14 September 2023
EMA/528959/2023
Committee for Medicinal Products for Human Use (CHMP)

Group of variations including an extension of indication assessment report

Invented name: **Ryeqo**

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

Procedure No. EMEA/H/C/005267/II/0013/G

Note

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

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List of abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUCss	area under the concentration-time curve at steady state
B&B	Biberoglu and Behrman
BMD	bone mineral density
BMI	body mass index
Cmax,ss	maximum concentration at steady state
Ctrough,ss	pre-dose (trough) concentration at the end of the dosing interval at steady state
CYP	cytochrome P450
DXA	dual x-ray absorptiometry
E2	estradiol (abbreviated only when referring to exogenously applied estradiol)
EHP-30	Endometriosis Health Profile-30
EOT	end of treatment
ESHRE	European Society of Human Reproduction and Embryology
FDA	(United States) Food and Drug Administration
FDC	fixed-dose combination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practices
GMR	geometric mean ratio
GnRH	gonadotropin-releasing hormone
ICH	International Council for Harmonisation
LH	luteinizing hormone
LS	least squares
NETA	norethisterone acetate
NMPP	non-menstrual pelvic pain
NRS	numerical rating scale
PopPK	population pharmacokinetic
PRO	patient-reported outcomes
SAP	Statistical Analysis Plan
SEMS	Symptoms of Endometriosis Scale
ULN	upper limit of normal
VAS	visual analog scale

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Gedeon Richter Plc. submitted to the European Medicines Agency on 11 October 2022 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderate to severe pain associated with endometriosis for RYEQO in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis, based on final results from studies MVT-601-3101 and MVT-601-3102 and final results up to 104 weeks from study MVT-601-3103. Studies MVT-601-3101 and 3102 are pivotal, phase III, randomised, double-blind, placebo-controlled, safety and efficacy studies to evaluate relugolix with E2 and NETA as a combination therapy for pain associated with endometriosis. Study 3103 is an open-label extension study including patients who completed one of the two pivotal studies and met the eligibility criteria, regardless of their treatment assignment in the pivotal studies. In the extension part all patients received relugolix combination therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC were updated. The Package Leaflet is updated in accordance.
Update of section 4.5 of the SmPC to update information regarding Drug-Drug Interaction based on final results of DDI studies MVT-601-054, MVT-601-055 and MVT-601-057. Study MVT-601-54 is a 2-part interventional open-label study to assess the potential effects of erythromycin on the PK of the 3 components of Ryeqo. Study MVT-601-55 is an interventional open label fixed single sequence cross-over study to assess whether a 6-hour dose separation is sufficient to mitigate absorption mediated increased exposure to relugolix and study MVT-601-057 is a 2-part study to assess the potential effect of relugolix on the PK of total dabigatran.
The updated RMP version (2.0) has also been submitted. As part of the application, the MAH also requests an extension of the market protection by one additional year.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-002428-PIP02-18 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 MAH 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Jean-Michel Race

Timetable	Actual dates
Submission date	11 October 2022
Start of procedure:	26 November 2022
CHMP Rapporteur Assessment Report	23 January 2023
PRAC Rapporteur Assessment Report	27 January 2023
PRAC members comments	1 February 2023
CHMP Co-Rapporteur Assessment	1 February 2023
PRAC Outcome	9 February 2023
CHMP members comments	13 February 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 February 2023
Request for supplementary information (RSI)	23 February 2023
CHMP Rapporteur Assessment Report	1 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur Assessment Report	16 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	18 August 2023
CHMP members comments	04 September 2023
Updated PRAC Rapporteur Assessment Report	06 September 2023
Opinion	14 September 2023

2. Scientific discussion

2.1. Introduction

Ryeqo is an orally active, nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist that has been developed as a fixed-dose combination (FDC) tablet with estradiol (E2) and norethisterone acetate (NETA) (referenced also as "relugolix combination therapy").

Ryeqo 40 mg once daily is approved on 16 Jul 2021 in the EU for the "*treatment of moderate-to-severe symptoms of uterine fibroids in adult women of reproductive age*".

This dossier is submitted to provide the efficacy and safety results of 2 pivotal phase 3 studies to support the use of Ryeqo 40 mg once daily for the treatment of endometriosis associated pain.

2.1.1. Problem statement

Disease or condition

Endometriosis is an inflammatory disease associated with pelvic pain and infertility characterized by extrauterine lesions of endometrial-like tissue, affecting 10% of women in their reproductive years (Dunselman et al. 2014; Vercellini et al. 2014; Kuznetsov et al. 2017; Zondervan et al. 2020).

Most commonly, the pain may occur with menses (dysmenorrhea), between menses (non-menstrual pelvic pain [NMPP]), and/or with sexual intercourse (dyspareunia). Some women also experience painful urination (dysuria) or painful bowel movements (dyschezia).

A definitive diagnosis requires surgery with direct visualization and/or biopsy with histologic confirmation, and women may see multiple healthcare providers over several years before endometriosis is diagnosed (Zondervan et al. 2020).

State the claimed the therapeutic indication

The MAH was initially asking approval to expand the use of relugolix combination therapy for the treatment of moderate to severe pain associated with endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis.

The population enrolled in the pivotal phase 3 endometriosis studies with relugolix combination therapy was consistent with the standard of care for endometriosis in treatment guidelines. Specifically, GnRH receptor antagonist therapy for endometriosis is considered a second line treatment after suboptimal response with other available pharmacologic interventions, including hormonal therapies (ESHRE Endometriosis Guideline Group et al. 2022). In the endometriosis phase 3 clinical program, nearly all patients had antecedent surgical procedures and/or prior medical management for their endometriosis. Administration of relugolix + E2/NETA as part of clinical trial participation represented de facto second-line treatment in the management of their disease. The MAH stated that the product labelling should reflect that Ryeqo is indicated for patients who have had prior management for endometriosis, which is consistent with treatment guidelines and the relugolix combination therapy clinical development program.

The initial wording of the indication has been revised into:

*"**Symptomatic** treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (see section 5.1)".*

Aetiology and pathogenesis

The pathogenesis of endometriosis is the presence of endometrial glands and stroma outside the uterine cavity. Retrograde menstruation is the classically described pathogenesis (Zondervan et al. 2020). Endometriosis-associated lesions remain sensitive to sex steroids and exhibit a pattern of hormonal responsiveness similar to that of the endometrium. Proliferation of endometriotic lesions requires estradiol, which is provided by systemic hormones and also locally from increased expression of aromatase and steroidogenic acute regulatory protein and decreased expression of 17β-hydroxysteroid dehydrogenase 2 in some women. Compared with normal endometrium, endometriotic implants are characterized by overproduction of prostaglandins and local production of estrogens and cytokines, which synergize the activities of each other and promote implantation of ectopic endometrium. In addition, the implants have upregulated estrogen synthesis pathways (Practice Committee of American Society for Reproductive Medicine 2014).

Management

Surgery

Treatment for endometriosis is often surgical resection and/or ablation with definitive surgery. Repeat surgeries are not uncommon as symptoms can recur after surgery. Conservative surgical management of endometriosis includes laparoscopic resection/laser ablation, drainage or resection of endometriomas, resection of rectovaginal nodules (eg, uterosacral nerves); however, symptoms can recur after conservative surgery. Definitive surgery, such as hysterectomy and bilateral oophorectomy for refractory disease, results in surgical menopause. In some patients, symptoms may recur after hysterectomy.

Medical management

This includes analgesics and therapies to lower estrogen, given that estradiol is a key driver of endometrial growth and contributes to local inflammation and pain.

- Combined (estrogen and progestin) oral contraceptives (off label) continuously used.
- Progestogens (e.g. medroxyprogesterone, norethisterone, and dienogest)
- Danazol
- GnRH agonists in the EU, with limited in duration of use to 6 months, due to the adverse effect on bone mineral density. The international endometriosis guidelines (ESHRE) recommends that GnRH agonists are prescribed as second line (for example if hormonal contraceptives or progestogens have been suboptimal in managing symptoms).
- Analgesics/ opioids, when current medical treatments and surgical interventions offer incomplete pain relief, patients may rely on opioid use to control pain

The clinical course in endometriosis can be challenging for the patient. Independent of treatment approach, 50% of patients have recurrence of symptoms over 5 years (Zondervan et al. 2020). Regardless of the type of management, long-term treatment to inhibit ovulation or reduce estrogen production is recommended for this chronic condition (Johnson et al. 2013; Dunselman et al. 2014; Practice Committee of American Society for Reproductive Medicine 2014; Zondervan et al. 2020). Continued pelvic pain, along with severity of disease, have been shown to have significant impact on

physical health-related quality of life and are associated with decreased work productivity (Nnoaham et al. 2011).

2.1.2. About the product

Relugolix is an orally active, nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist that has been developed as a fixed-dose combination (FDC) tablet with estradiol (E2) and norethisterone acetate (NETA) (referenced also as "relugolix combination therapy").

The relugolix combination therapy was approved on 16 Jul 2021 in the European Union (EU), for the "*treatment of moderate-to-severe symptoms of uterine fibroids in adult women of reproductive age*".

Pharmacotherapeutic action

Relugolix

Endometriosis is dependent on estrogen for proliferation.

It has been hypothesized that maintaining estradiol in a range of 20 to 50 pg/mL would lead to improvement of symptoms of endometriosis, while minimizing the risk of BMD loss and vasomotor symptoms due to a hypoestrogenic state, although the precise hormonal thresholds that define this therapeutic range likely vary across individuals (Barbieri 1992; Riggs et al. 2012). Estrogen concentrations consistent with the early follicular phase of the menstrual cycle (ie, estradiol ~ 10 to 70 pg/mL) (Cramer et al. 2002; Stricker et al. 2006) would be expected to accomplish this goal.

Relugolix is an orally active, potent, nonpeptide GnRH receptor antagonist that competitively binds to GnRH receptors on gonadotropic neurons, blocking the binding of endogenous GnRH and subsequent activation of GnRH receptors, preventing the release of LH and FSH from the anterior pituitary gland. Clinical pharmacology studies demonstrated that after oral administration of relugolix, a rapid and reversible, dose-dependent suppression of LH and FSH secretion is observed. The reduction in FSH concentration prevents natural follicular growth and development, limiting the production of estrogen by the developing ovarian follicles and secretion into the systemic circulation. Treatment with relugolix 40 mg leads to near-maximal inhibition of ovarian function with the subsequent reduction in ovarian production and secretion of estradiol. The resulting low systemic concentration of estradiol minimizes the hormone-related proliferative effects on endometriosis foci and the endometrium is stabilized. In addition, as shown in the phase 2 and phase 3 clinical studies, the low estradiol concentration effectively reduces symptoms associated with endometriosis, including dysmenorrhea, NMPP, and dyspareunia, and these observed reductions of pain have been shown to translate into improvements in daily function.

Estradiol

Exogenous administration of E2 1 mg ensures sufficient circulating estradiol concentrations to maintain BMD and minimize vasomotor symptoms.

Norethisterone acetate (NETA)

Exogenous administration of the progestin, NETA, leads to down-regulation of estrogen receptors in the uterus (Kuhl 2005; Levin et al. 2013), further limiting the proliferative effects of estrogens on the endometrium that can lead to endometrial hyperplasia or adenocarcinoma.

Rationale for relugolix combination treatment

At the proposed clinical dose (relugolix 40 mg, E2 1 mg, and NETA 0.5 mg), relugolix combination therapy provides estradiol concentrations within a therapeutically effective range that improves pain associated with endometriosis while minimizing the risk of bone mineral density (BMD) loss and vasomotor symptoms associated with a hypoestrogenic state as well as the risk of endometrial hyperplasia associated with unopposed estrogen.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek Scientific Advice at the CHMP, but national scientific advice was obtained and incorporated into the overall design of the studies, including the efficacy and safety analyses.

