	14.19 (6.76,29.79)
Race			
Black/African American	41 (65.1%)	11 (14.9%)	10.35 (4.50,23.79)
White	44 (75.9%)	7 (14.3%)	19.87 (7.17,55.12)
Uterine Vol at BL (cm3)			
< 300 cm3	54 (73.0%)	10 (15.4%)	15.18 (6.44,35.76)
>= 300 cm3	35 (68.6%)	9 (14.1%)	13.60 (5.31,34.81)
BMI (kg/m2) at BL			
< 30	40 (69.0%)	7 (11.5%)	17.69 (6.67,46.95)
>= 30	48 (72.7%)	12 (17.6%)	12.47 (5.38,28.88)
Max. NRS pain score at BL			
< 4	23 (76.7%)	3 (9.7%)	39.38 (7.87,197.02)
>= 4	65 (69.9%)	16 (16.8%)	11.45 (5.66,23.17)
Overall	89 (71.2%)	19 (14.7%)	14.23 (7.61,26.58)



Abbreviations: BL = baseline; E2 = estradiol; max = maximum; n = number of patients in subset; MBL = menstrual blood loss; NETA = norethindrone acetate.

[a] Odds ratio > 1 favors relugolix + E2/NETA over placebo based on logistic regression with treatment group, baseline MBL volume (< 225 mL or ≥ 225 mL), and geographic region (North America or Rest of World) as covariates.

Source: Table 7.2.1.2.

Across all subgroups, treatment differences were consistent with the primary analysis with a higher proportion of patients who received relugolix + E2/NETA meeting the definition for responder than patients who received placebo, as indicated by the point estimate and lower bound of the 95% CI for the odds ratios being above 1 favoring relugolix + E2/NETA over placebo. The magnitude of the responses across these subgroups was generally consistent with that observed in the analysis of the primary efficacy endpoint in the overall population, especially in the subgroups with larger sample sizes. Treatment effect was slightly higher in the rest of world than in North America and in White patients compared with Black or African American patients. Small sample sizes in Asian and other racial groups

made it difficult to make robust comparisons. Smaller treatment differences were observed in the subgroups of women with larger uterine volumes (≥ 300 cm3) relative to the rest of the subgroups; however, the odds ratio (95% CI) in these subgroups was still in favor of relugolix + E2/NETA.

Key secondary efficacy endpoints (MVT-601-3001 and MVT-601-3002)

In both phase 3 studies, six of the seven pre-defined, multiplicity-adjusted, key secondary endpoints were selected.

Treatment comparisons (relugolix combination therapy vs. placebo) of the seven key secondary efficacy endpoints for the individual relugolix combination therapy studies (MVT-601-3001 and MVT-601-3002) are presented below.

Table: Analyses of Primary and Key Secondary Efficacy Endpoints Adjusted for Multiplicity

	MVT-601-3001	MVT-601-3002
Endpoint Definition	**Relugolix+E2/NETA vs Placebo Diff (95% CI) p-value**	**Relugolix+E2/NETA vs Placebo Diff (95% CI) p-value**
Proportion of women with < 80mL and >=50% reduction in MBL	73.44% vs 18.90% 54.54% (44.30%, 64.78%) < 0.0001	71.20% vs 14.73% 56.47% (46.45%, 66.49%) < 0.0001
Proportion of women who achieved amenorrhea over the last 35 days of treatment.	52.34% vs 5.51% 46.83% (37.31%, 56.35%) < 0.0001	50.40% vs 3.10% 47.30% (38.04%, 56.56%) < 0.0001
Percent change from Baseline to Week 24 in menstrual blood loss volume	-84.3 vs -23.2 -61.1 (-73.5, -48.6) < 0.0001	-84.3 vs -15.1 -69.2 (-84.1, -54.3) < 0.0001
Change from Baseline to Week 24 in UFS QoL BPD scale score as measured by the UFS-QoL (Q1, Q2, Q5)	-45.0 vs -16.1 -28.9 (-36.3, -21.5) < 0.0001	-51.7 vs -18.3 -33.4 (-41.2, -25.5) < 0.0001
Proportion of women who achieved a maximum NRS score <= 1 for uterine fibroid-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	43.10% vs 10.14% 32.96% (18.36%, 47.56%) < 0.0001	47.06% vs 17.07% 29.99% (15.60%, 44.38%) < 0.0001
Proportion of women with a hemoglobin level <= 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24	50.00% vs 21.74% 28.26% (3.68%, 52.84%) 0.0377	61.29% vs 5.41% 55.88% (37.25%, 74.52%) < 0.0001
Percent change from Baseline to Week 24 in primary uterine fibroid volume	-12.4 vs -0.3 -12.1 (-26.3, 2.0) 0.0921	-17.4 vs -7.4 -10.0 (-25.8, 5.8) 0.2153
Percent change from Baseline to Week 24 in uterine volume	-12.9 vs 2.2 -15.1 (-23.0, -7.3) 0.0002	-13.8 vs -1.5 -12.2 (-21.3, -3.2) 0.0078

Abbreviations: BPD = Bleeding and Pelvic Discomfort; CI = confidence interval; MBL = menstrual blood loss; NRS = Numerical Rating Scale; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life; Q1 = question 1; Q2 = question 2; Q5 = question 5.

Note: Nominal p-values for pooled results.

In both phase 3 studies, six of the seven pre-defined, multiplicity-adjusted, key secondary endpoints were met. For all key secondary endpoints relugolix + E2/NETA was superior compared with placebo, except for reduction in uterine fibroid volume, where the reduction was not statistically significant in comparison with placebo.

Key secondary endpoints in the relugolix + delayed E2/NETA group 24 weeks

Mean Menstrual Blood Loss Volume

Percent Change from Baseline to Week 24 in MBL Volume

Percent change from baseline in MBL volume to Week 24 is presented below for studies MVT-601-3001 and MVT-601-3002:

Table: Summary of Percent Change from Baseline in MBL Volume to Week 24 (mITT Population)

	MVT-601-3001		MVT-601-3002	
	Relugolix + E2/NETA (N = 128)	**Placebo (N = 128)**	**Relugolix + E2/NETA (N = 126)**	**Placebo (N = 129)**
LS Means (SE)	-84.3 (4.72)	-23.2 (4.61)	-84.3 (5.45)	-15.1 (5.47)
95% CI	(-93.5, -75.0)	(-32.2, -14.1)	(-95.0, -73.6)	(-25.8, -4.3)
Difference of LS Means (SE) [1]	-61.1 (6.32)		-69.2 (7.58)	
95% CI	(-73.5, -48.6)		(-84.1, -54.3)	
p-value	< 0.0001		< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; LS = least square; MBL = menstrual blood loss; mITT = modified intent-to-treat; N = number of patients; NETA = norethindrone acetate; SE = standard error.

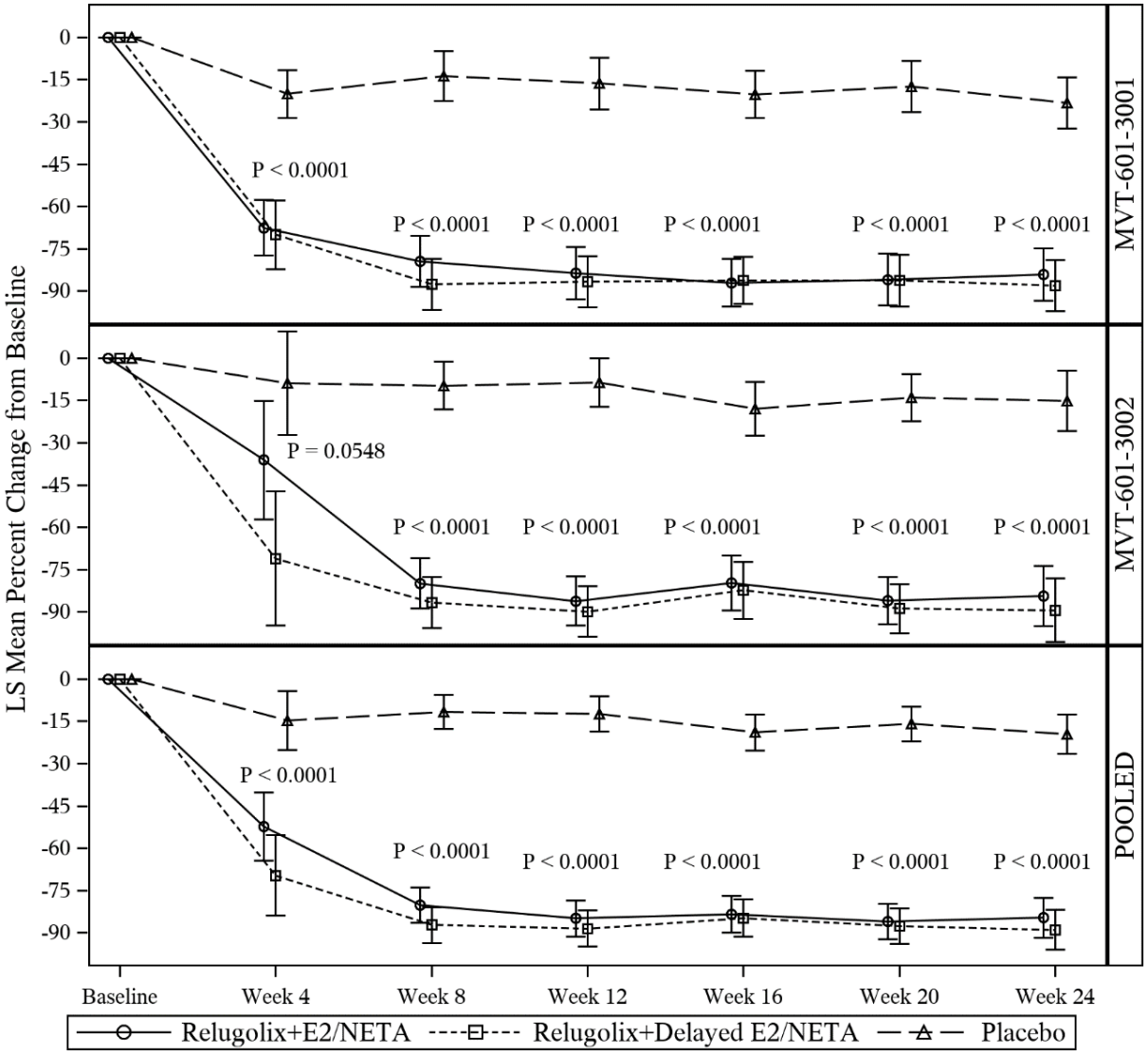
Note: Summary statistics are based on observed data. Patients with confirmed amenorrhea are assigned as 0 mL.

[1] LS means and p-value for test of difference is relugolix + E2/NETA minus placebo based on mixed-effect model with treatment, visit, region, baseline MBL and treatment by visit interaction included as fixed effects. The multiple visits for each patient were the repeated measures as random effect within each patient and an unstructured covariance.

Reduction in Menstrual Blood Loss Volume over time (24 weeks)

The reduction from baseline in least squares mean MBL volume over time is presented in the figures below for studies MVT-601-3001 and MVT-601-3002.

Figure: Summary of Reduction in Menstrual Blood Loss Volume by Visit mITT Population)



Abbreviations: CI = confidence interval; E2 = estradiol; LS = least squares; MBL = mean blood loss; mITT = modified intent-to-treat; NETA = norethindrone acetate.
Note: error bars represent 95% CI. The p-value represents the comparison of relugolix + E2/NETA and placebo groups. Except for percent change from baseline at Week 24 (a key secondary endpoint at study level), nominal p-values are shown.
LS means and p-value for test of difference is relugolix + E2/NETA minus placebo based on mixed-effect model with treatment, visit, region, baseline MBL and treatment by visit interaction included as fixed effects. The multiple visits for each patient were the repeated measures as random effect within each patient and an unstructured covariance.

In study MVT-601-3001, a considerable effect of relugolix+E2/NETA on MBL volume was observed by the first menstrual cycle (4 weeks) with maximal reduction in MBL volume at the second menstrual cycle (8 weeks). The effects sustained until the end of the study at Week 24. The difference between the relugolix combination therapy group and placebo was significant at all time points.

In study MVT-601-3002, reduction in MBL volume had not yet reached statistical significance in the relugolix + E2/NETA group at Week 4 (nominal p = 0.0548), but reductions were maximal by Week 8 and thereafter. At Week 4 the least squares mean change from baseline was heavily influenced by a single patient who had an extremely large MBL volume (2710.3 mL) at Week 4 (her baseline MBL volume was 190.2 mL).

In conclusion, the results from reduction in menstrual blood loss volume show that heavy menstrual bleeding, as the most important symptom of uterine fibroids, is significantly reduced starting at the first timepoint Week 4 through to Week 24.

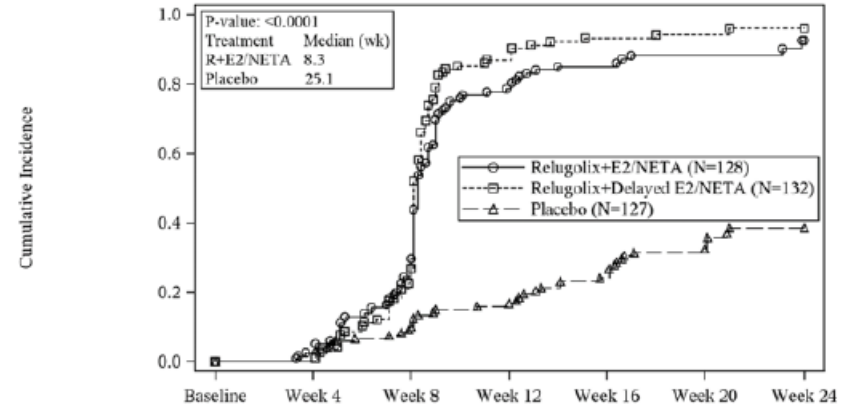
The decrease in **volume of menstrual blood loss** for relugolix + E2/NETA groups in both phase 3 studies) was statistically significant and reductions in menstrual blood loss volume (mean 84.3%, in both) were clinically relevant.

Time to Response

The median time to response (ie, MBL volume of < 80 and at least a 50% reduction from baseline MBL volume) in studies MVT-601-3001 and MVT-601-3002 is shown in the figure below.

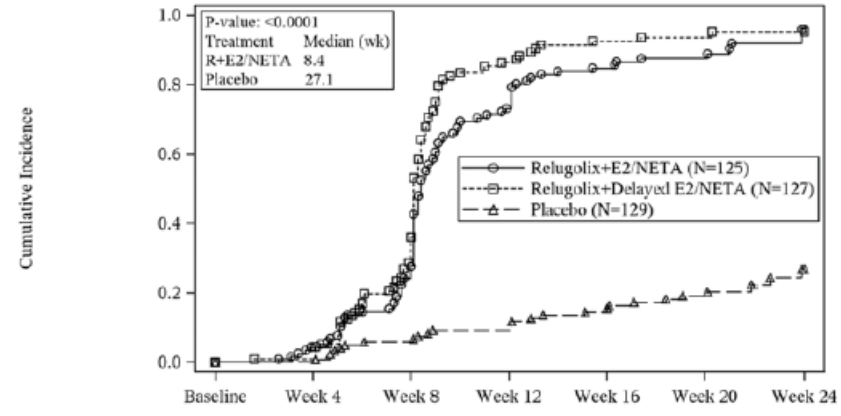
Figure: Time to Achieve Menstrual Blood Loss Volume < 80 mL and ≥ 50 % Reduction from Baseline (mITT Population)

Study MVT-601-3001



No. of Patients at Risk		Time to achieve MBL < 80 ml and at least 50% reduction					
R+E2/NETA	128	114	86	24	14	11	2
R+Delayed E2/NETA	132	120	89	15	7	6	2
Placebo	127	120	109	96	82	64	18

Study MVT-601-3002



No. of Patients at Risk		Time to achieve MBL < 80 ml and at least 50% reduction					
R+E2/NETA	125	112	87	30	17	10	1
R+Delayed E2/NETA	127	112	79	14	7	4	1
Placebo	129	123	112	105	93	77	29

In both studies, the median time to achieve a first response was consistently and significantly shorter in the relugolix + E2/NETA groups (8.3 weeks and 8.4 weeks in studies MVT-601-3001 and MVT-601-3002, respectively) when compared with the small number of patients who achieved a response in the placebo groups (25.1 weeks and 27.1 weeks, respectively; nominal p < 0.0001 in both studies).

When comparing the relugolix combination group with the relugolix + delayed E2/NETA group, the reduction in MBL volume appears, as expected, somewhat larger in the relugolix monotherapy group at week 12 (R-delayed E2/NETA group) in comparison to the relugolix combination group.

Amenorrhea (end of week 24)

The proportion of women who achieved amenorrhea over the last 35 days of 24 weeks treatment is presented in the table below for studies MVT-601-3001 and MVT-601-3002.

Table: Proportion of Patients Who Achieved Amenorrhea Over the Last 35 Days of Treatment (mITT Population)

	MVT-601-3001		MVT-601-3002	
	Relugolix + E2/NETA (N = 128)	**Placebo (N = 128)**	**Relugolix + E2/NETA (N = 126)**	**Placebo (N=129)**
Number (%) of patients with amenorrhea over the last 35 days of treatment	67 (52.34%)	7 (5.51%)	63 (50.40%)	4 (3.10%)
(95% CI) [1]	(43.34%, 61.24%)	(2.24%, 11.03%)	(41.32%, 59.46%)	(0.85%, 7.75%)
Difference from placebo	46.83%		47.30%	
(95% CI) [2]	(37.31%, 56.35%)		(38.04%, 56.56%)	
P-value [3]	< 0.0001		< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; MBL = menstrual blood loss; mITT = modified intent-to-treat; NETA = norethindrone acetate.

Note: Amenorrhea is defined as reported amenorrhea, spotting, or negligible bleeding (MBL < 5 mL) with supporting eDiary compliance at 2 consecutive visits.

[1] Based on exact binomial 95% CI (Clopper-Pearson).

[2] Difference is relugolix + E2/NETA minus placebo. 95% CI for difference is based on the normal approximation.

[3] p-value is based on Cochran-Mantel-Haenszel test stratified by baseline MBL volume (< 225 mL, >= 225 mL) and geographic region (North America, Rest of World).

Results in the relugolix + E2/NETA groups were generally similar between studies, with 52.34% and 50.40% of women in studies MVT-601-3001 and MVT-601-3002, respectively, achieving amenorrhea over the last 35 days of treatment compared with 5.51% and 3.10% in the placebo groups, respectively. The observed difference between the relugolix + E2/NETA and placebo groups of approximately 47% in both studies was statistically significant (p < 0.0001).

Time to Achieving Amenorrhea

The median time to achieving amenorrhea in the relugolix + E2 NETA group was 5.3 weeks in study MVT-601-3001 and 8.9 weeks in study MVT-601-3002. In the placebo groups, the median time to achievement of amenorrhea was not reached in either study due to the low event rates observed, as expected (nominal p < 0.0001).

Proportion of Women Achieving Amenorrhea per visit

In both studies, the proportion of women in the relugolix + E2/NETA groups who achieved amenorrhea was significantly higher (nominal $p < 0.0001$) than in the placebo groups at all assessed time points. The proportion of women achieving amenorrhea in the relugolix + E2/NETA groups increased over time from 29.7% and 17.6% of patients in studies MVT-601-3001 and MVT-601-3002 respectively at the Week 8 visit to more than half (52.3% and 50.4%, respectively) of patients by Week 24. Comparatively, in the placebo group, few patients achieved amenorrhea at any timepoint with 5.5% of patients in study MVT-601-3001and 3.1% of patients in study MVT-601-3002 by the Week 24 visit.

Time to achieve sustained amenorrhea

The median time to achieving sustained amenorrhea in the relugolix + E2 NETA groups was 11.3 weeks in study MVT-601-3001 and 16.3 weeks in study MVT-601-3002. In the placebo groups, the median time to sustained amenorrhea was not reached in either study due to low event rates observed, as expected (nominal $p < 0.0001$).

In conclusion, in studies MVT-601-3001 and MVT-601-3002, amenorrhea was achieved by 52.3% on relugolix+E2/NETA vs 5.5% on placebo in MVT-601-3001 and 50.4% vs 3.1% of women in MVT-601-3002, respectively. At Week 8 amenorrhea was only achieved by 29.7% and 17.6% of women on relugolix+E2/NETA, respectively. The median time to achieving sustained amenorrhea in the relugolix + E2 NETA groups was 11.3 weeks in study MVT-601-3001 and 16.3 weeks in study MVT-601-3002. The observed percentages of amenorrhea during use with relugolix + E2/NETA were statistically significantly greater and considered clinically relevant.

Improvement of anemia (subgroup analysis)

Hemoglobin increase of > 2 g/dL from baseline to Week 24 when ≤ 10.5 g/dL at baseline

The proportion in a subset of women with anemia (hemoglobin ≤ 10.5 g/dL at Baseline), i.e. (30 on relugolix+E2/NETA vs 23 patients on placebo in study 601-3001 and 31 vs 37 in study 601-3002) who achieved a hemoglobin increase of > 2 g/dL from baseline to Week 24 is presented in the table below for studies MVT-601-3001, MVT-601-3002, and the pooled population.

Table: Proportion of Women with Hemoglobin ⩽ 10.5 g/dL at Baseline and Achieved an Increase of > 2 g/dL at Week 24 (mITT Population)

	MVT-601-3001		MVT-601-3002		Pooled	
	Relugolix + E2/NETA (N = 128)	Placebo (N = 128)	Relugolix + E2/NETA (N = 126)	Placebo (N = 129)	Relugolix + E2/NETA (N = 254)	Placebo (N = 257)
Number of hemoglobin evaluable patients	30 (23.44%)	23 (18.11%)	31 (24.80%)	37 (28.68%)	61 (24.11%)	60 (23.44%)
Number of responders at Week 24	15 (50.00%)	5 (21.74%)	19 (61.29%)	2 (5.41%)	34 (55.74%)	7 (11.67%)
(95% CI) [1]	(31.30%, 68.70%)	(7.46%, 43.70%)	(42.19%, 78.15%)	(0.66%, 18.19%)	(42.45%, 68.45%)	(4.82%, 22.57%)
Difference from placebo	28.26%		55.88%		44.07%	
(95% CI) [2]	(3.68%, 52.84%)		(37.25%, 74.52%)		(29.19%, 58.95%)	
P-value [3]	0.0377		< 0.0001		< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; MBL = menstrual blood loss; mITT = modified intent-to-treat; N = number of patients; NETA = norethindrone acetate.

Notes: Hemoglobin-evaluable is also defined as anemia-evaluable. A responder is defined as a woman in the anemia-evaluable population (ie, those with hemoglobin ≤ 10.5 g/dL at baseline and who had a hemoglobin value at Week 24) who achieved hemoglobin increase > 2g/dL from baseline to Week 24.

[1] Based on exact binomial 95% CI (Clopper-Pearson).

[2] Difference is relugolix + E2/NETA minus placebo. 95% CI for difference is based on the normal approximation.

[3] p-value is based on Cochran-Mantel-Haenszel test stratified by baseline MBL volume (< 225 mL, ≥ 225 mL).

Percentages are based on number of patients with hemoglobin ≤ 10.5 g/dL at baseline and reported at Week 24 (anemia-evaluable population).

In each study, at least 50% of anemia-evaluable patients (i.e. those with hemoglobin ≤ 10.5 g/dL at baseline and who had a hemoglobin value at Week 24) in the relugolix + E2/NETA group demonstrated improvement in anemia (defined as hemoglobin increase of > 2 g/dL at Week 24). These results were statistically significant compared with the placebo group in both study MVT-601-3001 (p = 0.0377) and study MVT-601-3002 (p < 0.0001).

However, the treatment effect in the relugolix + E2/NETA group in study MVT-601-3001 was comparatively lower (28.26%) than that observed in study MVT-601-3002 (55.88%). This difference was not considered meaningful, as indicated by the overlapping 95% CIs for the responder rates (31.30%, 68.70% for MVT-601-3001 and 42.9%, 75.15% for MVT-601-3002), and may be driven by differences in the sizes of the placebo groups between the two studies (N = 23 in study MVT-601-3001 and N = 37 in study MVT-601-3002).

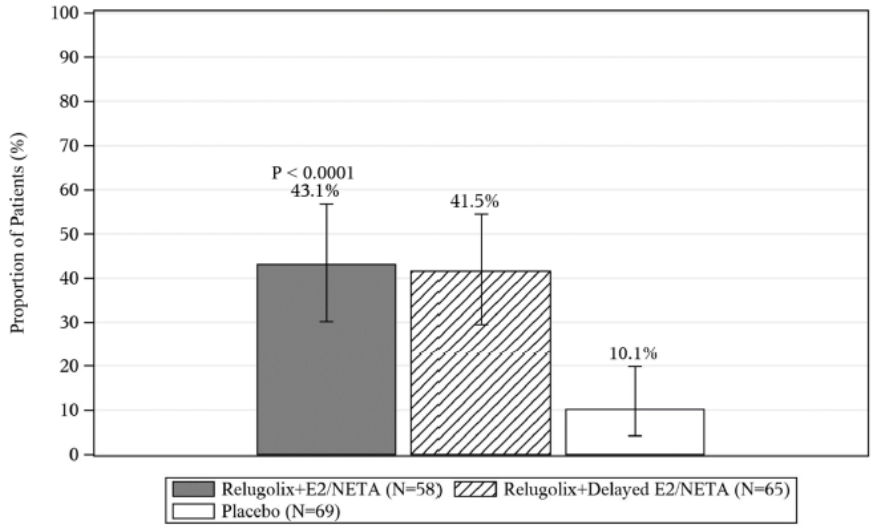
Uterine Fibroid-Associated Pain Endpoints (subgroup analysis)

After heavy menstrual bleeding, pain is the second most frequent and most burdensome symptom for women with uterine fibroids and is reported to have a significant impact on QoL.

Key secondary endpoint was Proportion of women who achieved a maximum NRS score ≤ 1 during the last 35 days of treatment in a subset of women with maximum NRS score ≥ 4 at baseline.

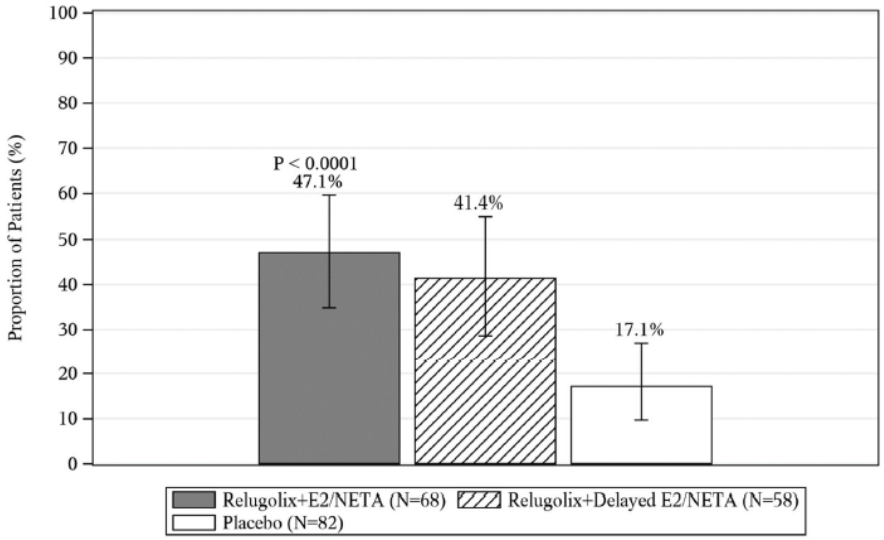
Proportion of women who achieved a maximum NRS score ≤ 1 are shown in the figures and table below:

Figure: MVT-301-3001: Proportion of Patients with a Maximum NRS Score ≤ 1 During the Last 35 Days of Treatment in a Subset of Pain Evaluable Patients (mITT Population)



Abbreviations: E2 = estradiol; N = number of patients; NETA = norethindrone acetate.
Source: Figure 7.2.8.1.

Figure: MVT-301-3002: Proportion of Patients with a Maximum NRS Score ≤ 1 During the Last 35 Days of Treatment in a Subset of Pain Evaluable Patients (mITT Population)



Abreviations: E2 = estradiol; N = number of patients; NETA = norethindrone acetate.
Source: Figure 7.2.8.4.

Table: Proportion of Patients with Maximum NRS Score ⩽ 1 During the Last 35 Days of 24 week Treatment in Subset of Pain-Evaluable Patients (mITT Population)

	MVT-601-3001		MVT-601-3002		Pooled	
	Relugolix + E2/NETA (N = 128)	Placebo (N = 128)	Relugolix + E2/NETA (N = 126)	Placebo (N = 129)	Relugolix + E2/NETA (N = 254)	Placebo (N = 257)
Number of pain evaluable patients	58 (45.31%)	69 (54.33%)	68 (54.40%)	82 (63.57%)	126 (49.80%)	151 (58.98%)
Patients who achieved maximum NRS score ≤ 1 during the last 35 days of treatment	25 (43.10%)	7 (10.14%)	32 (47.06%)	14 (17.07%)	57 (45.24%)	21 (13.91%)
(95% CI) [1]	(30.16%, 56.77%)	(4.18%, 19.79%)	(34.83%, 59.55%)	(9.66%, 26.98%)	(36.36%, 54.35%)	(8.82%, 20.47%)
Difference from placebo (95% CI) [2]	32.96% (18.36%, 47.56%)		29.99% (15.60%, 44.38%)		31.33% (21.04%, 41.63%)	
P-value [3]	< 0.0001		< 0.0001		< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; mITT = modified intent-to-treat; MBL = menstrual blood loss; N = number of patients; NETA = norethindrone acetate; NRS = Numerical Rating Scale.
Note: Pain-evaluable patients are defined as those who had maximum NRS score ≥ 4 at baseline and had at least 28 days (80% of the last 35 days of treatment) of pain scores recorded in the eDiary. Nominal p-value is shown for pooled results.
[1] Based on exact binomial 95% CI (Clopper-Pearson).
[2] Difference is relugolix + E2/NETA minus placebo. 95% CI for difference is based on the normal approximation.
[3] p-value is based on Cochran-Mantel-Haenszel test stratified by baseline MBL volume (< 225 mL, ≥ 225 mL).

Similar proportions in the subsets of patients in both studies MVT-601-3001 and MVT-601-3002 met the definition of responder (ie, achieving a maximal NRS score of ≤ 1 during the last 35 days of treatment in the pain-evaluable population) in the relugolix + E2/NETA (43.10% and 47.06%, respectively) and placebo groups (10.14% and 17.07%, respectively); the differences between groups were statistically significant ($p < 0.0001$) and consistent across studies.

Uterine fibroid volume

A summary of percent change from baseline in uterine fibroid volume at Week 24 in studies MVT-601-3001, MVT-601-3002, and the pooled population is shown in the table below:

Table: Summary of Percent Change from Baseline in Uterine Fibroid Volume at Week 24 (mITT Population)

	MVT-601-3001		MVT-601-3002		Pooled	
	Relugolix + E2/NETA (N=128)	Placebo (N=128)	Relugolix + E2/NETA (N=126)	Placebo (N=129)	Relugolix + E2/NETA (N=254)	Placebo (N=257)
LS Means (SE)	-12.4 (5.62)	-0.3 (5.40)	-17.4 (5.93)	-7.4 (5.92)	-15.4 (4.06)	-4.2 (3.98)
Difference of LS Means (SE) [1]	-12.1 (7.19)		-10.0 (8.03)		-11.2 (5.36)	
95% CI	(-26.3, 2.0)		(-25.8, 5.8)		(-21.7, -0.7)	
P-value	0.0921		0.2153		0.0374	

Abbreviations: CI = confidence interval; E2 = estradiol; LS = least squares; max = maximum; min = minimum; MBL = menstrual blood loss; mITT = modified intent-to-treat; N = number of patients; NETA = norethindrone acetate; SD = standard deviation; SE = standard error.
Note: Serial measurements of the largest uterine fibroid among those measurable at baseline were reported. Summary statistics are based on observed data. Nominal p-value for pooled results.
[1] LS means and p-value for test of difference is relugolix + E2/NETA minus placebo based on mixed-effect model with treatment, visit, region, baseline MBL and treatment by visit interaction included as fixed effects. The multiple visits for each patient were the repeated measures as random effect within each patient and an unstructured covariance.

Decrease in volume from baseline to Week 24 in uterine fibroid volume was lower in the relugolix + E2/NETA groups (-12.4% and -17.4% in studies MVT-601-3001 and MVT-601-3002, respectively) than on placebo (-0.3% and -7.4%, respectively), although the results were not statistically significant compared with placebo ($p = 0.0921$ and $p = 0.2153$, respectively). In the pooled data, statistical significance was reached with placebo (-15.4% vs. -4.2%; $p = 0.0374$). In summary, the greater decrease in fibroid volume, though not reaching statistical significance, can be considered supportive, but additional results are awaited collected during long-term treatment.

Uterine Volume

A summary of percent change from baseline in uterine fibroid volume at Week 24 for studies MVT-601-3001 and MVT-601-3002 is shown in the table below. Results of these analyses were further categorized by uterine volume at baseline; shown in Table 23 and Table 24 earlier in this report.

Table: Summary of Percent Change from Baseline in Uterine Volume at Week 24 (mITT Population)

	MVT-601-3001		MVT-601-3002	
	Relugolix+ E2/NETA (N = 128)	**Placebo (N = 128)**	**Relugolix+ E2/NETA (N = 126)**	**Placebo (N = 129)**
LS Means (SE)	-12.9 (3.08)	2.2 (3.01)	-13.8 (3.39)	-1.5 (3.37)
Difference of LS Means (SE) [1]	-15.1 (3.98)		-12.2 (4.57)	
95% CI	(-23.0, -7.3)		(-21.3, -3.2)	
P-value	0.0002		0.0078	

Abbreviations: CI = confidence interval; E2 = estradiol; LS = least squares; max = maximum; MBL = menstrual blood loss; min = minimum; mITT = modified intent-to-treat; N = number of patients; NETA = norethindrone acetate; SD = standard deviation; SE = standard error.
[1] LS means and p-value for test of difference is relugolix + E2/NETA minus placebo based on mixed-effect model with treatment, visit, region, baseline MBL and treatment by visit interaction included as fixed effects. The multiple visits for each patient were the repeated measures as random effect within each patient and an unstructured covariance.

In both studies, mean uterine volume decreased from baseline to Week 24 and was significantly greater in the relugolix + E2/NETA groups (-12.9% and -13.8% for MVT-601-3001 and MVT-601-3002, respectively) compared with the placebo groups (2.2% [p< 0.0002] and -1.5% [p< 0.0078], respectively.

Other Secondary Efficacy Endpoints

Consistent with improvement in heavy menstrual bleeding, the results of the other secondary efficacy endpoints evaluating patient-reported outcomes reflected improvement in patients treated with relugolix + E2/NETA compared with placebo:

- improvement in the Uterine Fibroids Symptoms (UFS)-QoL symptom severity scale (36.1 point improvement at Week 24 in the relugolix + E2/NETA group vs. 13.7 point improvement in the placebo group) and all health-related quality of life subscales (37.8 point vs. 13.8 point improvement at Week 24, respectively).
- Improvement in Patient Global Assessment (PGA) symptom scores in the relugolix + E2/NETA group (85.0% showing any improvement), compared with the placebo group (58.3% showing any improvement) as were PGA function scores (81.3% showing any improvement vs. 52.4%, respectively).

Exit interview study questionnaire

Further, study MVT-601-037, a substudy to MVT-601-3001 and MVT-601-3002 (exit study, see section Supportive studies), was conducted to obtain patient input via qualitative interviews of English-speaking patients who completed the pivotal phase 3 studies of 24 weeks on what constitutes a meaningful or relevant improvement on patient reported outcomes. Pain among subjects was among other, measured with the UFS QoL BPD scale to assess three symptoms associated with uterine fibroids that are common to most patients (i.e., heavy bleeding during the menstrual period, passing blood clots during the menstrual period, and feeling tightness or pressure in the pelvic area). The study results suggest that these women could distinguish a clinically meaningful change in their symptomatology. A limitation of the study was that the substudy population (N=30 from the US) was very small compared to the total number of subjects from MVT-601-3001 + MVT-601-3002 (total sample N=770, total US sample N=582).

Summary of main efficacy results (MVT-601-3001 and MVT-601-3002)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table: Summary of efficacy for trials MVT-601-3001 and MVT-601-3002

Summary of Efficacy for Trial MVT-601-3001

Title: 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			
Study Identifier	Study Number: MVT-601-3001 Eudra CT Number: 2016-003727-27 IND Number: 131161 NCT Number: 03049735		
Design	Randomized, multicenter, international, double-blind, placebo-controlled, efficacy and safety study.		
	Duration of Main Phase: Duration of Run-In Phase: Duration of Extension Phase:		24 weeks (randomized treatment period) 13 weeks (screening period) 30 days (follow-up period)
Hypothesis	Superiority		
Treatments Groups	Relugolix + Estradiol (E2) /Nrorethindrone Acetate (NETA)		Relugolix 40 mg tablet once daily (QD) + capsule containing a tablet of E2 1 mg and NETA 0.5 mg QD, 24 weeks, n = 128
	Relugolix + Delayed E2/NETA		Relugolix 40 mg tablet QD + placebo capsule QD for 12 weeks, followed by relugolix 40 mg tablet QD + capsule containing a tablet of E2 1 mg and NETA 0.5 mg QD for 12 weeks, n = 132
	Placebo		Relugolix placebo-to-match tablet QD + placebo capsule QD for 24 weeks, n = 127 (treated)
Endpoints and Definitions	Primary Endpoint	F1	The proportion of women who achieved a menstrual blood loss (MBL) volume < 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, referred to as responder rate
	Secondary Endpoint	F2_1	Proportion of women who achieved amenorrhea over the last 35 days of treatment
	Secondary Endpoint	F2_2	Percent change from baseline to Week 24 in MBL volume
	Secondary Endpoint	F2_3	Change from baseline to Week 24 in Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) bleeding and pelvic discomfort (BPD) scale score as measured by the UFS-QoL (Q1, Q2, Q5)

	Secondary Endpoint	F2_4	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
	Secondary Endpoint	F3_5	Proportion of women who achieved a maximum numerical rating scale (NRS) score ≤ 1 for uterine fibroid-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
	Secondary Endpoint	F3_6	Percent change from baseline to Week 24 in primary uterine fibroid volume
	Secondary Endpoint	F3_7	Percent change from baseline to Week 24 in uterine volume
Database Lock	08 May 2019		
Results and Analysis			
Analysis Description	**Primary Analysis (F1)**		
Analysis Population and Time Point Description	Modified Intent-to-Treat (mITT) The mITT population was defined as all randomized patients who received any amount of study drug (relugolix/placebo or E2/NETA/placebo). Time Point: Week 24/End of Treatment (EOT)		

Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	128	127
	Number (%) of Responders	94 (73.44%)	24 (18.90%)
	95% Confidence Interval (CI)	(64.91%, 80.85%)	(12.50%, 26.80%)
	Difference from Placebo (95% CI)	54.54% (44.30%, 64.78%)	
	P-value	< 0.0001	

Notes	In addition to the primary analysis, a secondary analysis was performed comparing the relugolix + delayed E2/NETA group with the placebo group with respect to the responder rate showing similar results, with 105 patients (79.55%) in the relugolix + delayed E2/NETA group meeting responder criteria compared with 24 patients (18.90%) in the placebo group. The observed difference between the two groups was 60.65% (95% CI: 50.97%, 70.33%) in favor of the relugolix + delayed E2/NETA group and was significant (nominal p < 0.0001). There were 7 secondary endpoints. The two-sided p-value was < 0.05 for each of the 4 endpoints sequentially tested in Testing Family 2 (F2_1, F2_2, F2_3, F2_4). Endpoints from Testing Family 3 (F3_5, F3_6, F3_7) were tested per Hochberg procedure with endpoints 5 and 7 meeting statistical significance at the 0.05 level. Per the pre-specified gate-keeping mixed sequence testing procedure, the study met six key secondary endpoints by demonstrating that relugolix + E2/NETA was statistically significantly superior to placebo. The study did not meet endpoint F3_6 (percent change in uterine fibroid volume), in which a numerical trend in reduction of uterine fibroids volume from baseline was observed compared with placebo.		
Analysis Description	**Secondary Analysis (F2_1), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	128	127
	Number (%) of Responders	67 (52.34%)	7 (5.51%)
	Difference from Placebo (95% CI)	46.83% (37.31%, 56.35%)	
	P-value	< 0.0001	
Notes	Results for the relugolix + delayed E2/NETA group were consistent with those in the relugolix + E2/NETA group.		
Analysis Description	**Secondary Analysis (F2_2), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	128	127
	% Change from Baseline	−84.3% (4.72)	−23.2% (4.61)
	Difference from Placebo (95% CI)	−61.1 (−73.5, −48.6)	
	P-value	< 0.0001	
Notes	Improvement from baseline in MBL volume was also observed in the relugolix + delayed E2/NETA group (−88.2%)		

Analysis Description	**Secondary Analysis (F2_3), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	128	127
	% Change from Baseline	−45.0 (2.88)	−16.1 (2.81)
	Difference from Placebo (95% CI)	−28.9 (−36.3, −21.5)	
	P-value	< 0.0001	
Notes	In the relugolix + E2/NETA group, the mean change from baseline to Week 24 UFS-QoL BPD scale score was -45.0 (indicating improvement), which was significantly greater than the change observed in the placebo group (-16.1; $p < 0.0001$). Results in the relugolix + delayed E2/NETA group (-51.3) were consistent with those observed in the relugolix + E2/NETA group (Table 7.2.5.1). Consistently, the proportion of responders on the UFS-QoL BPD scale at Week 24 was significantly higher in the relugolix + E2/NETA group (61.72%) compared with the placebo group (27.56%; nominal $p < 0.0001$). In the relugolix + delayed E2/NETA group 62.88% of patients were responders at Week 24.		
Analysis Description	**Secondary Analysis (F2_4), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		

Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	128	127
	Number (%) of Responders	15 (50.00%)	5 (21.74%)
	Difference from Placebo (95% CI)	28.26% (3.68%, 52.84%)	
	P-value	0.0377	
Notes	In the relugolix + delayed E2/NETA group, 18 patients (56.25%) had a > 2 g/dL increase in hemoglobin concentration from baseline to Week 24.		
Analysis Description	**Secondary Analysis (F3_5), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	128	127
	Number (%) of Responders	25 (43.10%)	7 (10.14%)
	Difference from Placebo (95% CI)	32.96% (18.36%, 47.56%)	
	P-value	< 0.0001	
Notes	A similar proportion of patients in each treatment group was part of the pain evaluable population (58 patients [45.31%] in the relugolix + E2/NETA group, 65 patients [49.24%] in the relugolix + delayed E2/NETA group, and 69 patients [54.33%] in the placebo group). In the relugolix + E2/NETA and placebo groups, 58 patients (45.31%) and 69 patients (54.33%), respectively, were included in the pain evaluable population. In the relugolix + E2/NETA group, 25 pain evaluable patients (43.10%) had a maximum NRS score ≤ 1 over the last 35 days of treatment, compared with 7 pain evaluable patients (10.14%) in the placebo group. The difference between the two groups was 32.96% and was statistically significant ($p < 0.0001$). Results in the relugolix + delayed E2/NETA group were consistent with those in the relugolix + E2/NETA group, with 27 of the 65 pain evaluable patients (41.54%) having a maximum NRS score ≤ 1 over the last 35 days of treatment.		
Analysis Description	**Secondary Analysis (F3_6), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics	Treatment Group	Relugolix + E2/NETA	Placebo

and Estimate Variability	Number of Subjects	128	127
	LS Mean % Change from Baseline	−12.4 (5.62)	−0.3 (5.40)
	Difference from Placebo (95% CI)	−12.1 (-26.3, 2.0)	
	P-value	0.0921	
Notes	Results in the relugolix + delayed E2/NETA group were consistent, with an LS mean percent change from baseline to Week 24 of −22.7%.		
Analysis Description	**Secondary Analysis (F3_7), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	128	127
	LS Mean % Change from Baseline	−12.9 (5.62)	2.2 (5.40)
	Difference from Placebo (95% CI)	−15.1 (-23.0, -7.3)	
	P-value	0.0002	
Notes	Results in the relugolix + delayed E2/NETA group were consistent, with an LS mean percent change from baseline to Week 24 of −17.9%		

Summary of Efficacy for Trial MVT-601-3002

Title: 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			
Study Identifier	Study Number: MVT-601-3002 Eudra CT Number: 2016-005113-50 IND Number: 131161 NCT Number: 03103087		
Design	Randomized, multicenter, international, double-blind, placebo-controlled, efficacy and safety study.		
	Duration of Main Phase: Duration of Run-In Phase: Duration of Extension Phase:		24 weeks (randomized treatment period) 13 weeks (screening period) 30 days (follow-up period)
Hypothesis	Superiority		
Treatments Groups	Relugolix + Estradiol (E2) /Nrorethindrone Acetate (NETA)		Relugolix 40 mg tablet once daily (QD) + capsule containing a tablet of E2 1 mg and NETA 0.5 mg QD, 24 weeks, n = 126
	Relugolix + Delayed E2/NETA		Relugolix 40 mg tablet QD + placebo capsule QD for 12 weeks, followed by relugolix 40 mg tablet QD + capsule containing a tablet of E2 1 mg and NETA 0.5 mg QD for 12 weeks, n = 127
	Placebo		Relugolix placebo-to-match tablet QD + placebo capsule QD for 24 weeks, n = 129
Endpoints and Definitions	Primary Endpoint	F1	The proportion of women who achieved a menstrual blood loss (MBL) volume < 80 mL and at least a 50% reduction from baseline MBL volume
	Secondary Endpoint	F2_1	Proportion of women who achieved amenorrhea over the last 35 days of treatment
	Secondary Endpoint	F2_2	Percent change from baseline to Week 24 in MBL volume
	Secondary Endpoint	F2_3	Change from baseline to Week 24 in Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) bleeding and pelvic discomfort (BPD) scale score
	Secondary Endpoint	F2_4	Proportion of women who achieved a maximum numerical rating scale (NRS) score ≤ 1 for uterine fibroid-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

	Secondary Endpoint	F3_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
	Secondary Endpoint	F3_6	Percent change from baseline to Week 24 in primary uterine fibroid volume
	Secondary Endpoint	F3_7	Percent change from baseline to Week 24 in uterine volume
Database Lock	16 July 2019		
Results and Analysis			
Analysis Description	**Primary Analysis (F1)**		
Analysis Population and Time Point Description	Modified Intent-to-Treat (mITT) The mITT population was defined as all randomized patients who received any amount of study drug (relugolix/placebo or E2/NETA/placebo). Time Point: Week 24/End of Treatment (EOT)		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	125	129
	Number (%) of Responders	89 (71.20%)	19 (14.73%)
	Difference from Placebo (95% CI)	56.47% (46.45%, 66.49%)	
	P-value	< 0.0001	
Notes	In addition to the primary analysis, a secondary analysis was performed comparing the relugolix + delayed E2/NETA group with the placebo group showing similar results, with 93 patients (73.23%) in the relugolix + delayed E2/NETA group meeting responder criteria compared with 19 patients (14.73%) in the placebo group. The observed difference between the two groups was 58.50% (95% CI: 48.67%, 68.33%) in favor of the relugolix + delayed E2/NETA group (nominal p < 0.0001). There were 7 secondary endpoints. The two-sided p-value was < 0.05 for each of the four endpoints sequentially tested in Testing Family 2 (F2_1, F2_2, F2_3, F2_4). Endpoints from Testing Family 3 (F3_5, F3_6, F3_7) were tested per Hochberg procedure with endpoints 5 and 7 meeting statistical significance at the 0.05 level. Per the pre-specified gate-keeping mixed sequence testing procedure, the study met six key secondary endpoints by demonstrating that relugolix + E2/NETA was statistically significantly superior to placebo. The study did not meet endpoint F3_6 (percent change in uterine fibroid volume), in which a numerical trend in reduction of uterine fibroids volume from baseline was observed compared with placebo.		
Analysis Description	**Secondary Analysis (F2_1), Pre-Specified**		

Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	125	129
	Number (%) of Responders	63 (50.40%)	4 (3.10%)
	Difference from Placebo (95% CI)	47.30% (38.04%, 56.56%)	
	P-value	< 0.0001	
Notes	In the relugolix + E2/NETA group, the median time to achievement of amenorrhea was 8.9 weeks while a median time to amenorrhea was not reached in the placebo group (nominal p < 0.0001). In the relugolix + delayed E2/NETA group, amenorrhea occurred more rapidly than in the relugolix + E2/NETA group, at a median time of 4.4 weeks.		
Analysis Description	**Secondary Analysis (F2_2), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	125	129
	% Change from Baseline	−84.3% (5.45)	−15.1% (5.47)
	Difference from Placebo (95% CI)	−69.2 (−84.1, −54.3)	
	P-value	< 0.0001	
Notes	Improvement from baseline in MBL volume was also observed in the relugolix + delayed E2/NETA group (−89.4%)		
Analysis Description	**Secondary Analysis (F2_3), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	125	129
	% Change from Baseline	−51.7 (2.89)	−18.3 (2.93)
	Difference from Placebo (95% CI)	−33.4 (−41.2, −25.5)	
	P-value	< 0.0001	

Notes	In the relugolix + E2/NETA group, the mean change from baseline to Week 24 in the BPD scale score was -51.7 (indicating improvement), which was significantly greater than the change observed in the placebo group (-18.3; $p < 0.0001$). Results in the relugolix + delayed E2/NETA group (-48.9) were consistent with those observed in the relugolix + E2/NETA group. Consistently, the proportion of responders on the BPD scale at Week 24 was significantly higher in the relugolix + E2/NETA group (63.20%) compared with the placebo group (28.68%; nominal $p < 0.0001$) (Table 7.2.5.7). In the relugolix + delayed E2/NETA group, 54.33% of patients were responders at Week 24.		
Analysis Description	**Secondary Analysis (F2_4), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	125	129
	Number (%)	32 (47.06%)	14 (17.07%)
	Difference from Placebo (95% CI)	29.99% (15.60%, 44.38%)	
	P-value	< 0.0001	

Notes	A similar proportion of patients in each treatment group was part of the pain evaluable population (93 patients [74.4%] in the relugolix + E2/NETA group, 92 patients [72.2%] in the relugolix + delayed E2/NETA group, and 95 patients [73.6%] in the placebo group). In the relugolix + E2/NETA group, 32 pain evaluable patients (47.06%) had a maximum NRS score ≤ 1 over the last 35 days of treatment, compared with 14 pain evaluable patients (17.07%) in the placebo group. The difference between the two groups (29.99%) was statistically significant ($p < 0.0001$). Results in the relugolix + delayed E2/NETA group were consistent with those in the relugolix+E2/NETA group, with 24 of the 58 pain-evaluable patients (41.38%) having a maximum NRS score ≤ 1 over the last 35 days of treatment.		
Analysis Description	**Secondary Analysis (F3_5), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	125	129
	Number (%) of Responders	19 (61.29%)	2 (5.41%)
	Difference from Placebo (95% CI)	55.88% (37.25%, 74.52%)	
	P-value	< 0.0001	
Notes	In the relugolix + delayed E2/NETA group, 18 patients (58.06%) had a > 2 g/dL increase in hemoglobin concentration from baseline to Week 24.		
Analysis Description	**Secondary Analysis (F3_6), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	125	129
	LS Mean % Change from Baseline	−17.4 (5.93%)	−7.4 (5.92%)
	Difference from Placebo (95% CI)	−10.0 (-25.8, 5.8)	

	P-value	0.2153	
Notes	Results in the relugolix + delayed E2/NETA group were consistent with those of the relugolix + E2/NETA group, with an LS mean percent change from baseline to Week 24 of −30.2%.		
Analysis Description	**Secondary Analysis (F3_7), Pre-Specified**		
Analysis Population and Time Point Description	mITT Time Point: Week 24/EOT		
Descriptive Statistics and Estimate Variability	Treatment Group	Relugolix + E2/NETA	Placebo
	Number of Subjects	125	129
	LS Mean % Change from Baseline	−13.8 (3,39%)	−1.5 (3.37%)
	Difference from Placebo (95% CI)	−12.2 (-21.3, -3.2)	
	P-value	0.0078	
Notes	Results in the relugolix + delayed E2/NETA group were consistent with those of the relugolix + E2/NETA group, with an LS mean percent change from baseline to Week 24 of −17.7%		

Analysis performed across trials (pooled analyses and meta-analysis)

Studies MVT-601-3001 and MVT-601-3002 of 24 weeks duration Pooled

Pooled subgroup analyses were conducted using data from the pivotal studies for the following subgroups:

Geographic region, baseline MBL volume, age, race, ethnicity, largest fibroid volume at baseline, uterine volume at baseline, baseline BMI, maximum NRS score at baseline, and history of prior pregnancy.