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

A comprehensive summary of individual studies in the clinical pharmacology program, including the pharmacokinetic (PK) and pharmacodynamic (PD) modelling and simulation analyses for relugolix combination therapy was previously provided in the original MAA for relugolix combination therapy (relugolix 40 mg, estradiol [E2] 1 mg, norethisterone acetate ([NETA] 0.5 mg [Ryeqo®]) for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age (EMEA/H/C/005267).

New information, including additional drug interaction studies that are relevant for both indications, and information specific to support the current extension of indication were included in this grouped type II variation. The additional studies and analyses were comprised of drug-drug interaction studies, pharmacokinetic (PK) and pharmacodynamic (PD) modelling and simulation analyses, and the justification for the lower comparability bound defining clinically meaningful decreases in relugolix exposure based on the exposure-response analysis in women with endometriosis.

Relugolix is a sensitive substrate of intestinal P-gp, which limits its oral bioavailability and is likely responsible for the greater than dose proportional increase in exposure for doses up to 80 mg till a plateau is reached and may govern absorption-mediated drug interactions. Since clinically meaningful increases in exposure to relugolix were observed at the therapeutic dose of Ryeqo, additional drug-drug interaction studies with P-gp inhibitors have been conducted to provide dosing recommendations when concomitant use of relugolix and an oral P-gp inhibitor cannot be avoided.

GCP

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

The MAH 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.

2.3.2. Pharmacokinetics

2.3.2.1. DDI victim interaction study with erythromycin MVT-601-054

The erythromycin drug interaction study (MVT-601-054 Clinical Study Report (CSR)) was a two-part (Part 1 and Part 2) study with each study part consisting of an open-label, single (fixed)-sequence, two-period crossover design to assess the potential effects of erythromycin on the pharmacokinetics of relugolix, estradiol, and norethindrone after administration of the relugolix/estradiol/norethindrone acetate fixed-dose combination tablet in healthy postmenopausal women (Part 1) and on the pharmacokinetics of relugolix after administration of a single 120-mg dose in healthy adult men (Part 2).For Part 1, the results of the analysis of pharmacokinetic parameters for relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet alone and co-administered with erythromycin (500 mg) are shown in Table 1.

Table 1. PK parameters of relugolix after single dose relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet and after co-administration with erythromycin (500 mg QID)**.**

Parameter	n	Geometric Mean (SE)[a]	Coadministration (Relugolix/E2/NETA + Erythromycin) / Relugolix/E2/NETA Alone		CV_b (%)[a]	CV_w (%)[a]
			Geometric Mean Ratio (SE)[a]	90% CI[a]		
$AUC_{0-\infty}$ (ng*hr/mL)						
Coadministration (Relugolix/E2/NETA + Erythromycin)	16	623.5 (1.121)	4.0631 (1.1369)	3.2447, 5.0879	28.3	37.5
Relugolix/E2/NETA Alone	16	153.5 (1.121)				
AUC_{0-t} (ng*hr/mL)						
Coadministration (Relugolix/E2/NETA + Erythromycin)	16	564.3 (1.122)	3.9915 (1.1368)	3.1881, 4.9972	28.7	37.5
Relugolix/E2/NETA Alone	16	141.4 (1.122)				
C_{max} (ng/mL)						
Coadministration (Relugolix/E2/NETA + Erythromycin)	16	80.19 (1.140)	3.8209 (1.1619)	2.9371, 4.9706	31.6	44.4
Relugolix/E2/NETA Alone	16	20.99 (1.140)				

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; AUC_{0-t} = AUC from time 0 to last quantifiable timepoint; CI = confidence interval; C_{max} = maximum observed concentration; CSR = clinical study report; CV_b = between-subject coefficient of variation; CV_w = within-subject coefficient of variation; E2 = estradiol; n = number of participants included in summary statistics; NET = norethisterone; NETA = norethisterone acetate; SE = standard error.

Note: $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} parameters were analyzed on a natural log scale.

a From a paired t-test for the log-transformed parameter results.

For Part 2, results of the analysis of pharmacokinetic parameters for relugolix (120 mg) tablet alone and co-administered with erythromycin (500 mg) are shown in Table 2.

Table 2. PK parameters of relugolix after single dose relugolix (120 mg) tablet and after co-administration with erythromycin (500 mg QID)**.**

Parameter	n	Geometric Mean (SE)[a]	Coadministration (Relugolix + Erythromycin) / Relugolix Alone		CV_b (%)[a]	CV_w (%)[a]
			Geometric Mean Ratio (SE)[a]	90% CI[a]		
$AUC_{0-\infty}$ (ng*hr/mL)						
Coadministration (Relugolix + Erythromycin)	24	1383 (1.145)	3.5298 (1.2016)	2.5767, 4.8354	18.8	70.6
Relugolix Alone	24	391.9 (1.145)				
AUC_{0-t} (ng*hr/mL)						
Coadministration (Relugolix + Erythromycin)	24	1281 (1.146)	3.5400 (1.2028)	2.5797, 4.8578	19.4	71.1
Relugolix Alone	24	362.0 (1.146)				
C_{max} (ng/mL)						
Coadministration (Relugolix + Erythromycin)	24	161.1 (1.179)	2.8858 (1.2461)	1.9792, 4.2078	26.2	88.8
Relugolix Alone	24	55.82 (1.179)				

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; AUC_{0-t} = AUC from time 0 to last quantifiable timepoint; CI = confidence interval; C_{max} = maximum observed concentration; CSR = clinical study report; CV_b = between-subject coefficient of variation; CV_w = within-subject coefficient of variation; n = number of participants included in summary statistics; SE = standard error.

Note: $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} parameters were analyzed on a natural log scale.

a: From a paired t-test for the log-transformed parameter results.

This interaction study with relugolix as a victim shows that after co-administration of a single relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet and multiple doses of 500 mg erythromycin, the AUC0-∞ and Cmax of relugolix were 4.1- and 3.8-fold higher, respectively, compared with administration of relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet alone (Table 1). This study also shows that after co-administration of a single 120-mg dose of relugolix and multiple doses of 500 mg erythromycin, the AUC0-∞ and Cmax of relugolix were 3.5- and 2.9-fold higher, respectively, compared with administration of a single 120-mg dose of relugolix alone (Table 2).

Taken together, adjusting the values for AUC and Cmax of relugolix to 4.1- and 3.8-fold increases, respectively, after concomitant use of a single relugolix/E2/NETA (40 mg/1 mg/0.5 mg) with erythromycin (P-gp and moderate CYP3A4 inhibitor) in the SmPC of Ryeqo is justified.

2.3.2.2. DDI victim interaction study with azithromycin MVT-601-055

The azithromycin drug interaction study (MVT-601-055 Clinical Study Report (CSR)) was an open-label, fixed (single)-sequence (ABC), three-period crossover study in healthy adult men to assess whether a 6-hour dose separation is sufficient to mitigate absorption-mediated increases in exposure to relugolix upon co-administration of relugolix and azithromycin.

Results of the analysis of PK parameters for relugolix (120 mg) alone and co-administered with azithromycin (500 mg) are shown in Table 3. Concentration-time profiles of Treatment A, Treatment B, and Treatment C are shown in Figure 1.

Table 3. Pharmacokinetic parameters of relugolix after relugolix (120 mg) tablet alone and after co-administration with azithromycin (500 mg).

Pharmacokinetic Parameter	n	Geometric Mean	(Relugolix + Azithromycin) / Relugolix Alone		CV_b (%)[a]	CV_w (%)[a]
			Geometric Mean Ratio	90% CI[a]		
$AUC_{0-\infty}$ (ng*hr/mL)						
Relugolix alone	18	627.78			48.0	68.5
Coadministration of relugolix and azithromycin	18	923.15	1.4705	1.0365, 2.0863		
Relugolix + azithromycin 6 hours postdose	18	899.59	1.4314	0.9700, 2.1123		
AUC_{0-t} (ng*hr/mL)						
Relugolix alone	18	576.80			47.9	69.6
Coadministration of relugolix and azithromycin	18	849.97	1.4736	1.0311, 2.1061		
Relugolix + azithromycin 6 hours postdose	18	830.80	1.4404	0.9703, 2.1381		
C_{max} (ng/mL)						
Relugolix alone	18	80.23			48.3	120.0
Coadministration of relugolix and azithromycin	18	130.10	1.6216	0.9487, 2.7718		
Relugolix + azithromycin 6 hours postdose	18	105.14	1.3105	0.7168, 2.3959		

Abbreviations: CI = confidence interval; CV_b = between-subject coefficient of variation; CV_w = within-subject coefficient of variation.

[a] From a mixed-effects model for the log-transformed pharmacokinetic parameters with treatment as a fixed effect and subject as a random effect.

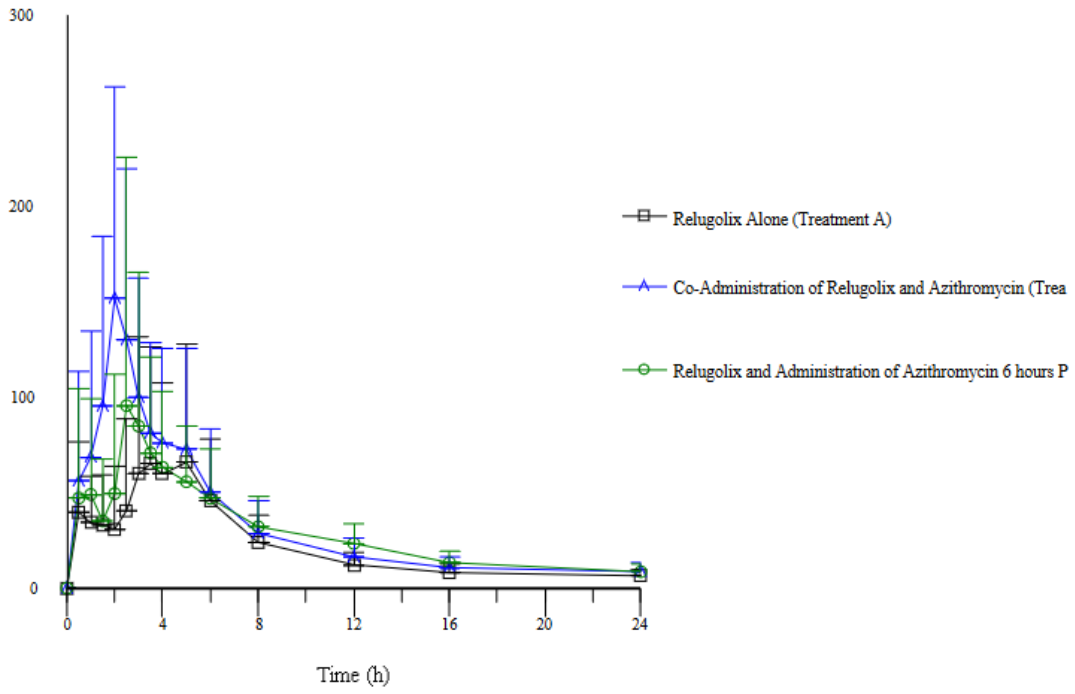


Figure 1. Mean (+SD) relugolix plasma concentration-time profiles from 0-24 hours after administration of a 120-mg dose of relugolix to healthy adult subjects: relugolix alone (Treatment A, black), co-administration of relugolix and azithromycin (Treatment B, blue), and relugolix and administration of azithromycin 6 hours later (Treatment C, green).

This interaction study with relugolix as a victim shows that the administration of relugolix (120 mg) and azithromycin (500 mg) administered 6 hours after relugolix administration, is found to be acceptable, as the calculated GMRs of the AUCs and Cmax in comparison to administration of 120 mg relugolix alone are found within the comparability bounds of 0.50 to 1.50 (established for 120 mg relugolix), which were established to conclude clinically meaningful changes. In other words, taking relugolix and azithromycin with a 6-hour interval does not lead to a clinically meaningful difference in total exposure to relugolix as compared to when relugolix is given alone. This decision is also taken on the mean relugolix vs concentration plot.