Homogeneity of demographics and baseline characteristics in MVT-601-3001 and MVT-601-3002, including geography, race, ethnicity, BMI, smoking status, prior pregnancy, MBL volume, hemoglobin, NRS, UFS-QoL, PGA, uterine volume, and uterine fibroid volume (see Demographics) justified pooling of these studies to analyze the primary endpoint.

Consistent with results for the primary analysis (proportion of responders relugolix + E2/NETA vs placebo) observed in the individual studies, treatment differences were consistent across all subgroups, with a significantly higher proportion of patients in the relugolix+ E2/NETA group meeting the definition for responder than patients in the placebo group. Additionally, for all subgroups, (except for the small subgroup of patients < 35 years old [n = 45]), the lower bound of the 95% CI for the odds ratios was above 1, favoring relugolix + E2/NETA over placebo. The results of these analyses are presented below.

Table: Studies MVT-601-3001 and MVT-601-3002 Pooled: Subgroup Analyses of Primary Endpoint, Number and Proportion of Responders at Week 24/EOT (mITT Population)

Subgroup	Relugolix+ E2/NETA (N=253)	Placebo (N=256)	Odds Ratio (95% CI)[a]
Overall	183 (72.3%)	43 (16.8%)	13.35 (8.65,20.60)
Geographic region			
North America	132 (69.1%)	32 (16.5%)	11.29 (6.92,18.42)
Rest Of World	51 (82.3%)	11 (17.7%)	25.54 (9.62,67.81)
MBL Vol at BL (mL)			
< 225 ML	124 (75.6%)	28 (16.4%)	16.67 (9.58,29.00)
>= 225 ML	59 (66.3%)	15 (17.6%)	9.26 (4.51,19.01)
Age (years)			
< 40 years	41 (66.1%)	11 (14.1%)	12.70 (5.29,30.46)
>= 40 years	142 (74.3%)	32 (18.0%)	13.59 (8.19,22.56)
Age (years)			
< 35 years (b)	9 (50.0%)	6 (22.2%)	3.50 (0.96,12.78)
35 to < 40 years	32 (72.7%)	5 (9.8%)	23.23 (7.32,73.68)
40 to < 45 years	63 (65.6%)	13 (15.5%)	11.26 (5.32,23.82)
>= 45 years	79 (83.2%)	19 (20.2%)	21.44 (9.98,46.06)
Race			
Black/African American	77 (63.1%)	19 (13.5%)	10.75 (5.83,19.84)
Not Black/African American	103 (80.5%)	24 (21.1%)	15.86 (8.39,29.95)
Index Fibroid Vol at BL (cm3)			
< 25 cm3	95 (77.2%)	20 (16.8%)	17.40 (9.07,33.36)
>= 25 cm3	88 (68.2%)	23 (16.8%)	10.83 (6.02,19.49)

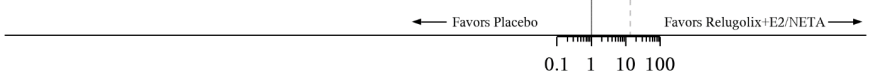
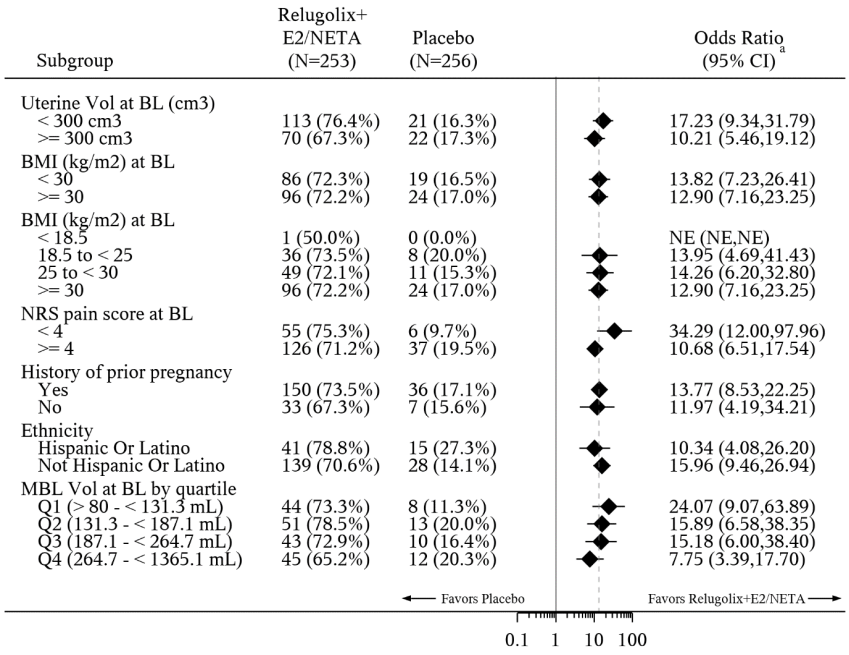


Table: Studies MVT-601-3001 and MVT-601-3002: Subgroup Analyses of Primary Endpoint, Number and Proportion of Responders at Week 24/EOT (mITT Population) Continued)



Abbreviations: BL = baseline; BMI = body mass index; CI = confidence interval; E2 = estradiol; EOT = end of treatment; MBL = menstrual blood loss; mITT = modified intent-to-treat; NE = Not evaluable; NETA = norethindrone acetate; NRS = numerical rating scale; Q = quarter; SD = standard deviation; SE = standard error; Vol = volume.
Note: A responder is defined as a woman achieving an MBL volume of < 80 mL and ≥ 50% reduction from baseline in MBL volume over the last 35 days of treatment. Summary statistics are based on observed data.
[a] Odds ratio > 1 favors relugolix+E2/NETA over placebo based on logistic regression with treatment group, baseline MBL volume and geographic region (North America, Rest of World) as covariates
[b] Odds ratio > 1 favors relugolix+E2/NETA over placebo based on logistic regression with treatment group as the only covariate.

Clinical studies in special populations

The potential effect of moderate and severe renal impairment (MVT-601-1003; MVT-601-041) and mild and moderate hepatic impairment (study MVT-601-1002) on the exposure to relugolix was evaluated in dedicated clinical pharmacology studies:

Table: Moderate and severe renal impairment in dedicated clinical pharmacology studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	MVT-601-1002	5.3.3.3	PK (hepatic impairment)	Open-label, parallel-group	Relugolix 40 mg, single dose, fasted	Control: 8 Mild Impairment: 8 Moderate Impairment: 8	Mild-moderate hepatic impairment or healthy subjects	Single-dose	Complete; Full Report
PK	MVT-601-1003	5.3.3.3	PK (renal impairment)	Open-label, parallel-group	Relugolix 40 mg single dose, fasted	Control: 8 Impaired: 8	Severe renal impairment or healthy subjects	Single-dose	Complete; Full Report
PK	MVT-601-040	5.3.3.3	PK (renal impairment)	Open-label, single-dose	Relugolix 40 mg single dose, fasted	Moderate Renal Impairment: 12 Control: 12	Moderate renal impairment or healthy subjects	Single-dose	Complete; Full Report

- **Renal impairment**

The effect on renal function was evaluated by population pharmacokinetic analysis of the pivotal phase 3 safety and efficacy studies that included patients with mild renal impairment.

After administration of a single 40-mg dose in patients with moderate or severe renal impairment, the total exposure ($AUC_{0-\infty}$) of relugolix was increased by 1.5-fold (the geometric mean ratio [GMR; renal impairment/normal renal function] and 90% CIs for the $AUC_{0-\infty}$ of relugolix were 1.4521 (0.9812, 2.1491) and 1.49 (0.9681, 2.2869), respectively). The C_{max} was similarly increased in patients with moderate renal impairment, whereas only a 1.1-fold increase was observed in patients with severe renal impairment. Based on inspection of the concentration-time data, the observed increases in relugolix exposure in both moderate and severe renal impairment appear to be due to an increase in absorption rather than a decrease in elimination, especially considering that the log-linear decline was parallel for both renal impairment groups compared with healthy patients with normal renal function. Moreover, the estimated elimination phase $t_{1/2}$ estimates were either the same in patients with moderate and shorter in patients with severe renal impairment, respectively, compared with healthy participants with normal renal function (mean $t_{1/2}$ estimates of 56.3 hours for both moderate renal impairment and normal renal function; 60.2 hours with severe renal impairment and 74.6 hours for normal renal function). Based on these observations, it is unlikely that greater than expected accumulation would occur after multiple-dose administration in either renal impairment group. Considering that relugolix is generally safe and associated with good overall tolerability at 2-fold or greater exposures than the proposed clinical dose of 40 mg and considering the upper bound of the 90% CI for the GMR of the $AUC_{0-\infty}$ for relugolix is only slightly greater than 2.0000, no dose adjustment in patients with moderate or severe renal impairment is required, based on the relugolix component of relugolix combination therapy. Furthermore, renal function did not have a statistically significant effect on the pharmacokinetic parameters of relugolix in the final PopPK model. Individual post-hoc estimates of the relugolix CL/F calculated by the final PopPK model also indicated no obvious difference in the relugolix CL/F between participants with mild renal impairment (CL_{CR} 60-89 mL/min; n = 103) and participants with normal renal function (CL_{CR} ≥ 90 mL/min; n = 848).

The impact of renal impairment on the pharmacokinetics of E2 and NET after administration of a E2/NETA (1 mg/0.5 mg) tablet have not been evaluated but because both moieties are primarily metabolized by the liver, an effect of renal impairment on the exposure to either of these components of the relugolix combination therapy is not expected.

- **Hepatic impairment**

After administration of a single 40-mg dose of relugolix to patients with mild or moderate hepatic impairment, no clinically meaningful effects on the rate or extent of absorption of relugolix were observed, although small numerical differences in the exposure-related pharmacokinetic parameters were noted. In patients with mild hepatic impairment, the $AUC_{0-\infty}$ and C_{max} of relugolix were decreased by 31% and 24%, respectively, and in patients with mild hepatic impairment, the $AUC_{0-\infty}$ was decreased by 5%, whereas the C_{max} was increased by 1.17-fold compared with healthy participants with normal hepatic function (GMR [hepatic impairment/normal hepatic function] and 90% CI for the $AUC_{0-\infty}$ of relugolix were 0.6860 (0.3543, 1.3282) and 0.9451 (0.4581, 1.9500) in patients with mild or moderate hepatic impairment, respectively. The terminal elimination $t_{1/2}$ estimates were nearly the same (51.7 and 50.6, 48.7 hours) in patients with mild or moderate hepatic impairment and healthy participants with normal hepatic function, respectively. Based on these results, no dose adjustment in mild or moderate hepatic impairment for the relugolix component of the FDC tablet is required. However, administration of E2/NETA in patients with hepatic disease is contraindicated, and as such administration of the FDC tablet to patients with presence or history of severe hepatic disease also is contraindicated, as long as liver function values have not returned to normal.

Supportive studies

Supportive studies for the proposed indication included three *s*tudies **in Japanese patients** conducted by Takeda: a completed phase 2 dose finding study for relugolix monotherapy ((**TAK-385/CCT-001) and** two completed phase 3 relugolix **monotherapy** (**TAK-385/CCT-002 [monotherapy vs GnRH agonist]**, **TAK-385-3008 [pain symptoms, vs placebo**]. Further, an exit questionnaire study **MVT-601-037** was performed, a substudy to MVT-601-3001 and MVT-601-3002 [patient input on the patient reported outcomes]).

TAK-385/CCT-001 (dose finding, Japan)

This phase 2, multicenter, randomized, double blind, parallel group study of 12 weeks duration evaluated three dose levels of relugolix (10 mg, 20 mg, 40 mg daily) administered orally for 12 weeks compared with placebo in Japanese patients with main age of 42 years with symptomatic uterine fibroids. The primary efficacy endpoint was an improvement in MBL volume, as assessed by the proportion of patients with a total PBAC score of < 10 from Week 6 to Week 12. The 40-mg dose group included 55 patients compared to a placebo group of 57 patients.

TAK-385/CCT-002 (relugolix monotherapy vs GnRH-agonist, Japan)

This phase 3, multicenter, randomized, double-blind, parallel-group study of 12 week duration evaluated the efficacy and safety of relugolix 40 mg compared with leuprorelin (once every 4 weeks, 1.88 or 3.75 mg subcutaneously) in Japanese patients with mean age of 42 years with symptomatic

uterine fibroids. The primary efficacy endpoint of this study was to evaluate the percentage of responders of relugolix 40 mg in comparison to leuprorelin group.

TAK-385/CCT-001 & TAK-385/CCT-002 (studies in Japanese patients)

Responder rate menstrual blood loss (MBL)

While the assessment of MBL volume was different between the pivotal relugolix combination studies (alkaline hematin method) and supporting relugolix monotherapy studies (PBAC method) in Japanese patients, both assessments are validated methods for MBL volume. Regardless of the differences in definitions of the primary endpoint, all studies assessed the proportion of responders using a high bar for defining a patient as a responder.

An overview of the responder rate at Week 12 for relugolix monotherapy [results at week 12 in the relugolix + delayed E2/NETA group in studies 9601-3001 and 601-300) and for relugolix monotherapy versus leuproreline (GnRH-agonist) in the Japanese studies 9TAK-385-001 and TAK 385/CCT-002)] across studies is provided below.

Table: Proportion of Responders at Week 12 with Relugolix Monotherapy Across Studies

Study	Treatment	N/group	Proportion of Responders [a]	P-value
Pivotal Phase 3 Studies				
MVT-601-3001	Relugolix 40 mg + delayed E2/NETA	128	77.3%	p < 0.0001
	Placebo	128	15.7%	
MVT-601-3002	Relugolix 40 mg + delayed E2/NETA	126	76.4%	p < 0.0001
	Placebo	129	8.5%	
Supportive Relugolix Monotherapy Studies in Japanese patients				
TAK-385/CCT-001	Relugolix 10 mg QD	48	20.8%	p = 0.0003[b]
	Relugolix 20 mg QD	54	42.6%	p < 0.0001[b]
	Relugolix 40 mg QD	54	83.3%	p < 0.0001[b]
	Placebo	57	0%	
TAK-385/CCT-002	Relugolix 40 mg	135	82.2%	p = 0.0013[c]
	Leuprolide (1.88 mg or 3.75 mg Q4W)	142	83.1%	

Abbreviations: CSR = clinical study report; E2 = estradiol; EOT = end of treatment; ISE = integrated summary of efficacy; MBL = menstrual blood loss; mITT = modified intent-to-treat; N = number of patients; NETA = norethindrone acetate; PBAC; Q4W = every 4 weeks; QD = daily.
Note: Women in the relugolix 40 mg + delayed E2/NETA group received relugolix monotherapy, administered daily for 12 weeks prior to introduction of E2/NETA. Nominal p-values are shown for MVT-601-3001 and MVT-601-3002.
[a] Responder defined as proportion of women who achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume at the Week 12 visit (MVT-601-3001 and MVT-601-3002) or with a PBAC score of < 10 from Week 6 to Week 12 (TAK-385/CCT-001 and TAK-385/CCT-002).
[b] p-value is based on Chi-square test.
[c] Non-inferiority p-value is based on the test using Farrington and Manning method with a non-inferiority margin of 15%.

In the pivotal phase 3 studies (MVT-601-3001 and MVT-601-3002), similarly greater proportions of women in the relugolix + delayed E2/NETA groups met the definition of responder at Week 12 (77.3% and 76.4%) compared with those in the placebo groups (15.7% and 8.5%). The differences between treatment and placebo groups were > 60% in both studies. These results were about 5% higher in comparison with the responder rate observed for the relugolix + E2/NETA group at Week 12.
In the phase 2 study TAK-385/CCT-001, a 12-week dose-finding study comparing the efficacy of relugolix 10-, 20-, and 40-mg doses with placebo, , 83.3% of women using the 40 mg relugolix met the definition of responder compared with 0% in the placebo group. In the phase 3 study TAK-385/CCT-002 the Week 12, the responder rate in the relugolix 40 mg group was 82.2%, non-inferior (using a non-inferiority margin of -15%) to the responder rate achieved with leuprorelin (83.1%, p = 0.0013).

TAK-385-3008 (pain, relugolix monotherapy vs placebo, Japan)

This phase 3, multicenter, randomized, double blind, placebo-controlled study that evaluated the efficacy and safety of relugolix 40 mg administered orally once daily for 12 weeks compared with placebo in Japanese patients of 20 years of age or older having pain symptoms associated with uterine fibroids. The study consisted of a screening period of approximately 1 to 6 weeks, a run in period of 3 to 6 weeks, a treatment period of 12 weeks, and a follow up period of 4 weeks. The primary endpoint was the proportion of patients with a maximum numerical rating scale (NRS) score of 1 or less during the 28 days before the final dose of study drug.

A total of 65 patients were randomized in the study to receive relugolix 40 mg (N = 33) or placebo (N = 32) and all randomized patients received study treatment. The mean age was 40.5 years in the relugolix 40 mg group and 42.6 years in the placebo group.

The primary efficacy endpoint for the study was the proportion of patients with a maximum NRS score ≤ 1 during the 28 days before the final dose of study drug.

Table: Primary Efficacy Analysis for Study TAK-385-3008

Primary Endpoint	Relugolix 40 mg (N = 33)	Placebo (N = 32)
Proportion of patients with NRS score of ≤ 1 during the 28 days before the final dose of study drug	57.6%	3.1%
Odds Ratio (Relugolix/Placebo [95% CI])	42.071 (5.113, 346.181)	< 0.0001[a]

Abbreviations: CI = confidence interval; CSR = clinical study report; FAS = full analysis set; N = number of patients; NRS = Numerical Rating Scale.

[a] Fisher's Exact Test p-value.

The study met the primary endpoint. The proportion of patients with a maximum NRS score of 1 or less during the 28 days before the final dose of study drug was higher in the relugolix group (57.6%) than in the placebo group (3.1%). The difference between the treatment groups was statistically significant (odds ratio, 42.071; 95% CI, 5.113 to 346.181; Fisher's exact test, p < 0.0001).

Although the definition of the endpoint is not fully identical, indirect comparison of the results obtained with the primary endpoint of pain in the relugolix monotherapy study TAK-385-3008 is approximately 10% higher than the results on pain relief in the subgroup analysis of the key secondary endpoint in the pivotal phase 3 studies with the relugolix combination, and in line with the suggestion that addition of E2/NETA has a small impact on efficacy.

For the key secondary endpoint 'Proportion of women who achieved a maximum NRS score <= 1 for uterine fibroid-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' the results were 43.10% vs 10.14% for relugolix combination therapy vs placebo, respectively in study MVT-601-3001 and 47.06% vs 17.07% for relugolix combination therapy vs placebo, respectively in study MVT-601-3002. Both differences were statistically significant ($p<0.0001$).

MVT-601-037 (exit questionnaire)

MVT-601-037, a substudy to MVT-601-3001 and MVT-601-3002, obtained patient input via qualitative interviews of English-speaking patients completing the pivotal phase 3 studies on what constitutes a meaningful or relevant improvement on several patient reported outcomes:

- Uterine Fibroid Symptom and Health Related Quality of Life (UFS QoL)
- Bleeding and Pelvic Discomfort (BPD) scale
- Patient Global Assessment (PGA) for function and symptoms
- Pain Numeric Rating Scale (NRS)
- UFS QoL revised activity subscale

Following Week 12 visits, patients who improved by at least one category from Baseline to Week 12 on the PGA for symptoms were identified by Myovant and the IDs of potentially eligible sub-study patients were provided to sites.

Thirty patients who completed MVT-601-3001 or MVT-601-3002 participated in this substudy. The mean age of these patients was 42.6 years, and more than half (70.0%; N = 21) self-reported as Black or African American. Most patients (80.0%; N = 24) were not Hispanic or Latino. The majority of patients (80.0%; N = 24) self-reported some college or higher education as their highest education level.

Long-term (upto 52 weeks) efficacy

Study MVT-601-3003

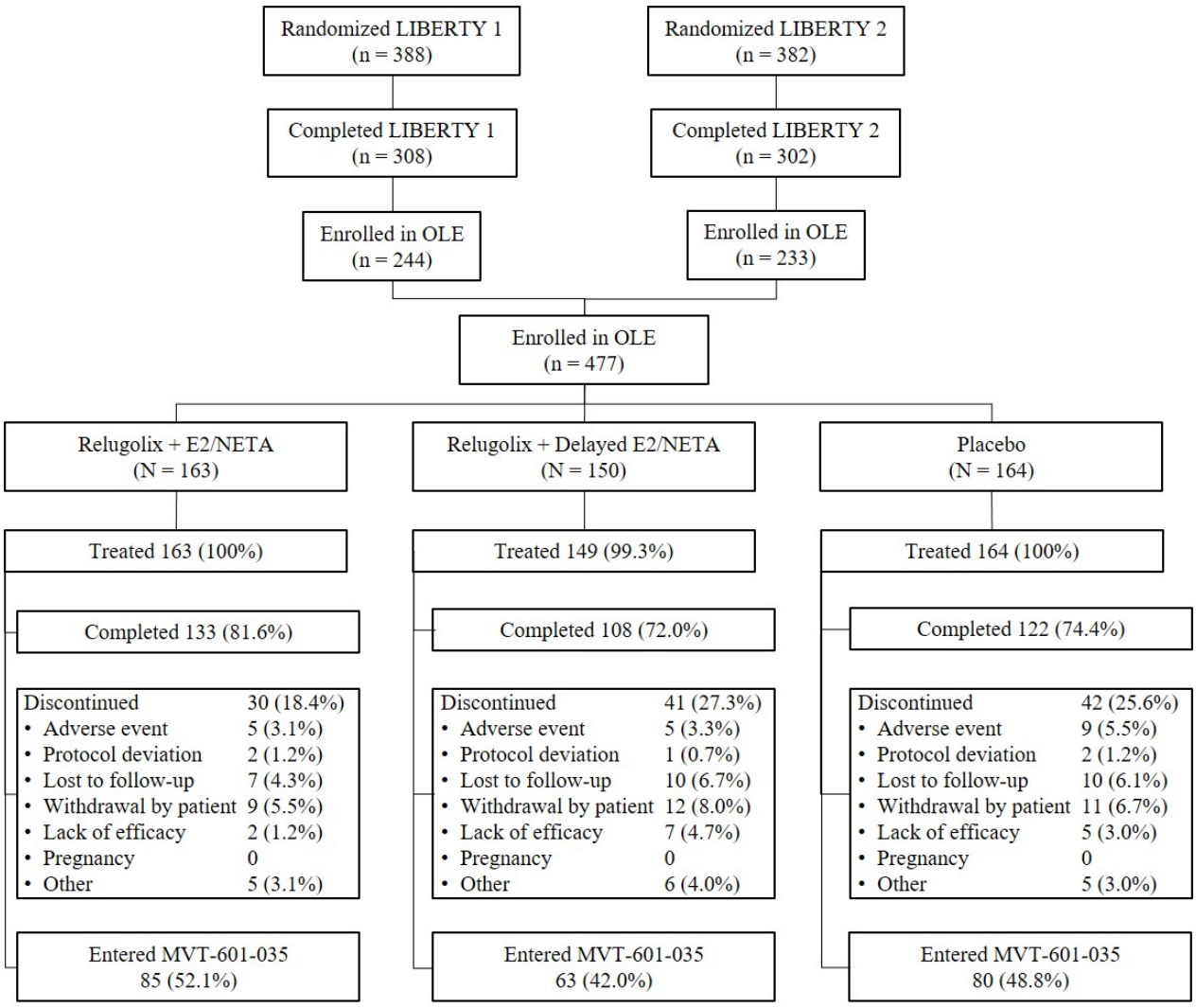
Study MVT-601-3003 was a multinational phase 3, open-label, single-arm, long-term efficacy and safety extension study that enrolled eligible patients who completed participation in one of the phase 3, 24 weeks randomized, placebo-controlled parent studies (MVT-601-3001 or MVT-601-3002).

All patients received oral relugolix 40 mg once a day co-administered with estradiol (E2) 1 mg and norethindrone acetate (NETA) 0.5 mg for up to 28 weeks in the extension study 3003.

The objectives of the study were to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including the 24 weeks of treatment during the parent study) with relugolix + E2/NETA.

A total of 477 patients were enrolled to receive open-label relugolix + E2/NETA, which were approximately 62% of patients randomized in the parent studies and > 75% of patients who completed those studies.

Figure: Disposition of Participants in MVT-601-3003



Abbreviations: E2 = estradiol; n = number of patients; NETA = norethindrone acetate; OLE = open-label extension. Note: One patient was enrolled in error and did not receive treatment.

In the relugolix + E2/NETA group, 81.6% of patients completed 52 weeks of treatment and 18.4% had discontinued from the study early. In the relugolix + delayed E2/NETA group that started relugolix + E2/NETA at Week 12 during the parent studies, 72.0% of patients had completed 52 weeks of treatment and 27.3% had discontinued from the study early. In the placebo group that started relugolix + E2/NETA upon

entering this open-label extension study, 74.4% of patients had completed 52 weeks of treatment and 25.6% had discontinued from the study early.

More patients in the relugolix + delayed E2/NETA and the placebo groups discontinued from the study relative to the relugolix + E2/NETA group. The differences observed between groups are mainly driven by patients who were lost to follow-up, patients who withdrew consent, or patients who experienced lack of efficacy.

Of the 363 patients who completed this study, 228 patients (47.8%) entered the randomized withdrawal study (MVT-601-035). The Applicant has indicated that the results of this study will not be submitted within the timeframe of this procedure and will not be part of the dossier.

The summary of patient demographics in MVT-601-3003 is presented below:

Table: Summary of Patient Demographics (MVT-601-3003 Extension Safety Population)

	Relugolix+ E2/NETA (N = 163)	Relugolix+ Delayed E2/NETA (N = 149)	Placebo (N = 164)	Total (N = 476)
Age (years)				
Mean (SD)	42.6 (5.08)	42.1 (5.58)	41.9 (5.43)	42.2 (5.36)
Age Category n (%)				
< 40 years	38 (23.3%)	47 (31.5%)	48 (29.3%)	133 (27.9%)
≥ 40 years	125 (76.7%)	102 (68.5%)	116 (70.7%)	343 (72.1%)
Geographic Region n (%)				
North America	113 (69.3%)	104 (69.8%)	117 (71.3%)	334 (70.2%)
Rest of World	50 (30.7%)	45 (30.2%)	47 (28.7%)	142 (29.8%)
Race n (%)				
American Indian or Alaska Native	2 (1.2%)	7 (4.7%)	1 (0.6%)	10 (2.1%)
Asian	0	3 (2.0%)	0	3 (0.6%)
Black or African American	69 (42.3%)	81 (54.4%)	88 (53.7%)	238 (50.0%)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	85 (52.1%)	51 (34.2%)	71 (43.3%)	207 (43.5%)
Other	2 (1.2%)	3 (2.0%)	2 (1.2%)	7 (1.5%)
Multiple	2 (1.2%)	2 (1.3%)	1 (0.6%)	5 (1.1%)
Not reported	3 (1.8%)	2 (1.3%)	1 (0.6%)	6 (1.3%)
Ethnicity n (%)				
Not Hispanic or Latino	122 (74.8%)	113 (75.8%)	126 (76.8%)	361 (75.8%)
Hispanic or Latino	38 (23.3%)	34 (22.8%)	36 (22.0%)	108 (22.7%)
Not reported	3 (1.8%)	2 (1.3%)	2 (1.2%)	7 (1.5%)

Abbreviations: E2 = estradiol; n = number of patients in subset; N = number of patients; NETA = norethindrone acetate; SD = standard deviation.
Note: Percentages are based on the number of patients in each parent study treatment group or total.
Source: Table 8.1.4.1.

In general, baseline characteristics (BMI, prior pregnancy, alcohol use, smoking) were similar across treatment groups with only small differences.

Disease-specific baseline characteristics (not shown) were similar across treatment groups with only small differences observed, except for MBL volume, which was higher in the two relugolix groups relative to the placebo group.

Primary Efficacy Analysis

The primary efficacy endpoint for this extension study was similar to that of the placebo-controlled studies of 24 weeks: the proportion of women who achieved an MBL volume < 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, referred to as a responder rate.

Table: Primary Efficacy Analysis: Proportion of Responders at Week 52/EOT (Extension Study Population)

	Relugolix + E2/NETA (N = 163)	Relugolix + Delayed E2/NETA (N = 149)	Placebo (N = 164)
Number (%) of responders[a]	143 (87.73%)	119 (79.87%)	124 (75.61%)
(95% CI)[b]	(81.69%, 92.34%)	(72.52%, 85.98%)	(68.30%, 81.97%)
Number (%) of patients with MBL < 80 mL over the last 35 days of treatment	142 (87.12%)	124 (83.22%)	124 (75.61%)
(95% CI)[b]	(80.98%, 91.84%)	(76.24%, 88.84%)	(68.30%, 81.97%)
Number (%) of patients with >= 50% reduction from baseline over the last 35 days of treatment	145 (88.96%)	127 (85.23%)	133 (81.10%)
(95% CI)[b]	(83.11%, 93.32%)	(78.50%, 90.51%)	(74.26%, 86.78%)

Abbreviations: E2 = estradiol; EOT = end-of-treatment; MBL = menstrual blood loss; N = number of patients; NETA = norethindrone acetate.

[a] Responders were patients with MBL volume < 80 mL and ≥ 50% reduction from baseline over the last 35 days of treatment. Menstrual blood loss volume was calculated as the sum of MBL volume from all feminine products (validated, unauthorized, and unvalidated) assessed by the alkaline hematin method at Week 52/EOT.

[b] Based on exact binomial 95% CI (Clopper-Pearson).

Source: Table 8.2.1.1.

In the former relugolix + E2/NETA group (patients who received the combination already at start of the double blind-phase), 143 patients (87.73%) achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment.

In the former relugolix + delayed E2/NETA group (patients who initially received relugolix monotherapy for 12 weeks in the double-blind phase), 119 patients (79.87%) achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment.

In the former placebo group (patients who initially revieved placebo for 24 weeks in the double blind phase), 124 patients (75.61%) achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment.

For all groups, the proportion of patients meeting the criteria for the individual components of the composite primary endpoint was similar, indicating no single component (i.e., MBL volume < 80 mL or percent change from baseline of at least 50%) drove results for the primary endpoint.

The applicant noted that there were six patients (two patients who were lost to follow-up and four who withdrew consent due to social reasons) deemed non-responders based on Week 24 MBL volumes, for whom last observation carried forward methodology was applied as part of the intent-to-treat analysis used for all treatment groups. Inclusion of these patients as non-responders may help explain the lower responder rate observed in the placebo group.

Efficacy analyses in Subgroups

Across all subgroups, the magnitude of the responder rates observed was generally consistent with that observed in the analysis of the primary efficacy of the overall population for each treatment.

For the relugolix + E2/NETA group, the proportion of responders (95% CI) for selected subgroups was as follows:

Geographic region:

- North America: 85.8% (78.03%, 91.68%);
- Rest of world: 92.0% (80.77%, 97.78%);

MBL volume at baseline:

- < 225 mL: 91.6% (84.63%, 96.08%);
- ≥ 225 mL: 80.4% (67.57%, 89.77%);

Race:

- Black/African American: 82.9% (71.97%, 90.82%);
- White: 91.8% (83.77%, 96.62%);

Uterine Volume:

- < 300 cm3: 92.7% (85.55%, 97.02%);
- ≥ 300 cm3: 80.6% (69.11%, 89.24%);

BMI at baseline:

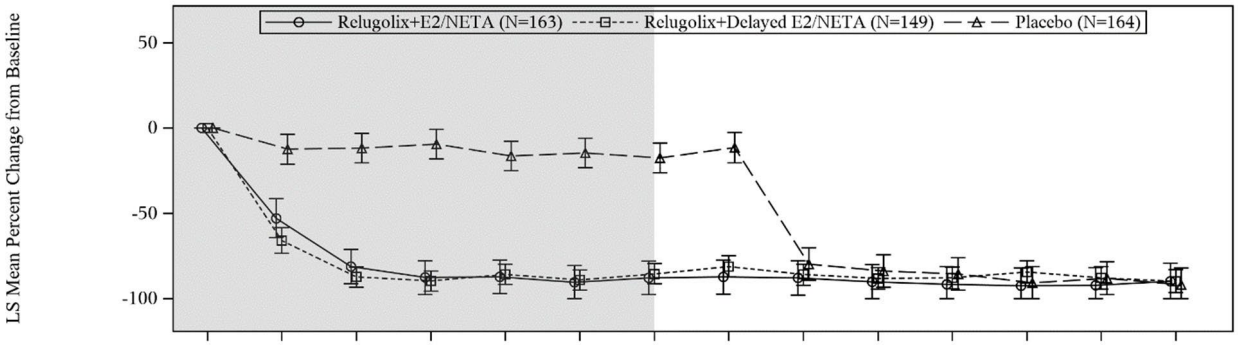
- < 30 kg/m2: 91.4% (82.27%, 96.79%);
- ≥ 30 kg/m2: 84.8% (75.79%, 91.42%).

Efficacy key secondary endpoints

Menstrual Blood Loss Volume

The decrease in MBL volume observed during the first 24 weeks of treatment was maintained during the open-label extension study with the LS mean percent change from baseline ranging from -81.1 at Week 28 to -89.8 at Week 52, demonstrating the durability of the effect of relugolix + E2/NETA treatment. In the placebo group, LS mean percent change in MBL volume decreased slightly during the first 24 weeks of treatment, ranging from -9.3% at Week 12 to -17.6% at Week 24. After transitioning to relugolix + E2/NETA treatment at Week 24, the LS mean percent change in MBL from baseline to Week 52 was -91.9%. From Week 32 to Week 52, the LS mean percent change from baseline ranged from -79.6% (Week 32) to -91.9% (Week 52).

Figure: Summary of Percent Change from Baseline in Menstrual Blood Loss Volume by Visit (Extension Study Population)



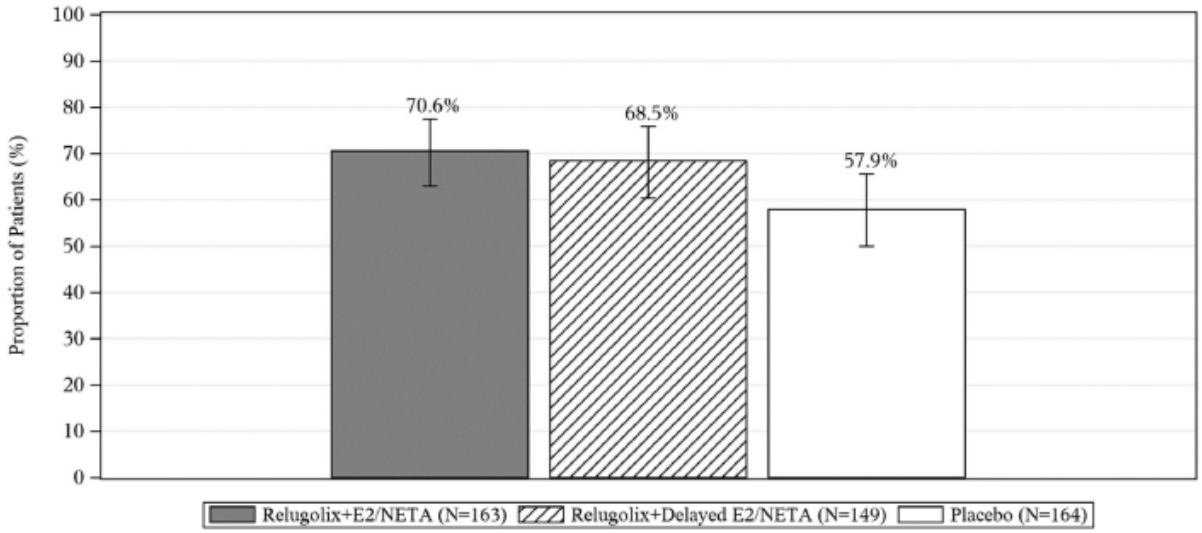
No. of Patients

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
R+E2/NETA	163	90	136	139	148	149	146	135	131	135	128	126	123	120
R+Delayed E2/NETA	149	65	124	135	134	131	130	106	107	109	109	106	97	103
Placebo	164	144	149	144	142	142	149	132	113	113	119	119	119	113

Amenorrhea

In the relugolix + E2/NETA group, 115 patients (70.55%) achieved amenorrhea over the last 35 days of treatment. In the relugolix + delayed E2/NETA group, 102 patients (68.46%) achieved amenorrhea over the last 35 days of treatment. In contrast, a lower response rate was observed in the placebo group with 95 patients (57.93%) having achieved amenorrhea over the last 35 days of treatment, which may reflect a shorter time of therapy compared with the longer term relugolix combination therapy groups.

Figure: Proportion of Patients Who Achieved Amenorrhea Over the Last 35 Days of Treatment (Extension Study Population)

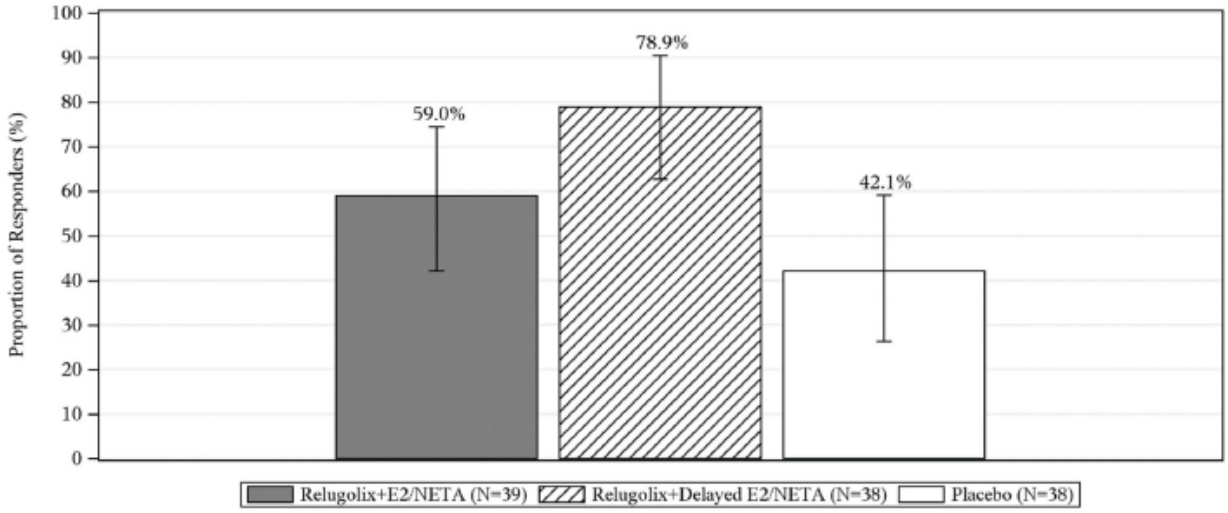


Abbreviations: E2 = estradiol; N = number of patients; NETA = norethindrone acetate.
Note: Error bars represent 95% CIs.
Source: Figure 8.2.3.1.

Improvement of Anemia

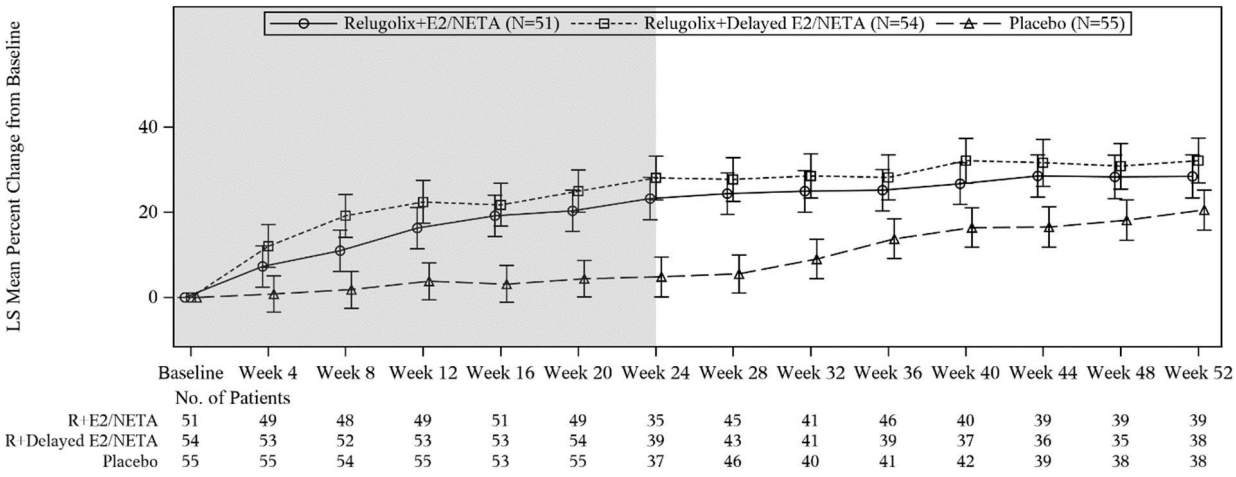
In the relugolix + E2/NETA group, of the 39 patients (23.93%) with a hemoglobin concentration ≤ 10.5 g/dL at baseline, 23 (58.97%) achieved an increase of > 2 g/dL at Week 52. In the relugolix + delayed E2/NETA group, of the 38 patients (25.50%) with a hemoglobin concentration ≤ 10.5 g/dL at baseline, 30 (78.95%) achieved an increase of > 2 g/dL at Week 52. The high proportion of responders in this group was attributable to the robust response observed during relugolix monotherapy over the first 12 weeks of the study and the continued exposure to relugolix combination therapy. In the placebo group, of the 38 patients (23.17%) with a hemoglobin concentration ≤ 10.5 g/dL at baseline, 16 (42.11%) achieved an increase of > 2 g/dL at Week 52.

Figure: Proportion of Patients with a Hemoglobin Concentration ⩽ 10.5 g/dL at Baseline Who Achieved > 2 g/dL Increase in Hemoglobin at Week 52 (Extension Safety Population)



Abbreviations: E2 = estradiol; N = number of patients; NETA = norethindrone acetate.
Note: Error bars represent 95% CIs.
Source: Figure 8.2.4.1.

Figure: Percent Change from Parent Study Baseline to Week 52 in Hemoglobin Concentration for Women with Hemoglobin ⩽10.5 g/dL (Extension Study Population)



No. of Patients

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
R+E2/NETA	51	49	48	49	51	49	35	45	41	46	40	39	39	39
R+Delayed E2/NETA	54	53	52	53	53	54	39	43	41	39	37	36	35	38
Placebo	55	55	54	55	53	55	37	46	40	41	42	39	38	38

Abbreviations: E2 = estradiol; LS = least squares; N = number of patients; NETA = norethindrone acetate; No. = number; R = relugolix. Note: Error bars represent 95% CIs. Note: Shaded area represents time in parent studies.

In summary, treatment with relugolix + E2/NETA was associated with clinically relevant improvements in anemia. A consistent trend in improved hemoglobin levels was observed with the increased duration of treatment over 52 weeks.

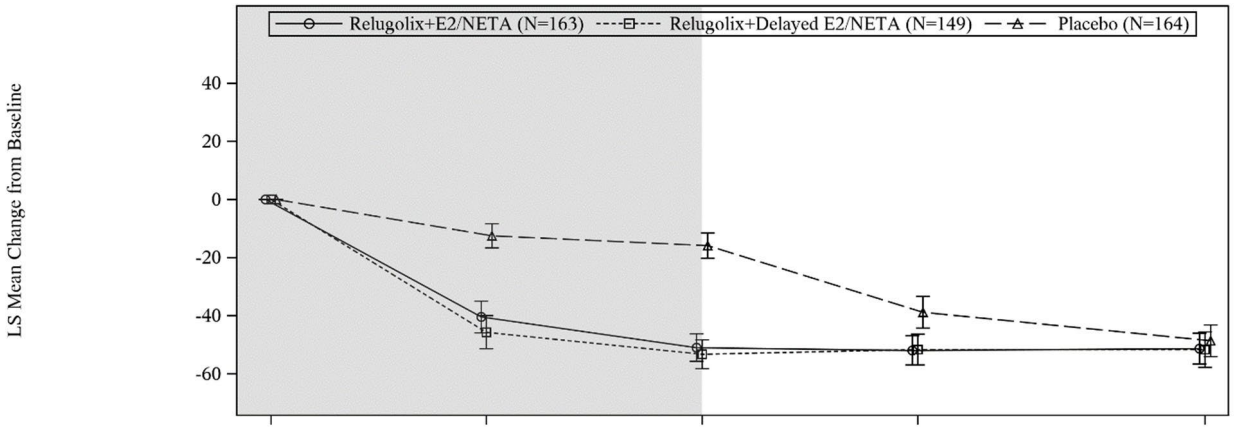
Patient-Reported Outcome Endpoints

In the extension study, the following patient-reported endpoints were analysed (not identical to the parent-studies): Changes in symptom severity and quality-of-life related to uterine fibroids, as measured by the UFS-QoL; and Impact of heavy menstrual bleeding on social, leisure, and physical activities, as measured by the MIQ.

Consistent with the improvement in heavy menstrual bleeding, patients treated with relugolix + E2/NETA reported sustained improvement in function and several quality-of-life measures related to the impact of uterine fibroids:

– Sustained mean change from baseline through Week 52 in the UFS-QoL BPD scale score of -51.3 indicating the durability of treatment effect in reducing distress due to bleeding and pain:

Figure: Summary of Change from Baseline in UFS-QoL Bleeding and Pelvic Discomfort Scale Score (Extension Study Population)



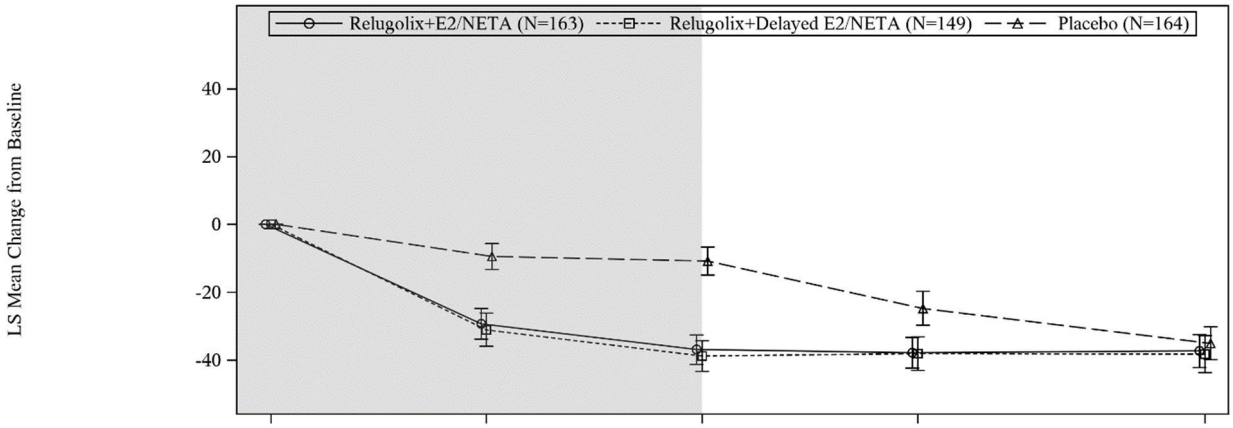
No. of Patients

	Baseline	Wk 12	Wk 24	Wk 36	Wk 52
Relugolix+E2/NETA	160	157	154	153	129
Relugolix+Delayed E2/NETA	147	143	142	128	108
Placebo	163	160	158	147	120

Abbreviations: E2 = estradiol; LS = least squares; N = number of patients; NETA = norethindrone acetate; No. = number.
Note: Error bars represent 95% CIs. Note: Shaded area represents time in parent studies.

– Sustained improvement throughout the extension study treatment period in UFS-QoL symptom severity scale scores to mean values observed in women without uterine fibroids (from an LS mean of 55.9 at baseline to 18.9 at Week 52) (Coyne et al. 2012):

Figure: Least Squares Mean Change from Baseline to Week 52 in UFS-QoL Symptom Severity Scale Over Time (Extension Study Population)



No. of Patients

	Baseline	Wk 12	Wk 24	Wk 36	Wk 52
Relugolix+E2/NETA	160	157	154	153	129
Relugolix+Delayed E2/NETA	147	143	142	128	108
Placebo	163	160	158	147	120

Abbreviations: E2 = estradiol; LS = least squares; N = number of patients; No. = number; NETA = norethindrone acetate; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life. Note: Error bars represent 95% CIs. Note: Shaded area represents time in parent studies.

– Sustained improvement throughout the extension study treatment period in the total health-related UFS-QoL score and in all sub-scale domains to values consistent with mild effects/impairment due to uterine fibroids.

Long-term efficacy beyond 52 weeks ('Top line data summary study MVT-601-035')

Study MVT-601-035

Note*: Only top-line efficacy results through 2 years of treatment with relugolix combination therapy have been provided. The full data set of this study will be submitted in a type II variation post-authorisation.*

The withdrawal study (MVT-601-035) was an international, phase 3, double-blind, placebo-controlled randomized study that enrolled eligible patients with uterine fibroids who had completed the 24-week treatment period in one of the pivotal studies (study MVT-601-3001 or study MVT 601-3002) and the 28-week treatment period of the long-term extension (LTE) study, MVT-601- 3003.

Objectives:

The objectives of study MVT-601-035 were to evaluate the long-term efficacy and safety of relugolix + E2/NETA, used once daily, for up to 104 weeks in patients with heavy menstrual bleeding associated with uterine fibroids.

Eligible women met the definition of a responder, which was a patient who demonstrated a menstrual blood loss (MBL) volume of < 80 mL and at least a 50% reduction from pivotal study baseline MBL volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the LTE study.

Women were randomized (1:1) at Week 52/Baseline to once-daily relugolix combination therapy or placebo for a 1-year double-blind treatment period.

For women who had a relapse of heavy menstrual bleeding during the study (MBL volume ≥ 80 mL), blinded treatment was stopped, and treatment with open-label relugolix combination therapy was offered.

Primary efficacy endpoint

The proportion of women who maintained an MBL volume of < 80 mL through **Week 76** (over the first 24 weeks of the randomized treatment period) as measured by the alkaline hematin method (referred to as *sustained responder rate at Week 76*), defined as the cumulative probability of MBL volume < 80 mL while on randomized treatment through Week 76.

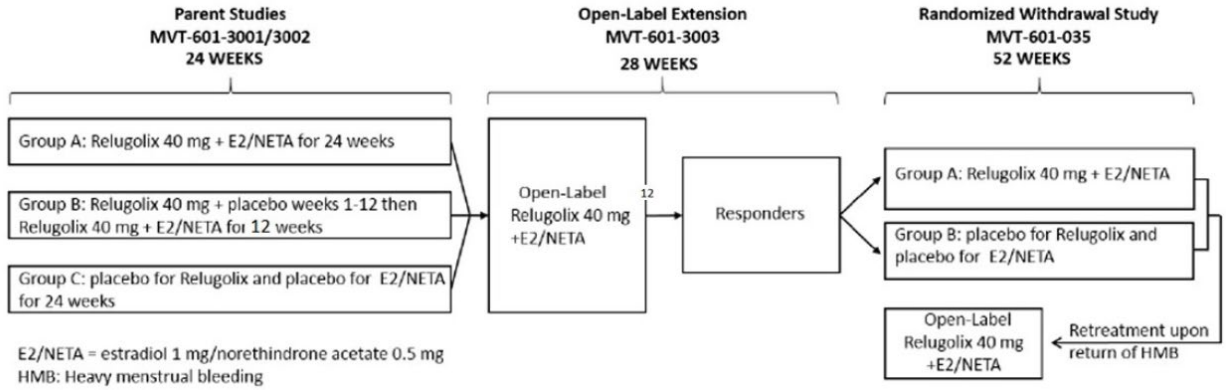
Key secondary endpoints:

- time to MBL volume ≥ 80 mL,
- proportion of women who maintained a MBL volume of < 80 mL through **Week 104** (over the 52-week randomized treatment period) as measured by the alkaline hematin method (referred to as sustained responder rate at Week 104), defined as the cumulative probability of MBL volume < 80 mL while on randomized treatment through Week 104,
- proportion of women achieving or maintaining amenorrhea at Week 76/end of treatment.