However, the study also shows that co-administration of relugolix (120 mg) and azithromycin (500 mg) at the same time leads to bigger increases in relugolix exposure as shown in Figure 1 (up to 5-fold in the window 1-3 hours after dosing), and the GMR of Cmax (1.62) is not found within the comparability bounds of 0.5 to 1.50. It is acknowledged that there is large variability within and between subjects in absorption of relugolix, and therefore due to the limited number of subjects (n=18) in this study total relugolix AUC may not be the most sensitive parameter to describe the effects of co-administration in this study. Therefore, the recommendation in the SmPC on concomitant use of relugolix (120 mg only) and the P-gp inhibitor azithromycin (500 mg) with 6 hours separation remains as it is in the current approved SmPC.

As administration of 40 mg relugolix and azithromycin with a 6-hour separation interval is not tested, and due to the non-linear PK of relugolix (more than dose-proportional) the effect of azithromycin on 40 mg relugolix cannot be estimated. Therefore, the information in the SmPC regarding the concomitant use of Ryeqo and a P-gp inhibitor (e.g. azithromycin) remains unchanged.

2.3.2.3. DDI perpetrator interaction study with dabigatran MVT-601-057

The dabigatran drug interaction study (MVT-601-057 Clinical Study Report (CSR)) was a two-part, open-label, fixed (single)-sequence, two-treatment, two-period crossover study in healthy adult men and woman to assess the effects of relugolix on the pharmacokinetics of total dabigatran upon co-administration of relugolix and dabigatran etexilate. This was a two-part (Part 1 and Part 2) drug interaction study to assess the potential effect of relugolix as a perpetrator on the pharmacokinetics of total dabigatran upon co-administration of a single 40-mg dose (Part 1) or a single 120 mg dose (Part 2) of relugolix and a 150 mg dose of dabigatran etexilate in healthy adult men and women (Part 1) or healthy adult men only (Part 2). There was a 6-day washout interval between study drug administration in each treatment period. As pre-specified in the protocol, Part 2 of the study (relugolix 120 mg) was conducted first, and if a clinically meaningful increase in exposure to total dabigatran was observed, relugolix 40 mg (Part 1) would be conducted, at the discretion of the study sponsor. Assessments of the results from Part 2 indicated that Part 1 of the study was not necessary, which is agreed upon

A summary of statistical comparisons of total dabigatran pharmacokinetic parameters after administration of dabigatran etexilate 150 mg alone or after co-administration with relugolix 120 mg is presented in Table 4 and Figure 2.

Table 4. Pharmacokinetic parameters of 150 mg dabigatran after dabigatran etexilate tablet alone and after co-administration with relugolix (120 mg).

Pharmacokinetic Parameter	n	Geometric Mean (SE)[a]	Coadministration (Relugolix 120 mg + Dabigatran Etexilate)/ Dabigatran Etexilate Alone		CV_b (%)[a]	CV_w (%)[a]
			Geometric Mean Ratio (SE)[a]	90% CI[a]		
$AUC_{0-\infty}$ (ng*h/mL)						
Coadministration (Relugolix 120 mg + Dabigatran Etexilate)	24	1208 (1.137)	1.1727 (1.1559)	0.9149, 1.5032	39.3	53.5
Dabigatran Etexilate Alone	24	1031 (1.137)				
AUC_{0-t} (ng*h/mL)						
Coadministration (Relugolix 120 mg + Dabigatran Etexilate)	24	1174 (1.140)	1.1766 (1.1617)	0.9101, 1.5212	39.2	55.6
Dabigatran Etexilate Alone	24	997.7 (1.140)				
C_{max} (ng/mL)						
Coadministration (Relugolix 120 mg + Dabigatran Etexilate)	24	158.0 (1.145)	1.1852 (1.1744)	0.8998, 1.5611	37.2	60.3
Dabigatran Etexilate Alone	24	133.3 (1.145)				

a: Paired t-test for the log-transformed parameter. SE=Standard error. CI=Confidence interval. CV_b=Between-subject coefficient of variation. CV_w=Within-subject coefficient of variation.

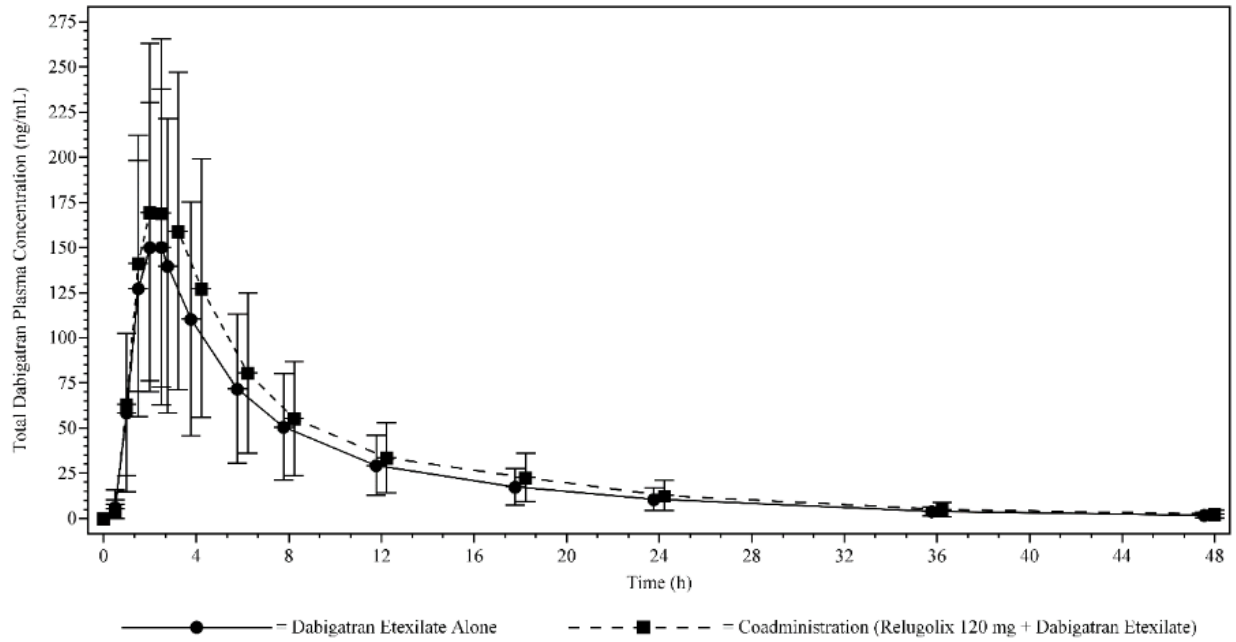


Figure 2. Mean (±SD) total dabigatran plasma concentrations (ng/mL) vs. time point to 48 hours post-dose by treatment.

This perpetrator interaction study shows that co-administration of a single dose 120 mg relugolix with a single dose 150 mg dabigatran etexilate did not lead to a clinically meaningful effect on total dabigatran, as the GMRs showed there was a 1.17- and 1.18-fold increase of total dabigatran AUC and Cmax, respectively. These values are within the criteria of 0.80 to 1.25, indicating that no clinically meaningful effect was established after one dose of relugolix.

Therefore, the addition of text to the SmPC of Ryeqo that Ryeqo has no effect on the P-gp substrate dabigatran etexilate is accepted.

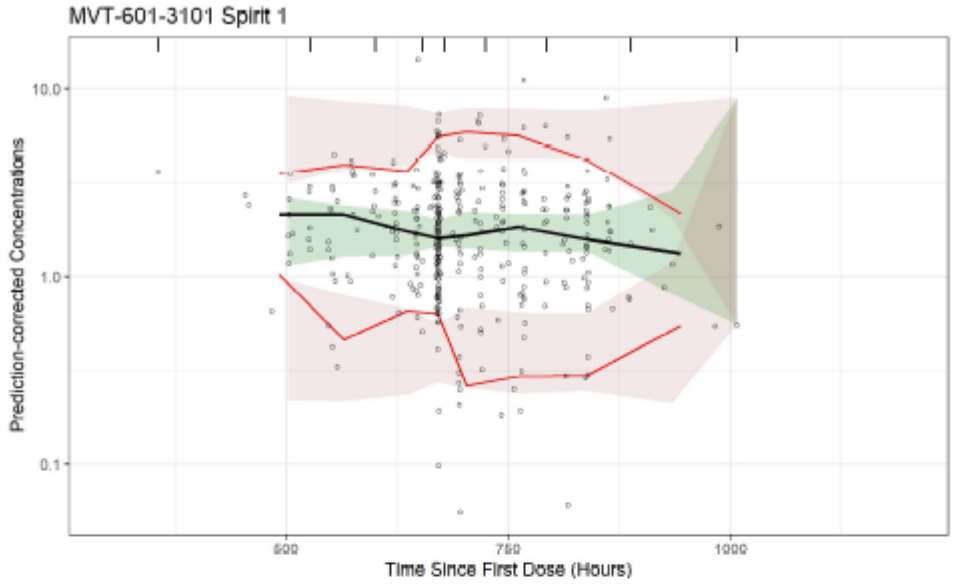
2.3.2.4. Population PK study

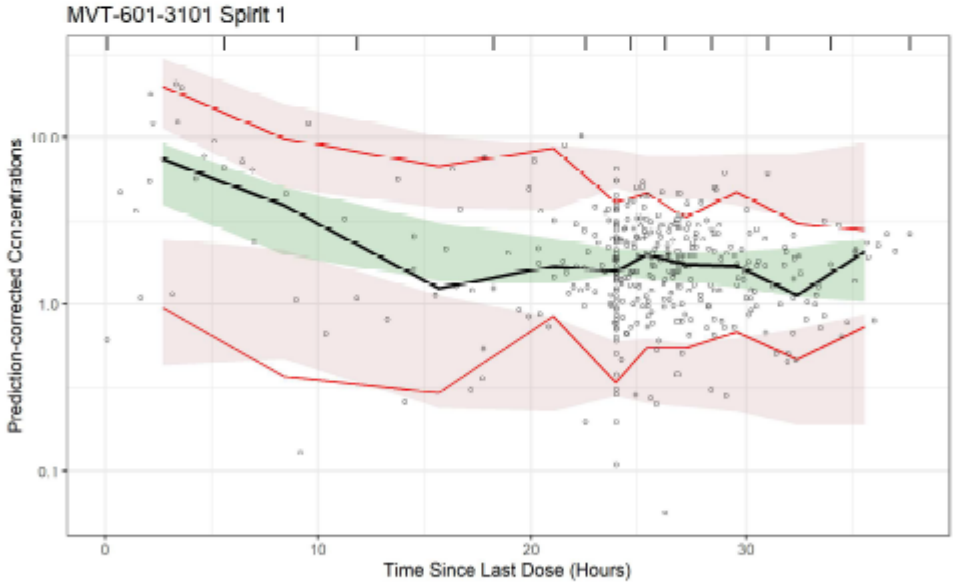
Two pivotal phase 3 studies (**MVT-601-3101** and **MVT-601-3102**) were conducted to evaluate the efficacy and safety of relugolix combination therapy in women with moderate to severe pain associated with endometriosis. Only relugolix concentration data from study **MVT-601-3101** were used for the external validation of the original PopPK model and the development of the exposure-response

(efficacy) model for women with endometriosis, because no relugolix PK concentrations were available from study **MVT-601-3102**.

Prediction- and simulated-based diagnostics were performed in order to assess whether the PopPK model was adequate to characterize the pharmacokinetics and variability in the validation dataset comprised of 376 women with endometriosis (Figure 3). Also, the impact of the addition of the validation dataset, PopPK parameters were re-estimated with the pooled dataset.