Re-treatment analyses (open-label):

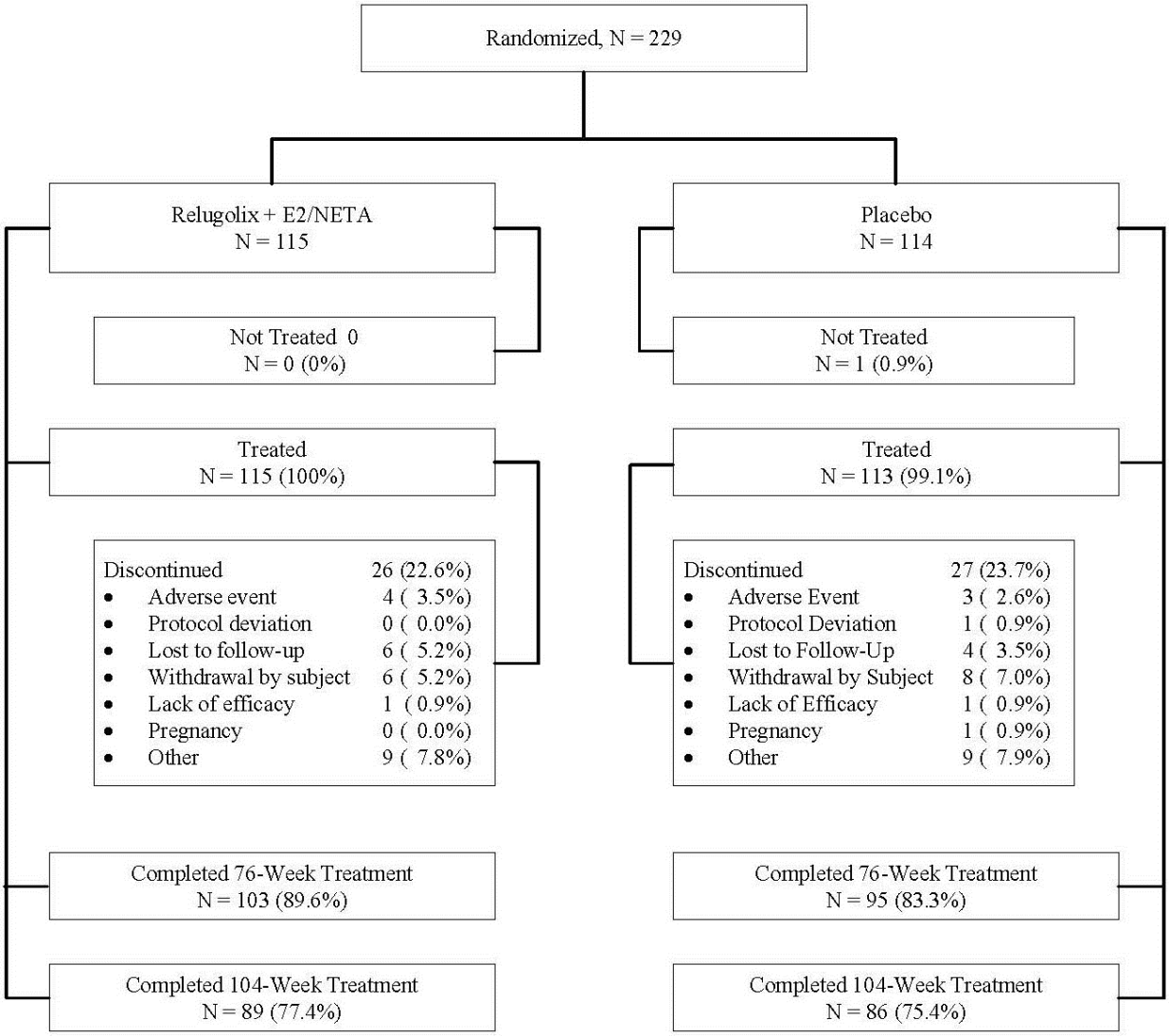
- proportion of patients who responded (MBL volume < 80mL) among those who had relapsed (MBL volume ≥ 80mL) during the randomized treatment period.

Figure: MVT-601-035 Study Design



A total of 229 patients were randomized to the study, 115 patients to relugolix + E2/NETA and 114 to placebo. A total of 175 patients (76.4%) completed, and the percentage who completed relugolix + E2/NETA (77.4%) and placebo (75.4%) were similar.

Figure Patient Disposition



Of the 229 randomized patients, 228 patients were treated and defined as the modified intent-to-treat (mITT) population for efficacy analysis and safety population for safety data analysis. The demographic and baseline characteristics of the participants at baseline were similar between the two treatment groups.

Table: Summary of Demographics (mITT Population)

Baseline Characteristic	Relugolix+E2/NETA (N = 115)	Placebo (N = 113)	Total (N = 228)
Age at Week 52/Baseline (years)			
n	115	113	228
Mean (SD)	43.3 (5.58)	44.2 (4.39)	43.8 (5.04)
Median	44.0	45.0	44.0
Min, Max	20, 52	34, 52	20, 52
Age at Week 52/Baseline category (years)			
n	115	113	228
< 40 years	25 (21.7%)	18 (15.9%)	43 (8.9%)
>= 40 years	90 (78.3%)	95 (84.1%)	185 (81.1%)
Race			
n	115	113	228
American Indian or Alaska Native	1 (0.9%)	0	1 (0.4%)
Asian	1 (0.9%)	1 (0.9%)	2 (0.9%)
Black or African American	49 (42.6%)	57 (50.4%)	106 (46.5%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	63 (54.8%)	52 (46.0%)	115 (50.4%)
Other	1 (0.9%)	2 (1.8%)	3 (1.3%)
Not Reported	0	1 (0.9%)	1 (0.4%)
Ethnicity			
n	115	113	228
Hispanic or Latino	29 (25.2%)	29 (25.7%)	58 (25.4%)
Not Hispanic or Latino	85 (73.9%)	84 (74.3%)	169 (74.1%)
Not Reported	1 (0.9%)	0	1 (0.4%)
Body mass index at Week52/Baseline (kg/m^2)			
n	115	112	227
Mean (SD)	30.6 (6.67)	31.4 (6.51)	31.0 (6.59)
Median	29.7	31.6	30.6
Min, Max	16.4, 46.9	19.1, 47.5	16.4, 47.5
Region			
n	115	113	228
North America	74 (64.3%)	73 (64.6%)	147 (64.5%)
Europe	26 (22.6%)	24 (21.2%)	50 (21.9%)
Latin America	8 (7.0%)	10 (8.8%)	18 (7.9%)
Rest of World	7 (6.1%)	6 (5.3%)	13 (5.7%)

Date of database lock: 17 Mar 2021.

Abbreviations: E2 = estradiol; Max = maximum; Min = minimum; mITT = modified intent-to-treat; N = number of patients in the treatment group; n = number of patients included in summary statistics; NETA = norethindrone acetate; SD = standard deviation.

Percentages are based on the total number of patients in each treatment group or total.

Overall, demographic characteristics were generally similar among the two treatment groups. The mean (SD) age for all patients in this study was 43.8 (5.04) years with the mean ages being similar among treatment groups. There were numerically more patients in the relugolix + E2/NETA group < 40 years compared with the placebo group. Additionally, baseline characteristics of the MVT-601-035 study population were generally comparable to the overall population enrolled into the two pivotal phase 3 studies except for age, which reflects the duration of the phase 3 programs and one year older from pivotal study entry.

Primary and Key Secondary Endpoint analysis

Study MVT-601-035 met the primary and all key secondary endpoints. A summary of results for the primary and key secondary endpoints is provided below.

Table: Primary and Key Secondary Efficacy Outcomes (mITT Population)

	Relugolix+E2/NETA (N = 115)	Placebo (N = 113)
Primary endpoint		
Sustained responder rate at Week 76	78.43%	15.08%
(95% CI)	(69.33%, 85.12%)	(8.91%, 22.76%)
Difference from placebo	63.36%	
95% CI	(52.85%, 73.86%)	
P-value	<.0001	
Key Secondary endpoints		
Time to MBL >= 80mL (weeks)		
25th percentile	34.7	4.6
Median (95% CI)	NE	5.9 (5.4, 6.3)
75th percentile	NE	15.7
Hazard ratio (95% CI)	0.13 (0.08, 0.20)	
P-value	< 0.0001	
Sustained responder rate at Week 104	69.79%	11.75%
(95% CI)	(59.72%, 77.80%)	(6.32%, 19.00%)
Difference from placebo	58.04%	
95% CI	(46.97%, 69.11%)	
P-value	<.0001	
Number (%) of patients achieved or maintained amenorrhea by Week 76	66 (57.39%)	15 (13.27%)
(95% CI)	(47.83%, 66.56%)	(7.62%, 20.95%)
Difference from placebo (95% CI)	44.12% (33.13%, 55.11%)	
P-value	< 0.0001	
Number (%) of patients were amenorrhea at Week 52/Baseline	62 (53.91%)	14 (12.39%)
Number (%) of patients were not amenorrhea at Week 52/Baseline	4 (3.48%)	1 (0.88%)

Date of database lock: 17 Mar 2021.

Abbreviations: CI = confidence interval; E2 = estradiol; MBL = menstrual blood loss; mITT = modified intent-to-treat; N = number of patients in the treatment group; NE = not estimable; NETA = norethindrone acetate.

Sustained responder rate at Week 76 (Week 104) is defined as the proportion of patients who maintained MBL volume < 80 through Week 76 (Week 104) and is calculated as the Kaplan-Meier estimate of the cumulative probability of MBL volume < 80 mL while on randomized treatment through Week 76 (Day 169) (Week 104 (365)).

Amenorrhea at a visit is defined as reported amenorrhea, spotting, or negligible bleeding (MBL < 5 mL) with supporting paper diary records and compliance.

Relugolix + E2/NETA vs. placebo week 76

For the primary endpoint, 78.4% of women who continued on relugolix + E2/NETA achieved a sustained responder rate (MBL < 80 mL) through **Week 76** compared with 15.1% of women who discontinued treatment and initiated placebo at Week 52 ($p < 0.0001$), see table above.

Relugolix + E2/NETA vs. Placebo week 104

Through Week 104, 88.3% (n=92) of women randomized to placebo at Week 52/Baseline relapsed with heavy menstrual bleeding (Table 8.2.2.2 in Appendix 1) with a median time to relapse of 5.9 weeks (Table). Among the 89 patients in the placebo group who relapsed and received open-label rescue treatment, 87 patients responded to relugolix + E2/NETA with a MBL < 80mL. In contrast, median time to relapse was not reached in the relugolix + E2/NETA group due to the small number of patients. Compared with the placebo group, women in the relugolix + E2/NETA group had 87% lower risk of relapse ($p < 0.0001$).

Through 2 years, 69.8% of women who continued on relugolix + E2/NETA remained responders compared with 11.8% of women who received placebo ($p < 0.0001$), supporting durability of treatment effect.

As expected, a larger proportion of women were amenorrheic at Week 76 with continued treatment with relugolix + E2/NETA relative to those receiving placebo (57.4% vs 13.3%, $p < 0.0001$).

No separate results have been presented regarding the primary efficacy endpoint in those patients who haver resieved relugolix + E2/NETA from baseline up to week 76, and week 104.

2.5.3. Discussion on clinical efficacy

The applicant initially applied for a MA in the following indications:

> *[TRADE NAME] is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.*
>
> *[TRADE NAME] maintains bone mineral density and protects the uterus from endometrial hyperplasia in women who choose to use [TRADE NAME] for uterine fibroid treatment.*

During the procedure, following the CHMP assessment of the data provided, the applicant withdrew the claim for the second indication as requested, and further information on bone mineral density and endometrial safety was added in SmPC section 5.1:

Claimed indication (revised)

- *[TRADE NAME] is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.*

For this indication initially the following studies were submitted*:*

- Two 24 week pivotal replicate, multi-national, pivotal randomized, double-blind, placebo-controlled phase 3 studies (**MVT-601-3001** and **MVT-601-3002**) in women with uterine fibroids.
- Open label extension efficacy and safety study **MVT-601-3003** (extension of MVT-601-3001 and MVT-601-3002) of in total 52 weeks.
- Study **MVT-601-034**, an observational (**natural history**) study evaluating BMD in women with uterine fibroids or endometriosis.
- Study **MVT-601-035** (only 'Top line data summary' submitted during the procedure): double-blind, placebo-controlled, randomized withdrawal study (Study MVT-601-035) to evaluate long-term efficacy and safety of relugolix 40 mg combined with E2/NETA (1 mg/0.5 mg) or placebo from week 52 to 104 weeks in patients with uterine fibroids. This study enrolled eligible patients who had completed MVT-601-

3003 and met the definition of a treatment response to relugolix with E2/NETA in women who completed the open label extension study MVT-601-3003 and who met the definition of responder.

The pivotal phase 3 studies of the relugolix + E2/NETA of 24 + 28 weeks long-term extension + additional 52 weeks of data are further supported by:

- Supportive studies for the proposed indication include two completed phase 3 relugolix *monotherapy s*tudies in Japanese patients conducted by Takeda
    - TAK-385/CCT-001 phase 2, multicenter, randomized, double blind, parallel group study of 12 weeks duration evaluated three dose levels of relugolix (10 mg, 20 mg, 40 mg daily) administered orally for 12 weeks compared with placebo in Japanese patients with main age of 42 years with symptomatic uterine fibroids.
    - TAK-385/CCT-002: phase 3, multicenter, randomized, double-blind, parallel-group study of 12 week duration evaluated the efficacy and safety of relugolix 40 mg compared with leuprorelin (once every 4 weeks, 1.88 or 3.75 mg subcutaneously) in Japanese patients with mean age of 42 years with symptomatic uterine fibroids.
    - TAK-385-3008: phase 3, multicenter, randomized, double blind, placebo-controlled study that evaluated the efficacy and safety of relugolix 40 mg administered orally once daily for 12 weeks compared with placebo in Japanese patients of 20 years of age or older having pain symptoms associated with uterine fibroids.
- An exit interview substudy (MVT-601-037), providing the patient's perspective on the patient-reported outcomes used in the pivotal studies in a subgroup of 30 patients.

Dose selection

Relugolix dose of 40 mg

Based on a PK/PD single and multiple dose study **TAK-385_101** in 120 healthy premenopausal women in the US, investigating single doses of 1- to 80-mg of relugolix, dose-dependent reductions in mean LH, FSH, and E2 serum concentrations with respect to both degree and duration were observed, consistent with the mechanism of action of relugolix as a GnRH receptor antagonist. As at 24 hours postdose, mean E2 concentrations for the 40- and 80 mg doses of relugolix were similar (30.2 pg/mL and 30.3 pg/mL, respectively), doses higher than 40 mg are unlikely to provide further suppression of E2 concentrations with once daily administration. Therefore, the 40 mg dose was selected for further development. Based on the presented data, the dose of 40 mg is agreed.

E2/NETA dose

The dose of E2 1mg + NETA 0.5 mg selected for combination with relugolix was based on data in the literature, particularly from published studies that supported the estradiol dose of 1 mg to have efficacy in prevention of bone loss in postmenopausal women. Further, the E2/NETA combination, Activelle, is registered in Europe for treatment of vasomotor symptoms and prevention of osteoporosis in postmenopausal women. The addition of this approved combination is therefore considered acceptable.

Design and conduct of clinical studies

Main efficacy studies (MVT-601-3001 and MVT-601-3002)

The two main studies were replicate pivotal phase 3 multi-national randomized, double-blind, placebo-controlled studies with relugolix combination therapy (MVT-601-3001 and MVT-601-3002) conducted in the US and rest of world. The studies consisted of a screening period (up to approximately 13 weeks), a randomized placebo-controlled treatment period (24 weeks), and an active control group of women who initially received relugolix monotherapy for 12 weeks, followed by 12 weeks of relugolix + E2/NETA in order to compare efficacy between relugolix monotherapy with relugolix +E2/NETA. Both studies were adequate and well-controlled studies.

All eligible women who completed the 24-week study were offered the opportunity to enroll in an open-label efficacy and safety extension study (MVT-601-3003) of another 28 weeks (in total 52 weeks).

Participants

The patient population was adequately selected to reflect the population of women with uterine fibroids.

In both studies, in total 770 women participated (388 and 382, respectively). The study population consisted of premenopausal women, aged 18 to 50 years with heavy menstrual bleeding associated with uterine fibroids (≥ 80 mL per cycle for two cycles or ≥ 160 mL for one cycle as measured by the alkaline hematin method during the screening period. The efficacy of relugolix treatment in women with uterine fibroids focused on reduction in heavy menstrual bleeding as this is the most common symptom of uterine fibroids. The inclusion criterion on heavy menstrual bleeding is suitable to evaluate the selected primary efficacy endpoint.

Women with a baseline BMD z-score < -2.0 at spine, total hip, or femoral neck or a history of or currently had osteoporosis or other metabolic bone disease were not allowed in the study.

It was noted that approximately 16% of patients were of European origin. Although it is not expected that the epidemiology and presentation of uterine fibroids in European women is different from the US and the rest of the world, a discussion was requested that the clinical data is also applicable for European women. The applicant provided sufficient arguments supporting that the clinical data from the development program are also applicable for European women. These arguments are based on pathophysiology, i.e. mutations in MED12 being present in ~70% of uterine fibroids, regardless of race/ethnicity and geography. Further, the standard of care for management of uterine fibroids is expected similar across geographies. No ethnicity-based polymorphisms are known for enzymes and transporters involved in relugolix exposure, including the intestinal P-glycoprotein (P-gp) efflux transporter, nor for the human GnRH receptor. Therefore, subsequent differences in biological effects are not expected. The demographic data of the EU population enrolled in the two pivotal phase 3 studies was generally comparable to that of the overall population (comprising of women from EU and US), except that the EU population is leaner, had smaller uterine volumes and index uterine fibroid volumes and had less moderate to severe pain. It is agreed that, despite these differences, the responder rate was consistent in the European women and the overall population, as was the effect on the pain reduction endpoint.

Contraception

Concomitant treatment with combined hormonal contraceptives is contraindicated, since the effect of additional hormones on the efficacy of relugolix combination therapy is unknown and the safety of concomitant use has not been established. Therefore use of barrier contraception was recommended. Use of

hormonal contraceptives was excluded and patients had to agree to use non-hormonal contraception throughout the study, including through 30 days following the last dose of study drug.

Primary efficacy endpoint

In the pivotal studies, the primary efficacy endpoint was the proportion of women in the relugolix + E2/NETA group versus the placebo group who achieved 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.

The primary efficacy analysis consisted of the comparison of the responder rate of the relugolix + E2/NETA group with the placebo group.

The secondary efficacy analysis consisted of the comparison of the responder rate of the relugolix + delayed E2/NETA group with the placebo group.

Additionally, further efficacy analyses were performed for the primary efficacy endpoint every 4 Weeks, including a comparison at 12 weeks, allowing a comparison of effects in the relugolix monotherapy against relugolix +E2/NETA up to 12 weeks.

Menstrual blood loss (MBL) volume was quantified using the alkaline hematin method. The alkaline hematin method to measure MBL is recognized as the most objective technique with which to measure MBL. The method requires the collection of feminine products. This validated method for determination of MBL volume is considered fit to investigate efficacy for relugolix-E2/NETA.

In the supportive efficacy studies (relugolix monotherapy) in Japanese women, the Pictorial Blood Loss Assessment Chart (PBAC) method was used, a validated semiquantitative measurement tool for diagnosing heavy menstrual bleeding that does not require the collection of feminine products. However, this method generally correlates with the qualitative measures of menstrual blood volume (e.g., alkaline hematin method).

The placebo group as comparator is considered adequate. There is no other product registered for this indication for long-term use in the US (75% of study population). Only in the EU (ca. 15% of study subjects), ulipristal acetate (Esmya) is registered for this indication for intermittent use.

The additional arm of relugolix monotherapy for 12 weeks followed by relugolix + E2/NETA for 12 weeks was included to assess the effectiveness of the addition of E2/NETA to relugolix in mitigating the adverse effects of the hypoestrogenic state (BMD loss and vasomotor symptoms) brought on by relugolix monotherapy. Additionally, a comparison of the efficacy in reducing blood loss obtained with relugolix monotherapy can be compared with the efficacy obtained with the relugolix +E2/NETA combination. This comparison will give insight in the loss of efficacy due to the addition of exogenous estradiol.

Key secondary efficacy endpoints

There were seven predefined key secondary endpoints. These were related to menstrual blood loss (MBL), percentage of women achieving amenorrhea, percentage reduction in uterine fibroid volume, improvement in Hb in a subgroup of women with anemia, abdominal pain, and patient-reported outcomes of quality-of-life. Measures chosen for assessment either are well established methods for evaluation of such endpoints or were validated to measure those outcomes.

Statistical methods

The sample size was based on having sufficient power for the **BMD safety endpoint** and more than sufficient for the efficacy endpoints. The assumptions are reasonable and the calculation is accepted.

The analysis populations and the primary and secondary endpoint analyses are considered adequate and are acceptable. Missing data in the analysis was imputed based on treatment exposure and compliance with feminine products and eDiary, imputing data as non-responder, responder or a value derived from a mixed-effects model, depending on the different missing data categories. Sensitivity analyses tested the assumptions of this pattern mixture model. This allowed assessment of the various assumptions and is sufficient. The primary and key secondary endpoints were tested hierarchically (first 5) followed by a Hochberg procedure (last 3), which will protect the type I error. The design is in accordance with legal requirements, available guidelines, and the several scientific advices that were held.

Efficacy data and additional analyses

Primary efficacy analysis

Efficacy relugolix + E2/NETA versus placebo at Week 24

Primary efficacy endpoint was the **proportion of women** in the relugolix + E2/NETA group versus the placebo group who achieved a 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.

Both studies MVT-601-3001 and MVT-601-3002 met their primary efficacy endpoint, in being statistically significantly superior compared with placebo, and results were consistent between studies. Relugolix combination therapy was associated with statistically significant and clinically relevant greater proportions of responders in the relugolix + E2/NETA groups in MVT-601-3001 and MVT-601-3002 studies (73.44% and 71.20%, respectively) compared to responses observed in the placebo groups (18.90% and 14.73%, respectively).

Secondary efficacy analysis at Week 24

In addition to the primary analysis, a secondary analysis was performed comparing the relugolix + delayed E2/NETA group with the placebo group with respect to the responder rate at week 24. In the MVT-601-3001, the proportion of responders was 79.55% in the relugolix + delayed E2/NETA group compared with to 18.90% in the placebo group. The observed difference between the two groups was 60.65% (95% CI: 50.97% to 70.33%) in favour of the relugolix + delayed E2/NETA group and was significant (nominal $p < 0.0001$). In study MVT-601-3002, the proportion of responders 73.23% in the relugolix + delayed E2/NETA group compared with 14.73% in the placebo group. The observed difference between the two groups was 58.50% (95% CI: 48.67% to 68.33%) in favour of the relugolix + delayed E2/NETA group and was statistically significant (nominal $p < 0.0001$).

Efficacy relugolix monotherapy vs. relugolix + E2/NETA and placebo at Week 12

The relugolix + delayed E2/NETA treatment arm (initial treatment with relugolix monotherapy for 12 weeks followed by 12 weeks relugolix + E2/NETA) was added to be able to evaluate the effect of addition of exogenous estrogen on the efficacy of relugolix and on prevention of bone loss. The difference is largest at Week 4 (about 20% difference), but from Week 4 onwards the difference between relugolix and relugolix+

E2/NETA diminishes to about 5% at week 12 (end of relugolix monotherapy). After Week 12 when these patients received relugolix + E2/NETA, this difference remained from Week 12 to Week 24. However, the difference in responders is only small and can be considered not clinically relevant in the light of the protective effect on bone mass (see safety section).

Onset of effect

At Week 4, about ~30% of patients were responding and >60% of patients had responded at Week 8. A total of >70% of responders remained constant between Week 12 to Week 24. It took approximately 12 weeks to reach maximum effect in reduction of blood loss.
The median time to achieve a first response (MBL volume < 80 mL and ≥ 50% reduction in MBL volume from baseline) was significantly shorter in the relugolix + E2/NETA group (8.3 weeks) when compared with the placebo group (25.1 weeks).

Key secondary efficacy endpoints

The key secondary endpoint outcomes are in support of the primary endpoint:

Results on the key secondary endpoints at Week 24:

The decrease in **volume of menstrual blood loss** for relugolix + E2/NETA groups in both phase 3 studies) was statistically significant and reductions in menstrual blood loss volume (mean 84.3%, in both) were clinically relevant.

Amenorrhea was achieved by 52.3% on relugolix+E2/NETA vs 5.5% on placebo in MVT-601-3001 and 50.4% vs 3.1% of women in MVT-601-3002, respectively. At Week 8 amenorrhea was only achieved by 29.7% and 17.6% of women on relugolix+E2/NETA, respectively. The median time to achieving sustained amenorrhea in the relugolix + E2 NETA groups was 11.3 weeks in study MVT-601-3001 and 16.3 weeks in study MVT-601-3002.

Uterine fibroid volume Decrease in volume from baseline to Week 24 in uterine fibroid volume was lower in the relugolix + E2/NETA groups (-12.4% and -17.4% in studies MVT-601-3001 and MVT-601-3002, respectively) than on placebo (-0.3% and -7.4%, respectively), although the results were not statistically significant compared with placebo (p = 0.0921 and p = 0.2153, respectively). In the pooled data, statistical significance was reached with placebo (-15.4% vs. -4.2%; p = 0.0374). Still, the decrease in fibroid volume can be considered supportive.

Uterine volume In both studies, mean uterine volume decreased from baseline to Week 24 and was significantly greater in the relugolix + E2/NETA groups (-12.9% and -13.8% for MVT-601-3001 and MVT-601-3002, respectively) compared with the placebo groups (2.2% [p< 0.0002] and -1.5% [p< 0.0078], respectively.

Key secondary endpoint analyses in subgroups of patients:

Hemoglobin was measured in a subgroup of women who had anemia with a hemoglobin ≤ 10.5 g/dL at baseline (30 (23.44%) patients on relugolix+E2/NETA vs 23 (18.11%) patients on placebo in study MVT-601-3001 and 31 (24.80%) vs 37 (28.68%) in study MVT-601-3002). In this group, hemoglobin had statistically significantly (> 2 g/dL) improved in 50.0% and 61.3% women, respectively. The observed improvements were statistically significant and considered clinically relevant. These improvements in women with anemia are supportive, although they represented only half the study population.

Pain was measured in the subset of women with a maximum Numerical Rating Scale (NRS) score ≥ 4 for pain associated with uterine fibroids during the 35 days prior to randomization (58 (45.31%) patients on relugolix+E2/NETA vs 58 (45.31%) patients on placebo in study MVT-601-3001 and 68 (54.40%) vs 82 (63.57%) in study MVT-601-3002). In this group, proportion of patients with maximum NRS score ≤ 1 during the last 35 days of treatment was reduced with relugolix combination therapy in 43.1% and 47.1% of patients compared with 10.1% and 17.1% with placebo, respectively. These improvements in women with a high pain score are supportive, although they represented only half the study population.

Ancillary analyses (subgroup analyses)

In the pivotal studies (MVT 601 3001 and MVT 601 3002), subgroup analyses of the primary efficacy endpoint comparing relugolix + E2/NETA versus placebo were performed to assess whether treatment effects were consistent across clinically important subgroups. Pooled subgroup analyses were conducted for the subgroups Geographic region, baseline MBL volume, age, race, ethnicity, largest fibroid volume at baseline, uterine volume at baseline, baseline BMI, maximum NRS (pain) score at baseline, and history of prior pregnancy.

Across all subgroups, treatment differences were generally consistent with the primary analysis with a higher proportion of patients who received relugolix + E2/NETA meeting the definition for responder than patients who received placebo, especially in the subgroups with larger sample sizes. Treatment effect was slightly higher in the rest of world than in North America and in White patients compared with Black or African American patients. Smaller treatment differences were observed in the subgroups of women with larger uterine volumes (≥ 300 cm3) relative to the rest of the subgroups.

Efficacy during open-label long-term use up to 52 weeks

Efficacy primary endpoint

At the end of the long-term extension study (Week 52), 143 of 163 patients (87.73%) in the relugolix + E2/NETA group achieved the primary endpoint: an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment. The 87.73% responder rate observed at Week 52 in the relugolix + E2/NETA group was consistent with that observed at Week 24 in the parent placebo-controlled studies among those who completed treatment (84.0% and 80.4% for MVT-601-3001 and MVT-601-3002, respectively. Similar to the parent studies, consistent treatment effects were observed across subgroups in the long-term extension study with responder rates generally consistent with those observed in the overall population.

Efficacy key secondary endpoints

- Menstrual Blood Loss Volume: The decrease in MBL volume observed during the first 24 weeks of treatment was maintained during the open-label extension study with the LS mean percent change from baseline ranging from -81.1 at Week 24 to -89.8 at Week 52, demonstrating the durability of the effect of relugolix + E2/NETA treatment.
- Amenorrhoea: The percentage of amenorrhoea was maintained in the relugolix + E2/NETA group, 115 patients (70.55%) achieved amenorrhea over the last 35 days of 52 weeks treatment.
- Anemia was improved with ≥ 2 g/dL in hemoglobin concentration at Week 52 for the subset of patients with hemoglobin concentrations ≤ 10.5 g/dL at baseline: In the relugolix + E2/NETA group, of the 39 patients (23.93%) with a hemoglobin concentration ≤ 10.5 g/dL at baseline, 23 (58.97%) achieved an increase of > 2 g/dL at Week 52.

- Uterine fibroid volume: In the relugolix + E2/NETA group, the LS mean percent change in uterine fibroid volume from baseline was -13.53% at Week 24 and -18.27% at Week 52, indicating that the reductions in uterine and fibroid volume observed at Week 24 were sustained through Week 52.
- Uterine volume: In the relugolix + E2/NETA group, the LS mean percent change in uterine volume from baseline was -12.93% at Week 24 and -14.10% at Week 52, indicating that the reductions in uterine volume were maintained.

Key secondary endpoints in subgroups:

Quality of life:

- Mean change from baseline was sustained through Week 52 in the UFS-QoL BPD scale score of -51.3 indicating the durability of treatment effect in reducing distress due to bleeding and pain;
- Improvement was sustained throughout the extension study treatment period in UFS-QoL symptom severity scale scores to mean values observed in women without uterine fibroids (from an LS mean of 55.9 at baseline to 18.9 at Week 52) (Coyne et al. 2012);
- Improvement was sustained throughout the extension study treatment period in the total health-related UFS-QoL score and in all sub-scale domains to values consistent with mild effects/impairment due to uterine fibroids.

Efficacy in double-blind long-term use from week 52 to up to 76 weeks + open-label to 104 weeks

(top-line summary study MVT-601-035)

Primary efficacy endpoint

At week 76, 78.4% of women who continued on relugolix + E2/NETA, achieved a sustained responder rate (the proportion of women who maintain a MBL of < 80 mL at Week 76 (24 weeks of the randomized treatment period)) compared with 15.1% of women who discontinued treatment with relugolix + E2/NETA and initiated placebo at Week 52.

The top-line summary did not provide separate results regarding the primary efficacy endpoint in those patients who haver resieved relugolix + E2/NETA from baseline up to week 76, and week 104.

Secondary efficacy endpoints

Through Week 104, 88.3% of women randomized to placebo at Week 52/Baseline relapsed with heavy menstrual bleeding with a median time to relapse of 5.9 weeks. In contrast, through Week 104, 30.2% of women randomized to relugolix + E2/NETA at Week 52/Baseline relapsed with heavy menstrual bleeding. The median time to relapse was not reached in the relugolix + E2/NETA group due to the small number of patients who relapsed.

Among the 26 and 89 patients in the relugolix + E2/NETA and placebo groups who relapsed and received open-label rescue treatment, 25 and 87 patients responded to relugolix + E2/NETA with an MBL < 80mL, respectively. Compared with the placebo group, women in the relugolix + E2/NETA group had 87% lower risk of relapse. Through 104 weeks of treatment, 69.8% of women who continued on relugolix + E2/NETA remained responders compared with 11.8% of women who received placebo, supporting durability of treatment effect.

A larger proportion of women were amenorrhoeic at Week 76 with continued treatment with relugolix + E2/NETA relative to those receiving placebo (57.4% vs 13.3%).

Supportive studies

Supportive studies for the proposed indication included three *s*tudies **in Japanese patients** conducted by Takeda: a phase 2 dose finding study for relugolix monotherapy versus placebo ((**TAK-385/CCT-001) and** two phase 3 relugolix **monotherapy** (**TAK-385/CCT-002 [monotherapy vs GnRH agonist]**, **TAK-385-3008 [pain symptoms, vs placebo**]. Further, an exit questionnaire (exit interview) study MVT 601 037 was performed, a substudy to the phase 3 studies (MVT-601-3001 and MVT-601-3002) [patient input on the patient reported outcomes]).

Two relugolix **monotherapy** *s*tudies **in Japanese patients** conducted by Takeda **TAK-385/CCT-001** (monotherapy versus placebo) and **TAK-385/CCT-002** (monotherapy vs GnRH agonist)], had similar primary efficacy endpoints, i.e. proportion of responders in reduction of MBL:

Comparison Proportion of Responders

While the assessment of MBL volume was different between the pivotal relugolix combination studies (alkaline hematin method) and supporting relugolix monotherapy studies (PBAC method) in Japanese patients, both assessments are validated methods for analyzing MBL volume and are highly correlated. A PBAC score of 150 represents an approximately 80 mL of blood loss (correlation coefficient of 0.75 to 0.85) measured by the alkaline hematin method (Higham et al. 1990; Zakherah et al. 2011). Regardless of the differences in definitions of the primary endpoint, all studies assessed the proportion of responders using a high bar for defining a patient as a responder.

In the pivotal phase 3 studies (MVT-601-3001 and MVT-601-3002), similarly greater proportions of women in the relugolix + delayed E2/NETA groups met the definition of responder at Week 12 (77.3% and 76.4%) compared with those in the placebo groups (15.7% and 8.5%). The differences between treatment and placebo groups were > 60% in both studies. In the phase 2 study TAK-385/CCT-001, a 12-week dose-finding study comparing the efficacy of relugolix 10-, 20-, and 40-mg doses with placebo, 83.3% of women using the 40 mg relugolix met the definition of responder compared with 0% in the placebo group. In the phase 3 study TAK-385/CCT-002 the Week 12, the responder rate in the relugolix 40 mg group was 82.2%, non-inferior (using a non-inferiority margin of -15%) to the responder rate achieved with leuprorelin (83.1%, p = 0.0013).

In conclusion, these comparisons across studies indicate that relugolix 40 mg monotherapy and leuprolin have comparable rate of responders, although measured with different MBL evaluation methods. As has been demonstrated in the comparison of responders in the relugolix monotherapy (relugolix + delayed E2/NETA group) versus relugolix + E2/NETA at 12 weeks treatment, the addition of E2/NETA results in a slightly lower, not clinically relevant percentage of responders, but with a clear advantage in mitigation of relugolix induced bone loss.

TAK-385-3008

In this phase 3, placebo-controlled relugolix monotherapy study (TAK-385-3008) of 12 weeks duration, the primary endpoint of the proportion of patients with a maximum numerical rating scale (NRS) score of 1 or less during the 28 days before the final dose of study drug was evaluated against placebo.
The study met the primary endpoint. The proportion of patients with a maximum NRS score of 1 or less was higher in the relugolix 40 mg group (57.6%) than in the placebo group (3.1%), which difference was

significant and clinically relevant (odds ratio, 42.071; 95% CI, 5.113 to 346.181). These results are in line with the pain relief results in the pivotal phase 3 studies.

- **Phase 3 Patient Experience (exit interview) Substudy (MVT-601-037)**

MVT-601 037, a substudy to MVT601-3001 and MVT-601-3002, was conducted to obtain patient input via qualitative interviews of English-speaking patients who completed the pivotal phase 3 studies of 24 weeks on what constitutes a meaningful or relevant improvement on patient reported outcomes. Pain among subjects was among other, measured with the UFS QoL BPD scale to assess three symptoms associated with uterine fibroids that are common to most patients (i.e., heavy bleeding during the menstrual period, passing blood clots during the menstrual period, and feeling tightness or pressure in the pelvic area). The study results suggest that these women could distinguish a clinically meaningful change in their symptomatology. A limitation of the study was that the population (N=30 from the US) was very small compared to the total number of subjects from MVT 601 3001 + MVT 601 3002 (total sample N=770, total US sample N=582).

2.5.4. Conclusions on the clinical efficacy

The initial phase 3 clinical program on efficacy supported a statistically and clinically relevant higher reduction in heavy menstrual blood loss associated with uterine fibroids in comparison to placebo over a treatment period of 24 weeks. This beneficial effect over placebo is further supported in clinically meaningful reductions in total menstrual blood loss volume, achievement of amenorrhea, and slight decrease in volume of uterine fibroids. As has been demonstrated in the comparison of responders in the relugolix monotherapy (relugolix + delayed E2/NETA group) versus relugolix + E2/NETA at 12 weeks treatment, the addition of E2/NETA results in a slightly lower, not clinically relevant percentage of responders but with a clear advantage in mitigation of relugolix induced bone loss.

Based on the results of the 28-week uncontrolled extension study, it was shown that the noted efficacy, as based on the primary efficacy endpoint, i.e. proportion of responders at week 24, has been sustained during 52 weeks. This was also the case for the key secondary efficacy endpoints. The number of women who received relugolix + E2/NETA up to 52 weeks in this efficacy analysis consisted of 163 women.

Based on the results of the top-line summary data of the withdrawal study, as based on the primary endpoint, i.e. the proportion of responders defined as proportion of women who maintain a MBL of < 80 mL at Week 76 (24 weeks of the randomized treatment period), efficacy was sustained during 76 weeks of treatment. Efficacy through week 104 (n=79), as a secondary endpoint, was based on the patients in the relugolix + E2/NETA and placebo groups who relapsed and received open-label rescue treatment. Of these, 69.8% of women who continued on relugolix + E2/NETA remained responders compared with 11.8% of women who received placebo, supporting maintenance of treatment effect in MBL reduction. The number of patients who received relugolix + E2/NETA for up to 104 weeks consisted of 32 women. The top-line summary did not provide separate results regarding the primary efficacy endpoint in these patients.

Only a small group of patients (approximately 16%) were of European origin. However, based on the applicant's requested clarification, assessment of data in European women in the pivotal studies, MVT-601-3001 and MVT-601-3002, demonstrates that demographics and baseline characteristics are generally comparable to the overall population, and standard of care was not substantially different prior to study entry. Clinical outcomes for the responder rate in reduction and heavy menstrual bleeding and pain reduction are consistent with the overall population.

2.6. Clinical safety

Introduction

In the relugolix clinical development program, safety was evaluated based on the assessment of:

- Adverse events
- Safety parameters of interest
    - Hepatic transaminase elevations
    - Gallbladder disease
    - Major adverse cardiovascular events
    - Thrombotic events
    - Tumors
    - Mood disorders
    - Hypersensitivity
    - Phospholipidosis
- Bone mineral density (BMD)
    - Adverse events related to BMD loss
    - BMD measurements by DXA
- Endometrial hyperplasia
- 12 lead electrocardiogram (ECG) parameters,
- Vital sign measurements including weight, physical examinations (including visual acuity).

The evaluation of the safety of relugolix combination therapy is primarily based on data from the two replicate placebo-controlled pivotal studies (MVT-601-3001 and MVT-601-3002) with duration of 24 week + 28 weeks long-term uncontrolled extension (MVT-601-3003) along with supportive information from studies with relugolix monotherapy and other clinical pharmacology studies.

Safety analyses were performed for the following populations based on studies included in the integrated safety database, see overview of the total safety base in the table below.

Table: Grouping of Studies and Treatments for the Integrated Analysis of Safety

Population	Pooling Rationale	Studies Included	Treatment Groups Displayed in Outputs
Phase 3 Uterine Fibroids 24-Week Combination Therapy Safety Population	To assess the safety and tolerability of relugolix combination therapy with E2 and NETA **for 24 weeks** in women with heavy menstrual bleeding associated with uterine fibroids	MVT-601-3001 MVT-601-3002	• relugolix + E2/NETA • relugolix + delayed E2/NETA • placebo

Population	Pooling Rationale	Studies Included	Treatment Groups Displayed in Outputs
Phase 3 + safety extension Uterine Fibroids Long-Term Combination Therapy Safety Population	To assess the long-term safety and tolerability of relugolix combination therapy with E2 and NETA for **up to 52 weeks** in women with heavy menstrual bleeding associated with uterine fibroids	MVT-601-3001 MVT-601-3002 MVT-601-3003	• relugolix + E2/NETA • relugolix + delayed E2/NETA • placebo
Phase 3 + safety extension + withdrawal study MVT-601-035 **Only summary, not integrated in the safety data sets.**	To assess the long-term efficacy and safety of relugolix + E2/NETA, for up to 104 weeks in patients with heavy menstrual bleeding associated with uterine fibroids.	MVT-601-3001 MVT-601-3002 MVT-601-3003 MVT-601-035	• relugolix + E2/NETA • placebo
Uterine Fibroids 12-Week Monotherapy Safety Population	To assess the safety and tolerability relugolix as **monotherapy for 12 weeks** exposure; applicable data from phase 3 studies MVT-601-3001 and MVT-601-3002 from the treatment group **that received an initial 12 weeks of relugolix** monotherapy were pooled with 12-week data from three relugolix monotherapy studies in women with heavy menstrual bleeding or pain associated with uterine fibroid	MVT-601-3001 MVT-601-3002 TAK-385/CCT-001 TAK-385/CCT-002 TAK-385-3008	• relugolix 10 mg • relugolix 20 mg • relugolix 40 mg • leuprorelin • placebo
Women's Health 12-Week Monotherapy Safety Population	To assess the safety and tolerability of relugolix as **monotherapy for 12 weeks** in women with heavy menstrual bleeding or pain associated with uterine fibroids and pain associated with endometriosis	MVT-601-3001 MVT-601-3002 TAK-385/CCT-001 TAK-385/CCT-002 TAK-385-3008 TAK-385/CCT-101	• relugolix 10 mg • relugolix 20 mg • relugolix 40 mg • leuprorelin • placebo
Women's Health 24-Week Monotherapy Safety Population	To assess the safety and tolerability of relugolix upon administration relugolix as **monotherapy for 24 weeks** in women with heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis	TAK-385/CCT-101 TAK-385/OCT-101 TAK-385/CCT-002	•

Population	Pooling Rationale	Studies Included	Treatment Groups Displayed in Outputs
Healthy Participants Single-Dose Safety Population	To assess the safety and tolerability of relugolix after administration of single 1 to 360 mg doses in healthy men and women (data are integrated based on dose)	TAK-385_101 (Cohorts 1-6) TAK-385/CPH-001 (Cohorts 1-6) C27001 (Part 1: Cohorts 1, 2, and 4) TAK-385_106	• relugolix 1-10 mg • relugolix 20 mg • relugolix 40 mg • relugolix 60 mg • relugolix 80-120 mg • relugolix > 120 mg • placebo
Healthy Participants Multiple-Dose Safety Population	To assess the safety and tolerability of relugolix after administration of 10 to 180 mg once daily for up to 28 days in healthy adult men and women (data are integrated based on dose and duration of exposure)	TAK-385_101 (Cohort 8-10: 14 days) TAK-385/CPH-001 (Cohort 8-10: 14 days) C27001 (Part 2: 14 days; Part 3 and 4: 28 days)	• relugolix 10 mg • relugolix 20 mg • relugolix 40 mg • relugolix 60 mg • relugolix 80-120 mg • relugolix > 120 mg • placebo

Abbreviations: E2 = estradiol; NETA = norethindrone acetate.

Patient exposure (relugolix mono or combination therapy)

The overall extent of exposure to relugolix alone or in combination with E2 and NETA in the clinical development program supporting this application is presented below:

Table: Number of Participants Who Received Any Dose of Relugolix in Completed Studies

Relugolix Treatment Group	Participants with ≥ 1 Dose	Participants with ≥ 6 Months	Participants with ≥ 12 Months
Any relugolix	3258	1509	795
Any relugolix ≥ 40 mg	2787	1414	795
Any relugolix monotherapy	2609	987	543
1 mg	20		
5 mg	20		
10 mg	189	50	
20 mg	242	45	
40 mg	944	120	
60 mg	86		
80 mg	132	63	57
120 mg	863	709	486
160 mg	25		
180 mg	12		
360 mg	76		

Relugolix Treatment Group	Participants with ≥ 1 Dose	Participants with ≥ 6 Months	Participants with ≥ 12 Months
Relugolix 40 mg + E2/NETA	888	451	141

Duration of exposure in days = (date of the last dose - date of the first dose) + 1.
Duration of exposure "≥ 24 weeks" is considered as "≥ 6 months" and "≥ 48 weeks" as "≥ 12 months."
Both co-administration and fixed-dose combination of relugolix 40 mg and E2/NETA are included in 'relugolix 40 mg + E2/NETA'.

A total of 888 patients received at least one dose of relugolix combination therapy. In studies in women with uterine fibroids, 634 patients received at least one dose of relugolix combination therapy, 451 were exposed for at least 6 months, and 130 were exposed for at least a year.

The patient exposure in studies MVT-601-3001, MVT-601-3002, and MVT-601-3003 is given below:

Table: Extent of Exposure: Uterine Fibroids Long-Term Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002, MVT-601-3003)

Category	Relugolix 40 mg + E2/NETA (N = 254)	Relugolix 40 mg + Delayed E2/NETA (N = 258)	Placebo (N = 256)	Total (N = 768)
Overall treatment duration (weeks)				
n	254	258	256	768
Mean (SD)	39.22 (18.505)	35.28 (19.003)	38.96 (17.643)	37.81 (18.458)
Median	52.21	33.43	50.36	47.71
Min, Max	0.1, 61.9	0.1, 58.7	0.1, 62.4	0.1, 62.4
Treatment duration in combination therapy (weeks)				
n	254	216	164	634
Mean (SD)	39.22 (18.505)	29.01 (14.506)	24.65 (8.769)	31.97 (16.314)
Median	52.21	39.07	28.36	29.29
Min, Max	0.1, 61.9	0.1, 46.7	0.1, 32.1	0.1, 61.9
Treatment duration category in combination therapy (weeks), n (%)				
⩽ 4	12 (4.7%)	6 (2.3%)	12 (4.7%)	30 (3.9%)
> 4 to ⩽ 12	19 (7.5%)	23 (8.9%)	9 (3.5%)	51 (6.6%)
> 12 to ⩽ 24	29 (11.4%)	61 (23.6%)	15 (5.9%)	105 (13.7%)
> 24 to ⩽ 36	39 (15.4%)	16 (6.2%)	128 (50.0%)	183 (23.8%)
> 36 to ⩽ 52	26 (10.2%)	110 (42.6%)	0	136 (17.7%)
> 52	129 (50.8%)	0	0	129 (16.8%)
Treatment duration in extension study (weeks)[a]				
n	163	149	164	476
Mean (SD)	26.19 (6.757)	23.56 (9.478)	24.65 (8.769)	24.83 (8.432)
Median	28.71	28.29	28.36	28.43
Min, Max	0.1, 35.9	0.1, 31.3	0.1, 32.1	0.1, 35.9
Treatment duration category in extension study (weeks),[a] n (%)				
⩽ 4	6 (2.4%)	11 (4.3%)	12 (4.7%)	29 (3.8%)
> 4 to ⩽ 12	5 (2.0%)	14 (5.4%)	9 (3.5%)	28 (3.6%)
> 12 to ⩽ 28	38 (15.0%)	36 (14.0%)	42 (16.4%)	116 (15.1%)
> 28	114 (44.9%)	88 (34.1%)	101 (39.5%)	303 (39.5%)

Abbreviations: E2 = estradiol; n = number of patients included in summary statistics; N = number of patients in the treatment group; NETA = norethindrone acetate; SD = standard deviation.
Treatment duration in weeks is calculated as (date of last dose - date of first dose + 1) / 7.
For patients enrolled in the extension study (MVT-601-3003), two treatment durations were calculated separately based on two dates of first dose, one for the date of the first dose in the parent study, one for the date of first dose in the extension study. The date of last dose is the date of last dose in the extension study.
[a]Only applies for patients enrolled in extension study.

In the uterine fibroids long-term safety population (studies MVT-601-3001, MVT-601-3002, MVT-601-3003), the mean duration of treatment exposure to relugolix combination therapy was 37.81 weeks. Mean exposure was similar in the relugolix + E2/NETA (39.22 weeks) and placebo (38.96 weeks) groups and shorter in the relugolix + delayed E2/NETA group (35.28 weeks). This difference is due to early discontinuations associated with the initial 12 weeks of relugolix monotherapy.

Mean duration of exposure to combination therapy across all groups was 31.97 weeks. This includes 129 patients who had exposure to more than 52 weeks of relugolix combination therapy. Across the three groups, 448 patients had exposure to more than 24 weeks of relugolix combination therapy.

Approximately 80% of patients who started the two pivotal phase 3 studies completed the study and of those who completed the study approximately 80% entered the extension study MVT-601-3003. Mean overall exposure during the extension study was 24.83 weeks (median 28.43 weeks) and was in line with between groups with the longest mean duration of treatment exposure in the relugolix + E2/NETA group (26.19 weeks).

Adverse events (24 weeks placebo-controlled)

- ***Treatment-emergent adverse events***

An overall summary of adverse events in the Uterine Fibroids 24-Week Combination Therapy Safety Population is presented below:

Table: Overall Summary of Adverse Events: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002)

Patients with ≥ 1 adverse event, n (%)	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Any	155 (61.0%)	186 (72.1%)	160 (62.5%)
Leading to study treatment discontinuation	10 (3.9%)	30 (11.6%)	11 (4.3%)
Leading to study treatment interruption	3 (1.2%)	3 (1.2%)	4 (1.6%)
Related to study drug	92 (36.2%)	144 (55.8%)	66 (25.8%)
Grade 2 or above	86 (33.9%)	108 (41.9%)	80 (31.3%)
Grade 2 or above related to study drug	46 (18.1%)	67 (26.0%)	21 (8.2%)
Serious adverse event	8 (3.1%)	5 (1.9%)	6 (2.3%)
Serious and related to study drug	2 (0.8%)	0	0
Serious and leading to study treatment discontinuation	0	0	1 (0.4%)
Fatal outcome	0	0	0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate.
Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.
Related adverse events are those rated by the investigators as possibly or probably related to study drug. Adverse events related to any one of the study drug treatments are considered related to study drug.
Patients with multiple events are counted once.

The overall incidence of adverse events was comparable between the relugolix + E2/NETA group (61.0%) and the placebo group (62.5%) but higher in the relugolix + delayed E2/NETA group (72.1%). Adverse events leading to study treatment discontinuations were reported at similar rates in the relugolix + E2/NETA group (3.9%) and the placebo group (4.3%), but at a higher rate in the relugolix + delayed E2/NETA group

(11.6%). This pattern continued for grade 2 or above adverse events, with similar incidences in the relugolix + E2/NETA group (33.9%) and the placebo group (31.3%), and a higher incidence in the relugolix + delayed E2/NETA group (41.9%).

The higher incidence in the latter group was due to the relugolix monotherapy treatment period (12 weeks) leading to a higher number of AEs related to postmenopausal symptoms, see discussion below on drug-related adverse events.

- ***Frequency of adverse events 24 weeks***

A summary of adverse events reported in at least 2% of patients in any treatment group and reported more frequently in any active group compared with placebo is presented in the table below:

Table: Summary of Adverse Events Reported in at Least 2% of Patients in Any Treatment Group and More Than Placebo Group by Preferred Term: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT 601-3001, MVT-601-3002)

	Relugolix 40 mg+E2/NETA	Relugolix 40 mg+Delayed E2/ NETA	Placebo
Preferred Term	**(N = 254)**	**(N = 258)**	**(N = 256)**
Patients with ≥ 1 adverse event, n (%)	155 (61.0%)	186 (72.1%)	160 (62.5%)
Headache	25 (9.8%)	42 (16.3%)	34 (13.3%)
Hot flush	21 (8.3%)	91 (35.3%)	15 (5.9%)
Hypertension	12 (4.7%)	10 (3.9%)	4 (1.6%)
Alopecia	9 (3.5%)	9 (3.5%)	2 (0.8%)
Abdominal pain	9 (3.5%)	5 (1.9%)	4 (1.6%)
Back pain	7 (2.8%)	10 (3.9%)	9 (3.5%)
Menorrhagia	7 (2.8%)	6 (2.3%)	1 (0.4%)
Libido decreased	7 (2.8%)	5 (1.9%)	1 (0.4%)
Irritability	6 (2.4%)	1 (0.4%)	0
Bronchitis	6 (2.4%)	0	4 (1.6%)
Arthralgia	5 (2.0%)	15 (5.8%)	8 (3.1%)
Fatigue	5 (2.0%)	13 (5.0%)	7 (2.7%)
Hyperhidrosis	5 (2.0%)	5 (1.9%)	2 (0.8%)
Dyspepsia	5 (2.0%)	2 (0.8%)	1 (0.4%)
Breast cyst	5 (2.0%)	0	0
Metrorrhagia	5 (2.0%)	6 (2.3%)	1 (0.4%)
Abdominal pain upper	4 (1.6%)	6 (2.3%)	3 (1.2%)
Urinary tract infection	3 (1.2%)	10 (3.9%)	8 (3.1%)
Anxiety	3 (1.2%)	7 (2.7%)	2 (0.8%)
Night sweats	3 (1.2%)	7 (2.7%)	0
Dizziness	1 (0.4%)	9 (3.5%)	8 (3.1%)
Pain in extremity	1 (0.4%)	9 (3.5%)	2 (0.8%)
Migraine	0	6 (2.3%)	1 (0.4%)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate.
Patients with multiple events for a given Preferred term are counted only once for each Preferred term.
MedDRA version 22.0.

For 24 weeks, any adverse events were reported in 61.0% of patients in the relugolix combination group, in 62.5% of patients on placebo and in 72.1% of patients in the relugolix+ delayed E2/NETA group.

The most frequently reported AEs on relugolix combination therapy and more than on placebo are hot flush (8.3% vs. 5.9%, respectively), hypertension (4.7% vs. 1.6%), alopecia (3.5% vs. 0.8%), abdominal pain (3.5% vs. 1.6%), menorrhagia (2.8% vs. 0.4%), libido decreased (2.8% vs. 0.4%), irritability (2.4% vs.

0%), bronchitis (2.4% vs. 1.6%, metrorrhagia (2.0% vs. 0.4), hyperhidrosis (2.0% vs. 0.8%), dyspepsia (2.0% vs. 0.4%), and breast cyst (2.0% vs. 0%).

- ***Drug-related (≥1%) TEAEs 24 weeks***

Any adverse drug reactions (ADRs) were reported in 36.25% of patients in the relugolix combination group, in 25.8% of patients on placebo and in 55.8% of patients in the relugolix+ delayed E2/NETA group. Most adverse events appear to be due to the menopausal state caused by relugolix alone or are due to the disease. A pattern can be observed, that most AEs occurring in the group with 12 weeks menopausal state, which are partly mitigated by the addition of exogenous estradiol.

Study drug-related adverse events reported in at least 1% of patients in the relugolix+E2/NETA group vs placebo were hot flush (7.9 vs 5.5%), headache (7.1 vs 7.0%), nausea (2.8 vs 3.9%), alopecia (2.8 vs 0.8%), menorrhagia (2.8 vs 0%), hypertension (2.4 vs 0.8%), abdominal pain (2.4 vs 0.4%), libido decreased (2.0 vs 0%), hyperhydrosis (2.0 vs 0.8%), anxiety (1.2 vs 0.4%), weight increased (1.2 vs 0.4%), blood creatine phosphokinase increased (1.2 vs 0.4%), insomnia (1.2 vs 0.8%), menstruation irregular (1.2 vs 0.4%), and mood swings (1.2 vs 0%).

Adverse events (52 weeks open label extension)

Note: All subjects in all three groups received relugolix+E2/NETA in this extension period (24-52 weeks). The group-name was what they received in the first 24 weeks of the study.

- ***Treatment-emergent adverse events***

In the relugolix + E2/NETA group, cumulatively over the 52-week treatment period, at least 1 adverse event was reported for 127 patients (77.9%). About half of the patients in this group (89 patients [54.6%]) had 1 adverse event during participation in the open-label extension study. Although half the patients in this group experienced additional events with increased duration of exposure to relugolix + E2/NETA, few patients were reported to have grade 3 or higher events (2.5% during the open-label extension study, 7.4% cumulatively), serious adverse events (0.6% during the open-label extension study, 3.7% cumulatively), and serious events assessed by the investigator as related to study drug (0.6% during the open-label extension study and 1.2% cumulatively).

In the former relugolix + delayed E2/NETA group, at least 1 adverse event was reported for 125 patients (83.9%) over the 52-week treatment period encompassing the parent and open-label extension studies. During participation in the open-label extension study, at least 1 adverse event was reported for 72 patients (48.3%). Patients continued to accrue grade 3 or higher events with increased exposure to relugolix + E2/NETA (7.4% during the open-label extension study and 14.1% cumulatively). Over the 52-week treatment period, serious adverse events were reported for 8 patients (5.4%) with reports occurring in the open-label extension study for 5 patients (3.4%).

In the former placebo group, at least 1 adverse event was reported for 138 patients (84.1%) during the parent and extension studies. During participation in the open-label extension study, at least 1 adverse event was reported for 103 patients (62.8%). Grade 3 or higher events were reported with initial exposure to relugolix + E2/NETA (11.0% during the extension [of which 3.0% were assessed by the investigator as

possibly related to open-label study drug] and 16.5% cumulatively). Over the 52-week treatment period, serious adverse events were reported for 15 patients (9.1%) with reports occurring in the open-label extension study for 11 patients (6.7%). The increased incidence of adverse events observed in the placebo group may have been related to ascertainment bias associated with the open-label nature of the extension study. Investigators and patients were aware that all patients were receiving relugolix combination therapy during this study and may have been more inclined to report adverse events, particularly when those potentially associated with hormonal changes were observed.

- ***Cumulative frequency of adverse events***

In the relugolix + E2/NETA group, cumulatively over the 52-week treatment period, at least 1 adverse event was reported for 127 patients (77.9%). About half of the patients in this group (89 patients [54.6%]) had 1 adverse event during participation in the open-label extension study.

In the former relugolix + E2/NETA group, over the 52-week treatment period in the parent studies and the open-label extension study, the most frequently reported adverse events included Headache (21 patients [12.9%]), Hot flush (18 patients [11.0%]), Nasopharyngitis (14 patients [8.6%]), Pelvic pain (11 patients [6.7%]), Hypertension (11 patients [6.7%]), Back pain (11 patients [6.7%]), Alopecia (10 patients [6.1%]), and Abdominal pain (9 patients [5.5%]). For most of these preferred terms, the adverse events were reported within the first 24 weeks of treatment and generally there was no evidence of a time-dependent increase in events.

Events that increased in incidence during the open-label extension, compared with the first 24 weeks of treatment, included Nasopharyngitis, which was reported for 4 patients (2.5%) during the first 24 weeks and for 10 patients (6.1%) with first onset during the open-label extension study; Dizziness, which was not reported in the first 24 weeks and was reported for 5 patients (3.1%) with first onset during the open-label extension study; Depression, which was reported for 1 patient (0.6%) and 3 patients (1.8%), respectively; and Pelvic pain, which was reported for 4 patients (2.5%) and 7 patients (4.3%), respectively.

- ***Drug-related (≥2%) TEAEs***

In the former relugolix + E2/NETA group, adverse events assessed as related to relugolix or E2/NETA were reported for 73 patients (44.8%). Over the 52-week treatment period in the parent studies and the open-label extension study, the most frequently reported adverse events assessed as related to study drug included Hot flush (18 patients [11.0%]) and Headache (15 patients [9.2%]). Of the patients with a reported event of Hot flush over the course of the 52-week treatment period, the event was first reported during the open-label extension study in 4 patients (2.5%). Of the patients with a reported event of Headache over the course of the 52-week treatment period, the event was first reported during the open-label extension study in 2 patients (1.2%). Of note, the incidence of adverse events of headache over 52 weeks in the relugolix + E2/NETA group was lower than that observed with placebo over the first 24 Weeks (13.3%).

In the former relugolix + delayed E2/NETA group, adverse events assessed as related to relugolix or E2/NETA were reported for 94 patients (63.1%). Over the 52-week treatment period in the parent studies and the open-label extension study, the most frequently reported adverse events assessed as related to study drug included Hot flush (55 patients [36.9%]) and Headache (20 patients [13.4%]). None of the Hot flush events were first reported during the open-label extension study. Of the patients with a reported event of Headache

over the course of the 52-week treatment period, the event was first reported during the open-label extension study in 1 patient (0.7%).

In the former placebo group, adverse events assessed as related to relugolix or E2/NETA were reported for 74 patients (45.1%). Over the 52-week treatment period in the parent studies and the open-label extension study, the most frequently reported adverse events assessed as related to study drug included Hot flush (21 patients [12.8%]) and Headache (18 patients [11.0%]). Of the patients with a reported event of Hot flush over the course of the 52-week treatment period, the event was first reported during the open-label extension study in 11 patients (6.7%). Of the patients with a reported event of Headache over the course of the 52- week treatment period, the event was first reported during the open-label extension study in 8 patients (4.9%).

Adverse events withdrawal study MVT-601-035 (104 weeks)

The frequency of adverse events over an additional 52 weeks of treatment is summarized below by treatment group. In the relugolix + E2/NETA group, women received relugolix combination therapy as blinded treatment or open label as rescue, after their MBL volume reached ≥ 80 mL. In the placebo group, women received placebo initially, and most transitioned to open-label as rescue relugolix + E2/NETA after their MBL volume reached ≥ 80 mL. Therefore, adverse event data in the placebo group are reflective of the sequence of placebo followed by relugolix + E2/NETA in most patients, which limits safety comparisons between groups. The mITT population is for efficacy data analysis according to randomized treatment, and the Safety population is for safety data analysis according to the actual treatment received. Both populations have the same total of patients (n = 228). Since one patient was randomized to placebo and was treated with relugolix + E2/NETA, she was counted as part of the safety population.

- ***Treatment-emergent adverse events***

Adverse events were reported in a similar proportion of women in both treatment groups (58.6% in the relugolix+E2/NETA group and 64.3% in the placebo group). AEs leading to discontinuation, AEs grade 3 or higher, and SAEs were reported infrequently and with generally similar frequency in both treatment groups. AEs in 22% to 24% of women were considered related to the study drug. No adverse events with fatal outcome were reported in this study.

Table: Overall Summary of Adverse Events (Safety Population MVT-601-035)

No. of Patients With at Least one AE n (%)	Relugolix+E2/NETA (N = 116)	Placebo (N = 112)
Any	68 (58.6%)	72 (64.3%)
Leading to study treatment discontinuation	2 (1.7%)	3 (2.7%)
Leading to study treatment interruption	1 (0.9%)	0
Related to study drug	26 (22.4%)	27 (24.1%)
Grade 3 or higher	3 (2.6%)	5 (4.5%)
Grade 3 or higher related to study drug	0	2 (1.8%)
Serious	2 (1.7%)	2 (1.8%)
Serious and related to study drug	0	1 (0.9%)
Serious and leading to treatment discontinuation	1 (0.9%)	1 (0.9%)
Fatal outcome	0	0

Date of database lock: 17 Mar 2021.
Abbreviations: AE = adverse event; E2 = estradiol; N = number of patients in the treatment group; n=number of patients with AE; NETA = norethindrone acetate.

Percentages are based on the total number of patients in each treatment group at time of randomization.
Adverse event grades are evaluated based on NCI-CTCAE (version 5).
Relationship to treatment was assessed by the investigators as possibly or probably related to study drug.
Patients with multiple events are counted once for each category.

- ***Frequency of adverse events 104 weeks***

The most frequently (≥ 3%) reported adverse events in patients taking relugolix + E2/NETA during 52 additional weeks of treatment were nasopharyngitis, headache, back pain, arthralgia, breast pain, cellulitis, and sinusitis.

Table: AEs by Decreasing Frequency ⩾ 3% in Any Group of Preferred Terms (Safety Population)

Preferred term	Relugolix+E2/NETA (N = 116)	Placebo (N = 112)
No. of patients with at least one AE n (%)	68 (58.6%)	72 (64.3%)
Nasopharyngitis	13 (6.9%)	12 (10.6%)
Headache	8 (6.9%)	5 (4.5%)
Backpain	5 (4.3%)	5 (4.5%)
Arthralgia	4 (3.4%)	2 (1.8%)
Breast pain	4 (3.4%)	0
Cellulitis	4 (3.4%)	0
Sinusitis	4 (3.4%)	2 (1.8%)
Pelvic pain	3 2.6%)	4 (3.6%)
Abdominal pain lower	2 (1.7%)	4 (3.6%)
Breast tenderness	2 (1.7%)	5 (4.5%)
Dysmenorrhoea	2 (1.7%)	8 (7.1%)
Hot flush	2 (1.7%)	8 (7.1%)
Hypertension	2 (1.7%)	6 (5.4%)
Upper respiratory tract infection	2 (1.7%)	6 (5.4%)
Anxiety	1 (0.9%)	4 (3.6%)
Urinary tract infection	1 (0.9%)	4 (3.6%)
Bronchitis	0	5 (4.5%)
Menorrhagia	0	5 (4.5%)

Date of database lock: 17 Mar 2021.
Abbreviations: AE = adverse event; E2 = estradiol; N = number of patients in the treatment group; n=number of patients with AE; NETA = norethindrone acetate. Percentages are based on the total number of patients in each treatment group. Patients with multiple events for a given preferred term are counted only once for each preferred term. Events are sorted by decreasing frequency of preferred term in the relugolix + E2/NETA treatment group.
MedDRA (version 22.0).

- ***Drug-related (≥1%) TEAEs 104 weeks***

In total, 26 (22.4%) in relugolix + E2/NETA and 27 (24.1%) of AES were considered treatment-related by the Investigator. No details were provided in this summary.

- ***Serious TEAEs and deaths 104 weeks***

Serious adverse events were reported for 4 patients, two (1.7%) in the relugolix + E2/NETA group and two (1.8%) in the placebo group as randomized. SAEs in the relugolix + E2/NETA group consisted of non-drug-related worsening anaemia, breast cancer. The 2 SAEs in the placebo-group consisted of myxoid liposarcoma,

and a transient global amnesia assessed of which the latter was assessed as possibly related to study drug by the investigator.

Description of Selected Adverse Reactions

- ***Vasomotor Symptoms Including Hot Flush and Night Sweats***

First 24 weeks (placebo-controlled)

The incidence of vasomotor symptoms through Week 24 is presented below:

Table: Vasomotor Symptoms by Preferred Term: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002)

Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Patients with ≥ 1 adverse event of vasomotor symptom, n (%)	27 (10.6%)	95 (36.8%)	17 (6.6%)
Hot flush	21 (8.3%)	91 (35.3%)	15 (5.9%)
Hyperhidrosis	5 (2.0%)	5 (1.9%)	2 (0.8%)
Night sweats	3 (1.2%)	7 (2.7%)	0
Flushing	0	1 (0.4%)	0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate.
Patients with multiple events for a given preferred term are counted only once for each preferred term.
Vasomotor symptoms includes preferred terms of hyperhidrosis, feeling hot, hot flush, night sweats, and flushing.

Hot flush was the most common drug-related adverse event reported. The difference between relugolix monotherapy (relugolix + delayed E2/NETA group, 12 weeks) and relugolix combination therapy (7.9% versus 36%) was statistically different ($p < 0.0001$) and indicates that the addition of E2/NETA can considerably reduce the frequency of postmenopausal symptoms.

Extension period (all patients received relugolix+E2/NETA)

In this population with relugolix combination treatment up to 52 weeks, in addition to the events described above in the Uterine Fibroids 24 Week Safety Population, vasomotor symptoms were reported for 4 new patients in the relugolix + E2/NETA group, no new patients in the relugolix + delayed E2/NETA group, and 15 new patients in the placebo group. These included adverse events of hot flush (4 patients) in the relugolix + E2/NETA group and adverse events of hot flush (13 patients) and night sweats (3 patients) in the placebo group.

One event of hot flush led to study drug discontinuation in a patient in the placebo group (MVT-601-3003).

- ***Abdominal Pain***

First 24 weeks (placebo-controlled)

Adverse events associated with abdominal pain were reported for 7.5% of patients treated with relugolix combination therapy and 5.9% of patients treated with placebo. The terms of abdominal pain and pelvic pain were the most frequently reported.

Table: Adverse Events Category - Abdominal Pain: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT 601-3001, MVT-601-3002)

Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Patients with ≥ 1 adverse event of abdominal pain, n (%)	19 (7.5%)	12 (4.7%)	15 (5.9%)
Abdominal pain	9 (3.5%)	5 (1.9%)	4 (1.6%)
Pelvic pain	5 (2.0%)	3 (1.2%)	6 (2.3%)
Abdominal pain lower	2 (0.8%)	2 (0.8%)	4 (1.6%)
Dysmenorrhoea	1 (0.4%)	1 (0.4%)	5 (2.0%)
Uterine pain	1 (0.4%)	1 (0.4%)	0
Abdominal tenderness	1 (0.4%)	0	0

Abbreviations:
E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate.
Patients with multiple events for a given Preferred term are counted only once for each Preferred term.
Abdominal pain includes Preferred terms of abdominal pain, abdominal pain lower, pelvic pain, dysmenorrhoea, uterine pain, abdominal tenderness, and abdominal discomfort.

Extension period (all patients received relugolix+E2/NETA)

Over the 52 weeks of pelvic and abdominal pain were reported for 24 patients (14.7%) in the relugolix + E2/NETA group. None of the events were serious. The events resolved in all but 3 patients and none led to discontinuation in either the parent or open-label extension studies. In the relugolix + delayed E2/NETA group, 16 patients (10.7%) were reported to have adverse events of abdominal pain, all non-serious, and only one leading to withdrawal. In the placebo group, 16 patients (9.8%) were reported to have adverse events of abdominal pain, 11 patients during the parent study and 5 patients (3.0%) during the openlabel extension study. One led to discontinuation. In summary, nonserious events related to pelvic and abdominal pain were reported in patients treated with relugolix + E2/NETA. The events generally resolved on treatment and rarely led to discontinuation.

- ***Alopecia***

First 24 weeks (placebo-controlled)

Adverse events of alopecia were reported more frequently in the relugolix + E2/NETA group compared with the placebo group (3.5% vs. 0.8%, respectively). In general, alopecia adverse events were grade 1 or 2 in severity. For two of nine patients treated with relugolix + E2/NETA for whom alopecia was reported, the adverse event resolved while the patients were still on study drug. No patients in the relugolix + E2/NETA group discontinued from the study due to an adverse event of alopecia compared with one patient in the placebo group and two patients in the relugolix + delayed E2/NETA group.

Extension period (all patients received relugolix+E2/NETA)

During the phase 3 long-term extension study MVT-601-3003, there were 7 reports of alopecia, 3 (1.8%) in patients who had previously received relugolix + E2/NETA including 1 patient with recurrent alopecia, 1

(0.7%) in a patient who had previously received relugolix + delayed E2/NETA, and 3 (1.8%) in patients who had previously received placebo. Outcome was not resolved in 4 of 7 cases. Study drug was withdrawn in 2 cases, and no action was taken with regard to study drug for the other 5 cases.

- ***Libido Decreased***

First 24 weeks (placebo-controlled)

Adverse events of libido decreased were reported for 2.8% of patients who received relugolix combination therapy and 0.4% of patients who received placebo. Adverse events of libido decrease were generally grade 1 and 2 in severity and did not lead to discontinuation in either group. One patient discontinued due to libido decreased in the relugolix + delayed E2/NETA group). None was reported as a serious adverse event.

Extension period (all patients received relugolix+E2/NETA)

During the phase 3 long-term extension study MVT-601-3003, there were 12 reports of study-drug related libido decreased, 3 (1.8%) in patients who had previously received relugolix + E2/NETA, 6 (4.0%) in a patient who previously received relugolix + delayed E2/NETA, and three (1.8%) in patients who had previously received placebo.

- ***Irritability***

First 24 weeks (placebo-controlled)

Adverse events of irritability were reported for 2.4% of patients in the relugolix + E2/NETA group and none in the placebo group. Adverse events of irritability were generally grade 1 and 2 in severity, and none was reported as a serious adverse event. One patient who received relugolix combination therapy discontinued due to an adverse event of irritability.

Extension period (all patients received relugolix+E2/NETA)

During the phase 3 long-term extension study MVT-601-3003, there were 4 reports of study-drug related irritability, 2 (1.2%) in patients who had previously received relugolix + E2/NETA, 1 (0.7%) in a patient who previously received relugolix + delayed E2/NETA, and 1 (0.6%) in patients who had previously received placebo.

- ***Breast Cysts***

First 24 weeks (placebo-controlled)

Breast cyst was reported for 5 patients (2.0%; rounded up from 1.96% and therefore not included in the table below) in the relugolix + E2/NETA group and none in the placebo group. Although simple breast cysts are common (up to 37.5% prevalence) in the female population aged 35 to 50 years (Brenner et al. 1994), adverse events of breast cyst are described herein given the difference between groups, the plausible temporal relationship, and the potential for influence of estrogen and progestins on breast cyst development. Of the five adverse events reported, three were grade 1 and two were grade 2, one led to discontinuation of study drug, four were considered related to study drug by the investigator, and none were reported as a serious adverse event.

Extension period (all patients received relugolix+E2/NETA)

During the phase 3 long-term extension study MVT-601-3003, there were 2 (1.2%) reports of study-drug related breast cyst, in patients who had previously received relugolix + E2/NETA.

- ***Dyspepsia***

First 24 weeks (placebo-controlled)

Dyspepsia is reviewed in consideration of the temporal relationship, and the potential for estrogens and progesterone to reduce the lower esophageal sphincter pressure (Fisher et al. 1978).

Dyspepsia was reported for 2.0% of patients in the relugolix + E2/NETA group and 0.4% of patients in the placebo group. Given the onset of mild to moderate dyspepsia within the first 2 months of treatment, albeit at low frequency, and the biological plausibility, dyspepsia is conservatively assessed as an adverse drug reaction.

Extension period (all patients received relugolix+E2/NETA)

During the phase 3 long-term extension study MVT-601-3003, there were 3 reports of study-drug related dyspepsia, 2 (1.2%) in patients who had previously received relugolix + E2/NETA, and 1 (0.7%) in a patient who previously received relugolix + delayed E2/NETA.

- ***Hypertension***

First 24 weeks (placebo-controlled)

A summary of hypertension-related adverse events in the uterine fibroids 24-week combination therapy safety population by PT is presented below.

Table: Adverse Event Category: Hypertension by Decreasing Frequency of Preferred Term: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002)

Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Patients with ≥ 1 adverse event of hypertension, n (%)	14 (5.5%)	12 (4.7%)	7 (2.7%)
Hypertension	12 (4.7%)	10 (3.9%)	4 (1.6%)
Blood pressure increased	1 (0.4%)	2 (0.8%)	1 (0.4%)
Essential hypertension	1 (0.4%)	0	0
Blood pressure diastolic increased	0	0	1 (0.4%)
Hypertensive crisis	0	0	1 (0.4%)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate.
Patients with multiple events for a given Preferred term are counted only once for each Preferred term.
Hypertension includes hypertension SMQ (narrow).
MedDRA version 22.0.

The overall frequency of hypertension for relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo was 5.5%, 4.7%, and 2.7%, respectively. The differences that were observed between study groups were not considered clinically relevant, however although hypertension may a comorbidity in a part of this population, it is not seen in the placebo group. Additionally, a dose-related increase in blood pressure was seen in earlier studies, albeit in higher doses. Therefore, a possible causal relationship is suggested.

Based on this, a warning has been added to the product information on the occurrence of hypertension.

52 weeks extension period (all patients received relugolix+E2/NETA)

Adverse events associated with hypertension were reported for a total of 12 patients (7.4%) in the relugolix + E2/NETA group, 8 patients (5.4%) in the former relugolix + delayed E2/NETA group, and 15 patients (9.1%) in the former placebo group. In the open-label extension study, new adverse events associated with hypertension were reported for 2 patients (1.2%) in the relugolix + E2/NETA group, 3 patients (2.0%) in the former relugolix + delayed E2/NETA group, and 11 patients (6.7%) in the former placebo group.

Hypertension events were reported for a total of 16 patients during the open-label extension study. All 16 patients had risk factors or pre-existing evidence of elevated blood pressure and 4 of the patients in the placebo group had pre-existing hypertension. Onset of the events was not temporally associated with initiation of open-label treatment with relugolix + E2/NETA in any of the cases.

Safety parameters of interest

Bone Mineral Density (BMD)

Adverse events related to loss of BMD

First 24 weeks (placebo-controlled)

A summary of all adverse events related to loss of BMD reported in the Uterine Fibroids 24-Week Combination Therapy Safety Population by PT is presented below.

Table: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002)

Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Patients with ≥ 1 adverse event of loss of bone mineral density, n (%)	2 (0.8%)	6 (2.3%)	3 (1.2%)
Ankle fracture	1 (0.4%)	1 (0.4%)	0
Avulsion fracture	1 (0.4%)	0	0
Wrist fracture	1 (0.4%)	0	0
Bone density decreased	0	4 (1.6%)	0
Bone loss	0	1 (0.4%)	0
Facial bones fracture	0	0	1 (0.4%)
Osteopenia	0	0	1 (0.4%)
Radius fracture	0	0	1 (0.4%)

Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)

Abbreviations:
E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate.
Patients with multiple events for a given Preferred term are counted only once for each Preferred term.
Loss of bone mineral density includes osteoporosis/osteopenia SMQ (broad) and fracture (custom SMQ) which with all Preferred terms including the term "fracture," excluding "Tooth fracture" and "Fracture of penis".

In the uterine fibroids 24-week combination therapy safety population, adverse events related to loss in bone mass were most commonly reported in the relugolix + delayed E2/NETA group compared with the relugolix + E2/NETA and placebo groups. The incidence of adverse events related to bone loss in the relugolix + E2/NETA and placebo groups was similar. The most commonly reported adverse event in this SMQ was bone density decreased in the relugolix + delayed E2/NETA group (4 patients; 1.6%) similar to what was observed with the Uterine Fibroid 12-Week Monotherapy Population. Adverse events of fracture were reported with similar frequency in all groups.

Week 52 extension period (all patients received relugolix+E2/NETA)

A summary of all adverse events related to loss of BMD reported in the uterine fibroids long-term combination therapy safety population is presented below:

Table: Adverse Event Category - Loss of Bone Mineral Density by Decreasing Frequency of Preferred Term: Uterine Fibroids Long-Term Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002, MVT-601-3003)

Preferred Term	Relugolix 40 mg + E2/NETA (N = 254)	Relugolix 40 mg + Delayed E2/NETA (N = 258)	Placebo (N = 256)	Any Relugolix + E2/NETA (N = 634)
Patients with ≥ 1 adverse event of loss of bone mineral density, n (%)	2 (0.8%)	10 (3.9%)	4 (1.6%)	10 (1.6%)
Ankle fracture	1 (0.4%)	2 (0.8%)	0	2 (0.3%)
Wrist fracture	1 (0.4%)	1 (0.4%)	0	2 (0.3%)
Avulsion fracture	1 (0.4%)	0	0	1 (0.2%)
Bone density decreased	0	4 (1.6%)	0	3 (0.5%)
Osteopenia	0	1 (0.4%)	1 (0.4%)	1 (0.2%)
Bone loss	0	1 (0.4%)	0	0
Forearm fracture	0	1 (0.4%)	0	1 (0.2%)
Tibia fracture	0	1 (0.4%)	0	1 (0.2%)
Facial bones fracture	0	0	2 (0.8%)	1 (0.2%)
Radius fracture	0	0	1 (0.4%)	0

Preferred Term	Relugolix 40 mg + E2/NETA (N = 254)	Relugolix 40 mg + Delayed E2/NETA (N = 258)	Placebo (N = 256)	Any Relugolix + E2/NETA (N = 634)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate; SMQ = Standardized MedDRA Query.
Treatment groups were as received in studies MVT-601-3001 and MVT-601-3002.
Any Relugolix + E2/NETA summarizes any adverse events reported in the treatment period of relugolix + E2/NETA

Patients with multiple events for a given preferred term are counted only once for each preferred term.

Events are sorted by decreasing frequency of categories.

For patients treated in relugolix + delayed E2/NETA group, only AEs reported on or after last dose of relugolix 40 mg in monotherapy are reported. For patients treated in placebo group and entered study MVT-601-3003, only AEs reported on or after the first dose in MVT-601-3003 are reported. All AEs are reported for patients treated in relugolix + E2/NETA group.
Loss of bone mineral density includes osteoporosis/osteopenia SMQ (broad) and fracture (custom SMQ) which with all preferred terms including the term "fracture", excluding "Tooth fracture" and "Fracture of penis".
MedDRA version 22.0.

Adverse events potentially related to loss of bone mass were most commonly reported in the relugolix + delayed E2/NETA group compared with the relugolix + E2/NETA and former placebo groups. The incidence of adverse events related to bone loss in the relugolix + E2/NETA and former placebo groups was similar. In the extension study, no additional adverse events were reported in the relugolix + E2/NETA group and one adverse event of facial bones fracture was reported for one patient in the placebo group. The most commonly reported adverse event was bone density decreased in the relugolix + delayed E2/NETA group with no additional reports with additional 6 months of relugolix + E2/NETA exposure in this group. The incidence of adverse events of fracture remained low and generally similar between groups with adverse events reported for two (0.8%) patients in the relugolix + E2/NETA group, five (2.0%) in the relugolix + delayed E2/NETA group (four new reports during the extension study), and three (1.2%) in the former placebo group (one new report in the extension study).

Week 104 (top=line summary withdrawal study)

No fracture events occurred during this 1-year study.

BMD measurements

Week 24 (separate 3001, 3002)

The percent changes in BMD as measured at the lumbar spine and total hip were assessed at Week 12 and Week 24 in studies MVT-601-3001 and MVT-601-3002. Comparisons were made between relugolix monotherapy and relugolix + E2/NETA, based on resuls in the Relugolix + Delayed E2/NETA group. This group initially received relugolix monotherapy, followed by another 12 weeks of relugolix + E2/NETA.

- *BMD measurements at lumbar spine by DXA at 12 and 24 weeks versus relugolix monotherapy:*

In the relugolix monotherapy at 12 weeks (relugolix monotherapy for 12 weeks followed by relugolix + E2/NETA for 12 weeks (relugolix delayed E2/NETA group), bone loss observed in lumbar spine was significantly greater than noted with relugolix+ E2/NETA (-2.0% vs -0.5%, study 601-3001 and -1.9% vs -0.8%, study 601-3002), suggesting the protective effect of this HRT as add-back therapy.

- *BMD measurements by DXA of lumbar spine at 12 weeks and 24 Weeks versus placebo:*

With the addition of E2/NETA only small decreases in BMD between relugolix + E2/NETA versus placebo BMD at the lumbar spine Week 12: −0.5% vs. 0.2%; Week 24: −0.4% vs. 0.1%, study 601-3001; Week 12: -0.8% vs 0.5%, Week 24: -0.1% vs 0.3%, study 601-3002) were noted, which further supports the protective effect. Comparable effects on bone loss were noted in study 601-3002. In total hip measurements a similar pattern was noted, see table on lumbar spine measurements and figures:

- *BMD measurements at **lumbar spine** by DXA at 12 and 24 weeks:*

Table: Studies MVT 601-3001 and MVT-601-3002, Least Square Mean Percent Change from Baseline in Lumbar Spine Bone Mineral Density

	MVT-601-3001			MVT-601-3002		
	Relugolix + E2/NETA (N = 128)	**Relugolix + Delayed E2/NETA (N = 132)**	**Placebo (N = 127)**	**Relugolix +E2/NETA (N = 126)**	**Relugolix + Delayed E2/NETA (N = 126)**	**Placebo (N = 129)**
Week 12						
n	101	103	103	103	95	104
LS mean percent change (95% CI)	-0.5 (-1.04, 0.10)	-2.0 (-2.56, -1.44)	0.2 (-0.36, 0.76)	-0.8 (-1.35, -0.29)	-1.9 (-2.463, -1.374)	0.5 (-0.01, 1.03)
Difference from placebo (95% CI)	-0.7 (-1.40, 0.07)	-2.2 (-2.92, -1.47)		-1.3 (-2.03, -0.625)	-2.4 (-3.14, -1.71)	
Difference from relugolix plus delayed E2/NETA (95% CI)	1.5 (0.79, 2.26)			1.1 (0.38, 1.82)		
Week 24						
n	100	100	102	95	94	95
LS mean percent change (95% CI)	-0.4 (-0.93, 0.22)	-1.8 (-2.39, -1.25)	0.1 (-0.52, 0.62)	-0.1 (-0.71, 0.46)	-2.1 (-2.71, -1.54)	0.3 (-0.27, 0.89)
Difference from placebo (95% CI)	-0.4 (-1.16, 0.34)	-1.9 (-2.61, -1.13)		-0.4 (-1.22, 0.34)	-2.4 (-3.23, -1.65)	
Difference from relugolix plus delayed E2/NETA (95% CI)	1.5 (0.71, 2.21)			2.0 (1.21, 2.99)		

- *BMD measurements at **total hip** by DXA at 12 and 24 weeks:*

Table: Studies MVT 601-3001 and MVT-601-3002, Least Square Mean Percent Change from Baseline in Total Hip Bone Mineral Density

	MVT-601-3001			MVT-601-3002		
	Relugolix + E2/NETA (N = 128)	**Relugolix + Delayed E2/NETA (N = 132)**	**Placebo (N = 127)**	**Relugolix +E2/NETA (N = 126)**	**Relugolix + Delayed E2/NETA (N = 126)**	**Placebo (N = 129)**

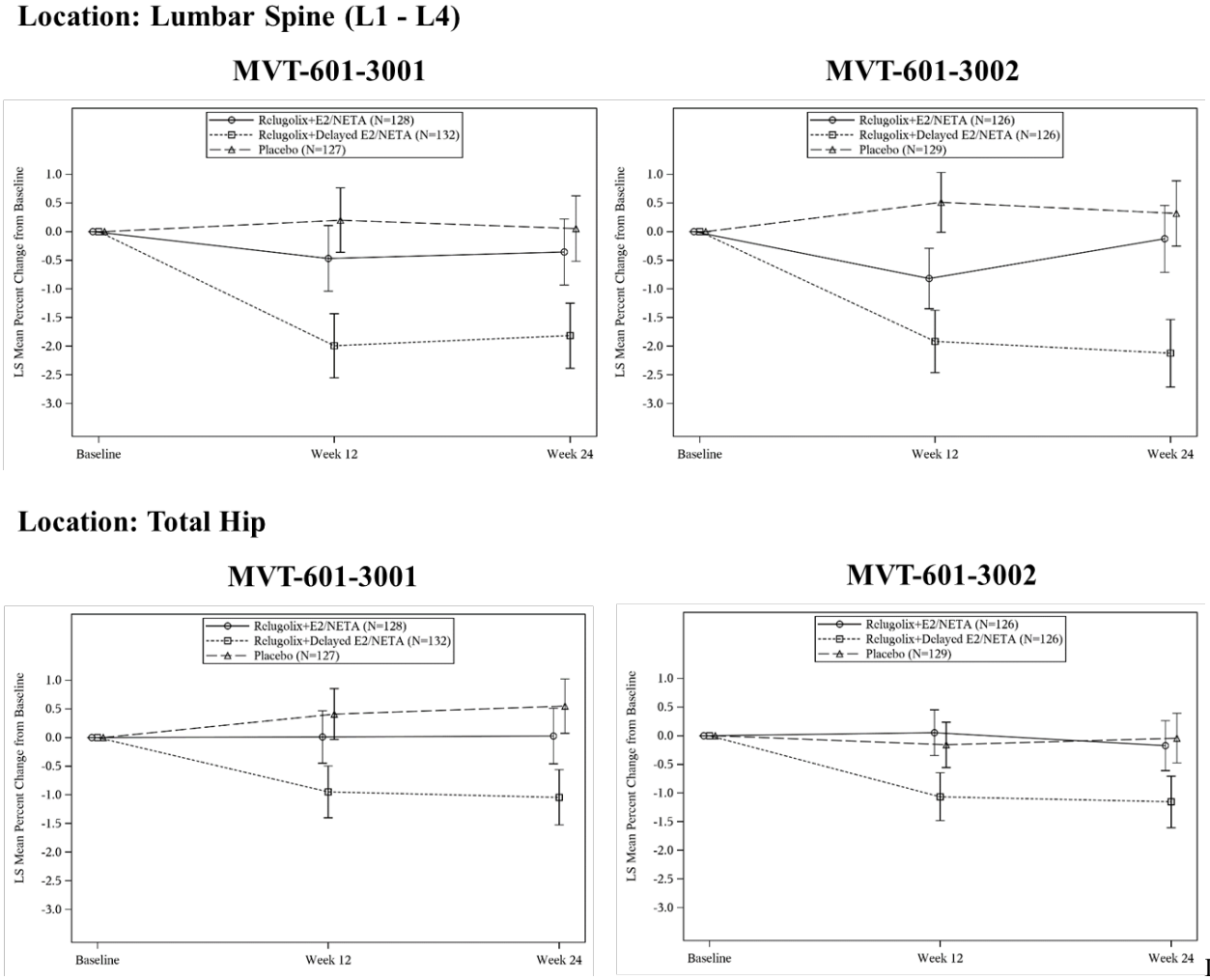
Week 12						
n	102	100	104	104	93	102
LS mean percent change (95% CI)	0.0 (-0.45, 0.47)	-1.0 (-1.40, -0.50)	0.4 (-0.03, 0.85)	0.1 (-0.35, 0.45)	-1.1 (-1.48, -0.65)	-0.2 (-0.56, 0.24)
Difference from placebo (95% CI)	-0.4 (-0.98, 0.18)	-1.4 (-1.94, -0.78)		0.2 (-0.32,0.75)	-0.9 (-1.46, -0.36)	
Difference from relugolix plus delayed E2/NETA (95% CI)	1.0 (0.37, 1.54)			1.1 (0.57, 1.67		
Week 24						
n	100	98	103	98	92	95
LS mean percent change (95% CI)	0.0 (-0.46, 0.51)	-1.0 (-1.52, -0.56)	0.6 (0.08, 1.02)	-0.2 (-0.61, 0.26)	-1.2 (-1.60, -0.71)	-0.0 (-0.48, 0.39)
Difference from placebo (95% CI)	-0.5 (-1.15, 0.10)	-1.6 (-2.22, -0.97)		-0.1 (-0.72, 0.46)	-1.1 (-1.71, -0.51)	
Difference from relugolix plus delayed E2/NETA (95% CI)	1.1 (0.43, 1.70)			1.0 (0.38, 1.58)		

LS mean percent changes from baseline to Week 12 and Week 24 in BMD at the total hip were slightly different in the relugolix + E2/NETA groups in comparison to the placebo groups (Week 12: 0.0% vs. -0.2% and -0.2 vs. 0.0%; Week 24: 0.0% vs. 0.6% and -0.2% vs. 0.0% in studies 601-3001 and 601-3002, respectively).

At Week 12, LS mean percent changes from baseline at the lumbar spine in the relugolix + E2/NETA groups (0.0% and -0.2%) were significantly smaller to those in the relugolix + delayed E2/NETA groups (-1.0% and -1.2%, repsectively), as women in the latter group initially were treated with relugolix monotherapy for the first 12 weeks. (difference of -1.7% and -1.0% at 12 weeks, repectively).

The differences observed between the relugolix + E2/NETA group and the relugolix monotherapy at Week 12 (relugolix+delayed E2/NETA group) at both anatomic locations, support the evidence that treatment with relugolix combination therapy has a protective effect on BMD loss.

Figure: Summary of Mean Percent Change from Baseline to Week 12 and Week 24 in Bone Mineral Density at the Lumbar Spine (L1-L4) and Total Hip (Safety Population)



Date of database lock: MVT-601-3001: 08 May 2019; MVT-601-3002: 16 July 2019.

[1] LS means and the difference in percent change from Baseline at Week 12 and Week 24 based on mixed-effect model with visit, region, Baseline menstrual blood loss volume, age at Baseline, body mass index at Baseline, bone mineral density at Baseline, race and treatment and treatment by visit interaction included as fixed effects. The multiple visits for each patient were the repeated measures as random effect within each patient and an unstructured covariance. Error bars represent 95% CI.

Week 24 (combined 3001+3002)

Table: Percent Change from Baseline in Bone Mineral Density at Lumbar Spine and Total Hip: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001 and MVT-601-3002)

Location Visit Category	Relugolix 40 mg + E2/NETA (N = 254)	Relugolix 40 mg + Delayed E2/NETA (N = 258)	Placebo (N = 256)
Location: Lumbar Spine (L1-L4)			
Week 12			
Percent Change from Baseline in BMD[a]			

Location Visit Category	Relugolix 40 mg + E2/NETA (N = 254)	Relugolix 40 mg + Delayed E2/NETA (N = 258)	Placebo (N = 256)
N	204	198	207
LS Mean Percent Change (SE)	-0.626% (0.1981)	-1.961% (0.1984)	0.342% (0.1941)
(95% CI)	(-1.0149%, -0.2370%)	(-2.3508%, -1.5716%)	(-0.0387%, 0.7236%)
Treatment Comparison			
Difference in LS Mean Percent Changes (SE)[b]	1.335% (0.2621)		
(95% CI)	(0.8205%, 1.8500%)		
p value[c]	< 0.0001		
Difference in LS Mean Percent Changes (SE) vs Placebo	-0.968% (0.2589)	-2.304% (0.2597)	
(95% CI)	(-1.4768%, -0.4600%)	(-2.8136%, -1.7937%)	
Week 24			
Percent Change from Baseline in BMD[a]			
N	195	194	197
LS Mean Percent Change (SE)	-0.233% (0.2076)	-1.972% (0.2070)	0.184% (0.2033)
(95% CI)	(-0.6402%, 0.1750%)	(-2.3784%, -1.5655%)	(-0.2147%, 0.5837%)
Treatment Comparison			
Difference in LS Mean Percent Changes (SE)[b]	1.739% (0.2760)		
(95% CI)	(1.1973%, 2.2814%)		
Difference in LS Mean Percent Changes (SE) vs Placebo	-0.417% (0.2741)	-2.156% (0.2738)	
(95% CI)	(-0.9553%, 0.1211%)	(-2.6940%, -1.6189%)	
Location: Total Hip			
Week 12			
Percent Change from Baseline in BMD[a]			
n	206	193	206
LS Mean Percent Change (SE)	0.014% (0.1531)	-1.016% (0.1554)	0.123% (0.1501)
(95% CI)	(-0.2868%, 0.3145%)	(-1.3212%, -0.7109%)	(-0.1720%, 0.4174%)
Treatment Comparison			
Difference in LS Mean Percent Changes (SE)[b]	1.030% (0.2038)		
(95% CI)	(0.6297%, 1.4300%)		
p value[c]	< 0.0001		
Difference in LS Mean Percent Changes (SE) vs Placebo	-0.109% (0.2000)	-1.139% (0.2029)	
(95% CI)	(-0.5017%, 0.2839%)	(-1.5371%, -0.7404%)	
Week 24			
Percent Change from Baseline in BMD[a]			
n	198	190	198
LS Mean Percent Change (SE)	-0.077% (0.1655)	-1.117% (0.1669)	0.252% (0.1623)
(95% CI)	(-0.4016%, 0.2483%)	(-1.4445%, -0.7889%)	(-0.0662%, 0.5712%)
Treatment Comparison			
Difference in LS Mean Percent Changes (SE)[b]	1.040% (0.2221)		
(95% CI)	(0.6039%, 1.4762%)		
Difference in LS Mean Percent Changes (SE) vs Placebo	-0.329% (0.2190)	-1.369% (0.2209)	
(95% CI)	(-0.7592%, 0.1010%)	(-1.8030%, -0.9353%)	

Location Visit Category	Relugolix 40 mg + E2/NETA (N = 254)	Relugolix 40 mg + Delayed E2/NETA (N = 258)	Placebo (N = 256)

Abbreviations: BMD = bone mineral density; CI = confidence interval; LS mean = least-squares mean; N = number of patients in the treatment group; n = number of patients with a baseline value and a postbaseline value for the given visit; NETA = norethindrone acetate; SE = standard error.
Summary is based on corrected bone mineral density data.
If multiple valid measurements for a visit are present, the measurement closest to the target visit day was used (earliest date in case of ties).
LS means and 95% CIs are based on a mixed-effects model with treatment group, age at baseline, visit, baseline BMD value, stratification factors (geographic region and menstrual blood loss volume), race group, and BMI at baseline as fixed effects using unstructured variance-covariance matrix. Visit is considered as a categorical variable.
a Baseline value is defined as the last measurement on or before the first administration (date and time) of study drug.
b The comparison is the relugolix 40 mg + E2/NETA group versus relugolix 40 mg + delayed E2/NETA group.
c The p-value is based on comparison of the least-squares means difference between relugolix 40 mg + E2/NETA group and relugolix 40 mg + delayed E2/NETA group.

Week 52 (24 week + 28 week extension)

BMD measurements in relugolix + E2/NETA group up to 52 weeks

The focus of the summary of BMD changes for the open-label extension study is on the changes in BMD in **the relugolix + E2/NETA group** (N=163) because this cohort represents longest treatment exposure (those patients who received relugolix + E2/NETA in the initial 24 weeks and entered into the open label extension).

Lumbar spine

As can be seen in the table and figures below, in the relugolix + E2/NETA group, LS mean percent changes from Baseline in BMD to Week 36 and Week 52 at the lumbar spine were -0.726% and -0.804%, respectively.

In the former placebo group, LS mean percent changes from Baseline to Week 36 and Week 52 in BMD at the lumbar spine were -0.246% and -0.775%, respectively.
In the former relugolix + delayed E2/NETA group (N=149), BMD values were -2.274% (Week 12) on relugolix monotherapy and -2.179% (Week 24), - 2.106% (Week 36) and -2.045% (Week 52) after addition of E2/NETA, indicating a slight improvement in BMD after addition of E2/NETA at Week 12, but no recovery of initial BMD loss.

Total hip

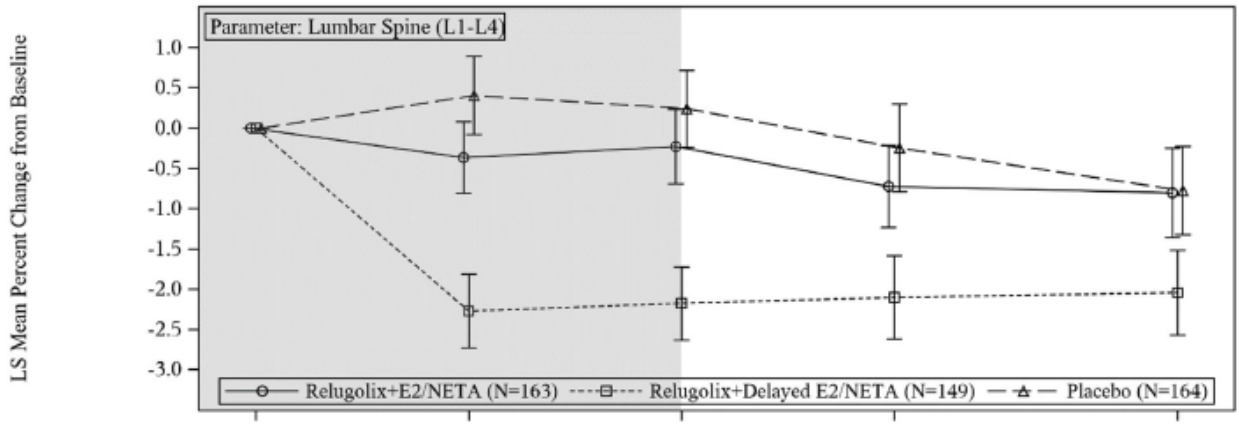
In the relugolix + E2/NETA group LS mean percent changes from Baseline in BMD to Week 36 and Week 52 at the total hip were -0.221% and -0.153%, respectively. In the former placebo group, LS mean percent changes in BMD from Baseline to Week 36 and Week 52 at the total hip were 0.187% and -0.065%, respectively. The former relugolix + delayed E2/NETA group showed LS mean percent changes from Baseline to Week 36 and Week 52 of -0.986% and -0.842%, respectively.

Table: Least Squares Mean Percent Change from Baseline in Bone Mineral Density (Extension Safety Population)

	Relugolix + E2/NETA (N = 163)	Relugolix + Delayed E2/NETA (N = 149)	Placebo (N = 164)
Lumbar spine (L1 - L4)			
Baseline			
N	163	149	164
LS Mean	1.194	1.219	1.251
(95% CI)	(1.1663, 1.2219)	(1.1884, 1.2492)	(1.2223, 1.2796)
Week 12			
N	145	137	146
LS mean percent change	-0.368	-2.274	0.403
(95% CI)	(-0.8117, 0.0757)	(-2.7279, -1.8192)	(-0.0811, 0.8866)
Week 24			
N	153	144	156
LS mean percent change	-0.229	-2.179	0.241
(95% CI)	(-0.6930, 0.2358)	(-2.6309, -1.7266)	(-0.2342, 0.7164)
Week 36			
N	145	120	138
LS mean percent change	-0.726	-2.106	-0.246
(95% CI)	(-1.2329, -0.2185)	(-2.6225, -1.5889)	(-0.7906, 0.2983)
Week 52			
N	132	108	120
LS mean percent change	-0.804	-2.045	-0.775
(95% CI)	(-1.3578, -0.2503)	(-2.5748, -1.5155)	(-1.3246, -0.2261)
Total hip			
Baseline			
N	163	149	164
LS Mean	1.053	1.061	1.082
(95% CI)	(1.0310, 1.0745)	(1.0372, 1.0847)	(1.0582, 1.1050)
Week 12			
N	146	131	145
LS mean percent change	0.065	-0.950	0.465
(95% CI)	(-0.3349, 0.4656)	(-1.3154, -0.5845)	(0.0924, 0.8376)
Week 24			
N	155	142	156
LS mean percent change	0.031	-1.011	0.609
(95% CI)	(-0.3609, 0.4231)	(-1.3664, -0.6547)	(0.2037, 1.0146)
Week 36			
N	147	122	137
LS mean percent change	-0.221	-0.986	0.187
(95% CI)	(-0.6117, 0.1691)	(-1.3963, -0.5750)	(-0.2024, 0.5758)
Week 52			
N	129	105	121
LS mean percent change	-0.153	-0.842	-0.065
(95% CI)	(-0.6148, 0.3085)	(-1.2983, -0.3856)	(-0.4772, 0.3469)

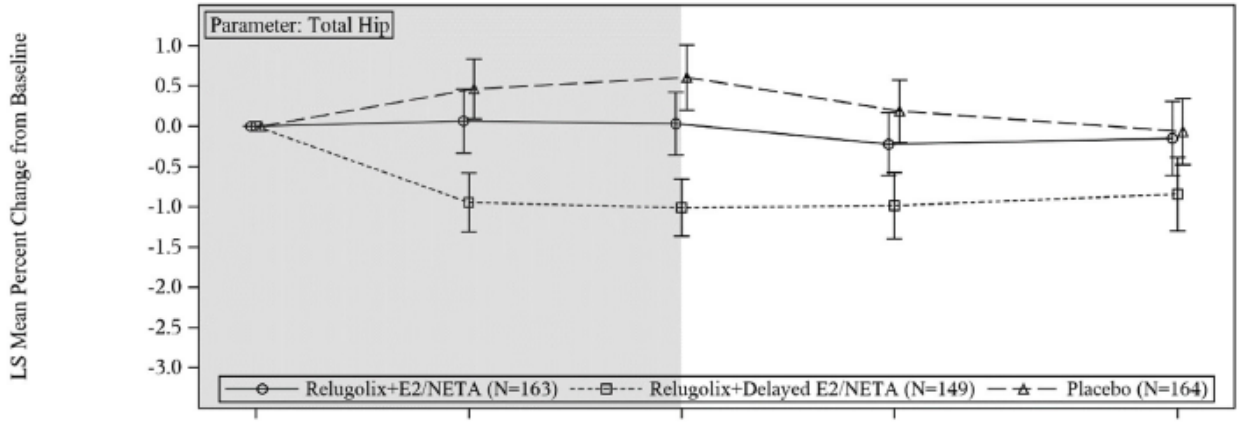
Abbreviations: CI = confidence interval; E2 = estradiol; LS = least squares; n = number of patients in subset; N = number of patients; NETA = norethindrone acetate.
Source: Table 8.3.12.2.