Figure 3. Prediction-Corrected Visual Predictive Checks to Externally Validate the Predictive Performance of the Population Pharmacokinetic Model





Note. Observed and simulated relugolix concentrations associated with time since first dose and last dose of relugolix (as monotherapy or combination therapy) were presented in the top and bottom panel, respectively. The markers represent the observed data. The solid black and solid red lines represent the median and the 5th and 95th percentiles of the observed data, respectively. The green- and red-shaded areas represent the 90% CI of the median and the 5th and 95th percentiles of the simulated data, respectively. Only women with endometriosis who participated in study MVT-601-3101 are included in the plots.

The previous PopPK model for Ryeqo in the original application (MAA EMEA/H/C/005267) was found fit for purpose to estimate the pharmacokinetics of relugolix. This model was a two-compartment model with first-order absorption, an absorption lag time and a first-order elimination. The data of the Phase 3 study in women with endometriosis (MVT-601-3101) was added to this model and used for external validation of this model. The PopPK model was used to estimate effects of covariates and to estimate individual exposure parameters of relugolix at steady state (Ctrough,ss, AUCss, and Cmax,ss) to implement in the exposure-response analyses.

The sensitivity analysis i.e. re-estimation of the model parameters of the pooled dataset vs. the old dataset showed that changes in most model parameter estimates were < 10%, and the parameter values previously estimated with the original dataset were all within the 95% CI of parameter values re-estimated with the pooled dataset.

In summary, the relugolix concentration data collected in the 376 women with endometriosis in the pivotal phase 3 study MVT-601-3101 were consistent with the original dataset. The previously developed PopPK model was able to capture the relugolix concentrations and the underlying variability in the 376 women with endometriosis. The PopPK model was considered fit for purpose and no further update of the old model was needed.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Primary pharmacodynamics were included in the dose response studies TAK-385/CCT-101 and TAK-385/OCT-101 in which TAK-385 was administered as monotherapy for 12 weeks, followed by an additional 12 weeks for completers of TAK-385/CCT-101.

TAK-385/CCT-101 (12 weeks of exposure)

LH, FSH, Progesterone and E2 plasma concentrations were studied.

For all pharmacodynamic efficacy parameters (for progesterone, the difference from baseline were small), the concentrations decreased in the 40 mg TAK-385 group and to a lesser extent in the 20 mg TAK-385 group. The decrease in the 40 mg TAK-385 group was comparable to the Leuprorelin group.

TAK-385/OCT-101 (total of 24 weeks of exposure)

LH, FSH, Progesterone and E2 plasma concentrations at 24 weeks are comparable to those reported at 12 Weeks, suggesting maintenance of the effect (for details see CSR TAK—385/OCT-101.

MVT-601-3101 and MVT-601-3103

Blood samples for determination of serum LH, FSH, estradiol, and progesterone were collected at baseline and at Day 1, and at Weeks 12 and 24 from patients in all treatment groups. Predose serum concentrations for all hormones were similar across all groups.

LH, FSH and progestogen concentrations declined at 12 and 24 weeks compared to baseline and placebo in the pivotal studies, as expected based on the mechanism of action of relugolix.
Estradiol declined the first 12 weeks in the relugolix + E2/NETA group and remained stable up to 104 weeks of treatment. Predose concentrations after 104 weeks of treatment were for around 50% of the patients between 20 to < 50 pg/ml.

2.3.4. PK/PD modelling

The following exposure-response relationships were investigated with PK/PD-modelling:

- The relationship between relugolix exposure and dysmenorrhea or non-menstrual pelvic pain (NMPP) using data from phase 2 and phase 3 studies in women with endometriosis
- An E2-bone mineral density (BMD) analysis for the phase 3 studies in women with endometriosis using the previously developed and validated exposure-BMD model

The primary objectives of the exposure-response model development and analysis were to assess the relationship between the exposure to relugolix and the effectiveness in the reduction of endometriosis-associated pain, as well as the effects of covariates on response. The specific aims were to develop exposure-response models with the response parameter (pain) as assessed by the visual analog scale (VAS) pain score in the phase 2 study and the numerical rating scale (NRS) pain score and responder criteria (primary study objective) from the phase 3 studies. Importantly, a sensitivity analyses to assess the impact of decreases in relugolix exposure on response was performed in order to establish the lower comparability bound to define a clinically meaningful decrease in exposure to relugolix.

Data from phase 2 study TAK-385/CCT-101 and phase 3 study MVT-601-3101 were used for the Exposure-Response Analysis. Data from phase 3 study MVT-601-3102 were not used, because no relugolix PK concentrations were available from study MVT-601-3102.

2.3.4.1. Exposure-Response (Efficacy, VAS pain score) model for relugolix

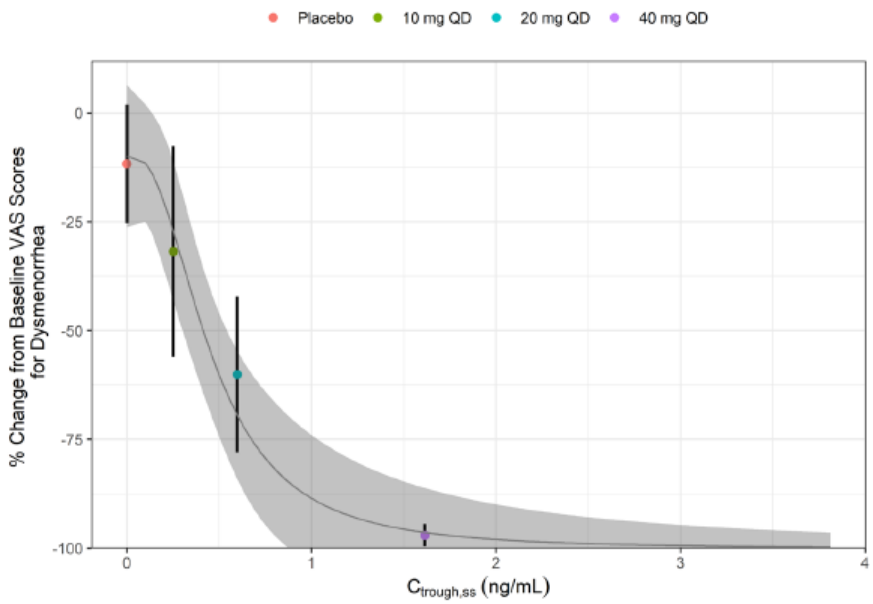
For the exposure-response analysis with a continuous response parameter, the relationship between the relugolix exposure parameters estimated by the PopPK model ($C_{trough,ss}$, AUC_{ss}, and $C_{max,ss}$) and the percent change from baseline in mean VAS score at the end of treatment (EOT) (Week 12) from the phase 2 study in women with endometriosis (TAK-385/CCT-101), in which participants received 10-, 20- or 40-mg doses of relugolix monotherapy (n = 103, 100, 103, respectively) or placebo (n = 97) once daily for 12 weeks, was described by an (sigmoidal) E_{max} model.

Maximum reduction in the percent change from baseline in VAS score for dysmenorrhea (-94%) and a near maximum reduction in the percent change from baseline in VAS score for NMPP (-73%) are achieved with the once daily 40-mg dose of relugolix as monotherapy (Figure 4).

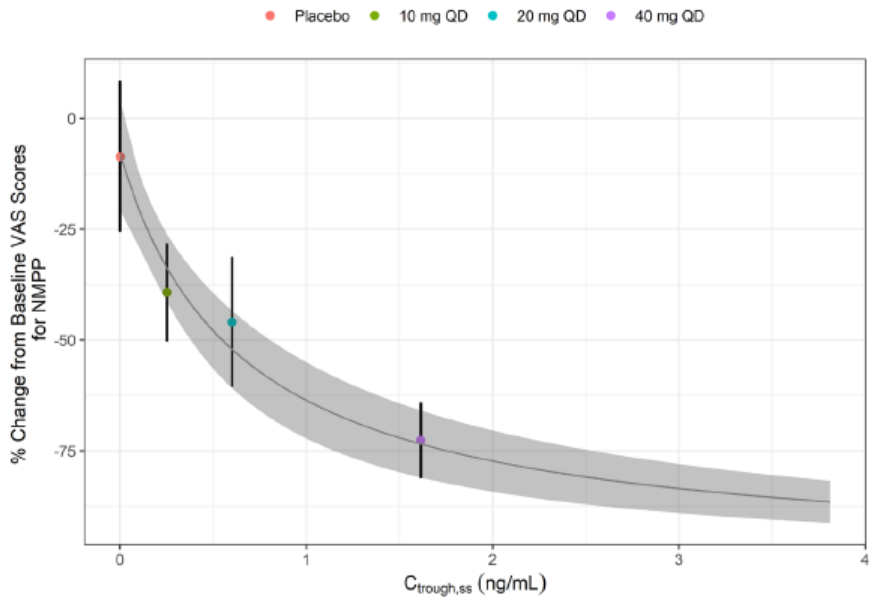
For each dose group and the placebo group, the observed mean percent change from baseline in VAS scores at the median relugolix exposure parameters were calculated and compared with the model-predicted percent change from baseline in VAS scores for dysmenorrhea and NMPP, respectively. The final exposure-VAS models using $C_{trough,ss}$ as exposure parameter are shown below (Figure 4). The model-predicted point estimates (grey line) for the percent change from baseline in VAS score fit adequately and provided an accurate characterization of the observed mean percent change from baseline in VAS score (filled colored-coded [by dose or placebo] circles). The 95% CI for the predicted percent change in VAS score (gray shaded area) was consistent with the 95% CI for the observed percent change in VAS score (solid black vertical line), indicating a good performance of the final exposure-VAS model.

Figure 4. Exposure ($C_{trough,ss}$)-Response (VAS score) Analysis for (A) Dysmenorrhea and (B) Non-Menstrual Pelvic Pain after Administration of 10, 20, 40 mg QD Relugolix or Placebo in Study TAK-385/CCT-101

(A) **Dysmenorrhea**



(B) **Non-Menstrual Pelvic Pain**

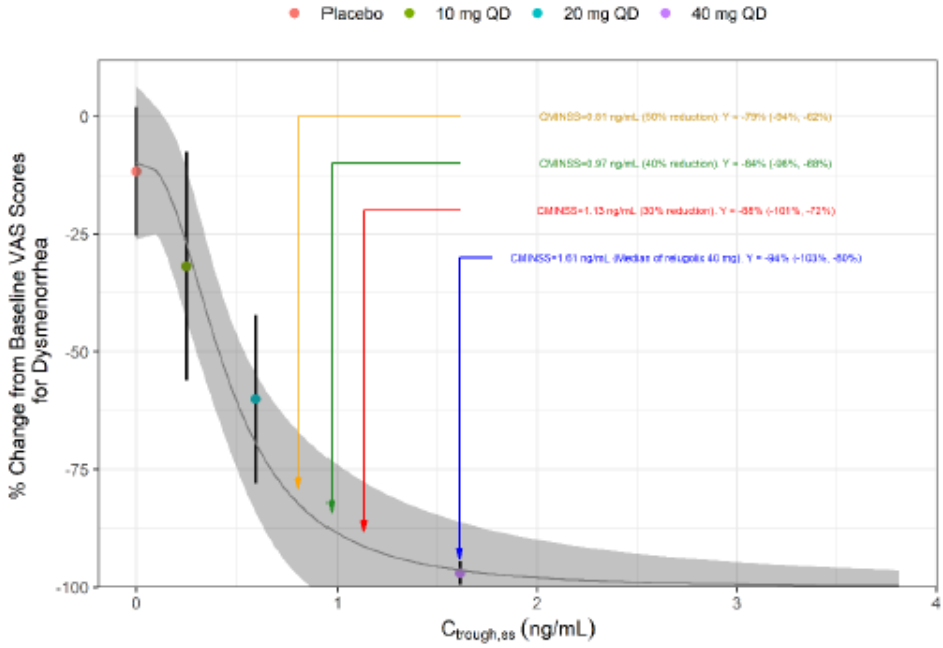


Abbreviations: CI = confidence interval; $C_{trough,ss}$ = pre-dose (trough) concentration at the end of the dosing interval at steady sate; NMPP = non-menstrual pelvic pain; VAS = visual analog scale.
Note: Solid dots represent the observed mean percent change from baseline in VAS score at the PopPK-model-based median $C_{trough,ss}$ from the placebo and relugolix 10 mg, 20 mg, and 40 mg dose groups, respectively. Solid vertical black lines are the 95% CI around the observed mean percent change from baseline in VAS score. Grey line represents model-predicted point estimate for the percent change from baseline in VAS score at end of treatment (Week 12). Shaded area represents 95% CI of the grey line (ie, model-predicted point estimates for the percent change from baseline in VAS score at end of the treatment (Week 12).