Figure: Least Squares Mean Percent Change from Baseline to Week 52 in Bone Mineral Density at the Lumbar Spine (L1 - L4) (Upper) and Total Hip (Lower) (Extension Safety Population)



No. of Patients

	Baseline	Week 12	Week 24	Week 36	Week 52
R+E2/NETA	163	145	153	145	132
R+Delayed E2/NETA	149	137	144	120	108
Placebo	164	146	156	138	120



No. of Patients

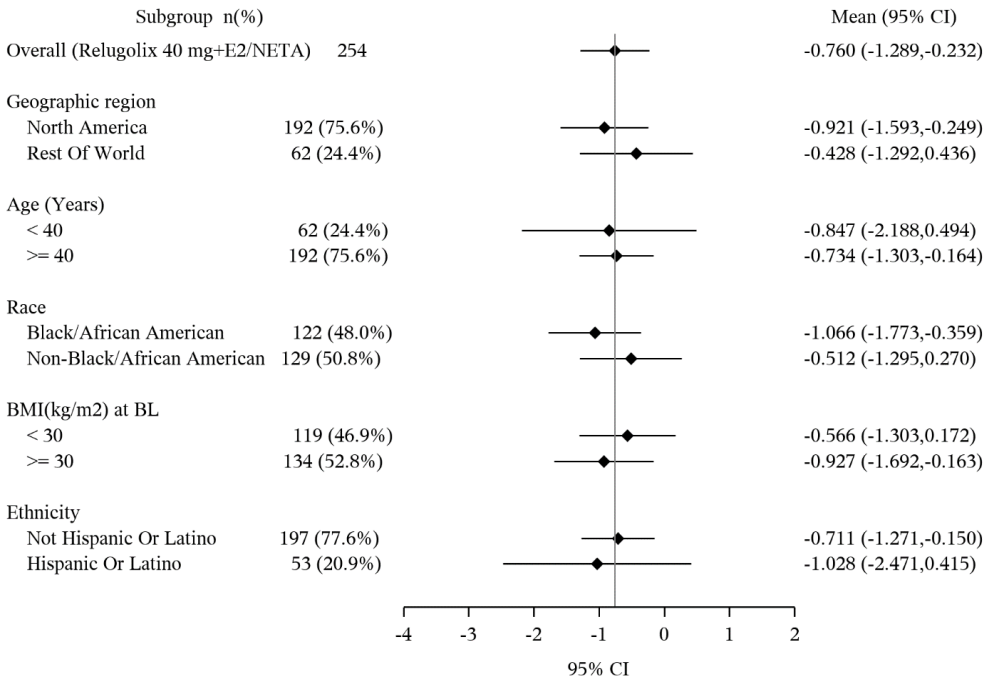
	Baseline	Week 12	Week 24	Week 36	Week 52
R+E2/NETA	163	146	155	147	129
R+Delayed E2/NETA	149	131	142	122	105
Placebo	164	145	156	137	121

Abbreviations: E2 = estradiol; LS = least squares; N = number of patients; NETA = norethindrone acetate; R = relugolix.
Note: Error bars represent 95% CIs.
Note: Shaded area represents time in parent studies.
Source: Figure 8.3.15.7.

BMD measurements in subgroups week 52

BMD and mean percent changes in BMD were provided for the following subgroups. The following figure presents the subgroup analyses for percent change in bone mineral density loss at Week 52 in the Relugolix + E2/NETA Treatment Group - Lumbar Spine:

Table: Subgroup analyses for percent change in bone mineral density loss at Week 52 in the Relugolix + E2/NETA Treatment Group - Lumbar Spine: Uterine Fibroids Long-Term Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002, MVT-601-3003)



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.

Trends in percent change from baseline in BMD in each subgroup were generally comparable with the overall population at Week 52 in the lumbar spine.

Natural history BMD measurements in study MVT-601-034

Study MVT-601-034 was an observational study evaluating BMD in women with uterine fibroids or endometriosis to characterize longitudinal BMD of premenopausal women aged 18-50 years with uterine fibroids or endometriosis over a 52 week observational period. This natural history study is conducted to support assessment of the long-term effects on BMD with relugolix combination therapy, by enrolling an age-matched concurrent reference group of women with uterine fibroids or endometriosis not receiving GnRH receptor agonists or antagonists, in whom BMD is assessed every 6 months for one year.

The primary objectives of this observational study were to characterize longitudinal assessment of BMD (lumbar spine [L1-L4], femoral neck, and total hip) in a concurrent cohort of premenopausal women, enrolled at the same sites as the pivotal studies and age-matched with the population of women with uterine fibroids or endometriosis in the pivotal studies.

The following two cohorts were recruited:

1. Premenopausal women with uterine fibroids confirmed by an ultrasound;
2. Premenopausal women with endometriosis diagnosed or confirmed by surgical or direct visualization, or histopathology within 10 years of the Screening Visit.

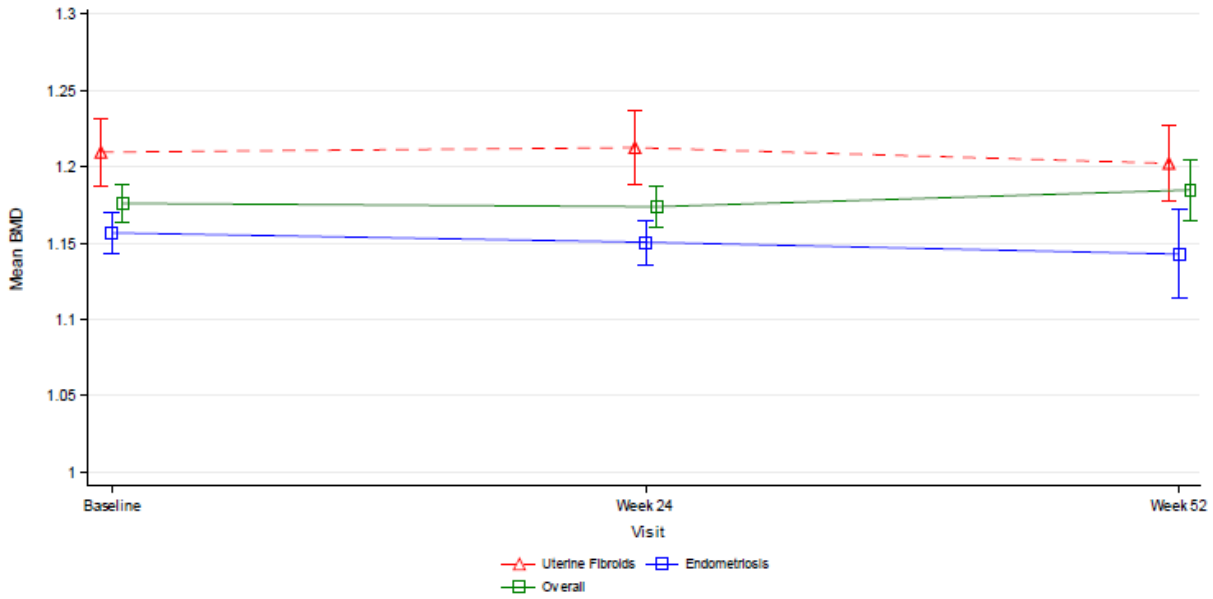
It was planned that approximately 660 participants would be recruited in the study (260 with uterine fibroids and 400 with endometriosis).

As age is a strong risk factor for BMD change over time, participants in this observational study were matched by age category (18–24,25–34,35–44, and ≥ 45 years old) with participants enrolled in the interventional studies for uterine fibroids (MVT-601-3001 and MVT-601-3002) and endometriosis (MVT-601-3101 and MVT-601-3102).

A total of 262 participants were enrolled in the uterine fibroid cohort and all were included in the BMD analysis population. The mean (standard deviation [SD]) age for all participants in the uterine fibroid cohort was 41.8 years (5.50) and the two predominant racial representations were Black or African American (58.0%) and White (37.4%).

At baseline, the mean BMD at the lumbar spine was 1.2095 g/cm3. At Weeks 24 and 52, the mean percent changes from baseline in BMD at the lumbar spine were 0% (95% confidence interval [CI]: -0.32%, 0.31%) and -0.41% (95% CI: -0.77%, -0.05%), respectively.

Figure: (*Figure 14.2.1.1) BMD Value in Lumbar Spine Over Time (BMD Analysis Population)*



The magnitude of the mean percent change in BMD from baseline observed over the 52 weeks at the lumbar spine was not clinically relevant in the overall population.

Age-related increases in the younger population (18-24 and 25-34 years of age; < 10% of participants) were observed (1.58% and 0.40%, respectively at week 52), and decreases in BMD in those 35-44 years and ≥45 years of age (-0.65% and -0.27%, respectively, at Week 52).

Table: Summary of Categorical Percent Change from Baseline to Week 52 in BMD at the Lumbar Spine (BMD Analysis Population)

Time Point Statistic	Uterine Fibroids (N = 262)
Baseline	
n	255
Mean (SD)	1.2095 (0.18052)
Week 24	
≤ 2% decline	183 (69.8)
> 2%-3% decline	16 (6.1)
> 3%-5% decline	19 (7.3)
> 5%-8% decline	4 (1.5)
> 8% decline	0
Week 52	
≤ 2% decline	158 (60.3)
> 2%-3% decline	18 (6.9)
> 3%-5% decline	28 (10.7)
> 5%-8% decline	7 (2.7)
> 8% decline	2 (0.8)

Abbreviations: BMD = bone mineral density; N = number of participants; n = number of participants in subset.
Source: Table 14.2.1.1.

Integration of BMD measurements clinical studies and observational natural history study

BMD measurements Week 52 (Integration study MVT-601-034 with MVT-601-3001+3002+3003)

An assessment integrating data across studies was conducted to contextualize the BMD changes observed in studies MVT-601-3001, MVT-601-3002, and MVT-601-3003 using the data from the uterine fibroids cohort from the observational study (MVT-601-034) as a benchmark.

MVT-601-034 and those of the population in the relugolix combination studies showed that the studies were generally well-matched by number of subjects included in the assessment, age, and BMI. Key differences include the higher percentage of Black or African American women in the uterine fibroid cohort compared with the relugolix combination studies and that the uterine fibroids cohort included only subjects from North America. Although mean BMI was similar across the relugolix combination therapy and uterine fibroid cohort groups, the relugolix combination therapy group included a higher preponderance of patients (52.8%) with BMI > 30 kg/m2 compared with the uterine fibroid cohort (42.4%). These differences were not expected to have impact on the comparison because the differences between the groups were small.

Table: Summary of Bone Mineral Density by Location and Visit: Long-Term Uterine Fibroids BMD Safety Population (MVT-601-3001, MVT-601-3002, MVT-601-3003, and MVT-601-034)

	Uterine Fibroids Cohort in MVT-601-034 (N = 262)		Relugolix 40 mg + E2/NETA (N = 254)		Relugolix 40 mg + Delayed E2/NETA (N = 258)	
Location Visit Statistics	Results	% Change from Baseline[a]	Results	% Change from Baseline[a]	Results	% Change from Baseline[a]
Location: Lumbar Spine (L1-L4)						
Baseline[a]						
n	255		254		258	
Mean (SD)	1.209 (0.1805)		1.193 (0.1695)		1.211 (0.1863)	

	Uterine Fibroids Cohort in MVT-601-034 (N = 262)		Relugolix 40 mg + E2/NETA (N = 254)		Relugolix 40 mg + Delayed E2/NETA (N = 258)	
Location						
Visit		**% Change from**		**% Change from**		**% Change from**
Statistics	**Results**	**Baseline[a]**	**Results**	**Baseline[a]**	**Results**	**Baseline[a]**
Median	1.202		1.177		1.188	
Min, Max	0.74, 1.82		0.81, 1.75		0.75, 1.87	
Week 12						
n	0	0	204	204	198	198
Mean (SD)			1.177 (0.1651)	-0.657 (2.5818)	1.198 (0.1954)	-1.991 (2.6325)
95% CI[b]				(-1.0134,-0.3005)		(-2.3594,-1.6216)
Median			1.159	-0.995	1.160	-1.787
Min, Max			0.81, 1.73	-7.58, 7.60	0.68, 1.86	-9.39, 4.71
Week 24						
n	226	222	195	195	194	194
Mean (SD)	1.212 (0.1855)	-0.002 (2.3855)	1.179 (0.1722)	-0.208 (2.6804)	1.183 (0.1811)	-2.070 (2.8275)
95% CI[b]		(-0.3174,0.3137)		(-0.5866,0.1705)		(-2.4703,-1.6695)
Median	1.205	-0.039	1.169	-0.214	1.162	-2.138
Min, Max	0.82, 1.80	-7.19, 6.82	0.81, 1.79	-7.34, 7.93	0.69, 1.87	-10.39, 6.76
Week 36						
n	0	0	145	145	120	120
Mean (SD)			1.180 (0.1608)	-0.696 (2.8708)	1.201 (0.1758)	-1.900 (2.7599)
95% CI[b]				(-1.1671,-0.2246)		(-2.3988,-1.4010)
Median			1.157	-0.776	1.171	-1.901
Min, Max			0.81, 1.59	-7.37, 6.80	0.86, 1.81	-7.93, 6.53
Week 52						
n	217	213	132	132	108	108
Mean (SD)	1.202 (0.1871)	-0.410 (2.6529)	1.169 (0.1606)	-0.760 (3.0686)	1.198 (0.1756)	-1.728 (2.6732)
95% CI[b]		(-0.7680,-0.0514)		(-1.2888,-0.2321)		(-2.2375,-1.2176)
Median	1.186	-0.186	1.156	-0.960	1.170	-1.506
Min, Max	0.81, 1.82	-8.96, 6.54	0.83, 1.59	-10.86, 9.00	0.82, 1.85	-8.56, 4.88
Location: Total Hip						
Baseline[a]						
n	252		254		257	
Mean (SD)	1.048 (0.1530)		1.048 (0.1451)		1.060 (0.1496)	
Median	1.026		1.048		1.048	
Min, Max	0.71, 1.52		0.69, 1.52		0.69, 1.48	
Week 12						
n	0	0	206	206	193	193
Mean (SD)			1.049 (0.1432)	-0.008 (2.1665)	1.055 (0.1522)	-1.002 (2.0043)
95% CI[b]				(-0.3058,0.2894)		(-1.2867,-0.7176)
Median			1.054	-0.103	1.044	-1.030
Min, Max			0.68, 1.43	-6.24, 7.82	0.68, 1.47	-7.11, 5.27
Week 24						
n	220	216	198	198	191	190
Mean (SD)	1.056 (0.1577)	-0.055 (2.1877)	1.042 (0.1436)	-0.091 (2.2188)	1.042 (0.1520)	-1.091 (2.0202)
95% CI[b]		(-0.3484,0.2384)		(-0.4022,0.2197)		(-1.3799,-0.8017)
Median	1.041	-0.138	1.039	-0.181	1.032	-1.104

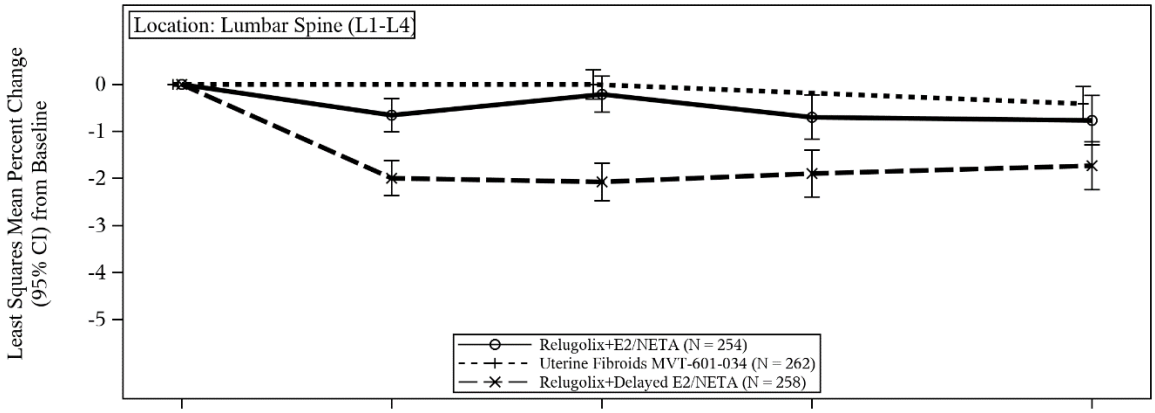
	Uterine Fibroids Cohort in MVT-601-034 (N = 262)		Relugolix 40 mg + E2/NETA (N = 254)		Relugolix 40 mg + Delayed E2/NETA (N = 258)	
Location						
Visit		**% Change from**		**% Change from**		**% Change from**
Statistics	**Results**	**Baseline[a]**	**Results**	**Baseline[a]**	**Results**	**Baseline[a]**
Min, Max	0.71, 1.50	-8.39, 6.33	0.69, 1.42	-7.59, 9.11	0.66, 1.46	-7.88, 3.44
Week 36						
n	0	0	147	147	122	122
Mean (SD)			1.039 (0.1391)	-0.214 (2.1543)	1.045 (0.1472)	-1.038 (2.1981)
95% CI[b]				(-0.5647,0.1376)		(-1.4319,-0.6439)
Median			1.047	-0.408	1.040	-0.948
Min, Max			0.69, 1.42	-6.18, 6.20	0.68, 1.44	-6.41, 4.86
Week 52						
n	219	214	129	129	105	105
Mean (SD)	1.052 (0.1556)	-0.240 (2.3676)	1.042 (0.1323)	-0.263 (2.5780)	1.047 (0.1474)	-0.879 (2.3807)
95% CI[b]		(-0.5589,0.0791)		(-0.7123,0.1859)		(-1.3398,-0.4183)
Median	1.042	-0.213	1.048	-0.361	1.044	-0.796
Min, Max	0.69, 1.48	-9.31, 7.40	0.70, 1.41	-5.16, 12.65	0.68, 1.49	-6.22, 6.56
Location: Femoral Neck						
Baseline[a]						
n	252		254		257	
Mean (SD)	0.968 (0.1854)		0.971 (0.1591)		0.991 (0.1718)	
Median	0.953		0.960		0.982	
Min, Max	0.59, 1.53		0.62, 1.41		0.59, 1.59	
Week 12						
n	0	0	206	206	193	193
Mean (SD)			0.961 (0.1595)	-0.724 (3.5333)	0.984 (0.1663)	-1.093 (3.2896)
95% CI[b]				(-1.2093,-0.2386)		(-1.5597,-0.6256)
Median			0.957	-0.718	0.978	-1.184
Min, Max			0.58, 1.44	-18.05, 12.73	0.60, 1.52	-13.37, 11.09
Week 24						
n	220	216	198	198	191	190
Mean (SD)	0.975 (0.1882)	-0.249 (3.3395)	0.956 (0.1613)	-0.490 (3.6498)	0.972 (0.1735)	-1.340 (3.8199)
95% CI[b]		(-0.6970,0.1987)		(-1.0012,0.0219)		(-1.8869,-0.7936)
Median	0.973	-0.446	0.954	-0.627	0.953	-1.458
Min, Max	0.59, 1.52	-10.73, 14.69	0.58, 1.42	-11.04, 14.70	0.55, 1.51	-11.90, 14.64
Week 36						
n	0	0	147	147	122	122
Mean (SD)			0.952 (0.1584)	-0.645 (3.3388)	0.979 (0.1605)	-0.800 (3.0501)
95% CI[b]				(-1.1888,-0.1003)		(-1.3470,-0.2536)
Median			0.943	-0.641	0.972	-0.930
Min, Max			0.62, 1.43	-9.05, 7.14	0.60, 1.43	-7.35, 9.87
Week 52						
n	219	214	129	129	105	105
Mean (SD)	0.971 (0.1846)	-0.248 (3.5513)	0.952 (0.1526)	-0.674 (3.3528)	0.980 (0.1724)	-0.565 (4.7805)
95% CI[b]		(-0.7263,0.2308)		(-1.2583,-0.0901)		(-1.4897,0.3606)
Median	0.968	-0.377	0.948	-1.063	0.962	-0.744
Min, Max	0.58, 1.58	-9.39, 11.37	0.62, 1.37	-10.73, 8.64	0.62, 1.63	-9.27, 27.37

	Uterine Fibroids Cohort in MVT-601-034 (N = 262)		Relugolix 40 mg + E2/NETA (N = 254)		Relugolix 40 mg + Delayed E2/NETA (N = 258)	
Location						
Visit		**% Change from**		**% Change from**		**% Change from**
Statistics	**Results**	**Baseline[a]**	**Results**	**Baseline[a]**	**Results**	**Baseline[a]**

The analysis data cutoff date of study MVT-601-034 was 23 Jan 2020.
Abbreviations: BMD = bone mineral density; CI = confidence interval; E2 = estradiol; 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.
Summary is based on corrected bone mineral density data.
If multiple valid measurements for a visit are present, the measurement closest to the target visit day will be used (earliest date in case of ti es).
[a]Baseline value is defined as the last measurement on or before the first administration (date and time) of study drug.
[b]Based on normal approximation.

The figure below summarizes the percent change from baseline to Week 52 in BMD for the uterine fibroid cohort from MVT-601-0034 and relugolix combination and relugolix delayed combination groups.

Figure: Percent Change from Baseline in Bone Mineral Density over Time at the Lumbar Spine: Long-Term Uterine Fibroids BMD Safety Population (MVT-601-3001, MVT-601-3002, MVT-601-3003, and MVT-601-034).

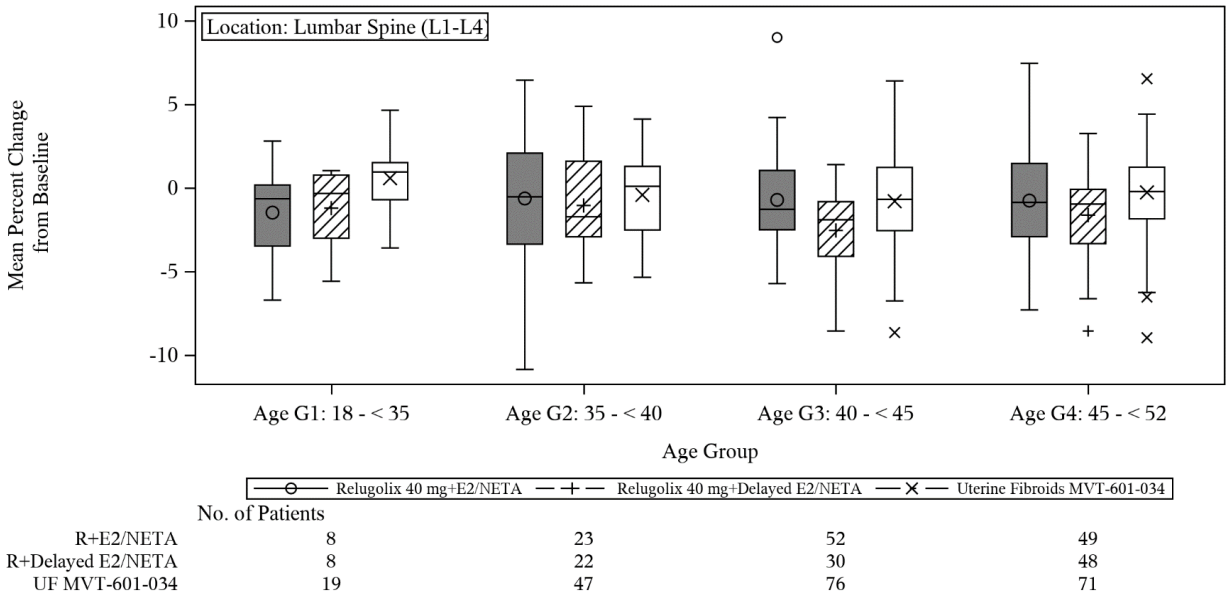


No. of Evaluable Patients					
R+E2/NETA	254	204	195	145	132
UF MVT-601-034	255	0	222	0	213
R+Delayed E2/NETA	258	198	194	120	108

Abbreviations: BMD = bone mineral density; CI = confidence interval; E2 = estradiol; NETA = norethindrone acetate; N – number of participants; No. = number; R = relugolix; UF = uterine fibroids.

Because bone mass accrual at the lumbar spine in women may occur up to age 30, subsequently plateaus, then declines in the fourth and fifth decades of life prior to menopause, change in BMD was assessed by age groups (18 to < 35 years, 35 to < 40 years, 40 to < 45 years, and 45 to < 52 years). Mean percent change in BMD by age group was consistent between the relugolix + E2/NETA group and uterine fibroids cohort when assessed at the lumbar spine:

Figure: Box Plot of Percent Change from Baseline to Week 52 in Bone Mineral Density at the Lumbar Spine and Age Group: Long-Term Uterine Fibroids BMD Safety Population (MVT-601-3003, and MVT-601-034).



No. of Patients				
R+E2/NETA	8	23	52	49
R+Delayed E2/NETA	8	22	30	48
UF MVT-601-034	19	47	76	71

Abbreviations: BMD = bone mineral density; G = group; E2 = estradiol; NETA = norethindrone acetate; No. = number; R = relugolix; UF = uterine fibroids.

Due to the small number of patients in the 18 to < 35-year-old cohort, conclusions are difficult to infer. In this age group, small gains were observed in the uterine fibroid cohort compared with the relugolix groups, where small reductions were observed. In the other age groups, no meaningful differences between the relugolix + E2/NETA and uterine fibroids cohort were observed. In contrast, in the relugolix + delayed E2/NETA, a trend towards bone loss was observed in most age groups that was reflective of the initial 12 weeks of treatment with relugolix monotherapy.

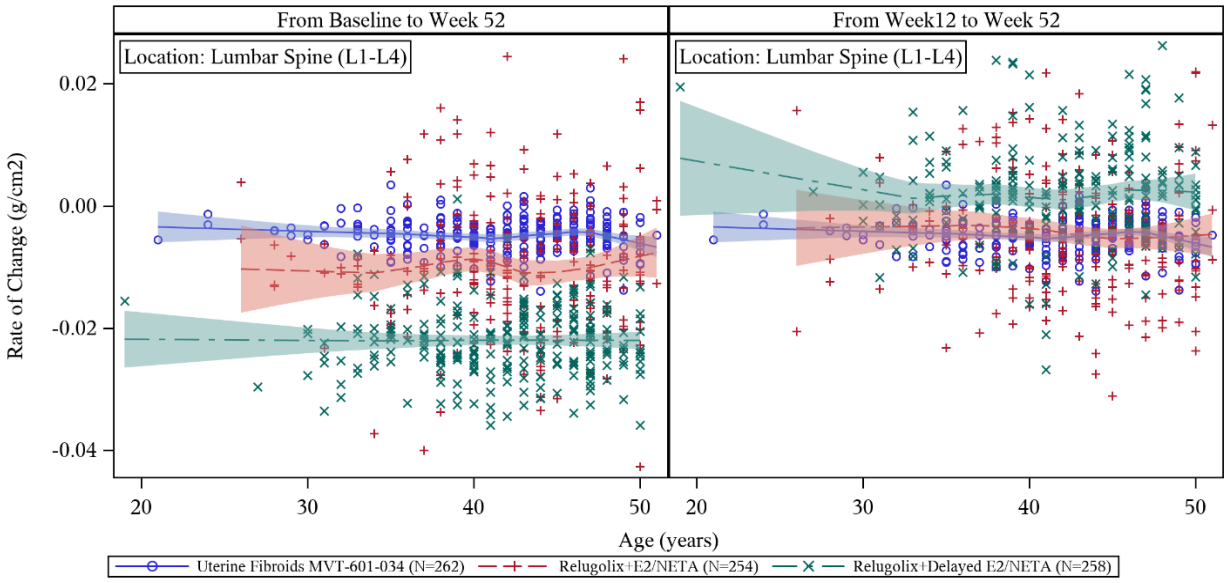
BMD: model-predicted effects of relugolix combination therapy on BMD

To further assess the potential long-term effect of relugolix combination therapy on BMD across the patient age range of the studies, the rate of change in BMD over 52 weeks for each patient was derived using a random-coefficients model and plotted against patient age to evaluate patterns across cohorts and age groups (Figure below). The random-coefficients model is a mixed-effects model with repeated measures of BMD that has visit time as a fixed effect and the random component consisting of intercept and slope (rate of change in BMD) over time for individual patients.

For the uterine fibroid cohort, the rate of change was assessed over 52 weeks from baseline. For the relugolix + E2/NETA group, the rate of change was assessed in two ways: starting at baseline and starting at Week 12, because the small changes observed at Week 12 in the relugolix + E2/NETA group, considered to be associated with adjustment to the new hormonal steady state, are not considered clinically significant and the rate of change from Week 12 onward is likely to be the determinant of long-term effect of relugolix combination therapy on BMD. Similarly, in the relugolix + delayed E2/NETA group, in which patients received

relugolix 40-mg monotherapy for 12 weeks, the assessment of the rate of change was also done in two ways: starting at baseline and starting at Week 12, when patients transitioned from relugolix monotherapy to relugolix + E2/NETA and where the onset of a plateau in BMD change was observed that continued through Week 52.

Figure: Bone Mineral Density Rate of Change at the Lumbar Spine by Age: Long-Term Uterine Fibroids BMD Safety Population (MVT-601-3001, MVT-601-3002, MVT-601-3003, and MVT-601-034).



Abbreviations: BMD = bone mineral density; E2 = estradiol; N = number of participants; NETA = norethindrone acetate. The rate of change from baseline to Week 52 for study MVT-601-034 is plotted in the figure for change from Week 12 to Week 52 as a reference. The rate of change within (-0.05, 0.05) is plotted.

As shown in the right panel, the rate of BMD change at the lumbar spine versus patient age in the relugolix + E2/NETA group and the uterine fibroids cohort overlap, indicating that, after Week 12, the rate of change in BMD at the lumbar spine in patients taking relugolix + E2/NETA for up to 52 weeks is consistent with that of an age-matched concurrent cohort.

Furthermore, transition from relugolix monotherapy to relugolix + E2/NETA was associated with a positive (> 0) rate of change in BMD. This finding helps support that the dose of E2 in relugolix + E2/NETA is adequate to mitigate bone loss associated with hypoestrogenism from gonadotropin-releasing hormone (GnRH) receptor antagonism.

Additionally, a semi-mechanistic exposure-BMD model was developed to support long-term use of relugolix combination therapy. The model was based on a model proposed by Riggs et al (Riggs et al. 2012), which characterized the relationship between suppression of E2 concentrations associated with commercially available GnRH agonists and antagonists and percent change from baseline in BMD for the lumbar spine over time.

Using the BMD data from both phase 3 studies it is demonstrated that relugolix monotherapy suppressed E2 levels and the rate of BMD change was well captured by the model. Transition from relugolix monotherapy to relugolix + E2/NETA was associated with stabilisation of BMD loss rather than reversibility of BMD loss.

Nevertheless, these data support the dose of E2 in relugolix + E2/NETA to minimize bone loss associated with hypoestrogenism.

Data from the long-term extension (LTE) study (MVT-601-3003), in which women who had participated in the phase 3 studies were treated with relugolix combination therapy for up to 12 months, were used for the validation of the E2-BMD model. The observed LTE data, in which the BMD at lumbar spine following a 9–12-month treatment period were captured, were compared with the corresponding predictions based on the E2-BMD model. The observed median BMD loss in the LTE study seemed to be reasonably captured by the E2-BMD model.

Overall, the model seems to indicate that there may be a sustained BMD effect with the addition of E2/NETA to the relugolix therapy. However, the clinical study data seem to indicate that the BMD decrease is not stabilized at the specific time point of 12 weeks, as BMD decreased further at month 9 and month 12.

How long the BMD effect is maintained according to the model is primarily dependent on the second assumption, that the changes in bone formation and resorption in the studied population remain at the same physiological steady state level. The model included E2 levels as the main driver of rate change in BMD; although trends were observed with baseline BMD, age and BMI, there were no statistically significant covariates in the model. Since in the model steady-state E2 levels are being reached within 1 to 2 months after start of relugolix + E2/NETA and remain stable over time, no change in rate of BMD change is to be expected for longer treatment based on the exposure-BMD model. However, small changes in BMD over time were observed in an age-matched cohort of premenopausal women with uterine fibroids (see above). It cannot be excluded that other factors not related to relugolix + E2/NETA treatment could contribute to changes in BMD over time, which are not captured by the model (see discussion on Clinical Efficacy and Safety).

Week 104 (24 week + 28 week extension + 52 week withdrawal study (summary only)

Note: Similar to adverse event data, BMD data in the placebo group is reflective of the sequence of placebo followed by relugolix + E2/NETA in most patients.

A summary of percent change from Week 52/Baseline to Week 104 at the lumbar spine and total hip is provided in Table and is represented in Figure for lumbar spine and total hip by randomized treatment groups. Percent change from pivotal baseline (prior to randomization into MVT-601-3001 or MVT-601-3002) in BMD at the lumbar spine and total hip for patients who received relugolix + E2/NETA for up to 2 consecutive years is presented below.

Table: Summary of Percent Change from Week 52/Baseline in BMD by Location and Visit (Safety Population)

Location Visit Statistics	Relugolix+E2/NETA (N = 116) Results	 % Change from Week52/Baseline	Placebo (N = 112) Results	 % Change from Week52/Baselin
Lumbar Spine (L1-L4)				
Week 52/Baseline				
n	112		111	
Mean (SD)	1.18 (0.172)		1.20 (0.148)	
Median	1.17		1.20	
Min, Max	0.82, 1.64		0.83, 1.52	
LS Means (SE)	1.19 (0.015)		1.20 (0.015)	
95% CI	(1.16, 1.22)		(1.17, 1.23)	
Week 104				
n	82	79	78	78
Mean (SD)	1.19 (0.174)	0.75 (2.386)	1.18 (0.145)	0.18 (2.893)
Median	1.18	0.67	1.19	0.12
Min, Max	0.87, 1.60	-3.92, 7.58	0.79, 1.49	-6.36, 8.79
LS Means (SE)	1.20 (0.017)	0.81 (0.309)	1.18 (0.018)	0.10 (0.315)
95% CI	(1.17, 1.24)	(0.20, 1.42)	(1.14, 1.21)	(-0.52, 0.72)
Difference of LS Means (SE)		0.71 (0.430)		
95% CI		(-0.14, 1.56)		
Total Hip				
Week 52/Baseline				
n	112		109	
Mean (SD)	1.04 (0.150)		1.04 (0.141)	
Median	1.04		1.03	
Min, Max	0.70, 1.49		0.74, 1.45	
LS Means (SE)	1.04 (0.013)		1.04 (0.013)	
95% CI	(1.02, 1.07)		(1.01, 1.06)	
Week 104				
n	83	79	78	76
Mean (SD)	1.04 (0.146)	0.32 (2.620)	1.03 (0.134)	-0.08 (2.985)
Median	1.03	0.28	1.02	0.09
Min, Max	0.76, 1.48	-6.17, 7.68	0.75, 1.40	-9.01, 8.30
LS Means (SE)	1.05 (0.014)	0.34 (0.299)	1.03 (0.015)	-0.10 (0.308)
95% CI	(1.02, 1.07)	(-0.25, 0.93)	(1.00, 1.06)	(-0.71, 0.51)
Difference of LS Means (SE)		0.44 (0.420)		
95% CI		(-0.39, 1.27)		

Date of database lock: 17 Mar 2021.

Abbreviations: CI = confidence interval; E2 = estradiol; Max = maximum; Min = minimum; LS = least squares; N = number of patients in the treatment group; n = number of patients included in summary statistics; NETA = norethindrone acetate; SD = standard deviation; SE = standard error.

Figure: Percent Change from Week 52/Baseline in BMD by Location and Visit (Safety Population)

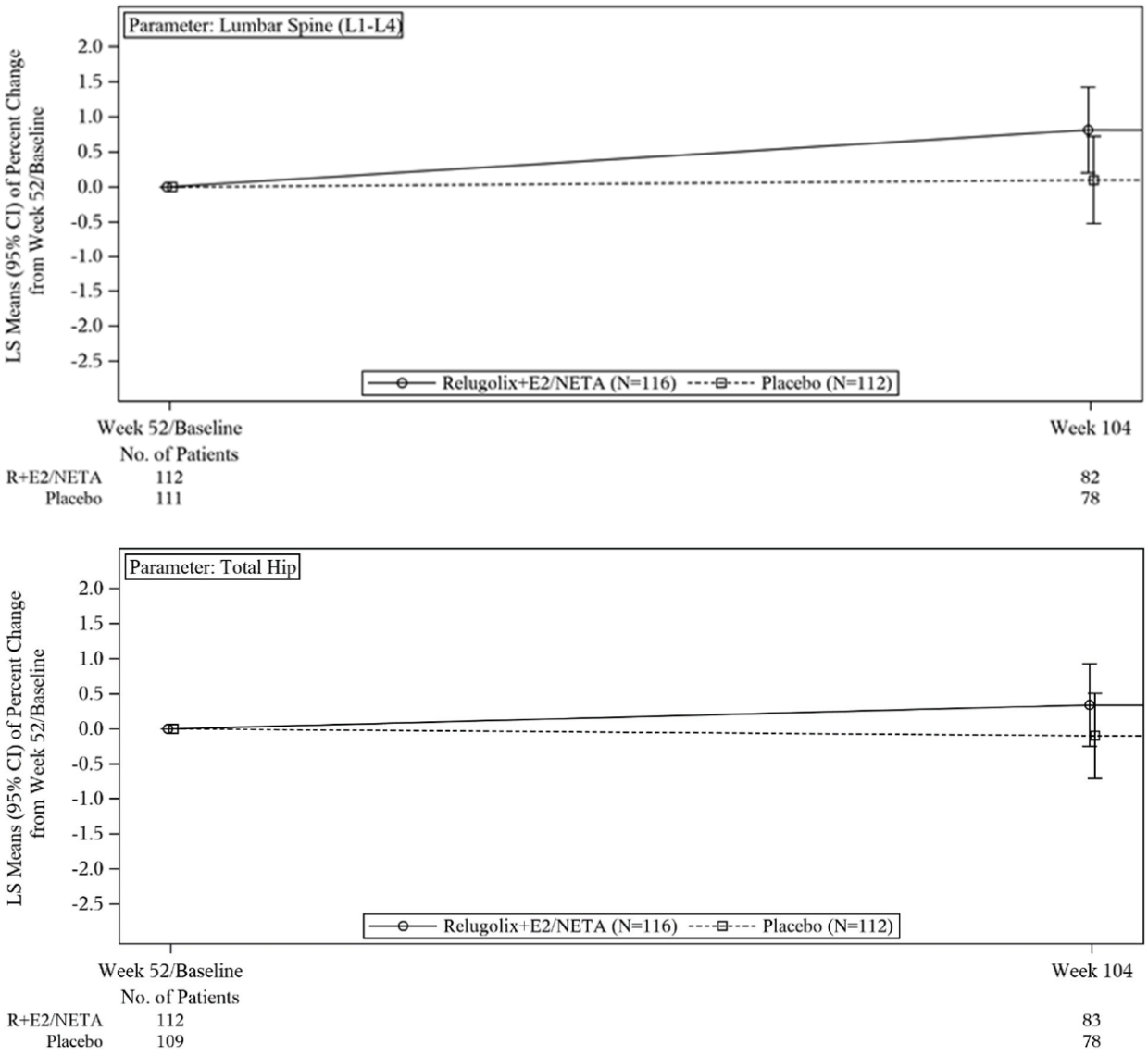
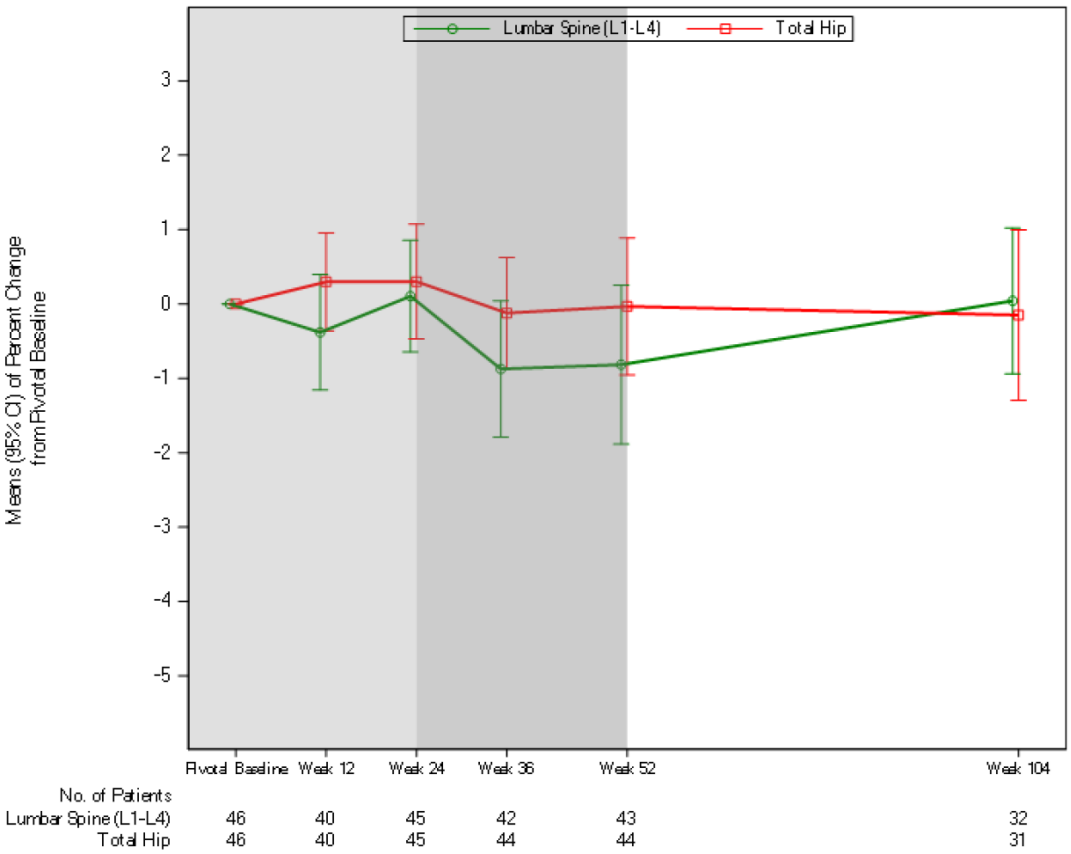


Figure: Summary of Percent Change from Pivotal Baseline in BMD by Location and Visit in Patients Who Were Treated with Relugolix + E2/NETA through Week 104 (Safety Population)



Date of database lock: 17 Mar 2021.

Abbreviations: CI = confidence interval; E2 = estradiol; N = number of patients in the treatment group; NETA = norethindrone acetate. 95% CIs were constructed based on the approximation to the normal distribution.

The bone mineral density data collected from pivotal baseline to Week 52 in studies MVT-601-3001, MVT-601-3002 and MVT-601-3003 are included. Error bars represent 95% CI.

All patients regardless of previous treatments

At the lumbar spine, the least squares mean percent change in BMD from Week 52/Baseline to Week 104 was 0.81% in all patients treated with relugolix + E2/NETA (regardless of previous treatment) compared with 0.10% in patients who were randomized to receive placebo.

Results on BMD presented per treatment category

Cumulatively, the mean percent change in BMD from pivotal study baseline to up to Week 104 in patients who received relugolix + E2/NETA (n = 32) was 0.04% (see Figure above).

In women who received placebo for 24 weeks followed by relugolix + E2/NETA for 80 weeks (n = 29), the mean percent change in BMD from pivotal study baseline to Week 104 was 0.45%. In addition, in women who received relugolix monotherapy for 12 weeks followed by relugolix + E2/NETA for 92 weeks (n = 21), the mean percent change in BMD from pivotal study baseline to Week 104 was -1.85%, see below.

Table: Summary of Percent Change from Pivotal Baseline in BMD by Location and Visit and by Combination Group (Safety Population)

	Relugolix+E2/NETA ||Relugolix+E2/NETA ||Relugolix+E2/NETA (N = 46)		Relugolix+ Delayed E2/NETA ||Relugolix+E2/NETA ||Relugolix+E2/NETA (N = 28)		Placebo ||Relugolix+E2/NETA ||Relugolix+E2/NETA (N = 42)	
Location Visit Statistics	Result	% Change from Pivotal Baseline	Result	% Change from Pivotal Baseline	Result	% Change from Pivotal Baseline
Lumbar Spine (L1-L4)						
Week 52						
n	43	43	28	28	42	42
Mean (SD)	1.15 (0.182)	-0.82 (3.470)	1.21 (0.197)	-2.29 (3.128)	1.20 (0.139)	-1.04 (2.843)
95% CI	(1.09, 1.20)	(-1.88, 0.25)	(1.13, 1.29)	(-3.50, -1.07)	(1.16, 1.25)	(-1.93, -0.16)
Median	1.14	-1.34	1.18	-1.24	1.19	-0.67
Min, Max	0.85, 1.51	-10.86, 7.46	0.82, 1.64	-8.56, 2.48	0.94, 1.49	-7.91, 7.20
Week 104						
n	32	32	21	21	29	29
Mean (SD)	1.16 (0.186)	0.04 (2.720)	1.24 (0.183)	-1.85 (2.996)	1.20 (0.148)	0.45 (3.419)
95% CI	(1.09, 1.22)	(-0.94, 1.02)	(1.15, 1.32)	(-3.21, -0.48)	(1.14, 1.26)	(-0.85, 1.75)
Median	1.14	-0.24	1.27	-1.96	1.20	0.07
Min, Max	0.87, 1.52	-5.65, 6.18	0.87, 1.60	-8.50, 5.32	0.93, 1.52	-6.56, 8.13

Date of database lock: 17 Mar 2021.

Abbreviations: CI = confidence interval; DXA = dual-energy x-ray absorptiometry; E2 = estradiol; EOT = end of treatment; 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. Summary statistics are based on observed data.

Corrected bone mineral density data was used for analysis as assessed by the central radiology laboratory.

The bone mineral density data collected from pivotal baseline to Week 52 in studies MVT-601-3001, MVT-601-3002 and MVT-601-3003 are included. 95% CIs were constructed based on the approximation to the normal distribution. The groups displayed and used for analysis are combinations of the treatments in pivotal study, extension study and that in randomized withdrawal study. Week 104/EOT also include patients who had DXA after Week 52 and prior to the visit window of Week 104.

At the total hip, the least squares mean percent change in BMD from Week 52/Baseline to Week 104 was 0.34% in patients treated with relugolix + E2/NETA compared with -0.10% in patients who were randomized to receive placebo. Cumulatively, the mean percent change in BMD from pivotal study baseline to Week 104 in patients who received relugolix + E2/NETA (n = 31) was -0.15%. In women who received placebo for 24 weeks followed by relugolix + E2/NETA for 80 weeks (n = 31), the mean percent change in BMD from pivotal study baseline to Week 104 was 0.25%. In addition, in women who received relugolix monotherapy for 12 weeks followed by relugolix + E2/NETA for 92 weeks (n = 21), the percent change in BMD from pivotal study baseline to Week 104 was -1.10%.

Table: Summary of Percent Change from Pivotal Baseline in BMD by Location and Visit and by Combination Group (Safety Population)

	Relugolix+E2/NETA ‖Relugolix+E2/NETA ‖Relugolix+E2/NETA (N = 46)		Relugolix+ Delayed E2/NETA ‖Relugolix+E2/NETA ‖Relugolix+E2/NETA (N = 28)		Placebo ‖Relugolix+E2/NETA ‖Relugolix+E2/NETA (N = 42)	
Location Visit Statistics	Result	% Change from Pivotal Baseline	Result	% Change from Pivotal Baseline	Result	% Change from Pivotal Baseline
Total Hip						
Week 52						
n	44	44	27	27	41	41
Mean (SD)	1.04 (0.146)	-0.03 (3.029)	1.01 (0.170)	-1.17 (2.799)	1.06 (0.143)	-0.10 (2.472)
95% CI	(1.00, 1.09)	(-0.95, 0.89)	(0.94, 1.08)	(-2.28, -0.07)	(1.01, 1.10)	(-0.88, 0.68)
Median	1.05	-0.40	0.97	-1.47	1.06	-0.51
Min, Max	0.70, 1.40	-4.19, 12.65	0.75, 1.49	-6.22, 6.56	0.83, 1.34	-5.02, 6.65
Week 104						
n	31	31	21	21	31	31
Mean (SD)	1.03 (0.144)	-0.15 (3.122)	1.04 (0.175)	-1.10 (2.629)	1.06 (0.127)	0.25 (2.732)
95% CI	(0.97, 1.08)	(-1.29, 1.00)	(0.96, 1.12)	(-2.29, 0.10)	(1.02, 1.11)	(-0.75, 1.25)
Median	1.04	-0.57	1.02	-0.87	1.06	0.69
Min, Max	0.76, 1.23	-6.49, 10.03	0.83, 1.48	-7.19, 3.93	0.86, 1.38	-6.29, 6.21

Date of database lock: 17 Mar 2021.

Abbreviations: CI = confidence interval; DXA = dual-energy x-ray absorptiometry; E2 = estradiol; EOT = end of treatment; 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. Summary statistics are based on observed data. Corrected bone mineral density data was used for analysis as assessed by the central radiology laboratory. The bone mineral density data collected from pivotal baseline to Week 52 in studies MVT-601-3001, MVT-601-3002 and MVT-601-3003 are included. 95% CIs were constructed based on the approximation to the normal distribution. The groups displayed and used for analysis are combinations of the treatments in pivotal study, extension study and that in randomized withdrawal study. Week 104/EOT also include patients who had DXA after Week 52 and prior to the visit window of Week 104.

Over 2 years of treatment with relugolix + E2/NETA, an initial reduction from baseline in BMD was observed at the lumbar spine up to Week 12 that was followed by stabilization beyond
week 52. At the total hip, changes were minimal for the duration of treatment fluctuating around zero. These data support that after an initial adaptation of bone to the new estrogenic steady state driven by exogenous administration of estradiol in the context of GnRH antagonism, BMD stabilizes over time while on treatment. No evidence of progressive BMD loss was observed.

Significant changes in BMD in patients in parent studies that met non-inclusion criteria of open-label 3003 (Z-score < -2.0 or ≥ 7% decrease in BMD)

- *After 24 weeks (study 3001+3002)*

Patients discontinuing due to bone loss at Week 24 or not eligible for the extension study:
A total of 610 patients in the three groups (N = 202, 201, and 207, respectively) completed Week 24. There were 40 patients (6.6%) from studies MVT-601-3001 and MVT-601-3002 who completed 24 weeks of treatment (N = 610) and had a Z-score < -2.0 and/or had a ⩾ 7% decrease in BMD from baseline at lumbar spine, total hip, or femoral neck, which made them ineligible to participate in MVT-601-3003.
The number of patients was similar between the relugolix combination therapy (N = 11) and placebo (N = 8) groups. The delayed relugolix combination therapy group had the highest number of patients (N = 21). There were 6 patients with ⩾ 7% decline in BMD only at the femoral neck. In addition, one patient had declines at both the femoral neck and total hip, and one patient with decline at the lumbar spine. A summary of these patients by treatment assignment is provided below in the table:

Table: Summary of Patients Who Met the BMD Decrease Exclusion Criteria for MVT-601-3003 (Studies MVT-601-3001 and MVT-601-3002)

		MVT-601-3001		MVT-601-3002		
		≥ 7% change BMD	Z -score < -2.0	≥ 7% change BMD	Z -score < -2.0	Total[a]
Relugolix + E2/NETA	Lumbar Spine	-	-	1	2[b]	11
	Total Hip	-	-	-	-	
	Femoral Neck	3	-	4	1	
Relugolix + delayed E2/NETA	Lumbar Spine	3	1[c]	6	2[c]	21
	Total Hip	-	1[d]	1[d]	-	
	Femoral Neck	7	1	3	-	
Placebo	Lumbar Spine	1	-	-	1[b,c]	8
	Total Hip	-	-	-	-	
	Femoral Neck	4	-	3	-	
Total[a]		**18**	**1**	**17**	**4**	**40**

Abbreviations: BMD = bone mineral density; E2 = estradiol; NETA = norethindrone acetate. a If the same subject were excluded due to meeting both BMD and Z-score criteria, only the BMD criterion was included in the total to avoid double-counting.

- *After 36 weeks and 52 weeks (open label extension study 3003)*

Patients discontinuing due to bone loss at Week 36 or not eligible for the withdrawal study (Z-score < -2.0 or ⩾ 7% decrease in BMD):

In the relugolix + E2/NETA group:

- 6 patients (3.7%) met criteria for discontinuation at Week 36 due to bone loss (BMD loss ≥ 7% at any anatomic site).
- Three patients (1.8%) were not eligible to continue into study MVT-601-035 at Week 52 due to bone loss (BMD loss > 7% at any anatomic site).
- Six patients (3.7%) had BMD loss > 3% at the lumbar spine or total hip and discontinued early or did not enter study MVT-601-035 and required safety follow-up.

In the relugolix + delayed E2/NETA group:

- 5 patients (3.4%) met criteria for discontinuation at Week 36 due to bone loss (BMD loss ≥ 7% at any anatomic site).
- Three patients (2.0%) were not eligible to continue into study MVT-601-035 at Week 52 due to bone loss (BMD loss ≥ 7% at any anatomic site).
- Eleven patients (7.4%) had BMD loss > 3% at the lumbar spine or total hip and discontinued early or did not enter study MVT-601-035 and required safety follow-up.

In the former placebo group,

- 5 patients (3.0%) met criteria for discontinuation at Week 36 due to bone loss (BMD loss ≥ 7% at any anatomic site).

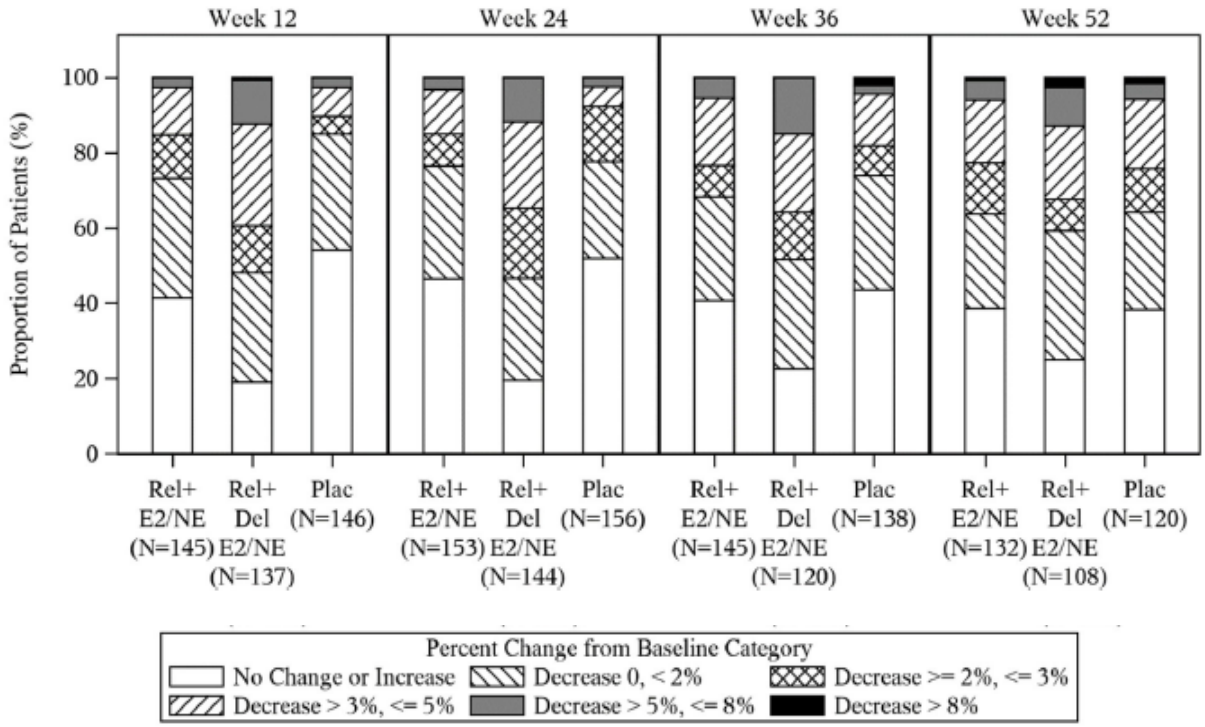
- Seven patients (4.3%) were not eligible to continue into study MVT-601-035 at Week 52 due to bone loss (BMD loss ≥ 7% at any anatomic site).
- Six patients (3.7%) had BMD loss > 3% at the lumbar spine or total hip and discontinued early or did not enter study MVT-601-035 and required safety follow-up.

Clinically significant changes in BMD of > 3% to ≤ 5% and > 5% to ≤ 8% (combined)

Relugolix + E2/NETA group

Proportion of patients at weeks 12, 24, 36 and 52 who had clinically meaningful (≥ 3%) bone loss and those with larger losses, so-called outliers, are presented by the number and proportion of patients who had BMD declines of < 2%, ≥ 2% to ≤ 3%, > 3% to ≤ 5%, > 5% to ≤ 8%, and > 8% by treatment group at lumbar spine:

Figure: Categorical Summary of Percent Change from Baseline Bone Mineral Density Over Time at the Lumbar Spine (L1 – L4) (Upper) by Category (Extension Safety Population)



Abbreviations: Del = delayed; E2 = estradiol; N = number of patients; NE = norethindrone acetate; Plac = placebo; Rel = relugolix.
Source: Table 8.3.12.3.

Relugolix + E2/NETA group (24 weeks of use):

At the lumbar spine in pooled studies MVT-601-3001 and MVT-601-3002 through 24 weeks, 45.1% of women in the relugolix + E2/NETA group and 51.8% of the placebo group had an increase in BMD (increase >0%); 2.1% and 0.5%, respectively, showed no change; or non-clinically significant decrease < 2% or decrease ⩾ 2% to ⩽ 3% (37% and 39% of patients in the relugolix + E2/NETA and placebo groups, respectively).

Smaller proportions of women had BMD loss of > 3% to ⩽ 5% (12.3% and 6.6% of patients, respectively) and > 5% to ⩽ 8% (3.6% and 2.5% of patients, respectively) in the relugolix + E2/NETA and placebo groups. No study patients in the relugolix + E2/NETA or placebo groups had losses > 8%.

Women who received relugolix + delayed E2/NETA showed a rapid decline in BMD in all categories that stabilized or improved with the addition of E2/NETA. Specifically, as compared with the relugolix+ E2/NETA and placebo groups, fewer women had gains in BMD defined as an increase > 0% (20.6%). A similar small number compared with the relugolix + E2/NETA and placebo groups had no change (0.5%) or non-clinically significant decline defined as a decrease < 2% or decrease ⩾ 2% to ⩽ 3% (42%). A higher proportion had changes of > 3% to ⩽ 5% and >5% to ⩽ 8% (21.6% and 12.4%, respectively); 2.6% of patients in the relugolix + delayed E2/NETA group had BMD losses at the lumbar spine > 8%.

Relugolix + E2/NETA group (52 weeks of use):

The majority of women in the relugolix + E2/NETA group (92 patients [68.7%]) continued to have clinically insignificant changes in BMD, defined as increase, no change, decrease < 2%, or decrease ⩾ 2% to ⩽ 3%. Smaller percentages of women had losses of > 3% to ⩽ 5% (34 patients [25.4%]) and > 5% to ⩽ 8% and (7 patients [5.2%]), respectively, that remained relatively unchanged over time. The following patient (0.8%) had losses that were > 8% at Week 52:

– One patient had 10.9% loss at the lumbar spine and 10.7% loss at the femoral neck. The patient was noted to have lost 5.5 kg and the Week 52 DXA was performed on a different scanner from the baseline study.

Former placebo group (24 weeks placebo followed by 28 weeks of relugolix + E2/NETA use):

The majority of women (61 patients [56.0%]) continued to have clinically insignificant changes in BMD, defined as increase, no change, decrease < 2%, or decrease ⩾ 2% to ⩽ 3%. Smaller percentages of women had losses of > 3% to ⩽ 5% and > 5% to ⩽ 8% (32 patients [29.4%]) and (13 patients [11.9%]), respectively, changes that may reflect the new steady state of estradiol with exogenous hormone administration as part of relugolix combination therapy. The following 2 patients (1.7%) had losses that were > 8% at Week 52:

- One patient had 8.5% loss at the lumbar spine (2.9% loss at Week 24). Low vitamin D and 7.16% weight loss were identified as a risk factor;
- One patient had 8.4% loss at the lumbar spine (5.2% loss at Week 24). Low vitamin D was identified as a risk factor. Additionally, the patient's high BMI (50.49 kg/m2) may have contributed to measurement error as a confounder.

Former relugolix + delayed E2/NETA group (12 weeks relugolix followed by 40 weeks relugolix + E2/NETA):

The categorical changes in BMD remained stable with continued E2/NETA exposure. The majority of women (89 patients [73.0%]) continued to have clinically insignificant changes in BMD, defined as increase, no change, decrease < 2%, or decrease ⩾ 2% to ⩽ 3%. Prolonged use of E2/NETA showed small changes in the percentages of women with losses of > 3% to ⩽ 5% and > 5% to ⩽ 8% (24 patients [19.7%]) and (7 patients [5.7%]), respectively. The following 3 patients (2.8%) had losses that were > 8% at Week 52:

– One patient had 8.6% loss at the lumbar spine. Elevated parathyroid hormone and vitamin D deficiency were noted as risk factors;
– One patient had 8.6% loss at the lumbar spine. No risk factors were identified;

– One patient had 8.2% loss at the lumbar spine. Vitamin D deficiency was identified as a risk factor.

Clinically significant changes in BMD of > 3% to ≤ 5% and > 5% to ≤ 8% after 104 weeks treatment (withdrawal study MVT-601-035)

Categorical changes in BMD over the 1-year treatment period of the randomized withdrawal study (all patients) and over the 2-year treatment period (patients who were treated with relugolix + E2/NETA for 104 weeks).

Table: Summary of Percent Change from Week 52/Baseline by Predefined Categories in Bone Mineral Density by Worst and Last Postbaseline Assessments (Safety Population)

	Relugolix+E2/NETA (N = 116)		Placebo (N = 112)	
	Result	95% CI for Proportion [1]	Result	95% CI for Proportion [1]
Lumbar Spine (L1-L4)				
Worst postbaseline				
n	85		85	
Increase > 0%	48 (56.5%)	(45.28%, 67.20%)	41 (48.2%)	(37.26%, 59.34%)
No change (0%)	1 (1.2%)	(0.03%, 6.38%)	5 (5.9%)	(1.94%, 13.20%)
Decrease < 2%	24 (28.2%)	(19.00%, 39.04%)	18 (21.2%)	(13.06%, 31.39%)
Decrease >= 2%, <= 3%	6 (7.1%)	(2.63%, 14.73%)	10 (11.8%)	(5.79%, 20.57%)
Decrease > 3%, <= 5%	6 (7.1%)	(2.63%, 14.73%)	7 (8.2%)	(3.38%, 16.23%)
Decrease > 5%, <= 8%	0	(0.00%, 4.25%)	4 (4.7%)	(1.30%, 11.61%)
Decrease > 8%	0	(0.00%, 4.25%)	0	(0.00%, 4.25%)
Last postbaseline				
n	85		85	
Increase > 0%	49 (57.6%)	(46.45%, 68.30%)	43 (50.6%)	(39.52%, 61.61%)
No change (0%)	1 (1.2%)	(0.03%, 6.38%)	5 (5.9%)	(1.94%, 13.20%)
Decrease < 2%	24 (28.2%)	(19.00%, 39.04%)	17 (20.0%)	(12.10%, 30.08%)
Decrease >= 2%, <= 3%	5 (5.9%)	(1.94%, 13.20%)	9 (10.6%)	(4.96%, 19.15%)
Decrease > 3%, <= 5%	6 (7.1%)	(2.63%, 14.73%)	7 (8.2%)	(3.38%, 16.23%)
Decrease > 5%, <= 8%	0	(0.00%, 4.25%)	4 (4.7%)	(1.30%, 11.61%)
Decrease > 8%	0	(0.00%, 4.25%)	0	(0.00%, 4.25%)

Date of database lock: 17 Mar 2021.

Abbreviations: CI = confidence interval; DXA = dual-energy x-ray absorptiometry; E2 = estradiol; N = number of patients in the treatment group; n = number of patients included in summary statistics; NETA = norethindrone acetate. Corrected bone mineral density data was used for analysis as assessed by the central radiology laboratory.

Based on lowest and last postbaseline bone mineral density assessment on treatment. [1] Based on exact binomial 95% confidence interval (Clopper-Pearson). Patients who had post-Week 52/Baseline DXA prior to the visit window of Week 104 are considered.

In the table above, reflecting all patients, regardless of their previous treatments, who received relugolix + E2/NETA and patients who received placebo for 24 weeks, followed by relugolix + E2 in the larger part of this group due to relapse of MBL >90 mL.

In the relugolix + E2/NETA group, 6 (7.1%) patients had BMD decrease of >3% -≤5% versus 10 (11.8%) in the placebo group, 0 patients had BMD increase of >5% -≤8%, versus 4 (4.7%) in the placebo group.

Table: Summary of Bone Mineral Density Loss from Pivotal Baseline by Predefined Categories, Location and Visit and by Combination Group (Safety Population)

	Relugolix+E2/NETA ||Relugolix+E2/NETA ||Relugolix+E2/NETA (N = 46)		Relugolix+ Delayed E2/NETA ||Relugolix+E2/NETA ||Relugolix+E2/NETA (N = 28)		Placebo ||Relugolix+E2/NETA ||Relugolix+E2/NETA (N = 42)	
Location Visit Statistics	Result	95% CI for Proportion [1]	Result	95% CI for Proportion [1]	Result	95% CI for Proportion [1]
Lumbar Spine (L1-L4)						
Week 104						
n	32		21		29	
Increase > 0%	15 (46.9%)	(29.09%, 65.26%)	5 (23.8%)	(8.22%, 47.17%)	15 (51.7%)	(32.53%, 70.55%)
No change (0%)	0	(0.00%, 10.89%)	0	(0.00%, 16.11%)	1 (3.4%)	(0.09%, 17.76%)
Decrease < 2%	10 (31.3%)	(16.12%, 50.01%)	7 (33.3%)	(14.59%, 56.97%)	7 (24.1%)	(10.30%, 43.54%)
Decrease >= 2%, <= 3%	2 (6.3%)	(0.77%, 20.81%)	2 (9.5%)	(1.17%, 30.38%)	1 (3.4%)	(0.09%, 17.76%)
Decrease > 3%, <= 5%	4 (12.5%)	(3.51%, 28.99%)	5 (23.8%)	(8.22%, 47.17%)	4 (13.8%)	(3.89%, 31.66%)
Decrease > 5%, <= 8%	1 (3.1%)	(0.08%, 16.22%)	1 (4.8%)	(0.12%, 23.82%)	1 (3.4%)	(0.09%, 17.76%)
Decrease > 8%	0	(0.00%, 10.89%)	1 (4.8%)	(0.12%, 23.82%)	0	(0.00%, 11.94%)

Date of database lock: 17 Mar 2021

Abbreviations: CI = confidence interval; E2 = estradiol; N = number of patients in the treatment group; n = number of patients included in summary statistics; NETA = norethindrone acetate. Corrected BMD data was used for analysis as assessed by the central radiology laboratory. [1] Based on exact binomial 95% confidence interval (Clopper-Pearson). The groups displayed and used for analysis are combinations of the treatments in pivotal study, extension study and that in randomized withdrawal study.

Based on the results presented in the table above, it is noted that at the end (Week 104) of the withdrawal study (MVT-601-035), in the subgroup of patients (n=32) who had taken the relugolix + E2/NETA for up to 104 weeks, 1 patient (3.1%) had a BMD loss of > 5% to ⩽ 8%.

Hepatic Transaminase Elevations

The applicant has selected increase in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 3 × upper limit of normal [ULN]) clinical laboratory tests as safety parameter of interest. The potential for hepatic transaminase elevations associated with relugolix is based on nonclinical observations, clinical trial data, and data reported for drugs that work on the hypothalamic-pituitary-gonadal axis (GnRH receptor agonists [eg, leuprolide] and the GnRH receptor antagonists [e.g., elagolix, degarelix]).

In nonclinical oral toxicology studies, administration of relugolix resulted in hepatic transaminase elevations (with and without accompanying histopathological findings) at doses associated with relugolix exposures that are 48 times the exposure associated with the proposed clinical dose of 40 mg (based on the area under the concentration-time curve [AUC] from the 39 week monkey toxicity study [most sensitive species]).

Hepatic transaminase elevations were monitored closely in accordance with FDA drug-induced liver injury guidelines (FDA 2009). The drug-related hepatic disorders SMQ (narrow) was run as a general safety screen for each analysis population. There was no pattern discerned in these populations over the 52-week period of observation.

- Uterine Fibroids 24-Week Combination Therapy short-term 24 weeks

In the first 24 weeks, elevated transaminases were reported for 7 patients (3 patients [1.2%] in the relugolix + E2/NETA group, 3 patients [1.2%] in the relugolix + delayed E2/NETA group and 1 patient [0.4%] in the

placebo group). None had concurrent elevated bilirubin, and all had confounding factors or alternative etiologies.

A summary of all increase in hepatic transaminase events of clinical interest reported in the Uterine Fibroids 24-Week Combination Therapy Safety Population is presented below.

Table: Adverse Events of Clinical Interest by Preferred Term (liver test abnormalities): Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001, MVT 601 3002)

Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Patients with ≥ 1 adverse event of clinical interest, n (%)	3 (1.2%)	3 (1.2%)	1 (0.4%)
Aspartate aminotransferase increased	2 (0.8%)	1 (0.4%)	1 (0.4%)
Alanine aminotransferase increased	1 (0.4%)	1 (0.4%)	0
Hepatic enzyme increased	0	1 (0.4%)	0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate.
Patients with multiple events for a given Preferred term are counted only once for each Preferred term.
Adverse events of clinical interest as defined in the protocol (any increase in ALT or AST ≥ 3 × ULN) are taken from the adverse event case report form. MedDRA version 22.0.

- Overall safety data on AST/ALT (24 weeks + extension)

During the 28 weeks of the open-label extension study, new cases were reported for an additional 7 patients (1 patient in the relugolix + E2/NETA group who was reported on Day 370 and was not included in the clinical database, 2 patients [1.3%] in the relugolix + delayed E2/NETA group and 4 patients [2.4%] in the placebo group). In total this were 14 of 634 (2.2%) patients while on relugolix + E2/NETA. One of the new events of alanine aminotransferase increased led to study drug discontinuation; no action was taken for four events, and study drug had already been discontinued at the time of onset for one of the events.

All events resolved or returned to baseline. None increased bilirubin and no events met Hy's law criteria. All events had confounding factors of comorbid conditions or concomitant medications. No serious adverse events were reported.

- Overall safety data on AST/ALT (withdrawal study – 104 weeks)

One patient in the relugolix + E2/NETA group was reported to have a grade 2 non-serious AE of clinical interest of AST/ALT increased. Bilirubin was not elevated. The event onset was approximately 31 days after the last dose of study drug.

Carbohydrate and Lipid Metabolic Effects

No clinically relevant changes in laboratory parameters of glucose (~2 mg/dL) and lipid metabolism (<1 mg/dL for total cholesterol and triglycerides) were observed in the relugolix combination group in the two pivotal studies. Changes were comparable to the placebo group.

Adverse events associated with carbohydrate or lipid metabolic effects in the relugolix + E2/NETA group, over the course of the 52-week treatment period, were reported for 8 patients (4.9%) with the events first being reported during the open-label extension study for 4 patients (2.5%). Reported events were generally in patients with a previous history of diabetes mellitus or evidence of impaired glucose tolerance at baseline. No meaningful changes were observed in mean changes from baseline or in the proportion of patients with laboratory values meeting predefined limits of change for glucose or lipid parameters.

Major Adverse Cardiovascular Events

No major adverse cardiovascular events were reported in premenopausal women with uterine fibroids treated with relugolix monotherapy and relugolix combination therapy. However, the incidence of MACEs in premenopausal women is extremely low, a limitation of this review is the relatively small number of women included in the analysis and short duration of treatment (up to 52 weeks). Also, it should also be noted that the relugolix program studies in women with uterine fibroids or endometriosis excluded patients with significant cardiovascular disease as a general safety exclusion.

Embolic and Thrombotic Events

In the clinical development program including studies with relugolix monotherapy and relugolix combination therapy, no embolic or thrombotic adverse events were reported in premenopausal women with uterine fibroids. In the Uterine Fibroids 12-Week Monotherapy Pooled Safety Population, one patient in the placebo group was reported to have an adverse event of lacunar infarction (phase 2 study TAK-385/CCT-001). In the ongoing endometriosis studies, a serious adverse event of deep vein thrombosis and pulmonary embolism was reported for one patient (long-term extension study MVT-601-3103) with significant risk factors for VTE (age, obesity, leg trauma, and immobilization).

However, as thrombotic and embolic events in premenopausal women are rare, a limitation is the relatively small number of women included in the analysis and short duration of treatment (up to 52 weeks).

Therefore, to further assess the potential risk of embolic or thrombotic events in patients treated with relugolix monotherapy or combination therapy, the incidence of VTE and ATE in premenopausal women taking CHCs was assessed using a meta-analysis:

Meta-analysis by ZEG Berlin

The use of relugolix + E2/NETA is associated with a reduction of systemic estrogen levels relative to the levels observed in a natural menstrual cycle. The incidence of thrombotic or embolic events with relugolix combination therapy has not been established but is expected to be at least similar if not lower to that observed with COCs containing E2 or estradiol valerate (Eval).

The use of combined hormonal contraceptives (COCs), which contain a combination of an estrogen + a progestogen, has been associated with an increased risk of VTEs compared with non-use, particularly at higher doses than those found in contraceptives containing E2.

The safety profile of COCs is dependent on the type and dose of estrogen, and the progestin used (Farris et al. 2017). There are no commercially available COCs containing both E2 and NETA. However, ethinylestradiol

(E2) and NETA are used (separately) in COCs. In some COCs, E2 or E2 valerate (E2val) or NETA have been used, but in higher doses than used in the relugolix + E2/NETA combination.

A meta-analysis was presented, which is conducted by ZEG Berlin (Center for Epidemiology and Health Research), to make use of the safety data on COCs in the target patient population for relugolix combination therapy to support the safety profile of E2/NETA. The meta-analysis was based on five prospective, non-interventional cohort studies comprising 235,437 pre-menopausal women and 30,077 menopausal women, who were followed up for a total of 571,163 WY and 101,715 WY, which allows for assessment of rare but serious adverse events that have been previously described in women taking COCs, particularly thromboembolic adverse events.

Evaluation of the safety profile of E2-containing COCs relative to the safety profile of ethinylestradiol (EE)-containing COCs (in the context of a standard progestin) and that of NETA-containing COCs relative to the safety profile of levonorgestrel (in the context of a standard dose of EE) provides data to define the potential safety profile of the E2/NETA included in relugolix combination therapy with respect to rare but severe events of venous thromboembolic event (VTE), deep venous thrombosis (DVT), and arterial thromboembolic event (ATE). Given the higher doses used for both components in COCs, their safety profiles likely represent a worst-case scenario.

The table below shows the distribution of study cohorts with respect to women years of exposure within the cohort. A woman may appear in both comparative sub-cohorts if she was exposed consecutively to both treatments during follow-up.

Table: Distribution of study cohorts, women years of exposure

Pre-menopausal women						Menopausal women	
Cohort A		Cohort B		Cohort C		Cohort D	
E2/E2Val (All)	EE≤30µg (All)	E2Val (DNG)	EE≤30µg (DNG)	NET/NETA (EE≤30µg)	LNG (EE≤30µg)	NET/NETA (E2/E2Val)	Other$_{w/o\ DRSP}$ (E2/E2Val)
23,312	449,604	21,058	43,263	61,976	84,816	12,345	19,368

These VTE and ATE endpoints were assessed in three separate cohorts:

Cohort A: E2/estradiol valerate (E2val) versus EE ≤ 30 mcg in combination with any progestin, referred to hereafter as E2/E2val (All) and EE ≤ 30 mcg (All);

Cohort B: E2val versus EE ≤ 30 mcg in combination with dienogest (DNG), referred to hereafter as E2val (DNG) and EE ≤ 30 mcg (DNG);

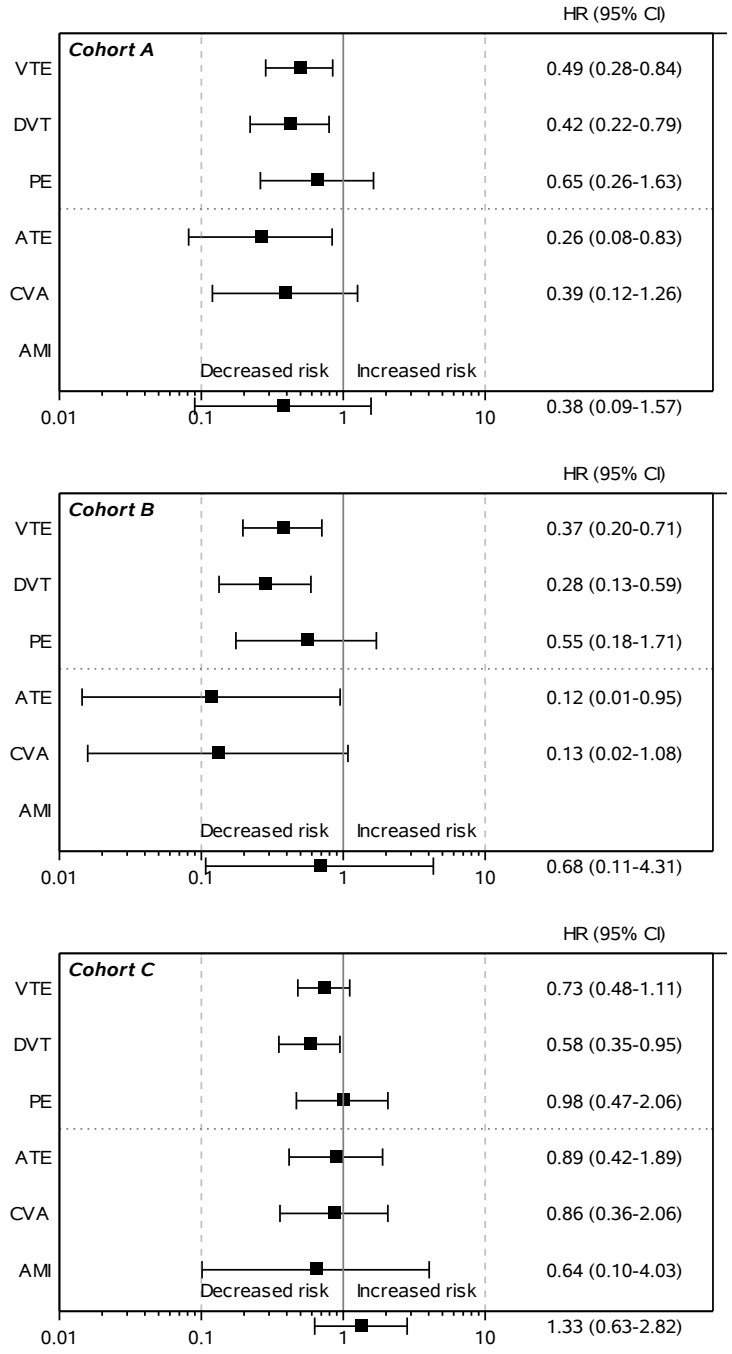
Cohort C: norethindrone (NET)/NETA versus levonorgestrel (LNG) in combination with EE ≤ 30 mcg, referred to hereafter as NET/NETA (EE ≤ 30 mcg) and LNG (EE ≤ 30 mcg).

Since the goal of this analysis was to estimate the expected safety profile of combined E2 1 mg and NETA 0.5 mg, the strategy of cohort selection was to compare safety profiles between different estrogens (E2/E2val vs. EE), while keeping the combined progestin (DNG) constant, as in Cohort B, or varying the progestin (NET/NETA vs. LNG) in combination with the same estrogen (EE ≤ 30 mcg), as in Cohort C. Cohort A is based on a comparison of E2/E2val versus EE ≤ 30 mcg in combination with any of the progestins used in the included studies.

A combination of E2 (E2 or $E2_{val}$) with any progestin is associated with significant reductions in the risk of venous thromboembolic event (VTE), deep venous thrombosis (DVT), and arterial thromboembolic event

(ATE) relative to a combined oral contraceptive containing ≤30 mcg of ethinylestradiol (EE) in combination with any progestin (Cohort A). When the same comparison is made using a standardized progestin (dienogest; Cohort B) the observed differences are even more meaningful. In a separate analysis of a combination of EE ≤30 mcg and NETA in premenopausal women (Cohort C) was associated with similar incidences of VTE and DVT and ATE relative to women receiving a combination of EE ≤ 30 mcg, and with EE ≤ 30mcg and any progestin including levonorgestrel. The combination of EE with NETA ≤ 30mcg was associated with similar incidences of VTE, DVT, ATE, and other parameters assessed to those observed with EE ≤ 30 mcg and levonorgestrel, confirming that NETA has a similar profile with regard to thrombotic and embolic events as that observed with levonorgestrel.

Table: Forest Plots of VTE and ATE Propensity Score–Stratified Hazard Ratios Including Upper and Lower Confidence Limits in Cohorts A to C



Abbreviations: AMI = acute myocardial infarction; ATE = arterial thromboembolic event; CI = confidence interval; CVA = cerebrovascular accident; DVT = deep vein thrombosis; HR = hazard ratio; PE = pulmonary embolism; VTE = venous thromboembolic event.

Phospholipidosis (PLD)

Data from nonclinical studies in rats and monkeys showed histological changes consistent with phospholipidiosis (PLD), or excess accumulation of phospholipids and drug in lysosomes. However, no clinical

evidence of relugolix-related PLD-associated toxicity has been identified in in any clinical study in the clinical development program of relugolix either as monotherapy or as relugolix combination therapy.

No clinical evidence of relugolix-related PLD-associated toxicity has been identified in in any clinical study in the clinical development program of relugolix either as monotherapy or as relugolix combination therapy. Therefore, the observation of PLD in rat and monkeys was not predictive of similar findings in human subjects.

Tumors (Breast, Liver)

In the relugolix clinical program, three participants had adverse events related to breast or liver tumors:

In ovulation study MVT-601-046, a breast mass/nodule was reported for one participant on Day 30 that resolved 2 days after the last dose of treatment and was considered by the investigator to be related to study drug.

In study MVT-601-3001, one patient in the relugolix + delayed E2/NETA group had a nonserious adverse event related to liver tumors (hemangioma of liver). The hemangioma was identified while the patient was on relugolix monotherapy during the first 12 weeks in the study; the event was discovered during evaluation of a nonserious event of gamma-glutamyltransferase increased that was considered by the investigator to be related to study drug and led to discontinuation of study drug. The event of hemangioma was ongoing at the end of the study and was considered not related to study drug.

In study MVT-601-3003, one patient from the former placebo group had a non-serious adverse event related to liver tumors (hemangioma of liver). The hemangioma was an incidental finding identified on ultrasound imaging during evaluation of hepatic transaminase elevations and was assessed by the investigator as not related to study drug; study drug was withdrawn due to this event.

No evidence of a pattern of tumor development was identified in the relugolix clinical program. No higher risk of breast and liver tumors with relugolix combination than with COCs is expected, as estradiol concentrations are lower than in the early follicular phase of the natural menstrual cycle (i.e. 20-60 pg/mL).

Mood-related disorders (depression/depressive mood)

Table: Mood-related disorders in studies MVT-601-3001 and MVT-601-3002 24 weeks

	Relugolix 40 mg+E2/NETA	**Relugolix 40 mg+Delayed E2/NETA**	**Placebo**
Preferred Term	**(N = 254)**	**(N = 258)**	**(N = 256)**
Patients with ≥ 1 AE of mood disorder, n (%)	6 (2.4%)	11 (4.3%)	4 (1.6%)
Mood swings	3 (1.2%)	2 (0.8%)	0
Depression	2 (0.8%)	4 (1.6%)	1 (0.4%)
Depressed mood	1 (0.4%)	2 (0.8%)	1 (0.4%)
Memory impairment	0	2 (0.8%)	0
Crying	0	1 (0.4%)	0
Affect lability	0	0	2 (0.8%)

Abbreviations: AE=adverse event;
E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified AE; NETA = norethindrone acetate.
Patients with multiple events for a given preferred term are counted only once for each preferred term.
Mood disorders includes depression and suicide/self-injury Standardised MedDRA Queries (SMQ) (broad).
Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

In studies MVT-601-3001 and MVT-601-3002, mood disorder-related adverse events generally associated with depression during 24 weeks of treatment were reported with similar frequency between the relugolix + E2/NETA 6 (2.4%) and placebo 4 (1.6%), with somewhat higher incidence in the relugolix + delayed E2/NETA group 11 (4.3%). The most commonly reported mood disorder-related events included mood swings, depression, and depressed mood.

In the Long-Term Combination Therapy Safety Population (including MVT-601-3003) mood disorders with onset during the extension period were reported with similar frequency across treatment groups: relugolix + E2/NETA 7 (4.7%), former relugolix + delayed E2/NETA group 5 (3.4%) and former placebo 5 (3.0%). In the extended relugolix+E2/NETA group, two patients withdrew from the open-label extension study due to events of depression.

In general, the overall incidence of mood disorders was low with relugolix combination therapy and there does not appear to be an increase in the risk of mood disorders.

However, a warning and precaution has been included as part of the SmPC, based on the potential class effect to warn women with a history of depression and discontinue relugolix combination therapy if depression recurs to a serious degree.

Gallbladder Disease

Gallstones are highly prevalent and the majority are asymptomatic. Prevalence rates vary by ethnicity, with the highest rates in US populations in Mexican American women (26.7%) and the lowest rates in US populations in non-Hispanic White women (16.6%) (Everhart et al. 1999).

Hormonal preparations, in the form of oral contraceptives, are reported to only have a transient effect on gallstone formation. Women under the age of 40 years and those taking high-dose estrogen (> 50 µg) preparations have the greatest added risk, per a retrospective cohort study with data from 1980 and 1981 (Strom et al. 1986). In support of this hypothesis, a case control study found a slightly higher incidence of gallstones shortly after oral contraceptives are started, an effect which disappeared after 10 years (Thijs et al. 1993). A similar relationship was noted in a meta-analysis of epidemiologic studies by the same authors (Thijs and Knipschild 1993). More recently, a claims database study found a small, statistically significant increase in the risk of gallbladder disease associated with desogestrel, drospirenone, and NET compared with levonorgestrel; however, small effect sizes compounded with the possibility of residual biases in this observational study led the authors to conclude that it was unlikely that these differences were clinically significant (Etminan et al. 2011). A more recent meta-analysis of 19 studies with approximately 556,620 patients concluded that oral contraceptives do not increase the risk of cholelithiasis (relative risk 1.19; (Wang et al. 2017)). The current FDA Guidance on contraceptive labeling includes a warning and precaution for gallbladder disease, citing that studies suggest a small increased relative risk of developing gallbladder disease among users of COCs (FDA 2017). Labeling for some oral contraceptive agents includes a Warning and Precautions statement that data for gallstone information are inconclusive (Qlaira SmPC 2018).

To evaluate gallbladder disease-related events, an assessment of the following MedDRA PTs in a Gallbladder related disorders SMQ (custom) was undertaken for the three phase 2 and 3 relugolix monotherapy integrated safety populations and the two phase 3 relugolix combination therapy integrated safety populations.

In the Uterine Fibroids 12-Week relugolix Monotherapy Safety Population, two gallbladder-related adverse events of biliary colic (nonserious) and cholecystitis acute (serious) were reported in two patients in the 40-mg relugolix monotherapy treatment group (2/484, 0.4%).

In the Uterine Fibroids 24-Week relugolix + E2/NETA Safety Population, one additional gallbladder disease-related adverse event of cholecystitis was reported in one patient in the relugolix + E2/NETA group. No events were reported for patients in the placebo group.

Two new adverse events of cholelithiasis and cholecystitis were reported for patients in the former relugolix + delayed E2/NETA group during the open-label extension study MVT-601-3003. Additionally, two new events of cholelithiasis were reported for patients in the former placebo group; these events had onset at approximately 4 months after initiation of relugolix combination therapy.

Summarized, 3 cases were reported in the pivotal studies of 24 weeks duration, and 4 additional events in the long-term extension.

The applicant concludes that, given the high prevalence of gallbladder disease in women of reproductive age (Stinton and Shaffer 2012 reporting highest rates in US populations in Mexican American women (26.7%) and the lowest rates in US populations in non-Hispanic White women (16.6%)), a single report of acute cholecystitis in clinical pharmacology studies, a single report of cholecystitis in the relugolix + E2/NETA group, and reports of gallbladder-related disease in the relugolix + delayed E2/NETA group (two with relugolix monotherapy and two with relugolix combination therapy including biliary colic, cholelithiasis and two reports of cholecystitis) and in the placebo group (two after initiation of relugolix combination therapy, both cholelithiasis) likely represents the background prevalence of the condition. Relugolix combination therapy decreases the systemic E2 concentrations relative to the average levels during a normal menstrual cycle (Stricker et al. 2006), maintaining E2 concentrations in a range consistent with that observed in the early follicular phase (10 - 70 pg/mL) and reduces progesterone concentrations by inhibiting ovarian function and ovulation.

No safety signal has been identified; monitoring for this potential risk will continue. Appropriate information has been included in the SmPC in this regard.

Hypersensitivity

In the Uterine Fibroids 24-Week Combination Therapy Safety Population, events of hypersensitivity found events in 2.0% (5/254) of patients treated with relugolix + E2/NETA, 0.8% (2/258) of patients treated with relugolix + delayed E2/NETA, and 3.9% (10/256) of patients treated with placebo. No serious adverse events were found.

In the Uterine Fibroids Long-Term Combination Therapy Safety Population, hypersensitivity-related adverse events were reported in 3.5% of women in the relugolix + E2/NETA group, 2.3% in the relugolix + delayed E2/NETA group, and 4.3% in the placebo group. There were no serious adverse events.

A contraindication statement for known hypersensitivity to any product components is included in the prescribing information.

Endometrial hyperplasia

Relugolix is combined with 1 mg dose of E2, and 0.5 mg dose of NETA, which provides systemic E2 concentrations, whereas the risk of endometrial hyperplasia associated with unopposed estrogen is mitigated by the addition of NETA. Endometrial histology is evaluated in the in the pivotal relugolix combination therapy studies and the extension study.

Endometrial biopsies were obtained using an endometrial suction curette (Pippelle) and read by a central laboratory for primary reading. The investigators received the results of the primary readings in real time. After the study was completed, endometrial biopsies were reviewed by a second pathologist for consensus diagnoses and when results were discordant with the first read, a third pathologist read the biopsy. In these cases, the final result was either the one provided by concordance between two of the three pathologists or the worst diagnosis in those cases were all three pathologists had discordant assessments. All pathologists were blinded to treatment assignment and to one another's assessments. In cases of three-way disagreement, the highest severity diagnosis was considered final. Any cases which included a single reviewer designation of hyperplasia or worse, or other disagreements that seemed to be significantly inconsistent, were escalated to an additional independent/blinded pathologist not involved in the review of that specific case to mediate agreement among the reviewers. Consensus endometrial biopsy data from the two replicate pivotal phase 3 studies were not pooled and are presented separately by study.

In Study MVT-601-3001

In study MVT-601-3001, endometrial biopsies were required at EOT for all patients who completed more than 6 weeks of treatment with study drug. The proportion of patients who completed the endometrial biopsy as required by the protocol was generally similar across treatment groups with only a small proportion of patients in each treatment group failing to complete the required procedures (10.2% in the relugolix + E2/NETA group, 11.4% in the relugolix + delayed E2/NETA group, and 9.4% in the placebo group) (MVT 601-3001 CSR). The consensus readings of the endometrial biopsies were generally concordant with the primary clinical readings.

Baseline and Week 24/EOT endometrial biopsy findings from consensus readings are summarized in the following table:

Table: Summary of Consensus Readings of Endometrial Biopsy Findings at Week 24/End of Treatment (Safety Population) (MVT-601-3001)

Primary Diagnosis	Relugolix + E2/NETA (N = 128)	Relugolix + Delayed E2/NETA (N = 132)	Placebo (N = 127)
Baseline			
Number of patients with biopsy findings	128 (100.0%)	132 (100.0%)	127 (100.0%)
Atrophy/Inactive	3 (2.3%)	6 (4.5%)	6 (4.7%)
Proliferative	52 (40.6%)	56 (42.4%)	40 (31.5%)
Mixed/Secretory/Menstrual	71 (55.5%)	60 (45.5%)	72 (56.7%)
Hyperplasia	0	1 (0.8%)	1 (0.8%)
Carcinoma	0	0	0
Other	0	2 (1.5%)	3 (2.4%)
Polyp	2 (1.6%)	4 (3.0%)	3 (2.4%)
Inadequate	0	3 (2.3%)	2 (1.6%)
Post baseline (Week24/EOT)			
Number of patients with biopsy findings	103 (80.5%)	101 (76.5%)	109 (85.8%)
Atrophy/Inactive	60 (46.9%)	54 (40.9%)	8 (6.3%)
Proliferative	18 (14.1%)	14 (10.6%)	51 (40.2%)
Mixed/Secretory/Menstrual	10 (7.8%)	9 (6.8%)	39 (30.7%)
Hyperplasia	0	0	2 (1.6%)
Carcinoma	0	0	0
Other	2 (1.6%)	1 (0.8%)	0
Polyp	1 (0.8%)	2 (1.5%)	0
Inadequate	12 (9.4%)	21 (15.9%)	9 (7.1%)
Missing	13 (10.2%)	15 (11.4%)	11 (8.7%)
Biopsy not required	12 (9.4%)	16 (12.1%)	7 (5.5%)

Data cut-off date: 01 Dec 2019.
Abbreviations: E2 = estradiol; N = number of patients in the treatment group; NETA = norethindrone acetate.
Percentages are based on the total number of patients in each treatment group.
Source: Table 7.1.1.4.

A greater proportion of patients in the relugolix + E2/NETA and relugolix + delayed E2/NETA groups had consensus diagnoses of atrophic/inactive endometrium compared with the placebo group. Conversely, in the placebo group, a larger proportion of patients had proliferative and mixed/secretory/menstrual findings compared with the relugolix treatment groups. The proportions of Week 24 biopsies considered inadequate according to the consensus reads were 9.4%, 15.9%, and 7.1% in the relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo groups, respectively, compared to the primary reads of 9.4%, 11.4%, and 4.7%, respectively. Two cases of endometrial hyperplasia were identified in patients in the placebo group as described below.

Endometrial hyperplasia

At screening/baseline biopsy, two patients with normal primary clinical readings (no evidence of hyperplasia) on the screening/baseline biopsy had consensus diagnoses of endometrial hyperplasia.

At the Week 24/EOT biopsy, two patients randomized to placebo had endometrial hyperplasia on the primary clinical readings, one of which was confirmed by the consensus reading.

One additional patient, , who had been randomized to placebo, had a consensus diagnosis of simple hyperplasia without atypia on the Week 24 biopsy.

No patients in the relugolix + E2/NETA or relugolix + delayed E2/NETA groups had treatment emergent endometrial hyperplasia or endometrial carcinoma.

Study MVT-601-3002

In study MVT-601-3002, endometrial biopsies were required for inclusion in extension study MVT-601-3003 but only required at the MVT-601-3002 Week 24/Early Termination visit if the endometrial thickness measured on transvaginal ultrasound at any location *was ≥ 4 mm or if any other endometrial abnormality was visualized.*

The proportion of patients not required to have a Week 24 biopsy based on protocol criteria for endometrial thickness was similar in the relugolix + E2/NETA group and the relugolix + delayed E2/NETA group (32.5% and 36.5%, respectively) while 18.6% were not required to undergo a Week 24 biopsy in the placebo group. The rate of missing biopsies was generally similar across treatment groups (16.7%, 15.1%, and 19.4% in the relugolix + E2/NETA, relugolix + delayed E2/NETA and placebo groups, respectively).

Baseline and Week 24/EOT endometrial biopsy findings from consensus readings are summarized in the following table:

Table: Summary of Consensus Readings of Endometrial Biopsy Findings at Week 24/End of Treatment (Safety Population) (MVT-601-3002)

Primary Diagnosis	Relugolix + E2/NETA (N = 126)	Relugolix + Delayed E2/NETA (N = 126)	Placebo (N = 129)
Baseline			
Number of patients with biopsy findings	126 (100.0%)	126 (100.0%)	129 (100.0%)
Atrophy/Inactive	5 (4.0%)	6 (4.8%)	4 (3.1%)
Proliferative	46 (36.5%)	48 (38.1%)	56 (43.4%)
Mixed/Secretory/Menstrual	72 (57.1%)	67 (53.2%)	67 (51.9%)
Hyperplasia	2 (1.6%)	0	0
Carcinoma	0	0	0
Other	0	2 (1.6%)	1 (0.8%)
Polyp	1 (0.8%)	2 (1.6%)	1 (0.8%)
Inadequate	0	1 (0.8%)	0
Post baseline (Week 24/EOT)			
Number of patients with biopsy findings	64 (50.8%)	61 (48.4%)	80 (62.0%)
Atrophy/Inactive	37 (29.4%)	32 (25.4%)	2 (1.6%)
Proliferative	8 (6.3%)	9 (7.1%)	32 (24.8%)
Mixed/Secretory/Menstrual	10 (7.9%)	10 (7.9%)	36 (27.9%)
Hyperplasia	0	0	1 (0.8%)
Carcinoma	0	0	0
Other	0	2 (1.6%)	0
Polyp	0	0	1 (0.8%)
Inadequate	9 (7.1%)	8 (6.3%)	8 (6.2%)
Missing	21 (16.7%)	19 (15.1%)	25 (19.4%)
Biopsy not required	41 (32.5%)	46 (36.5%)	24 (18.6%)

Abbreviations: E2 = estradiol; EOT = end-of-treatment; N = number of patients in the treatment group; NETA = norethindrone acetate.
Date of data cut-off date: 01 Dec 2019.
Percentages are based on the total number of patients in each treatment group.
Source: Table 7.1.1.4.

The consensus readings of the endometrial biopsies at end of study were generally concordant with the primary clinical readings. A greater proportion of patients in the relugolix + E2/NETA and relugolix + delayed E2/NETA groups had consensus diagnoses of atrophic/inactive endometrium compared with the placebo. Conversely, in the placebo group, a larger proportion had proliferative and mixed/secretory/menstrual findings compared with the relugolix treatment groups. The proportion of inadequate Week 24 biopsies according to the consensus reads was 7.1%, 6.3% and 6.2% in the relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo groups, respectively, compared with the primary reads of 6.3%, 4.8%, 5.4%, respectively. One case of endometrial hyperplasia was identified in a patient in the placebo group as described below.

Endometrial Hyperplasia

At screening/baseline, two patients with normal primary clinical readings (no evidence of hyperplasia) had consensus diagnoses of endometrial hyperplasia; both patients were randomized to relugolix + E2/NETA.

At the Week 24/EOT biopsy, one patient randomized to placebo had secretory cyclic type endometrium on the primary clinical reading and a consensus reading of simple hyperplasia without atypia.

No patients in the relugolix + E2/NETA or relugolix + delayed E2/NETA groups had endometrial hyperplasia or endometrial carcinoma.

Study MVT-601-3003 long-term 52 weeks

In study MVT-601-3003, an endometrial biopsy at Week 52/EOT for all patients was added in protocol Amendment 1, effective 18 Oct 2018 with implementation dependent on timing of ethical and regulatory

approval in each country. Of the 476 patients enrolled in the study, 168 patients (35.3%), were enrolled under the amendment. Patients who were enrolled under the original protocol were encouraged to comply with this requirement if the amendment were approved at their site during their participation; however, continued participation in the development program was not contingent upon their cooperation with this requirement.

A total of 216 of the 476 enrolled patients completed the Week 52/EOT endometrial biopsy as required by the protocol amendment. The proportion of patients who completed the endometrial biopsy was similar across the treatment groups (74 patients [45.4%] in the relugolix + E2/NETA group, 69 patients [46.3%] in the relugolix + delayed E2/NETA group, and 73 patients [44.5%] in the placebo group. While the endometrial biopsy was required by the protocol, some patients refused the procedure.

No cases of endometrial hyperplasia were identified at the assessments collected at the Week 52/EOT visit. There was one posttreatment endometrial biopsy collected 28 days after the last dose of study drug in MVT-601-3003, who had been randomized to relugolix + E2/NETA in MVT-601-3002 with a discordant consensus reading that included two diagnoses of benign endometrium and one diagnosis of complex hyperplasia without atypia. Additional expert assessment favoured benign endometrium.

Summarized, no cases of endometrial hyperplasia or endometrial carcinoma have been observed in patients treated with relugolix combination therapy for up to 52 weeks or initial treatment with relugolix monotherapy for 12 weeks followed by relugolix combination therapy for up to 40 weeks. Two patients in the placebo group in study MVT-601-3001 had endometrial biopsy findings of hyperplasia at Week 24. Since relugolix combination therapy leads to a reduction of systemic E2 concentrations in a range consistent with that observed in the early follicular phase of a natural menstrual cycle (Cramer et al. 2002; Stricker et al. 2006) and the inclusion in the combination of a 0.5 mg dose of NETA, it was expected that atrophic, inactive endometrium would be observed after treatment with relugolix combination therapy for up to 52 weeks.

Changes in bleeding pattern

Short-term (24 weeks)

In studies MVT-601-3001 and MVT-601-3002, changes in bleeding pattern data were used from the daily eDiary in which bleeding days and days with feminine product use were recorded, and from MBL volume measurement assessed each cycle using the alkaline hematin method. Patients were required to collect their feminine products daily in appropriately labeled and dated bags. Bleeding pattern at Week 24 is presented in the following table:

Table: Summary of Bleeding Pattern at Week 24: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002)

	Relugolix + E2/NETA (N = 254)	**Relugolix + Delayed E2/NETA (N = 258)**	**Placebo (N = 256)**
Overall n (%)	251 (98.8%)	256 (99.2%)	254 (99.2%)
Mean number of bleeding days (SD)	3.6 (5.55)	3.1 (5.32)	4.8 (2.82)
Amenorrhea n (%)	131 (51.6%)	138 (53.5%)	11 (4.3%)
Mean number of bleeding days (SD)	0.5 (1.33)	0.4 (1.02)	1.3 (1.68)
Cyclic Pattern n (%)	39 (15.4%)	39 (15.1%)	160 (62.5%)

	Relugolix + E2/NETA (N = 254)	Relugolix + Delayed E2/NETA (N = 258)	Placebo (N = 256)
Irregular Pattern n (%)	81 (31.9%)	79 (30.6%)	83 (32.4%)

Abbreviations: E2 = estradiol; eDiary = electronic diary; EOT = end-of-treatment; MBL = menstrual blood loss; N = number of patients; n = number of patients in subset; NE = not estimable; NETA = norethindrone acetate; SD = standard deviation.
Percentages are based on the total number of patients in each treatment group.
Bleeding days at Week 24/EOT is the number of days patients reported bleeding and feminine product use in eDiary during the Week 24/EOT window.
Patients with cyclic pattern did not meet definition of amenorrhea and had 3 to 12 days of bleeding per eDiary with no more than 2 consecutive non-bleeding days during the menstrual period.
Patients with irregular bleeding pattern did not meet the definition for amenorrhea or cyclic bleeding but had at least once eDiary entry during the Week 24/EOT window.

As expected with use of medication that change the systemic concentrations of sex hormones, changes in menstrual bleeding pattern were commonly observed in the relugolix treatment groups. In this population, a higher rate of amenorrhea over the last 35 days of treatment (Week 24 or end of treatment for patients who discontinued early) was observed in patients in the relugolix + E2/NETA group (51.6%) and the relugolix + delayed E2/NETA group (53.5%) compared with the placebo group (4.3%).

The proportion of patients who had a cyclic bleeding pattern during the last 35 days of treatment was 15.4% in the relugolix + E2/NETA group and 15.1% in the relugolix + delayed E2/NETA group, and the majority of these patients had spotting (< 5 mL), very light (5 - 10 mL), light bleeding (> 10 – 50 mL), or moderate bleeding (> 50 – 80 mL) rather than heavy bleeding (> 80mL). In contrast 62.5% of patients in the placebo group continued with cyclic bleeding which, in the majority of those patients, continued as heavy bleeding.

Irregular bleeding patterns were identified in about a third of patients across all three treatment groups. Although bleeding was lighter in the relugolix treatment groups, the mean number of days of bleeding for those with an irregular pattern was greater, with mean bleeding days across bleeding volume categories ranging from approximately 4-13 days in the relugolix + E2/NETA group, approximately 2-11 days in the relugolix + delayed E2/NETA group, and approximately 1-7 days in the combined placebo group.

Adverse events related to altered bleeding patterns

Adverse events related to altered bleeding patterns (PTs of menorrhagia, metrorrhagia, menometrorrhagia and menstruation irregular) were reported in 15 patients (5.9%) in the relugolix + E2/NETA group, 14 patients (5.4%) in the relugolix + delayed E2/NETA group, and 3 patients (1.2%) in the placebo group (see Table 63). Only one adverse event associated with expulsion of a uterine fibroid was reported as serious (study MVT-601-3001). This same patient reported also another serious adverse event: 'menorrhagia' .

Long-term treatment - Study MVT-601-3003

Of the 248 patients who prematurely discontinued from study treatment or did not continue into the randomized withdrawal study, menstruation status was known for higher proportions of patients in the relugolix + E2/NETA and relugolix + delayed E2/NETA groups (80.8% and 79.1%, respectively) than for the placebo group (72.6%). The proportion was lowest for the placebo group because a higher proportion in the placebo group were either lost to follow-up or declined further follow-up than in the relugolix groups

Of the patients for whom the menstruation status was available, 61 patients (96.8%), 66 patients (97.1%), and 57 patients (93.4%) in the relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo groups, respectively, reported having post-treatment menses. The median (mean) time from last dose of study

treatment to occurrence of menses was similar across the groups, 34 days (40.5), 33.5 days (40.6), and 34.0 days (36.9), respectively.

Amenorrhea over the last 35 days of treatment was reported by 60.3%, 64.7%, and 44.3% of patients in the relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo groups, respectively. The time to occurrence of post-treatment menses was longer in these patients than for patients without amenorrhea over the last 35 days of treatment in the relugolix groups (36 days [45.6] vs 30.0 days [32.6], respectively, for relugolix + E2/NETA; 35.0 days [44.3] vs 27.5 days [33.2] for relugolix + delayed E2/NETA) and similar in the placebo group (34.0 days [34.9] vs 34.0 days [38.7]).

Nine patients did not have return of menses after completing study treatment, due to surgery (n=7), menopause (n=1), or medication (n=1).