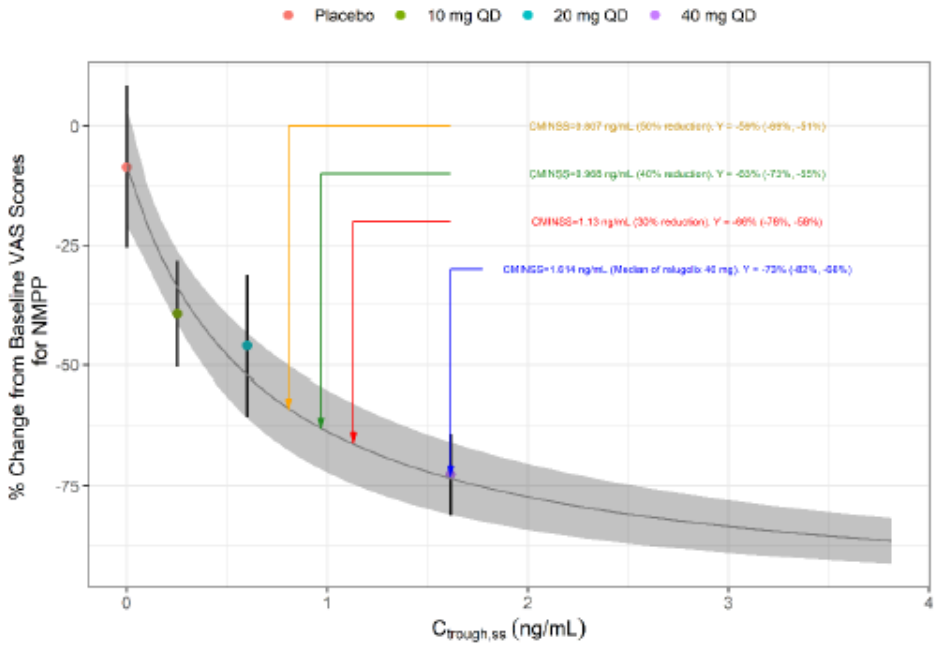
In order to define the lower effect boundary i.e. to quantify the degree to which relugolix exposure can be decreased without compromising efficacy, a sensitivity analysis using the exposure-response (efficacy) E_{max} models was conducted. The percent change from baseline in VAS score associated with reductions in $C_{trough,ss}$ by 30%, 40%, and 50% of the median of PopPK model-based $C_{trough,ss}$ values for the once daily 40-mg relugolix (monotherapy) dose group was estimated. Simulations showed that a 50% reduction in relugolix $C_{trough,ss}$ would still achieve an average decrease in the percent change from baseline in VAS score for dysmenorrhea and NMPP of 79% and 59%, respectively (Figure 5). Similar trend was observed for exposure-response analysis based on other PopPK model-based relugolix exposure parameters (AUC_{ss} and $C_{max,ss}$). Based on the 95% CI of reduction in VAS scores ([-94%, -62%] for dysmenorrhea; [-69%, -51%] for NMPP), the minimum percent change from baseline in VAS score associated with a 50% reduction in relugolix $C_{trough,ss}$ is 62% and 51% for dysmenorrhea and NMPP, respectively, supporting a lower bound of the 90% CI of the GMR for exposure-related pharmacokinetic parameters (AUC, C_{max}, and C_{trough}) of 0.5 as an acceptance criterion for clinically meaningful changes in the exposure to relugolix.

Figure 5. Predicted Percent Change from Baseline in VAS Score for (A) Dysmenorrhea and (B) Non-Menstrual Pelvic Pain and 95% CI for 30%, 40% and 50% Reductions in $C_{trough,ss}$ for Relugolix (Reference: $C_{trough,ss}$ for Relugolix 40 mg)

(A) Dysmenorrhea



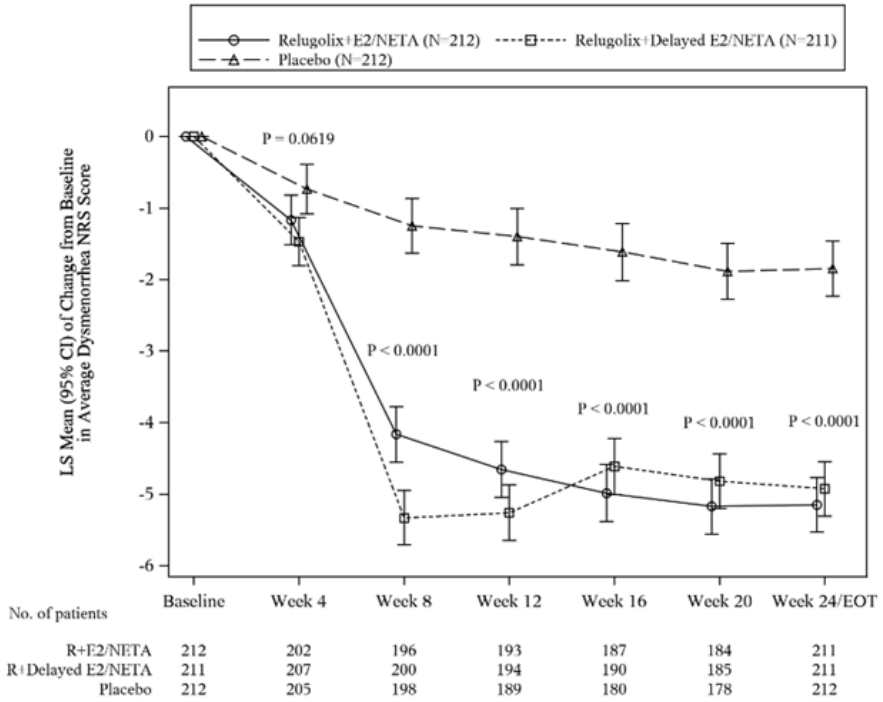
(B) Non-Menstrual Pelvic Pain



Abbreviations: CI = confidence interval; Ctrough,ss = pre-dose (trough) concentration at the end of the dosing interval at steady state; NMPP = non-menstrual pelvic pain; VAS = visual analogue scale.

The following plot shows the effect of adding E2/NETA to the 40 mg relugolix treatment (data from study MVT-601-3101), when the NRS pain score is investigated (see Figure 6 below). Studies have shown strong similarities between VAS and NRS pain scales.

Figure 6: MVT-601-3101: Change from baseline in average dysmenorrhea numerical rating scale score by visit (mITT population)



No. of patients	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/EOT
R+E2/NETA	212	202	196	193	187	184	211
R+Delayed E2/NETA	211	207	200	194	190	185	211
Placebo	212	205	198	189	180	178	212

This plot shows that addition of E2/NETA has a small antagonistic effect on the lowering of the NRS score by relugolix. The pharmacological effect of Ryeqo is based on maintaining estradiol concentration in a therapeutic range, with additional E2/NETA next to relugolix as combination therapy, in order to improve symptoms of endometriosis.

2.3.4.2. Exposure-Response (Efficacy, NRS Responder Rate) model for relugolix

The relationship between the relugolix exposure parameters estimated by the PopPK model ($C_{trough,ss}$, AUC_{ss}, and $C_{max,ss}$) and the proportion of NRS responders in the pivotal phase 3 study with observed relugolix concentration data (MVT-601-3101) was investigated graphically. NRS responders were defined as patients with the NRS score from baseline to Week 24/EOT declined by at least 2.8 and 2.1 points for dysmenorrhea and NMPP, respectively, without increased use of study-specified analgesics for pelvic pain at Week 24/EOT relative to baseline. In order to focus the evaluation on relugolix combination therapy, patients who received the relugolix + delayed E2/NETA were not included in this exposure-NRS responder rate analysis.

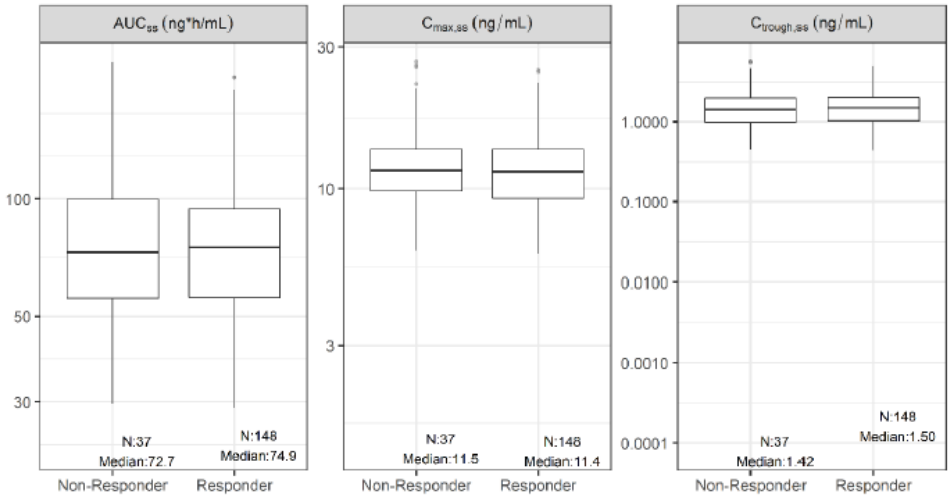
As shown in **7**, interquartile distribution of the three model-based relugolix exposure parameters ($C_{trough,ss}$, AUC_{ss}, and $C_{max,\ ss}$) overlapped between responders versus non-responders, suggesting that at the daily dose of 40 mg, relugolix exposure was not associated with responder rate. Further graphical investigation of the response rate versus different relugolix exposure parameters

demonstrated that the proportion of responders are similar between quartiles for all three exposure parameters.

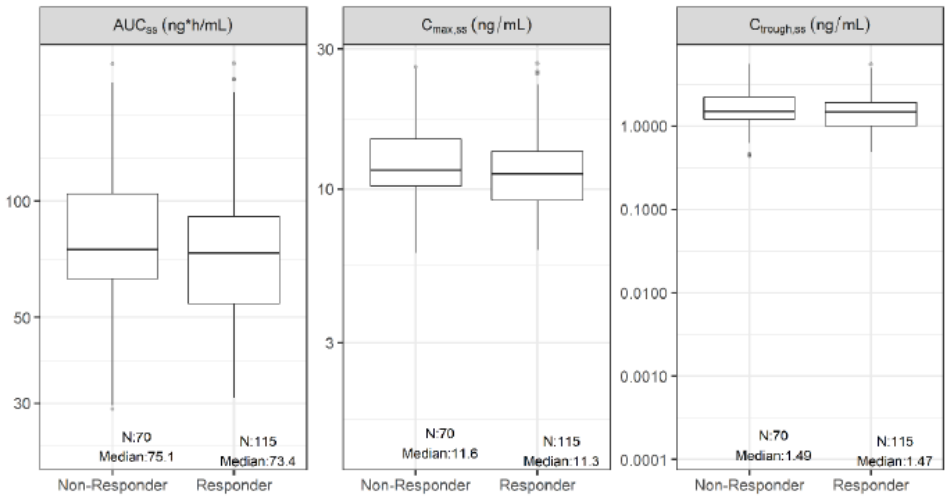
Logistic regression using a linear model or an E_{max} model were also evaluated. No clear exposure-response relationship was identified between quartiles of relugolix exposure parameters and the NRS responder rates.