Serious adverse events and deaths

No fatal cases have been reported in the studies conducted for women's health indications.

A summary of serious adverse events by SOC and PT for the Uterine Fibroids 24-Week Combination Therapy Safety Population is presented below.

Table: Serious Adverse Events by System Organ Class and Preferred Term: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002)

System Organ Class Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Patients with ≥ 1 serious adverse event, n (%)	8 (3.1%)	5 (1.9%)	6 (2.3%)
Blood and lymphatic system disorders	0	0	1 (0.4%)
Anaemia	0	0	1 (0.4%)
Endocrine disorders	1 (0.4%)	0	0
Hypothyroidism	1 (0.4%)	0	0
Eye disorders	1 (0.4%)	0	0
Vitreous detachment	1 (0.4%)	0	0
Gastrointestinal disorders	1 (0.4%)	0	0
Haematemesis	1 (0.4%)	0	0
Hepatobiliary disorders	1 (0.4%)	1 (0.4%)	0
Cholecystitis	1 (0.4%)	0	0
Cholecystitis acute	0	1 (0.4%)	0
Infections and infestations	0	1 (0.4%)	2 (0.8%)
Appendicitis	0	1 (0.4%)	0
Necrotising fasciitis	0	0	1 (0.4%)
Pneumonia	0	0	1 (0.4%)
Injury, poisoning and procedural complications	1 (0.4%)	1 (0.4%)	1 (0.4%)
Ankle fracture	1 (0.4%)	1 (0.4%)	0
Avulsion fracture	1 (0.4%)	0	0
Radius fracture	0	0	1 (0.4%)

System Organ Class Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Road traffic accident	0	0	1 (0.4%)
Musculoskeletal and connective tissue disorders	1 (0.4%)	1 (0.4%)	0
Rhabdomyolysis	1 (0.4%)	0	0
Intervertebral disc degeneration	0	1 (0.4%)	0
Intervertebral disc protrusion	0	1 (0.4%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.8%)	0	0
Uterine leiomyoma	1 (0.4%)	0	0
Uterine myoma expulsion	1 (0.4%)	0	0
Nervous system disorders	0	0	1 (0.4%)
Syncope	0	0	1 (0.4%)
Psychiatric disorders	0	1 (0.4%)	1 (0.4%)
Panic attack	0	1 (0.4%)	0
Acute psychosis	0	0	1 (0.4%)
Reproductive system and breast disorders	2 (0.8%)	0	0
Menorrhagia	1 (0.4%)	0	0
Pelvic pain	1 (0.4%)	0	0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate.
Patients with multiple events for a given Preferred term or System organ class are counted only once at each level of summarization.
MedDRA version 22.0.

Serious adverse events considered related to study drug were reported for two women (0.8%) in the relugolix + E2/NETA group: uterine myoma expulsion and pelvic pain. A uterine leiomyoma (prolapse) (not related) was reported in study MVT-601-3001 for a patient in the relugolix + E2/NETA group, considered not related.

Serious adverse events in the relugolix + delayed E2/NETA and placebo groups were all considered not related to study drug.

Long-term (up to 52 weeks) use

Serious adverse events with onset during the long-term extension study (MVT-601-3003) were reported for one patient in the former relugolix + E2/NETA group, five patients in the former relugolix + delayed E2/NETA group, and 11 patients in the former placebo group. The greater incidence of serious adverse events in the placebo group during the long-term extension study is mainly driven by serious adverse events across multiple SOCs. Except for the adverse events consistent with uterine bleeding in three patients after initiation of treatment with relugolix combination therapy, in general, all reported serious adverse events are reflective of general conditions that are unlikely to be related to treatment.

Serious adverse events assessed by the investigator as related to study drug were reported for four patients during the long-term extension study: a serious adverse event of uterine hemorrhage (Patient in the former

relugolix + E2/NETA group), a serious adverse event of cholecystitis (Patient in the former relugolix + delayed E2/NETA group), and serious adverse events of menorrhagia and blood pressure increased, both in the former placebo group.

Laboratory findings/vital signs/ECG findings

Laboratory findings

In the clinical program, there were no obvious treatment or dose-related trends in clinical laboratory test parameters and vital sign measurements at doses up to 360 mg (single dose) or 180 mg (multiple dose) for relugolix monotherapy.

Hematology

With relugolix combination therapy, assessment of results of clinical laboratory parameters in blood chemistry did not show a significant trend of concern. In hematology, over time, progressive increases in hemoglobin and hematocrit over time, with progressive reductions in platelet counts were observed with relugolix combination therapy group compared with no change with placebo. These changes were reflective of the improvement of heavy menstrual bleeding associated with relugolix combination therapy.

Following up to 52 weeks of treatment in the Uterine Fibroids Long-Term Combination Therapy Safety Population, there were clinically significant increases from baseline in hemoglobin and hematocrit levels and decreases in platelets as a result of the significant reductions in MBL volume observed with relugolix combination therapy. The proportions of patients meeting predefined limits of change for hematology parameters were consistent with the changes observed in mean changes from baseline.

Vital signs

In the relugolix monotherapy populations, no meaningful changes from baseline up to 24 weeks or proportions of patients with abnormal values in vital sign measurements were observed in any treatment group and no meaningful differences were observed between treatment groups.

Similarly, in the relugolix combination therapy populations, no meaningful changes from baseline up to 52 weeks or proportions of patients with abnormal values in vital signs were observed in any treatment group and no meaningful differences were observed between treatment groups.

BMI

Special attention was given to the body mass index (BMI). At baseline, BMI was comparable between groups in both studies MVT-601-3001 and MVT-601-3002. In study MVT-601-3001, mean BMI was 31.4 (range 17 to 63) in the relugolix + E2/NETA group, 31.4 (range 18 to 52) in the relugolix + delayed E2/NETA groups, and 32.3 (range 19 to 55) in the placebo group. In study MVT-601-3002, mean BMI was 31.0 (range 17 to 49) in the relugolix + E2/NETA group, 30.7 (range 19 to 50) in the relugolix + delayed E2/NETA group, and 32.1 (range 16 to 60) in the placebo group.

Change from baseline in BMI through up to 52 weeks of study drug treatment in the open-label extension study were consistent with those in studies MVT-601-3001 and MVT-601-3002 and there was no apparent trend in a disproportionate change over time.

In the relugolix combination therapy populations, no meaningful change from baseline in BMI up to 52 weeks was observed in any treatment group and no meaningful differences were observed among treatment groups.

In summary, changes from baseline in BMI were small and similar in the three treatment arms and over the 52 week period. No safety issues or trends could be observed.

ECG

During the two phase 3 relugolix 24-week combination therapy studies, ECGs were obtained at baseline, Week 12, and Week 24. No patients in any treatment group had a QTcF excursion > 501 msec at any of the assessed time points with up to 24 weeks of treatment with study drug. A change from baseline of ≥ 30 msec was reported in comparable number of patients across treatment groups, including 5.9% (15/254) of patients treated with relugolix + E2/NETA, 5.0% (13/258) of patients treated with relugolix + delayed E2/NETA, and 4.3% (11/256) of patients treated with placebo); these changes were not assessed as clinically meaningful.

A change from baseline of ≥ 60 msec was reported for one patient (MVT-601-3001) in the relugolix + delayed E2/NETA group. At baseline, the ECG showed normal sinus rhythm with normal T wave morphology with a heart rate of 68 bpm and QTcF of 383 msec. The patient was reportedly dosed 14 minutes before the baseline ECG, and therefore the screening ECG with QTcF of 367 msec was used as the reference baseline. At Week 12, this woman had a QTcF value of 439 msec, a 72 msec increase from the reference baseline (screening) and a 56 msec increase from the baseline visit. The prolongation relative to the reference baseline persisted; at Week 24 the QTcF interval was 440 msec (73 msec increase from reference baseline and 57 msec from the baseline visit), and at the safety follow-up visit the QTcF was 436 msec (69 msec increase from reference baseline and 53 msec from the baseline visit). No adverse events suggestive of arrhythmia were reported.

In the Uterine Fibroids Long-Term Safety Population (MVT-601-3003 extension study), QTcF results with the addition of up to 28 weeks of exposure are consistent with those in the Uterine Fibroids 24-Week Safety Population, with no clinically significant changes in QTcF identified in this population which received relugolix combination therapy for up to 52 weeks.

Overall, no clinically significant changes in QTcF were identified during these studies.

QTcF data in a thorough QT/QTc stud

This is in line with the results of a thorough QT/QTc study (TAK-385_106) that was performed. The study did not suggest for any QT prolonging effect of relugolix with point estimates for the corrected ddQTcF around 5 ms and thus far below the 10 ms for regulatory concern.

Safety in special populations

Pregnancy

Although during the use of relugolix+E2/NETA, pregnancy is not expected, as the results of the pharmacodynamic ovulation inhibition study MVT-601-046 indicated ovulation was inhibited in 100% of 84 women who participated, women had to use adequate contraception throughout the clinical studies.

However, concomitant treatment with combined hormonal contraceptives is contraindicated, since the effect of additional hormones on the efficacy of relugolix combination therapy is unknown and the safety of concomitant use has not been established. Therefore, in studies 601-3001, 601-3002, 601-3003, medication and devices containing hormones for contraception were excluded, and patients had to agree to use non-hormonal contraception throughout the study, including through 30 days following the last dose of study drug.

An overview of the clinical trial pregnancies reported in the relugolix clinical development program as of 31 Oct 2020, including contraceptive method used, dosing compliance, and pregnancy outcome is provided in the table below.

As of this data cut-off date, a total of 29 pregnancies have been reported overall in the relugolix clinical development program:

- 3 pregnancies in the phase 3 uterine fibroid program,
- 1 pregnancy in a phase 2 uterine fibroid dose-finding study, and
- 25 pregnancies in the phase 3 endometriosis program.

Of these 29 pregnancies:

- 13 were in women who became pregnant during treatment with relugolix (as monotherapy or in combination with E2/NETA or with delayed E2/NETA),
- 1 was in a woman who became pregnant prior to initiating treatment with relugolix,
- 4 were in women who became pregnant after completing treatment with relugolix,
- 10 were in women who were in a placebo group, and
- 1 was in a woman participating in the randomized withdrawal study (MVT-601-035) while the patient was receiving blinded treatment with relugolix combination therapy or placebo (the patient discontinued treatment; sponsor remains blinded to treatment assignment).

The contraceptive properties of relugolix combination therapy are driven by the action of relugolix on suppressing ovarian function. Noting that all clinical trial participants were to use nonhormonal contraception and that in the ovulation inhibition study with relugolix combination therapy (MVT-601-046) ovulation was inhibited 100% of the time, indicating that pregnancy is unlikely, an assessment was made of the pregnancies reported in women during treatment with relugolix.

Of the 13 pregnancies in women who became pregnant during treatment with relugolix, 3 were reported in women assigned to relugolix monotherapy (one on 10 mg relugolix and two on 40 mg relugolix), and 10 in women assigned to relugolix combination therapy:

- 1 pregnancy was reported in a participant assigned to treatment with relugolix 10 mg monotherapy, a dose that incompletely inhibits ovulation.
- 1 participant initiated relugolix monotherapy on Day 8 of her menstrual cycle and conceived 7 days later, suggesting relugolix may not have been started early enough in the cycle to suppress ovulation.
- 8 participants in the phase 3 endometriosis program were receiving relugolix (1 patient) or relugolix combination therapy (the 7 other patients) failed on multiple occasions in the 28 days prior to conception to make diary entries where they confirmed whether or not they were compliant with dosing and/or they made a diary entry where they confirmed doses were missed, suggesting compliance with study drug administration may have led to escape ovulation.
- 1 participant had an estimated date of conception on study Day 537 in the open label extension study. Patient stated compliance with use of condoms and diary entries indicated good compliance with relugolix combination therapy.

- 2 participants (; each randomized to relugolix combination therapy) reported that they were pregnant but were never seen at the site for pregnancy testing. Neither provided any information on compliance with study drug or contraceptive measures and were lost to follow-up, thus, conclusions are limited.

In five pregnancies, it was determined that estimated conception dates occurred either prior to first dose or after the last dose of relugolix:

- 1 participant had an estimated conception date that occurred prior to the first dose of relugolix combination therapy (during the placebo run-in period of endometriosis indication study MVT-601-3101);
- 4 participants had estimated conception dates that occurred after completing treatment with relugolix combination therapy (range: 13-24 days after the last dose of study drug).

Of the 10 pregnancies in women who became pregnant in the placebo group, 2 conceived during the placebo run-in period of endometriosis indication studies and 8 were the apparent result of noncompliance with or failure of nonhormonal contraception. One pregnancy is ongoing in blinded study MVT-601-035 as previously noted.

In summary, in 10 of the 13 participants who became pregnant during treatment with relugolix monotherapy or relugolix combination therapy for whom information is available, there is evidence to suggest that, in nearly all cases, issues with the dose (N = 1), timing of initiation of therapy (N = 1), or compliance with dosing (N = 8) were identified as reasons that ovulation was not suppressed during treatment and, in addition to failed barrier contraception, pregnancy occurred.

Immunological events

Not applicable

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to AES

Table: Adverse Events with Action Taken of Study Treatment Discontinuation in at Least 1% of Patients in Any Treatment Group by System Organ Class and Preferred Term: Uterine Fibroids 24-Week Combination Therapy Safety Population (MVT-601-3001, MVT-601-3002)

System Organ Class Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
Patients with ≥ 1 adverse event leading to study treatment discontinuation, n (%)	10 (3.9%)	30 (11.6%)	11 (4.3%)
Gastrointestinal disorders	1 (0.4%)	4 (1.6%)	2 (0.8%)
Nausea	0	3 (1.2%)	0

System Organ Class Preferred Term	Relugolix 40 mg+E2/NETA (N = 254)	Relugolix 40 mg+Delayed E2/NETA (N = 258)	Placebo (N = 256)
General disorders and administration site conditions	2 (0.8%)	10 (3.9%)	1 (0.4%)
Fatigue	1 (0.4%)	5 (1.9%)	0
Nervous system disorders	2 (0.8%)	7 (2.7%)	1 (0.4%)
Migraine	0	4 (1.6%)	0
Vascular disorders	1 (0.4%)	8 (3.1%)	0
Hot flush	1 (0.4%)	6 (2.3%)	0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate. Patients with multiple events for a given Preferred term or System organ class are counted only once at each level of summarization.
Adverse events with action taken of study treatment discontinuation are taken from the adverse event case report form. MedDRA version 22.0.

The incidence of adverse events leading to discontinuation over 24 weeks on relugolix+E2/NETA (3.9%) was low and similar to that observed with placebo (4.3%).

The differences observed in the incidence of AEs leading to discontinuation in patients who received relugolix monotherapy (even for only 12 weeks), suggest that the addition of E2/NETA as add-back therapy provides better tolerability.

MVT-601-3003

In the Uterine Fibroids Long-Term Combination Therapy Safety Population, adverse events leading to study drug discontinuation reported in the relugolix + E2/NETA group over up to 52 weeks of treatment were generally consistent with those reported over the initial 24 weeks of treatment, and the numerical increases in incidence are reflective of the increased exposure (up to 28 additional weeks). The proportion of patients in this treatment group who had adverse events leading to study drug discontinuation during the initial 24-weeks of treatment (3.9%) was similar to that in the long-term extension study (3.1%).

Post-marketing experience

Relugolix 40-mg monotherapy (Relumina) was launched in Japan on 01 March 2019 for the treatment of symptoms associated with uterine fibroids (hypermenorrhea, lower abdominal pain, lower back pain, and anemia). Label precautions include general limitation of treatment to a 6-month period due to the risk of loss of bone mineral density. Postmarketing data for the expected hypoestrogenic state associated with relugolix monotherapy do not apply directly to relugolix combination therapy, which was designed to prevent the hypoestrogenic risks associated with monotherapy.

A total of 6,293,000 of Relumina tablets have been shipped since launch (01 March 2019 to 07 July 2020). Assuming that one tablet was taken daily based on the product labelling, the estimated patient exposure was 6,293,000 patient days, or 17,241 patient years.

A search of the global safety database for post-marketing reports, using the Osteoporosis/osteopenia standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) (broad), Vasomotor symptoms SMQ (custom) and the preferred terms (PTs) of Alopecia, Arthralgia, and Oestrogen deficiency

(latter not otherwise specified) was performed with a data cut-off of 31 August 2020. All events were nonserious.

Table: Summary of Global Safety Database Search (Postmarketing)

MedDRA PT or SMQ	Search Results	Incidence in Patient-Years
Osteoporosis/osteopenia SMQ	0	0
Vasomotor symptoms SMQ (custom)[a]	22 (18 hot flush, 3 hyperhidrosis, 1 feeling hot)	1.3/1000
Alopecia (PT)	2	0.1/1000
Arthralgia (PT)	12	0.7/1000
Oestrogen deficiency (PT)	6	0.3/1000

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = standardised MedDRA query. a Vasomotor symptoms SMQ (custom) inclusive of PT Hyperhidrosis, Feeling hot, Hot flush, Night sweats, and Flushing.

Given the mechanism of action as a gonadotropin-releasing hormone (GnRH) receptor antagonist taken as monotherapy and consistent with the approved labelling, the use of relugolix (Relumina) 40 mg once daily for the indication of symptomatic uterine fibroids has been associated with signs and symptoms associated with a hypoestrogenic state. There have been no post-marketing reports of events associated with the identified risk of loss of bone mineral density, per the Osteoporosis/osteopenia SMQ.

The safety data from post-marketing reports with Relumina associated with a hypoestrogenic state have not identified a new signal for Ryeqo.

2.6.1. Discussion on clinical safety

Patient exposure

In the clinical program, a total of 888 patients received at least one dose of relugolix combination therapy. In studies in women with uterine fibroids, 634 patients received at least one dose of relugolix combination therapy, 451 were exposed for at least 6 months, and 130 were exposed for at least a year.

Studies MVT-601-3001 and MVT-601-3002 enrolled N=770 subjects for 24 weeks, extension study MVT-601-3003 enrolled N=477 subjects for 28 weeks (in total 52 weeks). For studies MVT-601-3001, MVT-601-3002, MVT-601-3003, the median duration of treatment exposure to daily relugolix combination therapy was 52.21 weeks for the relugolix+E2/NETA group, 39.07 weeks for the relugolix+delayed E2/NETA group and 28.36 for the placebo group.

Of the 363 patients who completed the extension study, 228 patients entered the 52-week, placebo-controlled withdrawal study MVT-601-035, which is completed in February 2021. A top-line summary of this study was provided during the procedure.

Safety profile

Relugolix is a GnRH antagonist which use leads to a postmenopausal state in premenopausal women, with consequent risk BMD loss (and occurrence of vasomotor symptoms). Addition of E2/NETA is meant to mitigate the BMD loss and to decrease postmenopausal symptoms.

Main safety data

The main safety data set of relugolix combination therapy is based on the pooled data of the two randomized, double-blind, phase 3 pivotal studies MVT-601-3001 and MVT-601-3002 with duration of 24 weeks and the data from the 52 week open label extension study MVT-601-3003 (which includes the patients who participated in the double blind period and continued in the open extension).

A prospective, observational study Study MVT-601-034 was undertaken to characterize longitudinal BMD in a cohort of premenopausal women aged 18-50 years with uterine fibroids. These women were enrolled concurrently with the clinical studies at a subset of the participating study sites.

As a top line summary of the double-blind placebo-controlled study MVT-601-035 (withdrawal study) was submitted during the procedure, this study is not included in the pooled safety data.

Pooled safety data of both phase 3 studies with 24 weeks treatment duration

Adverse events

Short term safety over 24 weeks in placebo-controlled setting

The overall incidence of AEs over a treatment period of 24 weeks was comparable between the relugolix + E2/NETA group (61.0%) and the placebo group (62.5%), but higher in the relugolix + delayed E2/NETA group (72.1%). The higher incidence in the latter group was due to the relugolix monotherapy treatment period (12 weeks) leading to a higher number of AEs related to postmenopausal symptoms.

Hot flush was the most common drug-related AE reported and inherent to the lowering of estrogen levels. The difference between relugolix monotherapy (relugolix + delayed E2/NETA group, 12 weeks) and relugolix combination therapy (7.9% versus 36%) was significant and indicates that the addition of E2/NETA considerably reduces the frequency of postmenopausal symptoms. The difference between relugolix +E2/NETA and placebo was small, i.e. 7.9 versus 5.9%, and as expected.

Other drug-related AEs reported >1% of patients in the relugolix+E2/NETA group vs placebo were headache (7.1 vs 7.0%), nausea (2.8 vs 3.9%), alopecia (2.8 vs 0.8%), menorrhagia (2.8 vs 0%), hypertension (2.4 vs 0.8%), abdominal pain (2.4 vs 0.4%), libido decreased (2.0 vs 0%), hyperhydrosis (2.0 vs 0.8%), anxiety (1.2 vs 0.4%), weight increased (1.2 vs 0.4%), blood creatine phosphokinase increased (1.2 vs 0.4%), insomnia (1.2 vs 0.8%), menstruation irregular (1.2 vs 0.4%), and mood swings (1.2 vs 0%).

Serious AEs were reported in 8 (3.1%) of the relugolix+E2/NETA group, in 5 (1.9%) of the relugolix + delayed E2/NETA group and 6 (2.3%) on placebo. Two (0.8%) SAEs related to study drug were reported in the relugolix + E2/NETA group: uterine myoma expulsion and pelvic pain. Serious adverse events considered related to study drug were reported for two women (0.8%) in the relugolix + E2/NETA group: uterine myoma expulsion and pelvic pain. A uterine leiomyoma (prolapse) (not related) was reported in study MVT-601-3001 for a patient in the relugolix + E2/NETA group, considered not related. Prolaps and expulsion is considered inherent to the disease and not related to the study medication. A warning has been included in the SmPC. No deaths were reported in the two pivotal phase 3 studies.

In general, the adverse events profile of relugolix-E2/NETA as reported during 24 weeks of treatment did not contain clear signals for concern. The adverse events are in line with the mechanism of action, (i.e. due to hypo-estrogenic state).

Long term safety (uncontrolled extension study MVT-601-3003)

In the relugolix + E2/NETA group, cumulatively over the 52-week treatment period, at least 1 adverse event was reported for 127 patients (77.9%). About half of the patients in this group (89 patients [54.6%]) had 1 adverse event during participation in the open-label extension study. In the relugolix + delayed E2/NETA group, at least 1 adverse event was reported for 125 patients (83.9%) over the 52-week treatment period encompassing the parent and open-label extension studies. During participation in the open-label extension study, at least 1 adverse event was reported for 72 patients (48.3%). In the placebo group, at least 1 adverse event was reported for 138 patients (84.1%) during the parent and extension studies. During participation in the open-label extension study, at least 1 adverse event was reported for 103 patients (62.8%).

In the patients who had received relugolix-E2/NETA for 52 weeks (the former relugolix + E2/NETA group), drug-related adverse events were reported for 73 patients (44.8%), of which 36 (22.1%) in the open-label extension study. The most frequently reported drug-related adverse events were hot flush (18 patients [11.0%]) and headache (15 patients [9.2%]). In 4 patients (2.5%), hot flush was first reported during the open-label extension study. Headache was first reported during the open-label extension study in 2 patients (1.2%). It should be noted that the incidence of headache over 52 weeks in the relugolix + E2/NETA group was lower than that observed with placebo over the first 24 Weeks (13.3%).

The adverse event profile over 52 weeks in any group was consistent with that observed over the first 24 weeks of treatment. No significant findings suggesting an exposure- or duration-related safety trend of concern were observed.

The top-line summary data suggest that the adverse event profile over 104 weeks in any group was consistent with that observed over the first 52 weeks of treatment. No significant findings suggesting an exposure- or duration-related safety trend of concern were observed.

Adverse events of special interest

Relugolix is a GnRH antagonist which use leads to a postmenopausal state in premenopausal women, with consequent risk of bone mineral density (BMD) loss and occurrence of vasomotor symptoms. Addition of E2/NETA is added to mitigate the BMD loss (and to decrease postmenopausal symptoms).

Bone mineral density loss

- ***Adverse events due to BMD loss:***

During 24 weeks, AEs related to bone loss were most commonly reported in relugolix + delayed E2/NETA group (6 (2.3%), when compared with the relugolix + E2/NETA: 2 (0.8%) and placebo: 3 (1.2%) group. A similar pattern was observed for the 28-week extension period, where no new adverse events related to bone loss (ankle fracture, avulsion fracture, wrist fracture, bone density decreased, bone loss, facial bones fracture, osteopenia, radius fracture) were reported for the patients in the relugolix + E2/NETA group, 4 new reports in the former relugolix + delayed E2/NETA group and 1 new report in the former placebo group.

The higher value in the former relugolix + delayed E2/NETA group may be attributed to the 12 initial weeks were relugolix was used without the protective effect of E2/NETA as add-back therapy.

- ***Loss of BMD (measurements by DXA):***

  - *Short-term up to 24 weeks*

In the 12 week relugolix monotherapy (relugolix + delayed E2/NETA group), bone loss observed in lumbar spine was significantly greater than noted with relugolix + E2/NETA (-2.0% vs -0.5%, p < 0.0001, study MVT-601-3001), suggesting the protective effect of this HRT as add-back therapy. Only small decreases in BMD between relugolix + E2/NETA versus placebo (BMD at the lumbar spine Week 12: −0.5% vs. 0.2%; Week 24: −0.4% vs. 0.1%, study 601-3001) were noted, which supports a protective effect of E2. Comparable effects on bone loss were noted in study 601-3002. For total hip measurements a similar pattern was noted.

  - *Long-term-term up to 52 weeks*

Regarding long-term use, the most informative patient group is the one in which patients were initially treated with relugolix + E2/NETA and entered the extension study 3003. They received up to a maximum of 52 weeks of treatment with relugolix + E2/NETA. In this patient group, LS mean percent changes from Baseline in BMD to Week 36 and Week 52 at the lumbar spine were -0.726% and -0.804%, respectively. These outcomes in both treatment arms indicate a slight decrease in BMD upon use up to 52 weeks, suggesting that further decrease in BMD cannot be excluded with use beyond 52 weeks. Further, a decrease in BMD is noted in the treatment group who initially received placebo in the 24 week double blind phase of both studies. In the patient group who initially received placebo for 24 weeks in the double-blind phase, BMD values were -0.293% (Week 36), and -0.823% (Week 52), also suggesting that further decrease in BMD cannot be excluded. Therefore, the conclusion of the Applicant that the observed BMD loss in the phase 3 studies with relugolix combination therapy displayed a plateau starting at Week 12 and continuing through Week 52, in the rate of change in BMD, is not shared. Based on the currently submitted data no definite conclusions can be drawn whether the decrease in BMD of around 1% noted over 52 weeks compared to baseline already has reached a plateau. Further data are needed beyond 52 weeks of treatment to establish whether the decrease in BMD remains in the range that is currently observed over 52 weeks of treatment. The provided BMD simulation based on E2 levels for a period of 36 months treatment is not considered robust evidence to overcome the lack of clinical data beyond 52 weeks of treatment.

  - *Comparison of BMD loss over 52 weeks (MVT-601-3003) versus natural history study (MVT-601-034)*

A 1-year prospective, observational study was undertaken to characterize longitudinal BMD in a cohort of premenopausal women with uterine fibroids (natural history study). These women were enrolled concurrently with the clinical studies at a subset of the participating study sites. As age is a risk factor for BMD change over time, the population was age-matched to interpret the extent of BMD change that may be attributed to drug treatment. Age-related BMD increases were observed in the younger population (< 10% of participants) and slight decreases in BMD were observed in those 35-44 years and ≥45 years of age. Compared to baseline values, the decrease in BMD noted over 52 weeks treatment in the relugolix + E2/NETA age groups of 35 to < 40 years, 40 to < 45 years, and 45 to < 52 years was only slightly larger in comparison to these age groups in the natural history study (MVT-601-034). This is reassuring, but does not provide data beyond 52-weeks. With regard to the uncertainty as to whether a plateau in BMD has been achieved by Week 52, the applicant conducted additional analyses on the available data over 52 weeks to further substantiate that there is a plateau in BMD to be seen after Week 12 through Week 52 and that this is expected to continue through an additional 52 weeks of observation in Study MVT-601-035.

However, the concerns regarding observed BMD loss remained, in the sense that these analyses, however well-performed, cannot replace actual long-term clinical data beyond 52 weeks.

In order to respond to these concerns, top-line summary results were submitted during the procedure of the recently completed double-blind, placebo-controlled withdrawal study (MVT-601-035), which provided information on BMD outcomes with a second year of treatment with Ryeqo:

- *BMD loss with Long term use up to 104 weeks*

- This top-line summary of results on BMD measurements over 104 weeks (from week 52 to week 104) treatment with relugolix + E2/NETA indicated that a plateau in BMD decrease has been reached after the first treatment year of around 1%, which is also seen in the subgroup of 32 patients who received relugolix + E2/NETA from for up to 104 weeks. Cumulatively, the mean percent change in BMD from pivotal study baseline to up to Week 104 in patients who received relugolix + E2/NETA (n = 32) was 0.04%. These results could support a registration for unlimited duration of use, but results are based on a selected population, as women with osteoporosis or risk factors for osteoporosis were not allowed to participate, women in the trials who experienced a Z-score of -2 or BMD loss ≥7% were discontinued and/or not allowed to enter the extension study or withdrawal study, and the final number of patients treated with relugolix + E2/NETA for up to 104 weeks is limited to 32 patients. Further, as women with significant effects on BMD had to discontinue, it is unknown whether in these women the observed decrease in BMD would further progress.
- In conclusion, the data from the BMD measurements sufficiently support the rationale of the addition of E2/NETA to relugolix to reduce the adverse effect of relugolix monotherapy on BMD for a period of 52 weeks treatment. The summary data on BMD effects of relugolix + E2/NETA over a treatment period of 104 weeks of study MVT-601-035, although limited, support that a plateau in BMD decrease of around 1% has been reached by showing no further decline and stability in BMD loss after treatment of 52 weeks, which could support a registration for unlimited duration of use. However, considering the selected population, the limited number of patients and lack of information whether in women, who had to discontinue due to significant BMD loss, decrease in BMD would further progress with continued treatment, an additional RMM is recommended in the SmPC; to perform a DXA after 12 month treatment.

- ***Significant BMD loss of >3%***

  - *At Week 24 (categorized per treatment group)*

The proportions of women who had BMD loss of > 3% to ≤ 5% (12.3% and 6.6% of patients, respectively) and > 5% to ≤ 8% (3.6% and 2.5% of patients, respectively) in the relugolix + E2/NETA and placebo groups. No study patients in the relugolix + E2/NETA or placebo groups had losses > 8%.

Women who received relugolix + delayed E2/NETA, a higher proportion had changes of > 3% to ≤ 5% and >5% to ≤ 8% (21.6% and 12.4%, respectively); 2.6% of patients in the relugolix + delayed E2/NETA group had BMD losses at the lumbar spine > 8%.

  - *At Week 52 (categorized per treatment group)*

In the relugolix + E2/NETA group after 52 weeks, the proportion of women who had BMD losses of >3% to ≤ 5% and >5% to ≤8% (34 patients [25.4%]) and (7 patients [5.2%]), respectively, that remained relatively unchanged over time.

In the former placebo group (after 28 weeks of relugolix + E2/NETA use), some women had losses of > 3% to ≤ 5% and > 5% to ≤ 8% (32 patients [29.4%]) and (13 patients [11.9%]). Two patients (1.7%) had losses that were > 8% at Week 52.

Relugolix + E2/NETA

Small percentages of women had losses of > 3% to ⩽ 5% (34 patients [25.4%]) and > 5% to ⩽ 8% and (7 patients [5.2%]), respectively, that remained relatively unchanged over time. The following patient (0.8%) had BMD loss that was > 8% after Week 52:

- One patient had 10.9% loss at the lumbar spine and 10.7% loss at the femoral neck. The patient was noted to have lost 5.5 kg and the Week 52 DXA was performed on a different scanner from the baseline study.

Former placebo group (24 weeks placebo followed by 28 weeks of relugolix + E2/NETA use):

Small percentages of women had losses of > 3% to ⩽ 5% and > 5% to ⩽ 8% (32 patients [29.4%]) and (13 patients [11.9%]), respectively, changes that may reflect the new steady state of estradiol with exogenous hormone administration as part of relugolix combination therapy. Two patients (1.7%) had losses that were > 8% at Week 52:

  - One patient had 8.5% loss at the lumbar spine (2.9% loss at Week 24). Low vitamin D and 7.16% weight loss were identified as a risk factor;
  - One patient had 8.4% loss at the lumbar spine (5.2% loss at Week 24). Low vitamin D was identified as a risk factor. Additionally, the patient's high BMI (50.49 kg/m2) may have contributed to measurement error as a confounder.

- *At Week 104 (categorized per treatment group) withdrawal study*

At the end (Week 104) of the withdrawal study (MVT-601-035), in the subgroup of patients (n=32) who had taken the relugolix + E2/NETA for up to 104 weeks, 1 patient (3.1%) had a BMD loss of > 5% to ≤ 8%.

Significant BMD loss (Z-score > -2 and/or ≥ 7% decrease in BMD at any site) in parent studies, which precluded entering long-term extension study 3003 or withdrawal study (035)

- *At Week 24 (categorized per treatment group)*

During the initial 24 week studies, 11 patients in the relugolix + E2/NETA group had Z-score > -2 and/or ⩾ 7% decrease in BMD, which made them not eligible for the extension study.

- *At Week 52 (categorized per treatment group)*

In the extension study 3003, 6 patients (3.7%) in the relugolix + E2/NETA group met criteria for discontinuation at Week 36 due to BMD loss ⩾ 7% at any anatomic site. Additionally, 3 patients (1.8%) were not eligible to continue into the withdrawal study MVT-601-035 at Week 52 due to BMD loss > 7%. Six patients (3.7%) had BMD loss >3% at the lumbar spine or total hip and discontinued early or did not enter study MVT-601-035 and required safety follow-up.

In the former placebo group, 5 patients (3.0%) met criteria for discontinuation at Week 36 due to bone loss (BMD loss ⩾ 7% at any anatomic site). Seven patients (4.3%) were not eligible to continue into study MVT-601-035 at Week 52 due to bone loss (BMD loss ⩾ 7% at any anatomic site). Six patients (3.7%) had BMD

loss > 3% at the lumbar spine or total hip and discontinued early or did not enter study MVT-601-035 (withdrawal study) and required safety follow-up.

- *At Week 104 (categorized per treatment group)*

In the withdrawal study, after 104 weeks of treatment, based on top line summary data, none of the patients had decrease in BMD >7%.

The applicant has previously shown that women experiencing BMD loss of >3% during treatment cannot be identified upfront. The factors age, race, BMI, tobacco use, and alcohol use showed no association between BMD loss >3% and any of these risk factors.

To address the concerns that women experiencing the BMD loss of (> 3%) could not be identified a priori, the following recommendation is made:

"In some women treated with Ryeqo, **who had normal bone mineral density (BMD) at start of treatment**, a bone loss **varying from > 3 - 8%** was reported.

Therefore, a dual x ray absorptiometry (DXA) scan is recommended after the first 52 weeks of treatment to verify that the woman does not have an unwanted degree of BMD loss, that exceeds the benefit of treatment with Ryeqo."

The rationale for having a DXA at 12 months is based on the following:

Taking the general category of >3% BMD loss, this is considered too wide, since it varies from 3% to >8% BMD loss. Attention should be on those women, who had normal BMD at baseline, but were not allowed to enter the open label extension study or the withdrawal study due to BMD loss (Z-score < -2.0 and/or had a ≥ 7% BMD decrease). The occurrence of this clinically relevant BMD loss may indicate that in some women relugolix + E2/NETA does not sufficiently preserve BMD. The highest frequency is noted in the first 24 weeks of treatment, with decreasing frequency after prolonged treatment. As these women had to discontinue from the studies, it is not known if they would experience further decrease in BMD with longer treatment.

Therefore, it is considered not justifiable to not have any measurement of BMD during the requested chronic use as unlimited treatment is based on a selected population, a limited number of 32 patients and lack of information whether women, who had to discontinue due to significant BMD loss, would experience further decrease in BMD with longer treatment.

It is acceptable to have no baseline DXA in all women starting Ryeqo as a reference BMD value for future DXA during treatment, as a clinically relevant BMD loss from baseline would not necessarily result in osteopenia or increased fracture risk and patients at the highest risk are excluded by the contraindication for known osteoporosis and patients with risk factors for osteoporosis or bone loss are recommended a DXA upon Ryeqo treatment. However, a DXA after 1 year of treatment is considered appropriate to verify that the woman does not have an unwanted low BMD, that exceeds the benefit of treatment. So, in order to support chronic use, i.e. no limitation in treatment duration, a DXA is recommended after 1 year of treatment in order to verify that the woman does not have an unwanted low BMD, that exceeds the benefit of treatment. SmPC sections 4.2 and 4.4 have been amended accordingly.

Embolic and Thrombotic Events (VTE/ATE)

No venous or arterial thrombo-embolic events (VTE/ATE) were reported during the 52-Week treatment in these women with uterine fibroids. However, the population included is far too small to assess a risk of VTE.

The combination of E2/NETA is used as HRT in postmenopausal women, but estradiol as well as NETA are used separately in several COCs.

The results of a submitted meta-analyis based on published studies evaluating VTE/ATE risk in women using COCs suggest that a combination of E2 with any progestin is associated with a reduction in the risk of VTE, and ATE relative to a COC containing ≤30 mcg of EE in combination with any progestin. However, the E2 dose in COCs is 2 or 3 times higher (2 mg or 3 mg) than used in the relugolix + E2/NETA combination. Further, estradiol levels in women treated with relugolix + E2/NETA are low, i.e. within 20-60 pg/mL, within early follicular phase of the menstrual cycle. Therefore, estradiol level is below the level of untreated women with a normal menstrual cycle. Although it is expected that for these reasons an increase in VTE risk would be lower than noted for COCs, definite conclusions cannot be drawn. Extensive warnings on risk of VTE/ATE are included in the SmPC.

Phospholipidosis

Data from nonclinical studies in rats and monkeys showed histological changes consistent with phospholipidosis (PLD). No clinical evidence of relugolix-related PLD-associated toxicity has been identified in in any clinical study in the clinical development program of relugolix either as monotherapy or as relugolix combination therapy. Therefore, the observation of PLD in rat and monkeys was not predictive of similar findings in human subjects.

Tumors (Breast, Liver)

Two patients were reported to have an adverse event related to breast or liver tumors (both with haemangioma of liver reported as incidental finding. One in the relugolix + delayed E2/NETA group while taking relugolix monotherapy and one in a patient taking relugolix + E2/NETA in the extension study (MVT-601-3003) after previously taking placebo for 24 weeks). Both events were considered not related to study drug, although the patients were withdrawn from the study (due to gamma-glutamyltransferase increased and hepatic transaminase elevations, respectively). In addition, in study MVT-601-046, a grade 1 adverse event of breast mass/nodule was reported for one participant that was considered by the investigator to be related to study drug.

No evidence of a pattern of tumor development was identified in the relugolix clinical program. No higher risk of breast and liver tumors with relugolix combination than with COCs is expected, as estradiol concentrations are lower than in the early follicular phase of the natural menstrual cycle (i.e. 20-60 pg/mL).

Mood disorders

Mood disorder-related adverse events generally associated with depression during 24 weeks of treatment were reported on relugolix + E2/NETA in 6 (2.4%) patients, on placebo in 4 (1.6%), and in the relugolix + delayed E2/NETA group in 11 patients (4.3%). During the extension period these events were reported on relugolix + E2/NETA 7 (4.7%), former relugolix + delayed E2/NETA group 5 (3.4%) and former placebo 5 (3.0%). In the extended relugolix+E2/NETA group, two patients withdrew from the open-label extension study due to events of depression.

Depression may be associated with the hypoestrogenic state induced by treatment with GnRH receptor antagonists and agonists. A warning has been included in the product information to warn about depression. The warning is agreed as depression be a class-effect of HRT and possibly also for GnRH-agonists and antagonists.

Gallbladder disease

Hormonal preparations are reported to have effect on gallstone formation. Therefore, gallbladder disease-related events were followed as AE of interest. In the Uterine Fibroids 24-Week treatment, 6 cases of gall bladder disease related AEs were reported, but none in the placebo group. In several cases, a relevant medical history could have contributed. Two new adverse events of cholelithiasis and cholecystitis were reported for patients in the 52 week former relugolix + delayed E2/NETA group during the open-label extension study MVT-601-3003. Additionally, two new events of cholelithiasis were reported for patients in the former placebo group.

The number of cases in this specific population might be consistent with the epidemiology of gallbladder disease in obese fertile women, but although gallstones are highly prevalent, most are reported asymptomatic. Although the hormonal environment is changed when relugolix + E2/NETA is used, and concentrations of estradiol and progesterone may be lower, the net effect is as yet unclear. An appropriate warning has been included in section 4.4 of the SmPC.

Endometrial hyperplasia

The combination of E2/NETA is approved for the treatment of symptoms due to estrogen deficiency. The addition of NETA 0.5 mg to prevent endometrial hyperplasia has been established in the registration dossier of this product. Therefore, occurrence of endometrial hyperplasia is considered very unlikely. However, endometrial histology is evaluated in the pivotal relugolix combination therapy studies and the ongoing extension study. No findings of endometrial hyperplasia or carcinoma have been observed during 52 weeks of treatment in the former relugolix + E2/NETA group and the former relugolix + delayed E2/NETA group.

The majority of patients across the treatment groups had normal-atrophic/indeterminate/inactive endometrium as would be expected on relugolix combination therapy. The outcome of endometrial biopsy evaluations is added in section 5.1 of the SmPC.

Hepatic Transaminase Elevations

The evaluation of potential for hepatic transaminase elevations (ALT/AST) is based on non-clinical observations in monkeys exposed to an 48-times higher dose of relugolix, the clinical trial data, and data reported for drugs that work on the hypothalamic-pituitary-gonadal axis (GnRH receptor agonists [eg, leuprolide] and the GnRH receptor antagonists [e.g., elagolix, degarelix]). In the first 24 weeks, elevated ALT/AST were reported for 7 patients (3 patients [1.2%] in the relugolix + E2/NETA group, 3 patients [1.2%] in the relugolix + delayed E2/NETA group and 1 patient [0.4%] in the placebo group). During the 28 weeks of the open-label extension study, 7 new cases were reported (1 patient in the relugolix + E2/NETA group who was reported on Day 370 and was not included in the clinical database, 2 patients [1.3%] in the former relugolix + delayed E2/NETA group and 4 patients [2.4%] in the former placebo group). In total this were 14 of 634 (2.2%) patients while on relugolix + E2/NETA. One of the ALT elevations led to study drug discontinuation; no action was taken for four events, and study drug had already been discontinued at the time of onset for one of the events. All events resolved or returned to baseline, with no serious adverse events. None had increased bilirubin and no events met Hy's law criteria. It is noted that most events had confounding factors of comorbid conditions or concomitant medications. Increased transaminases were added to the PI as a warning in SmPC section 4.4.

Pregnancy and contraceptive effect

Although during the use of relugolix+E2/NETA, pregnancy is not expected, as the pharmacodynamic ovulation inhibition study MVT-601-046 indicated a 100% inhibition of ovulation in 84 women who participated, women had to use adequate contraception throughout the clinical studies.
However, concomitant treatment with combined hormonal contraceptives is contraindicated, since the effect of additional hormones on the efficacy of relugolix combination therapy is unknown and the safety of concomitant use has not been established. Therefore, patients had to agree to use non-hormonal contraception throughout the study, including through 30 days following the last dose of study drug. As of 31 Oct 2020, a total of 29 pregnancies have been reported overall in the relugolix clinical development program, of which 13 were in women who became pregnant during treatment with relugolix (as monotherapy or in combination with E2/NETA or with delayed E2/NETA), For 10 of the 13 pregnancies, information is available:

- Dosing issue (n = 1): This subject received 10 mg relugolix in the phase 2 study, which dose is too low to inhibit ovulation. This dose is not applicable with the recommended dose, as the dose to be registered is 40 mg.
- Timing of initiation of relugolix (n = 1): This subject started on menstrual cycle-day 8. In the clinical studies, the patient was to start within 5 days of the onset of the menstrual bleeding (which is cycle-day 1). Starting too late in the follicular phase may be too late to suppress ovulation.
- Compliance with dosing and/or failure of non-hormonal contraception (n = 8)

The additional background information indicated that compliance problems with contraceptive measures were the major cause for pregnancy occurrence. Dosing non-compliance or non-hormonal contraception failure (in the first month) cannot be ruled out. This cannot be avoided completely but should be anticipated as much as possible by correctly informing physician and patient in the PI.

Contraceptive properties of Ryeqo

- Recommendation to use a non-hormonal method of contraception for one month after initiation of treatment.

Based on PK and PD data from phase 1 studies, i.e. the single- and multiple-rising dose study (TAK-385-101) and the 6-week PK, and safety study (MVT-601-1001), and results from the ovulation inhibition study (MVT-601-046), the antagonist action and associated biological response to relugolix and relugolix combination therapy have a rapid onset and offset of action, including ovulation inhibition. Antagonist effects of relugolix are shown to occur rapidly with a decreases of estradiol concentration observed within hours after administration of a single 40-mg dose of relugolix. In the ovulation inhibition study, ovulation was inhibited in 100% of women within the first month of treatment, by a Hoogland-Scooby (HS) score of < 5 (consistent with an absence of luteal activity), but with a slight trend for higher scores (HS of 4) in 5 women. In the second treatment month a HS of 4 was noted in two women and in a single woman in the third month of administration. Pituitary and ovarian hormone concentrations were demonstrated to have effectively suppressed pituitary secretion of FSH and LH and ovarian production of estradiol and progesterone within the first treatment month and fairly consistent across all treatment periods. This study also showed that ovulation rapidly returned following discontinuation of treatment with the earliest ovulation observed after 15 days (median time to return to ovulation of 23.5 days). However, it is noted that all women started on the first day of their menstrual cycle. It is therefore agreed with the Applicant, that it is possible that ovulation could occur within the first cycle after initiation of treatment when starting later in the menstrual cycle.

Therefore, a conservative recommendation for use a non-hormonal method of contraception for one month after initiation of treatment to establish full suppression of ovulation is justified and supported.

- The initial recommendation for use of a non-hormonal method of contraception for 7 days after missed doses for ***three or more consecutive days*** has been changed into ***two or more consecutive days***, based on the conservative rule, which is also applied for missed tablets of combined oral contraceptive (additional contraceptive measures after one terminal half-life), one terminal half-life of 61 hours for relugolix would conservatively translate into two or more consecutive days.
- The recommendation to ***use a non-hormonal method for 7 days***

The recommendation to use a non-hormonal method for 7 days is based on results obtained in the ovulation inhibition study. Although the earliest ovulation was observed 15 days after administration of the last dose, this data is too limited to conclude that up to 15 days is required for sufficient follicular development to occur. In the ovulation inhibition study, pituitary secretion of FSH, evidence of follicular growth, and increases in serum estradiol concentrations became apparent within 3 to 6 days after discontinuation of relugolix combination therapy. This shows a rapid return to biological function of the HPG axis and ovarian activity. However, these data support that 3 days is the minimum duration of time required for biological activity to be re-initiated upon consecutive missed doses, but 2 days would by a safer margin.

The recommendation to use of a non-hormonal method of contraception for at least 7 consecutive days of dosing with Ryeqo following a period of 2 or more consecutive days of missed doses will minimize the risk of pregnancy is acceptable when Ryeqo is re-initiated immediately.

However, when Ryeqo is discontinued and the woman does not wish to become pregnant, she needs to immediately start with an alternative a contraceptive. However, as the SmPC now states that alternative contraception needs to be started immediately after discontinuation of treatment, this issue is already adequately covered.

In conclusion, the Applicant has sufficiently substantiated the contraceptive measures recommended in section 4.2 of the SmPC, and has changed the recommendation to take additional contraceptive measures after missed doses for two or more consecutive days.

Considering that the recommendations regarding contraceptive measures are rather complicated, SmPC section 4.2 (Posology) has been further rearranged to strengthen the message on the need for treatment compliance, timing of initiating treatment and handling of missed doses.

Pregnancy outcome

Pregnancy is a contraindication for relugolix-E2/NETA. Embryo-foetal toxicity is included in the RMP as an important potential risk for relugolix. Congenital anomalies are included as important potential risk of other GnRH antagonists (but not all). Regarding the combination of estrogen/progestogen, up to now there appears to be little or no increased risk of birth defects in children born to women who have used oestrogens and progestogens as an oral contraceptive inadvertently during early pregnancy, as stated in SmPCs of combined hormonal contraceptives (section 4.6).

Until now, in the very limited data, no pregnancy outcomes have been seen indicative of an increased risk of birth defects. However, pregnancies and pregnancy outcomes should be closely followed.

Changes in bleeding pattern

It is noted that the protocol instructed that adverse events related to heavy menstrual bleeding were only to be reported if the event met criteria for a serious adverse event; thus, the incidence of adverse events related to bleeding is not a suitable metric for assessment of the effect on menstrual bleeding in these studies.

A higher rate of amenorrhea over the last 35 days of treatment (Week 24 or end of treatment for patients who discontinued early) was observed in patients in the relugolix + E2/NETA group (51.6%) and the relugolix + delayed E2/NETA group (53.5%) compared with the placebo group (4.3%). The proportion of patients who had a cyclic bleeding pattern during the last 35 days of treatment was 15.4% in the relugolix + E2/NETA group and 15.1% in the relugolix + delayed E2/NETA group and 62.5% of patients in the placebo group.

At Week 52, amenorrhea over the last 35 days of treatment was reported by 60.3%, 64.7%, and 44.3% of patients in the relugolix + E2/NETA, former relugolix + delayed E2/NETA, and former placebo groups, respectively. Of the patients for whom the menstruation status was available, 61 patients (96.8%), 66 patients (97.1%), and 57 patients (93.4%) in the relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo groups, respectively, reported having post-treatment menses. The median (mean) time from last dose of study treatment to occurrence of menses was similar across the groups, 34 days (40.5), 33.5 days (40.6), and 34.0 days (36.9), respectively.

Dyspepsia

Dyspepsia is reviewed in consideration of the temporal relationship, and the potential for estrogens and progesterone to reduce the lower esophageal sphincter pressure. Given the onset of mild to moderate dyspepsia within the first 2 months of treatment, albeit at low frequency, and the biological plausibility, the applicant assessed dyspepsia conservatively as an adverse drug reaction. This is accepted.

Hypertension

The overall frequency of hypertension for relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo was 5.5%, 4.7%, and 2.7%, respectively. The differences that were observed between study groups were not considered clinically relevant, however although hypertension may a comorbidity in a part of this population, it is not seen in the placebo group. Additionally, a dose-related increase in blood pressure was seen in earlier studies, albeit in higher doses. Therefore, a possible causal relationship is suggested.

Hypertension events was reported for a total of 16 patients during the open-label extension study. All 16 patients had risk factors or pre-existing evidence of elevated blood pressure and 4 of the patients in the placebo group had pre-existing hypertension. Onset of the events was not temporally associated with initiation of open-label treatment with relugolix + E2/NETA in any of the cases.

Currently, a warning has been added to the product information on the occurrence of hypertension.

Uterine fibroid prolapse or expulsion

In view of the fact that prolapse or expulsion is a known complication inherent to the disease and possible related to treatment with Ryeqo, appropriate information has been included in the SmPC sections 4.4 and 4.8.

2.6.2. Conclusions on the clinical safety

Relugolix + E2/NETA indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age appeared to be generally well tolerated with only 3.9% of patients discontinued due to an adverse event over a treatment period of 24 weeks, which remained consistent over 52 weeks (3.1%).

The adverse events pattern was consistent with the adverse event pattern that is expected for a GnRH-antagonist, as most frequently reported treatment related adverse events consisted of symptoms due to the lower estradiol levels, of which hot flushes had highest frequency. However, these symptoms were considerably lower than noted with relugolix monotherapy, indicating a beneficial effect of the addition of E2/NETA on these symptoms. Beneficial effects of E2/NETA have been noted in mitigation of relugolix induced BMD loss over a placebo-controlled period of 24 weeks, showing that the decrease in BMD observed was less that noted in the relugolix monotherapy arm. Newly submitted uncontrolled extension data covering a total treatment duration of up to 52 weeks show a protective effect of E2/NETA as add-back therapy, as the decrease in BMD was around 1% over a period of 52 weeks in the 163 patients who received relugolix + E2/NETA from start to up to 52 weeks. The BMD simulation based on E2 levels for a period of 36 months treatment and the new analyses provided were not considered robust evidence to overcome the lack of clinical data beyond 52 weeks of treatment. In response to this uncertainty whether the plateau in BMD decrease already has been reached in the first treatment year, further data have been submitted by means of a top-line summary of the results obtained in the recently completed withdrawal study MVT-601-035. These data provided a 2nd year of treatment with Ryeqo which supported that the decrease in BMD remains in the range of around 1% that is currently observed over 52 weeks of treatment, which is also seen in the subgroup of 32 patients who received relugolix + E2/NETA from for up to 104 weeks. Cumulatively, the mean percent change in BMD from pivotal study baseline to up to Week 104 in patients who received relugolix + E2/NETA (n = 32) was 0.04%. These results could support a registration for unlimited duration of use, but results are based on a selected population, as women with osteoporosis or risk factors for osteoporosis were not allowed to participate, women in the trials who experienced a Z-score of -2 or BMD loss ≥7% were discontinued and/or not allowed to enter the extension study or withdrawal study, and the final number of patients treated with relugolix + E2/NETA for up to 104 weeks is limited to 32 patients.

Further, in some women with normal BMD at baseline, a clinically relevant decrease in BMD (>3% decrease in BMD) was noted during treatment with relugolix + E2/NETA. Additional analyses indicated that these women experiencing the BMD loss of (>3%) cannot be identified upfront. This category of >3% varies from 3% to >8% BMD loss. Within this category, women who had a Z-score < -2.0 and/or had a ≥7% BMD decrease had to discontinue and/or were not allowed to enter the open label extension study or the withdrawal study. The occurrence of this clinically relevant BMD loss may indicate that in some women relugolix + E2/NETA does not sufficiently preserve BMD. The highest frequency is noted in the first 24 weeks of treatment, with decreasing frequency after prolonged treatment.

Therefore, it is considered not justifiable to not have any measurement of BMD during the requested chronic use as unlimited treatment is based on a selected population, a limited number of 32 patients and lack of information whether these women, who had to discontinue due to significant BMD loss, would experience further decrease in BMD with longer treatment.

It is acceptable to have no baseline DXA in all women starting Ryeqo as a reference BMD value for future DXA during treatment, as a clinically relevant BMD loss from baseline would not necessarily result in osteopenia or increased fracture risk and patients at the highest risk are excluded by the contraindication for

known osteoporosis and patients with risk factors for osteoporosis or bone loss are recommended a DXA upon Ryeqo treatment. However, a DXA after 1 year of treatment is considered appropriate to verify that the woman does not have an unwanted low BMD, that exceeds the benefit of treatment. This recommendation is reflected in the PI.

Thorough evaluation of several adverse events of interest that may be related to changes in sex hormone balance have not revealed any clear signal and the pattern was in line with that observed with comparable medicinal products such a GnRH agonists and GnRH antagonists.

The important potential risks depression/suicidal ideation, venous or arterial thromboembolic events, hepatic transaminase elevations, tumors (breast, liver), and gallbladder disease have been sufficiently characterised before and extensive warnings are included in the product information. No additional risk minimisation measures or pharmacovigilance measures are planned with respect to those risks that are to be reflected in the RMP. Also information regarding uterine fibroid prolapse or expulsion, a known complication inherent to the disease and possible related to treatment with Ryeqo, is included in the SmPC Sections 4.4 and 4.8. These issues should be closely monitored for relevant spontaneous reports by means of routine pharmacovigilance. To ensure that aggregate reports should be provided with each PSUR, they should be included in the summary of safety concerns in the PSUR.

Although E2 1mg/NETA 0.5 mg is a known HRT (Activelle) of which the endometrial safety has been evidenced at registration, thorough evaluation of the endometrial histology evaluation confirmed an atrophic pattern with no cases of endometrial hyperplasia.

Regarding contraceptive properties, the occurrence of 13 pregnancies during the study trials has been clarified as due to dosing issues, non-compliance in most cases with non-hormonal contraception.

As to contraceptive properties of Ryeqo, pharmacodynamic data adequately confirmed consistent inhibition of ovulation. However, contraceptive efficacy has not been evaluated within a phase 3 clinical trial setting. However, further detailed discussion on PK/PD date adequately substantiated the contraceptive measures recommended in SmPC section 4.2.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	Loss of bone mineral density Embryo-foetal toxicity
Missing information	Long-term use beyond 12 months

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation *(key to benefit risk)*				
None				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances *(key to benefit risk)*				
None				
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
MVT-601-035: An international Phase III double-blind, placebo-controlled, randomised withdrawal study of relugolix co-administered with E2+NETA in women with heavy menstrual bleeding associated with uterine fibroids *Ongoing*	To evaluate the efficacy and safety of long-term use of relugolix	Loss of BMD Long-term use beyond 12 months	Final study report	Q4 2021

Risk minimisation measures

Safety concern	Risk minimisation measures
Loss of BMD	**Routine risk minimisation measures**: SmPC section: 4.2, 4.3, 4.4, 4.5, 5.1 PL section: 2 Prescription only medicine **Additional risk minimisation measures**: None
Embryo-foetal toxicity	**Routine risk minimisation measures**: SmPC section: 4.2, 4.3, 4.4, 4.6, 5.3 PL section: 2, 4 Contraindication in pregnancy is provided in SmPC section 4.3 and advice regarding the need to discontinue treatment should if pregnancy occurs is provided in SmPC section 4.6. Prescription only medicine **Additional risk minimisation measures**: None

Safety concern	Risk minimisation measures
Long-term use beyond 12 months	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of relugolix with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers relugolix to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ryeqo (relugolix / estradiol / norethisterone acetate) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Uterine fibroids (also called uterine myomas and leiomyoma) are benign, monoclonal, hormone-sensitive, smooth muscle tumors of the uterus. The hormonal sensitivity of uterine fibroids is indicated on the same clinical observations as observed with endometriosis: development during the reproductive (hormonally active) years and regression after menopause. Most of the uterine fibroids are not symptomatic. When symptomatic, the clinical symptoms are heavy uterine bleeding, abdominal pressure, abdominal pain, anaemia, increased urinary frequency and infertility. In particular, heavy menstrual blood loss is one of the most frequently disabling symptoms of uterine fibroids. Beyond their physical morbidity, they are a frequent cause of significant impairment of quality of life (QoL).

The claimed indication for the fixed-dose combination 'relugolix 40mg +E2 1mg /NETA 0.5mg' is:

Therapeutic indication

- *[TRADE NAME] is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.*

The posology is 1 tablet daily taken orally. The claimed duration of treatment is "can be used long-term without interruption".

Ryeqo consists of three active ingredients, the GnRH antagonist relugolix 40 mg, estradiol 1 mg (E2) and norethisterone acetate (NETA, also known as norethindrone acetate) 0.5 mg. Relugolix is a new active substance. Relugolix can be taken orally by which it differs from GnRH agonists which are administered as monthly depot by a subcutaneous implant. E2 and NETA are well known and well used active substances, either alone or in combination (Activelle) for hormone replacement therapy i.e. treatment of postmenopausal symptoms of estrogen deficiency.

The relugolix-component is a GnRH antagonist, which blocks the hypothalamic–pituitary–adrenal axis (HPA axis), thereby preventing release of LH and FSH. The subsequent decrease of estradiol and progesterone to postmenopausal levels, reduce symptoms associated with uterine fibroids, like heavy menstrual bleeding, anemia, and pain, and to some extent fibroid size.

The estradiol/progesterone (1mg E2 / 0.5mg NETA) component, an existing hormone replacement therapy (HRT, Activelle) that has been added to mitigate the important risk of long term decreased estrogen, which is bone mineral density loss leading to osteoporosis. In this HRT a progestin component (norethisterone) is included to avoid proliferative effects of unopposed estrogen on the endometrium that can lead to endometrial hyperplasia.

3.1.2. Available therapies and unmet medical need

Surgery

The mainstay of symptomatic myoma treatment is surgery. The most common procedure is hysterectomy, but less invasive procedures have been developed especially when the patient wishes to preserve fertility and/or her uterus. Less invasive procedures include myomectomy and uterine artery embolization. Endometrial ablation can also be used if the dominant symptom is bleeding, the fibroid size relatively small, and fertility is not an issue.

Approved medicinal treatments

Currently, only two effective medicinal options are available for women with symptoms associated with uterine fibroids.

Ulipristal acetate (Esmya) for intermittent treatment

Ulipristal acetate (Esmya), a selective progesterone receptor modulator, is available in the EU for treatment of women when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.

GnRH agonists for short-term pre-operative treatment

The only other pharmaceutical treatment currently registered in Europe for the preoperative treatment of symptomatic fibroids are gonadotropin releasing hormone (GnRH) agonists, i.e. goserelin, leuprorelin, nafarelin and triptorelin.

GnRH agonists suppress oestrogen to castration levels resulting in symptoms of menopause such as hot flushes. Their use is restricted to 3-6 months as they lead to loss of bone mineral density, an effect which is partially reversible after discontinuation. Various GnRH combination therapies to reduce effects on BMD and postmenopausal symptoms are used (e.g., combined estrogen and progestins, medroxyprogesterone acetate, tibolone, etc), in order to allow a longer duration of treatment with GnRH agonists (Pérez-López et al. 2014), though none are approved for use in combination with a GnRH-agonist in the EU.

GnRH antagonists

Relugolix (active ingredient of the product under discussion) monotherapy (40 mg oral tablet, trade name Relumina) has been approved in Japan since Jan 2019 and is indicated for the improvement of symptoms associated with uterine myoma (hypermenorrhea, lower abdominal pain, lower back pain and anemia). Another oral GnRH antagonist (elagolix monotherapy) has been approved in the US for endometriosis pain since July 2018. A 150 mg dose once daily for up to 24 months or 200 mg twice daily for up to 6 months has been approved. Earlier GnRH antagonists (cetrorelix [1999], ganirelix [2000]) need to be administered parenterally and are only approved in assisted fertility treatment, to inhibit the LH-surge during ovarian stimulation.

Unmet medical need

Long-term treatment of uterine fibroids

Currently Esmya is approved for treatment of women when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed. GnRH agonists are only approved for short-term preoperative use (3-6 months) because of the adverse effects on BMD. A medicinal treatment for long-term use of symptoms of uterine fibroids that can safely be given for a longer period without adverse effects on BMD would fulfill an unmet medical need in women of childbearing age who still want to have children and are therefore reluctant to have surgery.

3.1.3. Main clinical studies

Main placebo-controlled studies with duration of 24 weeks

Two large double-blind, placebo-controlled phase 3 trials with a duration of 24 weeks have been performed in the US and Rest of World (Belgium, Brazil, Chile, Czech Republic, Hungary, Italy, Poland, South Africa, and the United Kingdom) (studies MVT-601-3001 and MVT-601-3002). The studies are similar in design. The studies compared relugolix-E2/NETA (n=254) with placebo (n=256) in premenopausal women 18 to 50 years of age with a confirmed diagnosis of uterine fibroids and heavy menstrual bleeding associated with uterine fibroids. The primary and several key secondary endpoints focus on a reduction in heavy menstrual bleeding (MBL), the most common symptom of uterine fibroids, measured by the validated alkaline hematin method.

Testing for multiplicity for the efficacy endpoints was adequately handled by a combination of hierarchical testing and a Hochberg procedure. The studies also contained a treatment arm with Relugolix monotherapy for 12 weeks in order to compare efficacy and safety results with the relugolix +E2/NETA arm. This comparison was made to evaluate the claimed protective effect on bone mineral density of the addition of estradiol 1 mg and to evaluate whether the addition of exogenous estradiol would reduce efficacy of relugolix on uterine fibroid symptoms of bleeding. The type I error protection did not include these safety endpoints.

The design is in accordance with legal requirements, available guidelines, and the several scientific advices that were given, and in accordance with the ICH E1 guideline for extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions.

Uncontrolled efficacy and safety extension study of 28 weeks

The two main double-blind, placebo-controlled phase 3 studies were followed by an uncontrolled, long-term efficacy and safety extension study (MVT-601-3003) of 28 weeks enrolling eligible patients who had completed participation in study MVT-601-3001 or MVT-601-3002 of 24 weeks duration.

Supportive studies

A prospective observational (natural history) study (MVT-601-034) of bone mineral density in women aged 18-51 years with uterine fibroids or endometriosis, to characterize longitudinal BMD of premenopausal women with uterine fibroids or endometriosis over a 52 week observational period.

Three *s*tudies **in Japanese patients** conducted by the company Takeda: a completed phase 2 dose finding study for relugolix monotherapy and two completed phase 3 relugolix monotherapy [relugolix monotherapy vs GnRH agonist], relugolix monotherapy vs placebo].

An exit questionnaire study **MVT-601-037** was performed, being a substudy to MVT-601-3001 and MVT-601-3002 [patient input on the patient reported outcomes]).

Ongoing study

An additional placebo-controlled study, MVT-601-035, a 52-week randomized withdrawal study including patients who completed MVT-601-3003, is ongoing. However, top level results were provided during the procedure upon request by the CHMP.

3.2. Favourable effects

Selection of dose

Based on a PK/PD single and multiple dose study **TAK-385-101** in 120 healthy premenopausal women in the US, investigating single doses of 1- to 80-mg of relugolix, dose-dependent reductions in mean LH, FSH, and E2 serum concentrations with respect to both degree and duration were observed, consistent with the mechanism of action of relugolix as a GnRH receptor antagonist. As at 24 hours post-dose, mean E2 concentrations for the 40- and 80 mg doses of relugolix were similar (30.2 pg/mL and 30.3 pg/mL, respectively), doses higher than 40 mg are unlikely to provide further suppression of E2 concentrations with once daily administration. Therefore, the 40 mg dose was selected for further development. Based on the presented data, the dose of 40 mg is agreed.

The selection of the dose of E2 1mg + NETA 0.5 mg for combination with relugolix was based on data in the literature, particularly from published studies that supported the estradiol dose of 1 mg to have efficacy in prevention of bone loss in postmenopausal women. Further, the E2/NETA combination, Activelle, is registered in Europe for treatment of vasomotor symptoms and prevention of osteoporosis in postmenopausal women. The addition of this approved combination is therefore considered acceptable.

Pivotal phase 3 studies (MVT-601-3001 and MVT-601-3002) of 24 week duration

Efficacy in Reduction in menstrual blood loss

Efficacy relugolix + E2/NETA vs placebo

Evaluation of efficacy in reduction of menstrual blood loss was based on the primary endpoint of the **proportion of women** in the relugolix + E2/NETA group versus the placebo group who achieved a 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.

With the selected dose combination of relugolix 40 mg + E2 1mg/NETA 0.5 mg, a statistically significant and clinically relevant greater proportion of responders in both placebo-controlled trials (73.44% and 71.20%, respectively) was obtained compared to placebo (18.90% and 14.73%, respectively) after 24 weeks of treatment.

Efficacy relugolix + E2/NETA vs relugolix without E2/NETA

The relugolix + delayed E2/NETA treatment arm (initial treatment with relugolix monotherapy for 12 weeks followed by 12 weeks relugolix + E2/NETA) was added to be able to evaluate the effect of addition of exogenous estrogen on the efficacy of relugolix and on prevention of bone loss. A difference between the percent of responders in the relugolix + E2/NETA group versus percent of responders in relugolix + delayed E2/NETA group was observed. The difference is largest at Week 4 (about 20% difference), but from Week 4

onwards the difference between relugolix and relugolix+ E2/NETA diminished to about 5% at Week 12 (end of relugolix monotherapy). After Week 12 when these patients received relugolix + E2/NETA, this difference remained from Week 12 to Week 24. However, this potential difference in responders can be considered not clinically relevant, in particular in the light of the protective effect on bone mass.

The results from the two phase 3 studies obtained at Week 24 for relevant key secondary efficacy endpoints appeared supportive of the primary endpoint findings:

- The decrease in **volume of menstrual blood loss** for relugolix combination therapy (in both phase 3 studies) was statistically significant with reductions in menstrual blood loss volume of > 80% (mean 84.3%, in both studies) versus placebo (23% and 15%) and considered clinically relevant.
- **Amenorrhea** was achieved by 52.3% and 50.4% of patients on relugolix + E2/NETA, respectively, versus 5% and 3% in placebo groups.
- In a subgroup of women with **anaemia** (hemoglobin ≤ 10.5 g/dL at baseline), a higher percentage of these patients on relugolix+E2/NETA reported improvement in Hb levels (increase > 2 g/dL) of 50.0% and 61.3%, respectively versus 5% and 3% in the placebo groups.
- For **pain** associated with uterine fibroids**,** measured in a subset of women with a maximum Numerical Rating Scale (NRS) score ≥ 4, the proportion of patients with maximum NRS score ≤ 1 during the last 35 days of treatment was greater with relugolix + E2/NETA (>40%) compared with placebo 10.1% and 17.1%, respectively.

For both studies, for all key secondary endpoints relugolix + E2/NETA superiority was noted compared with placebo, except for reduction in uterine fibroid volume, where the reduction was not statistically significant.

Long term efficacy over 52 weeks (28-week Extension study MVT-601-3003)

A total of 477 patients from the two parent studies were enrolled to receive open-label relugolix + E2/NETA. The proportion of women who received relugolix + E2/NETA up to 52 weeks in this efficacy analysis consisted of 163 women.

Efficacy analyses showed that efficacy over 52 weeks of treatment was maintained as shown by the outcomes on the primary efficacy endpoint in the three different treatment groups:

In the former relugolix + E2/NETA group, 143 patients (87.73%) achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment.

In the former relugolix + delayed E2/NETA group this end point was met for 119 patients (79.87%) and in the former placebo group 124 patients (75.61%).

The former placebo group, actually being a replication of the cohort that started initially on relugolix-E2/NETA, had a similar percentage of responders at week 24 compared to the former relugolix + E2/NETA group.

For all groups, the proportion of patients meeting the criteria for the individual components of the composite primary endpoint was similar, indicating no single component (i.e., MBL volume < 80 mL or percent change from baseline of at least 50%) drove results for the primary endpoint.

Across all subgroups (geographic region, baseline, race, uterine volume, BMI), the responder rates observed were consistent with those observed in the analysis of the primary efficacy of the overall population for each treatment.

The results from the key secondary efficacy endpoints were supportive of these primary endpoint findings.

For this application in the EU, only a small group of patients (16%) were of European origin. Although it is not expected that the epidemiology and presentation of uterine fibroids in European women is different from the US and the rest of the world, a discussion was provided by the applicant on pathophysiology, ethnicity-based polymorphisms, demographic data and adverse events. Sufficient data was supporting that the results from the clinical development program is applicable for European women.

3.3. Uncertainties and limitations about favourable effects

While the newly presented top-line data on longer duration up to 104 support maintenance of efficacy, the number of patients who were treated with relugolix + E2/NETA (Ryeqo) for a second year is limited to 32 patients.

3.4. Unfavourable effects

Pooled safety data of both phase 3 studies with 24 weeks treatment duration

Adverse events

Short-term safety over 24 weeks in placebo-controlled setting

The overall incidence of AEs over a treatment period of 24 weeks was comparable between the relugolix + E2/NETA group (61.0%) and the placebo group (62.5%), but higher in the relugolix + delayed E2/NETA group (72.1%). The higher incidence in the latter group was due to the relugolix monotherapy treatment period (12 weeks) leading to a higher number of AEs related to post-menopausal symptoms.

Hot flush was the most common drug-related AE reported and inherent to the lowering of estrogen levels. The difference between relugolix monotherapy (relugolix + delayed E2/NETA group, 12 weeks) and relugolix combination therapy (7.9% versus 36%) was significant and indicates that the addition of E2/NETA considerably reduces the frequency of postmenopausal symptoms. The difference between relugolix +E2/NETA and placebo was small, i.e. 7.9 versus 5.9%, and as expected.

Other drug-related AEs reported >1% of patients in the relugolix+E2/NETA group vs placebo were headache (7.1 vs 7.0%), nausea (2.8 vs 3.9%), alopecia (2.8 vs 0.8%), menorrhagia (2.8 vs 0%), hypertension (2.4 vs 0.8%), abdominal pain (2.4 vs 0.4%), libido decreased (2.0 vs 0%), hyperhydrosis (2.0 vs 0.8%), anxiety (1.2 vs 0.4%), weight increased (1.2 vs 0.4%), blood creatine phosphokinase increased (1.2 vs 0.4%), insomnia (1.2 vs 0.8%), menstruation irregular (1.2 vs 0.4%), and mood swings (1.2 vs 0%).

Serious AEs were reported in 8 (3.1%) of the relugolix+E2/NETA group, in 5 (1.9%) of the relugolix + delayed E2/NETA group and 6 (2.3%) on placebo. Two (0.8%) SAEs related to study drug were reported in the relugolix + E2/NETA group: uterine myoma expulsion and pelvic pain. (In the long term study, 4 SAEs related to study drug were reported: uterine hemorrhage and cholecystitis.) No specific safety concern was identified over 24 weeks treatment. No deaths were reported in the two pivotal phase 3 studies.

In general, the adverse events profile of relugolix-E2/NETA as reported during 24 weeks of treatment did not give rise to concern. The adverse events are in line with the mechanism of action, (i.e. due to hypo-oestrogenic state).

Long-term safety (uncontrolled extension study MVT-601-3003)

In the relugolix + E2/NETA group, cumulatively over the 52-week treatment period, at least 1 adverse event was reported for 127 patients (77.9%). About half of the patients in this group (89 patients [54.6%]) had 1 adverse event during participation in the open-label extension study. In the relugolix + delayed E2/NETA group, at least 1 adverse event was reported for 125 patients (83.9%) over the 52-week treatment period encompassing the parent and open-label extension studies. During participation in the open-label extension study, at least 1 adverse event was reported for 72 patients (48.3%). In the placebo group, at least 1 adverse event was reported for 138 patients (84.1%) during the parent and extension studies. During participation in the open-label extension study, at least 1 adverse event was reported for 103 patients (62.8%).

In the patients who had received relugolix-E2/NETA for 52 weeks (the former relugolix + E2/NETA group), drug-related adverse events were reported for 73 patients (44.8%), of which 36 (22.1%) in the open-label extension study. The most frequently reported drug-related adverse events were hot flush (18 patients [11.0%]) and headache (15 patients [9.2%]). In 4 patients (2.5%), hot flush was first reported during the open-label extension study. Headache was first reported during the open-label extension study in 2 patients (1.2%). It should be noted that the incidence of headache over 52 weeks in the relugolix + E2/NETA group was lower than that observed with placebo over the first 24 Weeks (13.3%).

The adverse event profile over 52 weeks in any group was consistent with that observed over the first 24 weeks of treatment. No significant findings suggesting an exposure- or duration-related safety trend of concern were observed.

Adverse events of special interest

Relugolix is a GnRH antagonist which use leads to a postmenopausal state in premenopausal women, with consequent risk of bone mineral density (BMD) loss and occurrence of vasomotor symptoms. Addition of E2/NETA is added to mitigate the BMD loss (and to decrease postmenopausal symptoms).

Bone mineral density loss

– Adverse events due to BMD loss:

During 24 weeks, AEs related to bone loss were most commonly reported in relugolix + delayed E2/NETA group (6 (2.3%), when compared with the relugolix + E2/NETA: 2 (0.8%) and placebo: 3 (1.2%) group. A similar pattern was observed for the 28-week extension period, where no new adverse events related to bone loss were reported for the patients in the relugolix + E2/NETA group, 4 new reports in the former relugolix + delayed E2/NETA group and 1 new report in the former placebo group.

The higher value in the former relugolix + delayed E2/NETA group may be attributed to the 12 initial weeks were relugolix was used without the protective effect of E2/NETA as add-back therapy.

Loss of BMD (measurements by DXA):

Short-term data up to 24 weeks

In the 12 week relugolix monotherapy (relugolix + delayed E2/NETA group), bone loss observed in lumbar spine was significantly greater than noted with relugolix + E2/NETA (-2.0% vs -0.5%, $p < 0.0001$, study MVT-601-3001), suggesting the protective effect of this HRT as add-back therapy. Only small decreases in BMD between relugolix + E2/NETA versus placebo (BMD at the lumbar spine Week 12: −0.5% vs. 0.2%; Week 24: −0.4% vs. 0.1%, study 601-3001) were noted, which supports a protective effect of E2.

Comparable effects on bone loss were noted in study 601-3002. For total hip measurements a similar pattern was noted.

Long-term data up to 52 weeks
Regarding long-term use, the most informative patient group is the one in which patients were initially treated with relugolix + E2/NETA and entered the extension study 3003. These patients received up to a maximum of 52 weeks of treatment with relugolix + E2/NETA and the LS mean percent changes from Baseline in BMD to Week 36 and Week 52 at the lumbar spine were -0.726% and -0.804%, respectively. These outcomes at week 36 and week 52 indicate a slight decrease in BMD upon use up to 52 weeks, suggesting that further decrease in BMD cannot be excluded with use beyond 52 weeks. Further, a decrease in BMD is noted in the treatment group who initially received placebo in the 24 week double blind phase of both studies. In the patient group who initially received placebo for 24 weeks in the double-blind phase, BMD values were -0.293% (Week 36), and -0.823% (Week 52), also suggesting that further decrease in BMD cannot be excluded. Therefore, the conclusion of the Applicant that the observed BMD loss in the phase 3 studies with relugolix combination therapy displayed a plateau starting at Week 12 and continuing through Week 52, in the rate of change in BMD, was not shared. The provided BMD simulation results based on E2 levels for a period of 36 months treatment is not considered robust evidence to overcome the lack of clinical data beyond 52 weeks of treatment.

To contextualize BMD outcomes from the relugolix combination studies, a 1-year prospective, observational study was undertaken to characterize longitudinal BMD in a cohort of premenopausal women with uterine fibroids (natural history study). Age-related BMD increases were observed in the younger population (< 10% of participants) and slight decreases in BMD were observed in those 35-44 years and ≥45 years of age. Compared to baseline values, the decrease in BMD noted over 52 weeks treatment in the relugolix + E2/NETA age groups of 35 to < 40 years, 40 to < 45 years, and 45 to < 52 years was only slightly larger in comparison to these age groups in the natural history study (MVT-601-034).

Long-term data up to 104 weeks (top-line summary data only)

During the procedure, the applicant provided top-line summary results of the recently completed double-blind, placebo-controlled withdrawal study (MVT-601-035), which provided a second year of treatment with Ryeqo. This summary of results on BMD over 104 weeks treatment with relugolix + E2/NETA indicated that a plateau in BMD decrease has been reached after the first treatment year of around 1%. Cumulatively, the mean percent change in BMD from pivotal study baseline to up to Week 104 in patients who received relugolix + E2/NETA (n = 32) was 0.04%. In women who received placebo for 24 weeks followed by relugolix + E2/NETA for 80 weeks (n = 29), the mean percent change in BMD from pivotal study baseline to Week 104 was 0.45%.

- *Significant loss of BMD >3%*

In the phase 3 studies, there were individual women with significant losses in BMD (>3%). In the relugolix + E2/NETA group after 52 weeks, some women had BMD losses of >3% to ≤5% and >5% to ≤8% (34 patients [25.4%]) and (7 patients [5.2%]), respectively, that remained relatively unchanged over time. In the former placebo group (after 28 weeks of relugolix + E2/NETA use), some women had losses of > 3% to ≤ 5% and > 5% to ≤ 8% (32 patients [29.4%]) and (13 patients [11.9%]). Two patients (1.7%) had losses that were > 8% at Week 52.

- *Significant BMD loss (Z-score > -2 and/or ≥ 7% decrease in BMD at any site) in parent studies, which precluded entering long-term extension study 3003 or withdrawal study (035)*

During the initial 24 week studies, 11 patients in the relugolix + E2/NETA group had Z-score > -2 and/or ⩾ 7% decrease in BMD, which made them not eligible for the extension study.

In the extension study, 6 patients (3.7%) in the relugolix + E2/NETA group met criteria for discontinuation at Week 36 due to BMD loss ⩾ 7% at any anatomic site. Additionally, 3 patients (1.8%) were not eligible to continue into the withdrawal study MVT-601-035 at Week 52 due to BMD loss > 7%. Six patients (3.7%) had BMD loss >3% at the lumbar spine or total hip and discontinued early or did not enter study MVT-601-035 and required safety follow-up.

In the former placebo group, 5 patients (3.0%) met criteria for discontinuation at Week 36 due to bone loss (BMD loss ⩾ 7% at any anatomic site). Seven patients (4.3%) were not eligible to continue into study MVT-601-035 at Week 52 due to bone loss (BMD loss ⩾ 7% at any anatomic site). Six patients (3.7%) had BMD loss > 3% at the lumbar spine or total hip and discontinued early or did not enter study MVT-601-035 and required safety follow-up.

In the withdrawal study, summary data presented indicated that none of the patients had experienced a decrease ⩾ 7%.

Risk of VTE/ATE

No venous or arterial thrombo-embolic events (VTE/ATE) were reported during the 52-Week treatment in these women with uterine fibroids. However, the population included is far too small to assess a risk of VTE. The combination of E2/NETA is used as HRT in postmenopausal women, but estradiol as well as NETA are used separately in several COCs.

The results of a submitted meta-analyis based on published studies evaluating VTE/ATE risk in women using COCs suggest that a combination of E2 with any progestin is associated with a reduction in the risk of VTE, and ATE relative to a COC containing ≤30 mcg of EE in combination with any progestin. However, the E2 dose in COCs is 2 or 3 times higher (2 mg or 3 mg) than used in the relugolix + E2/NETA combination. Further, estradiol levels in women treated with relugolix + E2/NETA are low, i.e. within 20-60 pg/mL, within early follicular phase of the menstrual cycle. Therefore, estradiol level is below the level of untreated women with a normal menstrual cycle. Although it is expected that for these reasons an increase in VTE risk would be lower than noted for COCs, definite conclusions cannot be drawn. The risk of VTE (and ATE) is included in the SmPC.

Tumors (Breast, Liver)

No evidence of a pattern of tumor development was identified in the relugolix clinical program. No higher risk of breast and liver tumors with relugolix combination than with COCs is expected, as estradiol concentrations are lower than in the early follicular phase of the natural menstrual cycle.

Mood disorders/Depression

Mood disorders may be associated with the hypoestrogenic state induced by GnRH receptor antagonists and agonists. Mood disorder related adverse events were reported in a low frequency, but not relevantly higher in comparison to placebo. A warning is included in the SmPC, which is accepted as depression might be a class-effect of GnRH-agonists and antagonists.

Gallbladder disease

Hormonal preparations are reported to have effect on gallstone formation. Therefore, gallbladder disease-related events were followed as AE of interest. In the Uterine Fibroids 24-Week treatment, 6 cases of gall

bladder disease related AEs were reported, but none in the placebo group. In several cases, a relevant medical history could have contributed. Two new adverse events of cholelithiasis and cholecystitis were reported for patients in the 28 week extension period in the former relugolix + delayed E2/NETA group. Additionally, two new events of cholelithiasis were reported for patients in the former placebo group.

The number of cases in this specific population might be consistent with the epidemiology of gallbladder disease in obese fertile women, but although gallstones are highly prevalent, most are reported asymptomatic. Although the hormonal environment is changed when relugolix + E2/NETA is used, and concentrations of estradiol and progesterone may be lower, the net effect is as yet unclear. The occurrence of gallbladder disease during use of Ryeqo is added as a warning in section 4.4. of the SmPC.

Endometrial hyperplasia

The combination of E2/NETA is approved for the treatment of symptoms due to estrogen deficiency. The addition of NETA 0.5 mg to prevent endometrial hyperplasia has been established in the registration dossier of this product. Therefore, occurrence of endometrial hyperplasia is considered very unlikely. However, endometrial histology is evaluated in the pivotal relugolix combination therapy studies and the ongoing extension study. No findings of endometrial hyperplasia or carcinoma have been observed during 52 weeks of treatment. The majority of patients across the treatment groups had normal-atrophic/indeterminate/inactive endometrium as would be expected on relugolix combination therapy. The outcome of endometrial biopsy evaluations is added in section 5.1 of the SmPC.

Hepatic Transaminase Elevations

The evaluation of potential for hepatic transaminase elevations (ALT/AST) is based on non-clinical observations in monkeys exposed to an 48-times higher dose of relugolix, the clinical trial data, and data reported for drugs that work on the hypothalamic-pituitary-gonadal axis (GnRH receptor agonists [eg, leuprolide] and the GnRH receptor antagonists [eg, elagolix, degarelix]). In the first 24 weeks, elevated ALT/AST were reported for 7 patients (3 patients [1.2%] in the relugolix + E2/NETA group, 3 patients [1.2%] in the relugolix + delayed E2/NETA group and 1 patient [0.4%] in the placebo group). During the 28 weeks of the open-label extension study, 7 new cases were reported (1 patient in the relugolix + E2/NETA group who was reported on Day 370 and was not included in the clinical database, 2 patients [1.3%] in the former relugolix + delayed E2/NETA group and 4 patients [2.4%] in the former placebo group). In total this were 14 of 634 (2.2%) patients while on relugolix + E2/NETA. One of the ALT elevations led to study drug discontinuation; no action was taken for four events, and study drug had already been discontinued at the time of onset for one of the events. All events resolved or returned to baseline, with no serious adverse events. None had increased bilirubin and no events met Hy's law criteria. It is noted that most events had confounding factors of comorbid conditions or concomitant medications. Increased transaminases were added to the PI as a warning in section 4.4 of the SmPC.

Pregnancy

Based on the mechanism of action relugolix in a dose of 40 mg is supposed to be completely suppress ovarian function. This was confirmed with the ovulation inhibition study with relugolix combination therapy (MVT-601-046) where ovulation was inhibited 100%. In the SmPC it is recommended that nonhormonal methods of contraception should be used for at least one month after initiation of treatment, or for 7 days after missed doses for two or more consecutive days. This advice is not evaluated in the clinical phase 3 studies, as non-hormonal contraception was to be taken during the trials. Despite this advice, thirteen pregnancies have been reported during studies in women with uterine fibroids or endometriosis. Additional

information by the applicant learned that 10 of the 13 pregnancies (one was on placebo) during treatment with relugolix monotherapy or relugolix combination therapy were due to a dosing issue (n=1), timing of initiation of therapy (n = 1), or non-compliance with dosing and/or failure of non-hormonal contraception (n = 8). The additional background information indicated that compliance problems with contraceptive measures were the major cause for pregnancy occurrence. Regarding contraceptive properties of relugolix, pharmacodynamic data adequately confirmed consistent inhibition of ovulation.

Recommendations regarding contraceptive measures in section 4.2 of the SmPC have been included to strengthen the message on the need for treatment compliance, timing of initiating treatment and handling of missed doses.

Pregnancy outcome

Pregnancy is a contraindication for relugolix-E2/NETA. Embryo-foetal toxicity is included in the RMP as an important potential risk for relugolix. Congenital anomalies are included as important potential risk of other GnRH antagonists (but not all). Regarding the combination of estrogen/progestogen, up to now there appears to be little or no increased risk of birth defects in children born to women who have used oestrogens and progestogens as an oral contraceptive inadvertently during early pregnancy, as stated in SmPCs of combined hormonal contraceptives (section 4.6).

Until now, in the very limited data, no pregnancy outcomes have been seen indicative of an increased risk of birth defects. However, pregnancies and pregnancy outcomes should be closely followed.

3.5. Uncertainties and limitations about unfavourable effects

- In some women, a clinically relevant decrease in BMD (>3% decrease in BMD) was noted during treatment with relugolix + E2/NETA. These women cannot be identified upfront; the factors age, race, BMI, tobacco use, and alcohol use showed no association between BMD loss >3%. Within this category, women who had a Z-score < -2.0 and/or had a ≥7% BMD decrease had to discontinue and/or were not allowed to enter the open label extension study or the withdrawal study. The highest frequency is noted in the first 24 weeks of treatment, with decreasing frequency after prolonged treatment.

  Therefore, it is considered not justifiable to not have any measurement of BMD during the requested chronic use taking into account that unlimited treatment is based on a selected population, a limited number of 32 patients and lack of information whether these women, who had to discontinue due to significant BMD loss, would experience further decrease in BMD with longer treatment.

  It is acceptable to have no baseline DXA in all women starting Ryeqo as a reference BMD value for future DXA during treatment, as a clinically relevant BMD loss from baseline would not necessarily result in osteopenia or increased fracture risk and patients at the highest risk are excluded by the contraindication for known osteoporosis and patients with risk factors for osteoporosis or bone loss are recommended a DXA upon Ryeqo treatment. However, a DXA after 1 year of treatment is considered appropriate to verify that the woman does not have an unwanted low BMD, that exceeds the benefit of treatment. This recommendation is reflected in the PI.

3.6. Effects Table

Table: Effects Table for relugolix+E2/NETA for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age and to maintain bone mineral density and protects the uterus from endometrial hyperplasia in women who choose to use relugolix+E2/NETA for uterine fibroid treatment (data cut-off: 07 January 2020).

Effect	Short Description	Relugolix +E2/NETA	Relugolix+delayed E2/NETA	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects (24 weeks, placebo-controlled)						
Efficacy population	MVT-601-3001 MVT-601-3002	N=128 N=126	N-128 N=126	N=128 N=129		MVT-601-3001 MVT-601-3002
Primary endpoint Week 24	Proportion of women with < 80mL and >=50% reduction in MBL Week 24	73.44% 71.20%	79.5% 73.2%	18.90% 14.73%	The delayed group received 12 weeks relugolix mon and 12 weeks the combination. P<0.0001 for both relugolix+E2/NETA vs placebo (primary endpoint) as relugolix +delayed E2/NETA SoE: Effect was maintained after all 3 groups received relugolix +E2/NETA for 28 weeks until week 52 (MVT-601-3003): 87.7%, 79.9%, and 75.6% resp.	MVT-601-3001 MVT-601-3002
Primary endpoint at Week 12 (secondary)	Proportion of women with < 80mL and >=50% reduction in MBL Week 12	70.3% 70.4%	77.3% 76.4%	15.7% 8.5%	After 12 weeks, the delayed group only received relugolix monotherapy. For both studies , p<0.0001 for both relugolix+E2/NETA vs placebo as relugolix +delayed E2/NETA	MVT-601-3001 MVT-601-3002
Key secondary endpoint*	Proportion of women who achieved amenorrhea over the last 35 days of treatment.	52.34% 50.40%		5.51% 3.10%	For both studies , p<0.0001 for relugolix+E2/NETA vs placebo	MVT-601-3001 MVT-601-3002
Key secondary endpoint*	Percent change from Baseline to Week 24 in menstrual blood loss volume	-84.3% -84.3%		-23.2% 15.1%	For both studies , p<0.0001 for relugolix+E2/NETA vs placebo	MVT-601-3001 MVT-601-3002
Key secondary endpoint*	Change from Baseline to Week 24 in UFS QoL BPD scale score as measured by the UFS-QoL (Q1, Q2, Q5)	-45.0% -51.7%		-16.1% -18.3%	For both studies , p<0.0001 for relugolix+E2/NETA vs placebo	MVT-601-3001 MVT-601-3002
Key secondary endpoint*	Proportion of women who achieved a maximum NRS score <= 1 for uterine fibroid-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	43.10% 47.06%		10.14% 17.07%	For both studies , p<0.0001 for relugolix+E2/NETA vs placebo	MVT-601-3001 MVT-601-3002

Effect	Short Description	Relugolix +E2/NETA	Relugolix+delayed E2/NETA	Placebo	Uncertainties/ Strength of evidence	References
Key secondary endpoint*	Proportion of women with a hemoglobin level <= 10.5 g/dL at Baseline who achieve an increase of > 2 g/dL from Baseline at Week 24	50.00% 61.29%		21.74% 5.41%	For MVT-601-3001 , p<0.0377 for relugolix+E2/NETA vs placebo For MVT-601-3002, p<0.0001 for relugolix+E2/NETA vs placebo	MVT-601-3001 MVT-601-3002
Key secondary endpoint*	Percent change from Baseline to Week 24 in primary uterine fibroid volume	-12.4% -17.4%		-0.3% -7.4%	For MVT-601-3001 , p<0.0921 for relugolix+E2/NETA vs placebo (not statistically significant) For MVT-601-3002, p<0.2153 for relugolix+E2/NETA vs placebo (not statistically significant)	MVT-601-3001 MVT-601-3002
Key secondary endpoint*	Percent change from Baseline to Week 24 in uterine volume	-12.9% -13.8%		2.2% -1.5%	For MVT-601-3001 , p<0.0002 for relugolix+E2/NETA vs placebo For MVT-601-3002, p<0.0078 for relugolix+E2/NETA vs placebo	MVT-601-3001 MVT-601-3002

*: alpha-protected

Unfavourable Effects (24 weeks, placebo-controlled)

Safety population	MVT-601-3001 + MVT-601-3002	N=254	N=258	N=256		MVT-601-3001-/3002 pooled
Patients with ≥ 1 adverse event, Week 24	Any / serious / treatment-related, n (%)	155 (61.0%) 8 (3.1%) 92 (36.2%)	186 (72.1%) 5 (1.9%) 144 (55.8%)	160 (62.5%) 6 (2.3%) 66 (25.8%)		MVT-601-3001-/3002 pooled
AEs related to loss of BMD, Week 24	Including ankle fracture, avulsion fracture, wrist fracture, bone density decreased, bone loss, facial bones fracture, osteopenia, radius fracture	2 (0.8%)	6 (2.3%)	3 (1.2%)		MVT-601-3001-/3002 pooled
% change from baseline in BMD, Week 24	Lumbar spine LS Mean Percent Change (SE)	-0.233%	-1.972%	0.184%		MVT-601-3001-/3002 pooled
% of patients with clinically meaningful bone loss at lumbar spine at Week 24	Decrease >3%,≤5% >5%, ≤8% >8%	24 (12.3%) 7 (3.6%) 0	42 (21.6%) 24 (12.4%) 5 (2.6%)	13 (6.6%) 5 (2.5%) 0		MVT-601-3001-/3002 pooled

Effect	Short Description	Relugolix +E2/NETA	Relugolix+delayed E2/NETA	Placebo	Uncertainties/ Strength of evidence	References
No of Patients who met the BMD decrease exclusion criteria for MVT-601-3003	Z-score < -2.0 and/or had a ≥ 7% decrease in BMD	11	21	8		MVT-601-3001-/3002 pooled
Vasomotor symptoms, Week 24	Including hot flush, hyperhidrosis, night sweats, flushing	27 (10.6%)	95 (36.8%)	17 (6.6%)	SoE: Effect was maintained after all 3 groups received relugolix +E2/NETA for 28 weeks until week 52 (MVT-601-3003): 31 (12.2%), 95 (36.8%), 32 (12.5%), resp.	MVT-601-3001-/3002 pooled
Unfavourable Effects (52 weeks, all 3 groups received relugolix +E2/NETA for 28 weeks (MVT-601-3003):						
Safety population	Patients enrolled in open-label extension study	N=163	N=149	N=163	relugolix+E2/ NETA in all 3 arms	(MVT-601-3003)
% change from baseline in BMD, Week 36	Lumbar spine LS Mean % Change Week 36	-0.726%	-2.106%	-0.246%	After 52, 40, and 28 weeks relugolix+E2/ NETA, respectively	(MVT-601-3003)
% change from baseline in BMD, Week 52	Lumbar spine LS Mean % Change Week 52	-0.804%	-2.045%	-0.775%	After 52, 40, and 28 weeks relugolix+E2/ NETA, respectively	(MVT-601-3003)
Proportion of patients with clinically meaningful bone loss at lumbar spine at Week 52	Decrease >3%,≤5% >5%, ≤8% >8%	34 (25.4%) 7 (5.2%) 1 (0.8%)	24 (19.7%) 7 (5.7%) 3 (2.8%)	32 (29.4%) 13 (11.9%) 2 (1.7%)	After 52, 40, and 28 weeks relugolix+E2/ NETA, respectively	(MVT-601-3003)
Unfavourable Effects (104 weeks, most patients received relugolix +E2/NETA (MVT-601-035):						
Safety population 035	Patients enrolled in withdrawal study	N = 116		N = 112*		(MVT-601-035)
% change from baseline in BMD, Week 104	Lumbar spine LS Mean % Change Week 104	0.81%		0.10%		

Effect	Short Description	Relugolix +E2/NETA	Relugolix+delayed E2/NETA	Placebo	Uncertainties/ Strength of evidence	References
Proportion of patients with clinically meaningful bone loss at lumbar spine at Week 104	Decrease >3%,≤5% >5%, ≤8% >8%	4/79 (5.1%) - -		6/78 (7.7%) 4/78 (5.1%) -		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethindrone acetate; ULN = upper limit of normal
Notes: The treatment groups are as follows:
MVT-601-3001 and MVT-601-3002:

- relugolix+E2/NETA for 24 weeks
- relugolix+delayed E2/NETA : 12 weeks relugolix only followed by 12 weeks relugolix+E2/NETA
- Placebo for 24 weeks

MVT-601-3003: one-arm 28-week extension study where ALL subjects who wished to enrol from studies MVT-601-3001 and MVT-601-3002 received relugolix+E2/NETA.
*MVT-601-035: double-blind, placebo-controlled for 24 weeks, open-label 30 weeks (in this part, subjects with relapse of HMB >80 ml allowed to restart Ryeqo, 88% of placebo subjects restarted Ryeqo)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Relugolix in fixed combination with estradiol 1 mg/norethisterone 0.5 mg (E2/NETA) is proposed for *"treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age".*

The proposed duration of use is as follows *"As Ryeqo maintains estradiol and progestogen concentrations in a range that maintains bone mineral density, it can be used without interruption."*

Relugolix is a new GnRH antagonist while E2/NETA, is a known hormone replacement therapy (Activelle). Relugolix is a GnRH-antagonist, which blocks the hypothalamic–pituitary–adrenal axis (HPA axis), thereby preventing release of LH and FSH. The subsequent decrease of estradiol and progesterone to postmenopausal levels, reduces symptoms associated with uterine fibroids, like heavy menstrual bleeding, anemia, and pain, and to some extent fibroid size.

Relugolix monotherapy leads to suppression of oestrogen concentration to postmenopausal levels, which induces bone mineral density loss and postmenopausal symptoms. 'Add-back' therapy is combined with relugolix in order to mitigate bone loss with the aim to make longer use possible.

Regarding benefit, the phase 3 clinical program on efficacy supported a statistically and clinically relevant higher reduction in heavy menstrual blood loss associated with uterine fibroids in comparison to placebo over a treatment period of 24 weeks. This benefit is reflected by a significantly greater proportion of women in the relugolix + E2/NETA group versus the placebo group who achieved a 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 versus placebo. This beneficial effect over placebo is further supported in clinically meaningful reductions in total menstrual blood loss volume, achievement of amenorrhea, and slight decrease in volume of uterine fibroids.

Based on the results of the completed uncontrolled extension of the parent studies with 28 weeks, and the top-line summary data of the withdrawal study, it is concluded that the efficacy, as based on the primary

efficacy endpoint, i.e. proportion of responders at week 24, has been maintained over a period of 104 weeks treatment.

With regard to the adverse event profile up to 24 weeks of treatment, Relugolix + E2/NETA appeared to be generally well tolerated with only 10 (3.9%) patients discontinued due to an adverse event over a treatment period of 24 weeks. The number of discontinuations remained consistent over 52 weeks of treatment (3.1%). The adverse events pattern was consistent with the adverse event pattern that is expected for a GnRH-antagonist based on its mechanism of action, as most frequently reported treatment related adverse events consisted of symptoms due to the low estradiol levels, of which hot flushes had highest frequency. But these symptoms were considerably lower than noted with relugolix monotherapy, indicating a positive effect of the addition of E2/NETA.

Regarding BMD loss, over a period of 24 weeks, positive effects of E2/NETA have been noted in mitigation of relugolix induced BMD loss, as has been demonstrated in comparison to patients treated with relugolix for 12 weeks. BMD measurements at week 24 indicated maintenance of these effects.

Over a period of 52 weeks, BMD data show a protective effect of E2/NETA as add-back therapy, as the decrease in BMD was around 1% over a period of 52 weeks in the 163 patients who received relugolix + E2/NETA from start to up to 52 weeks. However, the LS mean percent change in BMD measured by DXA of -0.726% at week 36 and -0.804% at week 52 suggested that the maximum percent decrease in BMD may not have been reached at 52 weeks.

Additional top-line summary data on a second treatment year from the withdrawal support that a plateau in BMD loss of around 1% is maintained with longer treatment , which could support a registration for unlimited duration of use (up to menopause).

In some women, a clinically relevant decrease in BMD (>3% decrease in BMD) was noted during treatment with relugolix + E2/NETA. Of these women, a small percentage had a Z-score of -2 or a decrease in BMD of ≥ 7% decrease in BMD, which led to discontinuation or made them ineligible to enter the extension study or the withdrawal study. The highest frequency is noted in the first 24 weeks of treatment, with decreasing frequency after prolonged treatment up to 104 weeks, The occurrence of this clinically relevant BMD loss may indicate that in some women relugolix + E2/NETA does not sufficiently preserve BMD. As these women had to discontinue from the studies, it is not known if they would experience further decrease in BMD with longer treatment. Additional analyses showed that these women cannot be identified upfront.

Therefore, it is considered not justifiable to not have any measurement of BMD during the requested chronic use taking into account that unlimited treatment is based on a selected population, a limited number of 32 patients and lack of information whether these women, who had to discontinue due to significant BMD loss, would experience further decrease in BMD with longer treatment.

It is acceptable to have no baseline DXA in all women starting Ryeqo as a reference BMD value for future DXA during treatment, as a clinically relevant BMD loss from baseline would not necessarily result in osteopenia or increased fracture risk and patients at the highest risk are excluded by the contraindication for known osteoporosis and patients with risk factors for osteoporosis or bone loss are recommended a DXA upon Ryeqo treatment. However, a DXA after 1 year of treatment is considered appropriate to verify that the woman does not have an unwanted low BMD, that exceeds the benefit of treatment. This recommendation is reflected in the PI.

It is noted that pregnancy is a contraindication for relugolix-E2/NETA. Embryo-foetal toxicity is included in the RMP as an important potential risk for relugolix. Congenital anomalies are included as important potential

risk of other GnRH antagonists (but not all). Regarding the combination of estrogen/progestogen, there appears to be little or no increased risk of birth defects in children born to women who have used oestrogens and progestogens as an oral contraceptive inadvertently during early pregnancy, as stated in SmPCs of combined hormonal contraceptives (section 4.6). Until now, in the very limited data, no pregnancy outcomes have been seen indicative of an increased risk of birth defects. However, pregnancies and pregnancy outcomes should be closely followed.

3.7.2. Balance of benefits and risks

In terms of benefit, there is sufficient evidence that the combination therapy of relugolix 40 mg+E2 1 mg/NETA 0.5 mg provides adequate, and clinically relevant efficacy in the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age over a treatment period of 24 weeks, as primarily shown by a greater improvement in the proportion of women who achieved a menstrual blood loss volume of <80 mL and at least a 50% reduction from baseline MBL volume versus placebo and that this effect is maintained up to 104 weeks treatment in an open label setting. Additionally, based on its mechanism of action and detailed PK/PD data, it has been sufficiently substantiated that Ryeqo has adequate contraceptive properties, when recommendations are correctly followed.

The use of relugolix + E2/NETA appears to be well-tolerated with an acceptable safety profile and without unexpected safety signals over a period of 104 weeks' treatment. Therefore, on clinical grounds no major safety issues have been identified that preclude conclusions on the balance of benefits and risks in the treatment period of 104 weeks.

Based on the currently submitted data and additional analyses based on these data, the noted decrease in BMD of around 1% after 52 weeks of treatment compared to baseline BMD has reached a plateau as further clinical data up to 104 weeks of treatment have established that the decrease in BMD remains in the range that is currently observed over 52 weeks of treatment. Cumulatively, the mean percent change in BMD from pivotal study baseline to up to Week 104 in patients who received relugolix + E2/NETA (n = 32) was 0.04%. In women who received placebo for 24 weeks followed by relugolix + E2/NETA for 80 weeks (n = 29), the mean percent change in BMD from pivotal study baseline to Week 104 was 0.45%. These results could support a registration for unlimited duration of use, but results are based on a selected population, as women with osteoporosis or risk factors for osteoporosis were not allowed to participate, women in the trials who experienced a Z-score of -2 or BMD loss ≥7% were discontinued and/or not allowed to enter the extension study or withdrawal study, and the final number of patients treated with relugolix + E2/NETA for up to 104 weeks is limited to 32 patients.

Therefore, it is considered not justifiable to not have any measurement of BMD during the requested chronic use taking. It is acceptable to have no baseline DXA in all women starting Ryeqo as a reference BMD value for future DXA during treatment, as a clinically relevant BMD loss from baseline would not necessarily result in osteopenia or increased fracture risk and patients at the highest risk are excluded by the contraindication for known osteoporosis and patients with risk factors for osteoporosis or bone loss are recommended a DXA upon Ryeqo treatment. However, a DXA after 1 year of treatment is considered appropriate to verify that the woman does not have an unwanted low BMD, that exceeds the benefit of treatment. This recommendation is reflected in the PI.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Ryeqo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ryeqo is favourable in the following indication:

"Treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that relugolix is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.