Figure 7. Distribution of Relugolix Exposure Parameters Stratified by Overall Responder Category for (A) Dysmenorrhea and (B) Non-menstrual Pelvic Pain in Women with Endometriosis in the Phase 3 Study MVT-601-3101 (boxplots on logarithmical scale)

Dysmenorrhea

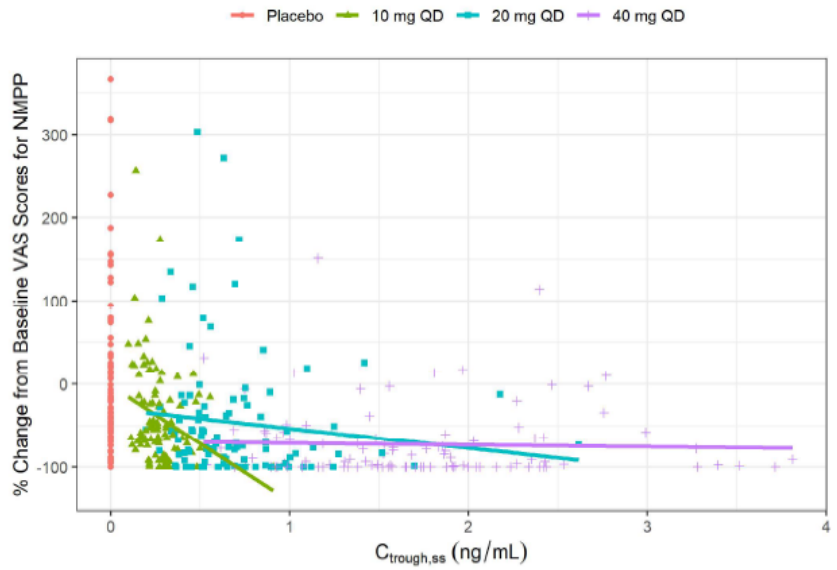


Non-Menstrual Pelvic Pain



The applicant also compared the demographics and baseline characteristics of responders and non-responders in the pivotal phase 3 studies (MVT-601-3101 and MVT-601-3102). No clinically relevant differences between responders and non-responders were found. Also, no clinically relevant correlation between demographic parameters and E2 suppression was observed.

Figure 8 Percent change from baseline in VAS score for Non-Menstrual Pelvic Pain (NMPP) at EOT versus model-based $C_{through,ss}$ by dose group



Notes: Orange, green, cyan and purple dots represent the observed VAS pain score for NMPP from the placebo and relugolix 10 mg, 20 mg and 40 mg QD cohorts, respectively. Solid green, cyan and purple lines are the linear regression lines of the percent change from baseline in VAS pain score versus $C_{trough,ss}$ for relugolix 10 mg, 20 mg and 40 mg cohorts, respectively.
Source: myovant-vas-er-analysis-without-outliers-V2.Rmd

2.3.4.3. Exposure-BMD Analysis for the Phase 3 Studies in Women with Endometriosis

Changes in circulating E2 concentrations during relugolix combination therapy (40 mg relugolix with 1 mg E2 and 0.5 mg NETA) are a result of relugolix-mediated suppression of endogenous E2 production and exogenous E2 administration. Treatment-induced changes in E2 concentrations during various relugolix treatment regimens were assessed in phase 2 and 3 clinical studies and were used to establish a model-based relationship between E2 suppression and change in BMD. In addition to the characterization of the short-term effects on BMD, the modelling and simulation analysis also aimed to support the understanding of the long term (i.e. > 12 months) changes in BMD expected upon treatment with relugolix combination therapy.

The model by Riggs (Riggs et al. 2012), which describes BMD loss (percent decrease) in the lumbar spine over time during treatment with GnRH agonists and antagonists for treatment of endometriosis, was previously used as a basis to develop a predictive exposure-BMD model for relugolix. This model was used to characterize changes in BMD over time, based on E2 concentrations associated with relugolix treatment, in women with endometriosis.

An exposure-BMD model previously developed and validated to support the original MAA for Ryeqo for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age adequately described the circulating E2 concentrations, which result from the combined effects from relugolix-mediated suppression of endogenous E2 production and exogenous E2 administration as part of relugolix combination therapy, and subsequent changes in BMD.

In the current analysis, the E2-BMD model was applied to the E2 and BMD data from various relugolix regimens (monotherapy dose range 10 - 40 mg; 40 mg alone or in combination with E2/NETA [1.0 mg/0.5 mg]) from phase 2 and phase 3 studies in women with endometriosis or uterine fibroids, including the newly added data from the two phase 3 studies in women with endometriosis (MVT-601-3101 and MVT-601-3102). The active control group was excluded for this model-based analysis. In the

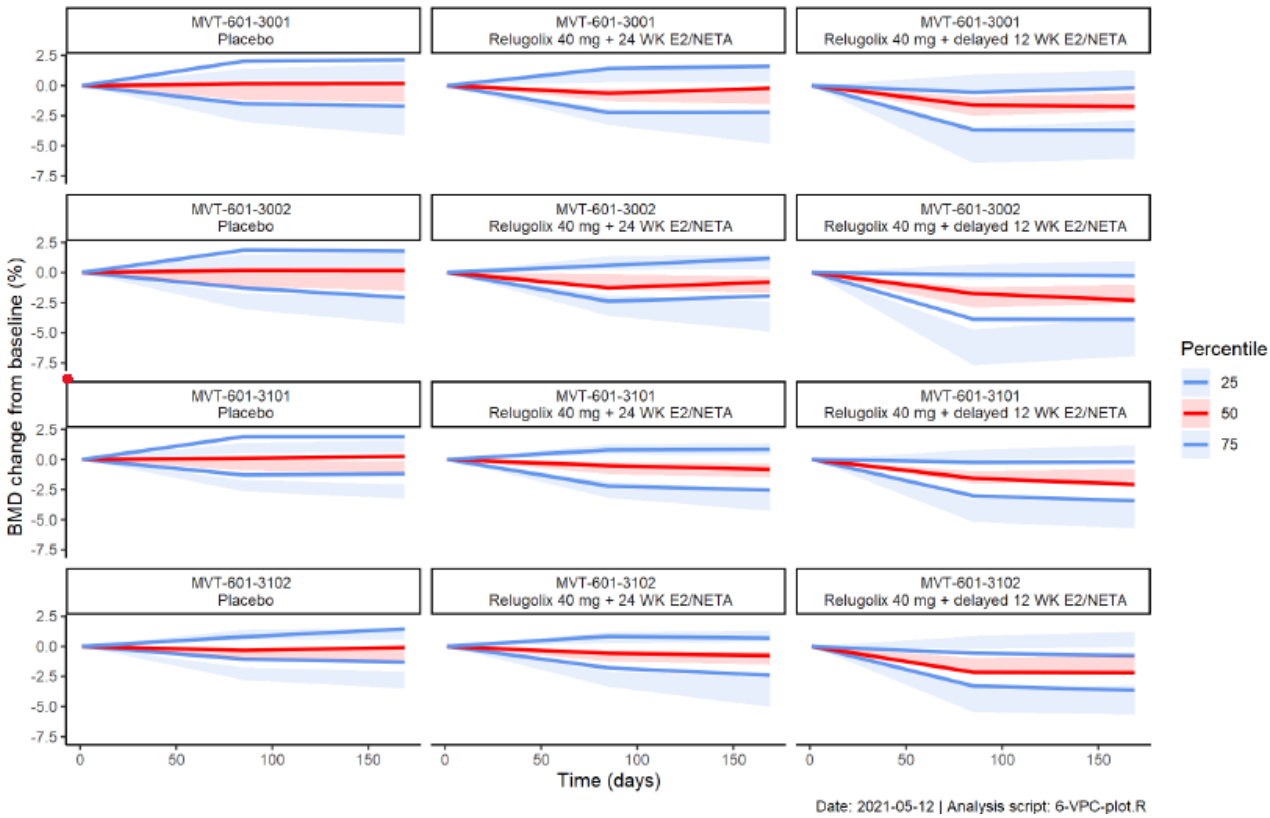
exposure-BMD analysis for women with endometriosis, 626 women with endometriosis from the phase 3 study MVT-601-3101, and 619 women with endometriosis from the phase 3 study MVT-601-3102, provided a total of 1711 and 1689 observed BMD measurement for analysis, respectively. The new data were consistent with the original dataset used to develop the E2-BMD model.

The performance of the exposure-BMD model to describe the phase 3 data in women with endometriosis was evaluated by comparing observed BMD loss and model-predicted BMD loss in several visual summaries (e.g. scatterplots, box plots, and visual predictive checks [VPC]) by study, treatment arm, and time point (3 months and 6 months), as appropriate. Additionally, covariates including demographic parameters (age, weight, BMI) and baseline BMD were explored for their potential impact on E2 suppression (assessed as % relative to baseline and placebo-corrected) or BMD change (assessed as % change from baseline).

The previously developed and validated exposure-BMD model was also able to describe the BMD loss based on E2 concentrations over time observed in the pivotal phase 3 studies in women with endometriosis for the BMD data included in the analysis until 6 months (24 weeks) after start of treatment.

Figure 9 shows that the 95% CI of the model-predicted median and 25th and 75^{th} percentiles for BMD loss generally well-estimated the corresponding values observed in the phase 3 studies. Specifically, in MVT-601-3101 and MVT-601-3102, the median and 25th percentile of the BMD percent change observed in the relugolix + E2/NETA groups were well captured by the E2-BMD model, while the model moderately over-predicted the 75th percentile of the BMD percent change observed in relugolix + E2/NETA groups and relugolix + delayed E2/NETA groups, and also over-predicted the overall BMD loss observed in the placebo groups. Additionally, for all cohorts in phase 3 studies including MVT-601-3101 and MVT-601-3102, the model moderately over-predicted the percentage of patients with substantial (>5%) loss of BMD.

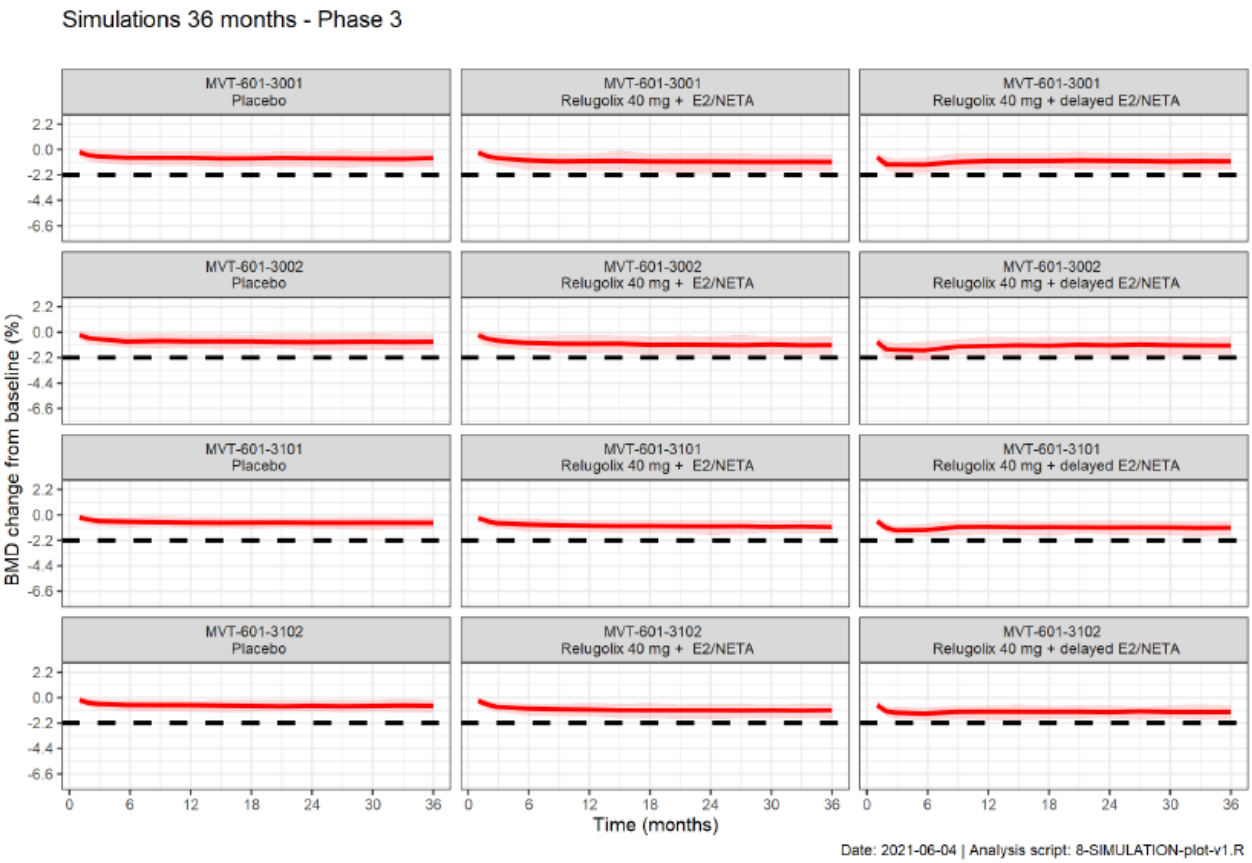
Figure 9. Observed Median, 25th and 75th Percentile Values vs. Model-Predicted 95% Confidence Intervals of BMD Change over Time up to 24 Weeks in Phase 3 Studies (MVT-601-3001, MVT-601-3002, MVT-601-3101, MVT-601-3102) (Exposure-BMD Model)



Abbreviations: BMD = bone mineral density; CI = confidence interval; E2 = estradiol; NETA = norethisterone acetate. Note: Median, 25th and 75th percentiles of the observed BMD percent change are shown in solid lines; median, 25th and 75th percentile of the model-predicted BMD percent change (as 95% CI) are shown in shaded areas.

Lastly, model-based simulations of the change from baseline in BMD over time were performed for a 36-month treatment period, with cohort size (200 replicate study cohorts) and patient characteristics identical to actual study cohorts in the pivotal phase 3 studies for endometriosis (MVT-601-3101, MVT-601-3102). The model predictions showed that the change from baseline in BMD at the lumbar spine for relugolix combination therapy is similar to placebo, and the plateau of the change from baseline in BMD observed in relugolix combination therapy is expected to be maintained for up to 36 months (3 years) of treatment, with median and lower bound of the 95% CI for the predicted BMD loss from baseline over 3 years (36 months) of -1.1% and -1.8%, respectively, see Figure 10.

Figure 10. Simulations of BMD Loss over Time for Up to Three Years of Treatment of Relugolix Combination Therapy



Abbreviations: BMD = bone mineral density; CI = confidence interval; E2 = estradiol; NETA = norethisterone acetate. Note: median and 95% CI of the model-predicted BMD percent change are shown in solid lines and shaded areas, respectively.

The applicant added data up to 104 weeks as an external validation, obtained from a long-term phase 3 study (MVT-601-3103), to the model. The data fitted the model reasonably, which confirmed the maintenance of the plateau of change from baseline in BMD at the lumber spine for at least two years. It was also noted that the observed change in BMD (specifically at two years) appears to be less than that observed in the population of the original indication of uterine fibroids (see also further discussion on Bone Mineral Density).

2.3.5. Conclusions on clinical pharmacology

Since the original MAA for Ryeqo, three additional drug-drug interaction studies, and pharmacokinetic (PK) and pharmacodynamic (PD) modelling and simulation analyses in women with endometriosis have been conducted. Relugolix is a sensitive substrate of intestinal P-gp, which limits its oral bioavailability and is thought to be responsible for the greater than dose-proportional increase in exposure and may govern absorption-mediated drug interactions. Relugolix is also a P-gp inhibitor.

Drug-drug interaction studies with relugolix as victim

There were two drug-drug interaction studies conducted. The first study (MVT-601-054) showed 4.1- and 3.8-fold increases in the values for AUC and C_{max} of relugolix to, respectively, after concomitant

use of a single relugolix/E2/NETA (40 mg/1 mg/0.5 mg) with multiple 500 mg erythromycin (P-gp and moderate CYP3A4 inhibitor) doses.

The second study (MVT-601-055) included the administration of relugolix 120 mg together with 500 mg azithromycin. However, due to the non-linear PK of relugolix (more than dose proportional), the study results cannot be easily translated to Ryeqo (40 mg relugolix). Therefore, the recommendation on separation between administration of Ryeqo and certain P-gp inhibitors (e.g. azithromycin) remains based on theoretical reasoning only. The SmPC of Ryeqo is not adjusted with respect to this study.

Drug-drug interaction study with relugolix as perpetrator

One additional dedicated drug-drug interaction study (MVT-601-057) since the original MAA for Ryeqo was conducted with relugolix as the perpetrator of the interaction, as there is potential for relugolix, which is a P-gp substrate and inhibitor, to cause clinically meaningful inhibition of intestinal P-gp.

The study showed that co-administration of 120 mg relugolix with 150 mg dabigatran etexilate did not lead to a clinically meaningful effect on total dabigatran, as the 1.17- and 1.18-fold increases of total dabigatran AUC and C_{max}, respectively, were found within the general acceptance criteria of 0.80 to 1.25. Therefore, the addition of text to the SmPC of Ryeqo that Ryeqo has no effect on the P-gp substrate dabigatran etexilate is accepted.

PopPK and PopPK/PD modelling

The previously developed PopPK model for Ryeqo in the original application (MAA EMEA/H/C/005267) was also used to describe the pharmacokinetics for the new indication for women with endometriosis. The PopPK model was used to estimate effects of covariates and to estimate individual exposure parameters of relugolix at steady state ($C_{trough,ss}$, AUC_{ss}, and $C_{max,ss}$) to implement in the exposure-response analyses. This model was able to capture the relugolix concentrations and the underlying variability in the 376 women with endometriosis. The PopPK model seems fit for purpose and no further update of the old model is needed.

PopPK/PD models were used to describe the relationship between relugolix exposure and dysmenorrhea or non-menstrual pelvic pain (NMPP) using data from phase 2 and phase 3 studies in women with endometriosis. Also, an E2-bone mineral density (BMD) analysis was performed for the phase 3 studies in women with endometriosis to support an extrapolation of clinical data on BMD to 3 years.

The relationship between relugolix exposure estimated by the PopPK model ($C_{trough,ss}$, AUC_{ss}, and $C_{max,ss}$) and percent change from baseline in the VAS score from the phase 2 study in women with endometriosis (TAK-385/CCT-101) was described by an E_{max} model for dysmenorrhea and NMPP. Based on this study 40 mg of relugolix was selected and studied in the phase 3 studies combined with NETA and E2. In the phase 3 studies, 40 mg relugolix was also administered alone for the first 12 weeks followed by relugolix + E2/NETA combination therapy in the so-called "Relugolix Delayed E2/NETA" arm. The data show that addition of E2/NETA has a small antagonistic effect on the lowering of the pain score by relugolix. The pharmacological effect of Ryeqo is based on maintaining estradiol concentration in a therapeutic range, with additional E2/NETA next to relugolix as combination therapy, in order to improve symptoms of endometriosis.

Furthermore, boxplots between NRS responders and non-responders overlapped with each other for dysmenorrhea and NMPP, suggesting that at the daily dose of 40 mg relugolix combination therapy, there are responders and non-responders, which cannot be predicted from PK. The applicant compared the demographics and baseline characteristics of responders and non-responders in the pivotal phase 3

studies and showed no clinically relevant differences between responders and non-responders in demographics and baseline characteristics.

The previously developed exposure-BMD model for Ryeqo in the original application (MAA EMEA/H/C/005267) was used to support long-term use of relugolix combination therapy based on the predicted risk for BMD loss over time for the endometriosis indication. The new data from the two phase 3 studies in women with endometriosis (MVT-601-3101 and MVT-601-3102) were included in this model. The previously developed and validated exposure-BMD model was able to describe the BMD loss over time observed in the pivotal phase 3 studies in women with endometriosis studies for the BMD data included in the analysis until 6 months (24 weeks) after start of treatment. The model seems to over-predict the 75th percentile of the BMD percent change observed. The model was used to extrapolate the BMD data from up to 24 weeks (6 months) included in the model to 3 years. Simulation demonstrated that the plateau of the change from baseline in BMD at the lumbar spine observed for a maximum up to 6 months in the phase 3 studies was expected to be maintained for up to 3 years of treatment, with median and lower bound of the 95% CI for the predicted BMD loss from baseline over 3 years (36 months) of -1.1% and -1.8%, respectively. Further BMD data up to 104 weeks from one phase 3 study (MVT-601-3103) were used for external validation and confirmed that the clinical data fitted the model reasonably. It is also noted that the observed change in BMD appears to be less than observed in the population of the original indication of uterine fibroids.

2.4. Clinical efficacy

The clinical development programme consisted of:

- Two replicate, multi-national, pivotal phase 3 studies (MVT-601-3101 and MVT-601-3102) in which relugolix is combined with E2/NETA.
- An open-label extension study (MVT-601-3103) of 80 weeks for all eligible women who completed the 24-week studies MVT-601-3101 and MVT-601-3102
- An exit interview substudy (MVT-601-038), providing the patient's perspective.
- One dose-response study conducted by Takeda (TAK-385/CCT-101).
- One long-term extension study conducted by Takeda of 12 weeks (TAK-385/OCT-101), for eligible women who completed the 12 week study TAK-385/CCT-101.
- One phase 3 active-controlled study conducted by Takeda, comparing relugolix monotherapy with Leuprorelin (TAK-385/3A)
- One observational (natural history) study of BMD (MVT-601-034), evaluating BMD in women with endometriosis also submitted in initial MAA.
- One instrument development study (MVT-601-3104)
- A PRO dossier specifically requested by the FDA

A short description of the studies is given below in the following table:

Table 5. Overview of Clinical Studies Providing Efficacy Data for Relugolix Combination Therapy

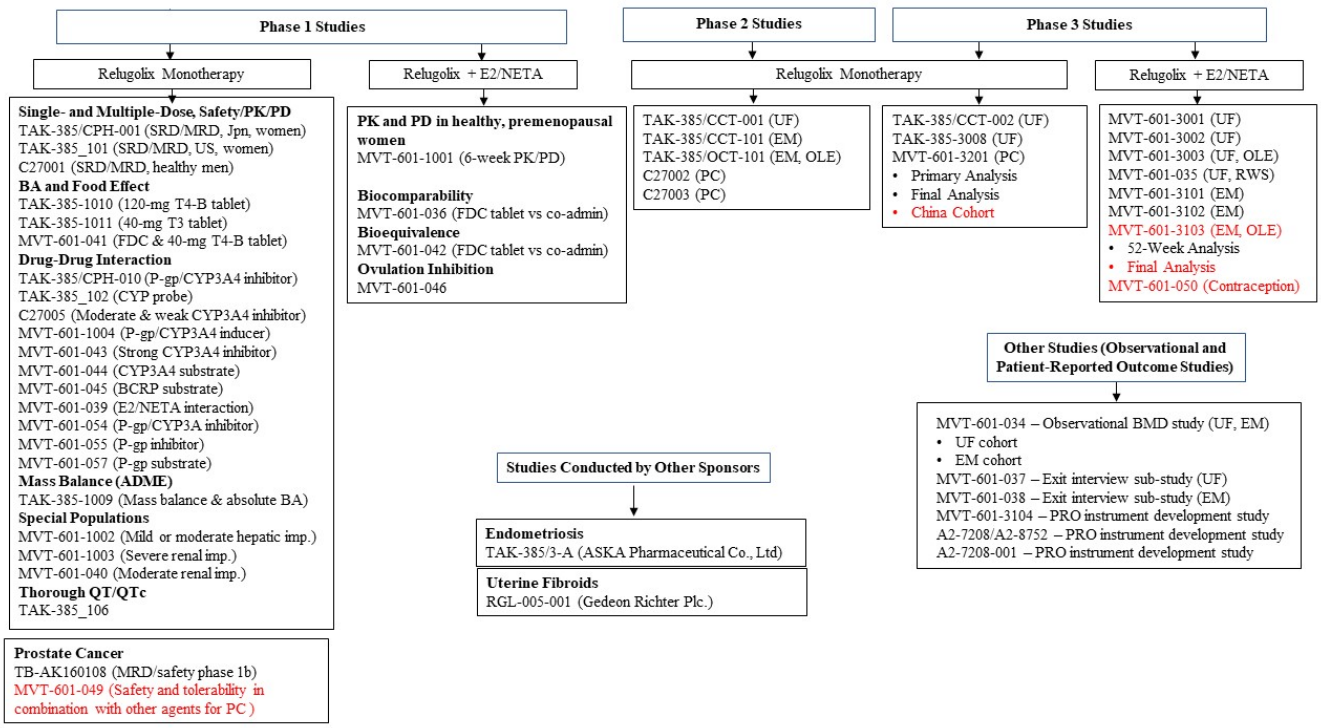
Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Duration of Treatment
Phase II – dose finding studies					
TAK-385/ CCT-101	Efficacy and safety	Multicenter, randomized, double-blind, parallel-group	Relugolix Relugolix 10, 20, 40 mg QD for 12 weeks plus leuprorelin acetate placebo Q4W Placebo Placebo QD for 12 weeks plus leuprorelin acetate placebo Q4W Leuprorelin Placebo QD for 12 weeks plus leuprorelin acetate 3.75 mg Q4W	Total: 487 10 mg: 103 20 mg: 100 40 mg: 103 Placebo: 99 Leuprorelin: 82	12 weeks
TAK-385/ OCT-101	Safety and efficacy (exploratory)	Long-term extension to study TAK-385/ CCT-101 (over 12 additional weeks)	Relugolix Relugolix 10, 20, 40 mg QD for 12 weeks plus leuprorelin acetate placebo Q4W Placebo Placebo QD for 12 weeks plus leuprorelin acetate placebo Q4W Leuprorelin Placebo QD for 12 weeks plus leuprorelin acetate 3.75 mg Q4W	Total: 397 10 mg: 84 20 mg: 78 40 mg: 89 Placebo: 77 Leuprorelin: 69	12 weeks
Phase III – pivotal studies					
MVT-601-3101	Efficacy and safety	Randomized, double-blind, placebo-controlled efficacy and safety study to evaluate oral relugolix 40 mg QD co-administered with 12 or 24 weeks of E2/NETA (1 mg/0.5 mg) compared with placebo in women with pain associated endometriosis.	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 213 Group B 212 Group C 213	24 weeks

MVT-601-3102	Efficacy and safety	Randomized, double-blind, placebo-controlled efficacy and safety study to evaluate oral relugolix 40 mg QD co-administered with 12 or 24 weeks of E2/NETA (1 mg/0.5 mg) compared with placebo in women with pain associated endometriosis.	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 207 Group B 208 Group C 208	24 weeks
Phase III – long-term extension study					
MVT-601-3103	Long-term efficacy and safety	Open-label, single-arm, long-term efficacy and safety extension study that enrolled participants who completed participation in studies MVT601-3101 or MVT-601-3102.	Relugolix 40 mg plus E2/NETA (1 mg/0.5 mg) QD for 80 weeks	Relugolix +E2/NETA 802	80 weeks
Supportive studies **Observational (natural history study)**					
MVT-601-034	Observational (natural history)	Prospective, observational	None	262	52 weeks
Phase III – patient-reported outcome substudy to MVT-601-3101 and MVT-601-3102					
MVT-601-038	To assess meaningful improvement as perceived by patients on the PGA for dysmenorrhea and NMPP, the PGIC for dysmenorrhea, the PGA for function, the NRS for dysmenorrhea and NMPP, and the EHP30 pain (impact) domain via exit interviews	Web/internet based video platform or telephone exit interviews of women with endometriosis recruited from MVT-601-3101 or MVT-601-3102	Not applicable. No study drug was administered during this study.	40	Not applicable. No study drug was administered during this study
Patient-reported outcome developmental study					

MVT-601-3104	To confirm the understandability of the SEMS. To confirm that there were no gaps in the EHP-30 Pain Domain. To confirm the understandability of the EHP-30 Pain Domain and additional instruments to be used in the phase 2studies (sB&B, PGA, and PGIC for dysmenorrhea, NMPP, and dyspareunia. To test the usability of the ePRO phone and tablet devices to be used in the Myovant phase 3 studies.	Qualitative (concept elicitation, cognitive debriefing, usability testing)	Not applicable. No study drug was administered during this study.	15	Not applicable. No study drug was administered during this study

Abbreviations: ADME = absorption, distribution, metabolism, excretion; BA = bioavailability; BC = biocomparability; BCRP = breast cancer resistance protein; BE = bioequivalence; BMD = bone mineral density; CSR = clinical study report; CYP = cytochrome P450; DDI = drug-drug interaction; E2 = estradiol; Endo = endometriosis; FDC = fixed-dose combination; IV = intravenous; MRD = multiple-rising dose; NA = not applicable; NETA = norethindrone acetate; PD = pharmacodynamics; P-gp = P-glycoprotein; PK = pharmacokinetics; QD = daily; Q4W = every 4 weeks; Q12H = every 12 hours; SC = subcutaneous. a Patients completing 48 weeks of relugolix treatment in study TB-AK160108 and in study C27002 (Arm 1 and Arm 2) had the option to continue for up to 48 additional weeks (ie, 96 weeks total) at their originally assigned relugolix dose levels.

Figure 11. Overview of Relugolix Clinical Development Program



Abbreviations: ADME = absorption, distribution, metabolism, and excretion; 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 = norethisterone acetate; OLE = open-label extension; PC = prostate cancer; PD = pharmacodynamics; P-gp = P-glycoprotein; PK = pharmacokinetics; PRO = patient-reported outcome; QT = QT interval; QTc = corrected QT interval; RWS = randomized withdrawal study; SRD = single-rising dose; UF = uterine fibroids; US = United States. Clinical pharmacology and biopharmaceutics

(phase 1) studies evaluated relugolix as monotherapy or combination therapy in healthy men, premenopausal or postmenopausal women, and patients with renal or hepatic impairment. Phase 3 studies MVT-601-038 (substudy to MVT-601-3101 and MVT-601-3102 in women with endometriosis) and MVT-601-037 (substudy to MVT-601-3001 and MVT-601-3002 in women with uterine fibroids) are qualitative exit interview studies. Study MVT-601-034 is an observational study evaluating BMD changes in untreated women with uterine fibroids or endometriosis. Red text denotes ongoing studies as of 1 Dec 2021.

2.4.1. Dose response studies

Since the initial aim of the endometriosis clinical development program was to develop relugolix as monotherapy in women for the short-term management of pain associated with endometriosis, single and multiple rising dose studies with relugolix monotherapy were conducted to establish initial safety and tolerability, and to inform dose selection from phase 2 studies. The results of these studies were reported in detail in the original MAA for Ryeqo for the management of heavy menstrual bleeding associated with uterine fibroids.

In women with endometriosis, phase 2 studies TAK-385/CCT-101, a 12-week, randomized, double-blind, placebo-controlled study and the associated double-blind extension study TAK-385/OCT-101 were performed. These studies examined 3 dose levels of relugolix (10-, 20-, and 40-mg), placebo, and leuprorelin, as a therapeutic benchmark.

2.4.1.1. Phase II study TAK-385/CCT-101

TAK-385/CCT-101 was a phase 2, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of 3 dose levels (10 mg, 20 mg, and 40 mg) of TAK-385 administered orally for 12 weeks compared with placebo in women with endometriosis. In addition, the pharmacokinetic and pharmacodynamic effects of TAK-385 were to be assessed. Leuplin (GnRH-agonist leuprorelin) was used as a reference to explore the clinical context of TAK-385. The study consisted of a pretreatment period of approximately 4 to 12 weeks and a treatment period of 12 weeks. 487 subjects were randomized (63%) into treatment period. Thereafter, patients could enter a long-term extension study (TAK 385/CCT-101), if not participating in this study, there was a 4-week follow-up after the treatment period.

The primary efficacy endpoint was the Change from baseline of visual analogue scale (VAS) score for pelvic pain at the end of treatment.

Secondary endpoints included VAS score and modified Biberoglu & Behrman (B&B) scores for pelvic pain and dyspareunia, use of pain killers, decrease in menstrual blood loss, QoL (Endometriosis Health Profile-30), plasma concentrations of unchanged TAK-385, blood concentrations of LH, FSH, E2 and progesterone and the biochemical endometriosis marker (CA125).

Safety endpoints included: BMD, AEs, vital signs, weight, ECG, clinical laboratory tests, and biochemical bone metabolism markers.

Efficacy Results

Primary Efficacy Endpoint

The change from baseline in mean of VAS score for pelvic pain at the end of 12-week treatment period in the full analysis set (FAS) was evaluated as the primary endpoint. The changes from baseline in mean of VAS score (mean ± SD) were -3.753 ± 10.5018 mm in placebo, -6.168 ± 9.1411 mm in TAK-

385 10-mg, -8.070 ± 13.3707 mm in TAK-385 20-mg, -10.418 ± 11.0171 mm in TAK-385 40-mg, and -10.460 ± 10.3013 mm in Leuprorelin groups, respectively. A statistically significant difference was observed between each TAK-385 treatment group and placebo group in the change from baseline in mean of VAS score for pelvic pain at the end of treatment period. The change from baseline in mean of VAS score in TAK-385 40-mg group was comparable with that in Leuprorelin group.

Secondary Efficacy Endpoints

The VAS scores of pelvic pain, dysmenorrhea, and dyspareunia during the treatment period were evaluated as the secondary endpoints.

While the mean of baseline VAS scores for pelvic pain were around 15 mm in each treatment group, the mean of VAS score (mean ± SD) at the end of treatment period in placebo group was 11.857 ± 12.3269 mm, and was 8.427 ± 10.2500 mm, 7.519 ± 12.1572 mm, 4.841 ± 9.1060 mm, for TAK 385 10, 20 and 40 mg, respectively. In the Leuprorelin group this was 4.721 ± 11.4952 mm at the end of treatment.

Whereas the mean of baseline VAS scores for dysmenorrhea were 27 to 30 mm in each treatment group, the mean of VAS score (mean ± SD) at the end of treatment this was 23.170 ± 18.4665 mm, 14.001 ± 15.8103 mm, 7.849 ± 14.3748 mm, 0.745 ± 3.3770 mm, and 0.174 ± 1.1623 mm, for placebo, TAK-385 10, 20, 40 mg and Leuprorelin, respectively.

Whereas the mean of baseline VAS scores for dyspareunia were 8.8 to 12.5 mm in each treatment group, the mean of VAS score (mean ± SD) at the end of treatment period were 11.111 ± 15.2339 mm, 8.843 ± 16.2414 mm, 8.660 ± 15.8146 mm, 4.966 ± 8.8931 mm, 3.791 ± 8.9426 mm, for placebo, TAK-385 10, 20, 40 mg and Leuprorelin, respectively.

Modified B&B scores

The changes from baseline in mean of M-B&B score (mean ± SD) for pelvic pain at the end of treatment period were -0.178 ± 0.3609 in placebo, -0.209 ± 0.3005 in TAK-385 10-mg, -0.218 ± 0.4395 in TAK-385 20-mg, -0.325 ± 0.4140 in TAK-385 40-mg, and -0.408 ± 0.4483 in Leuprorelin groups, respectively.

Those for dysmenorrhea were -0.172 ± 0.5380 in placebo, -0.478 ± 0.6455 in TAK-385 10-mg, -0.759 ± 0.6730 in TAK-385 20-mg, -1.160 ± 0.4869 in TAK-385 40-mg, and -1.160 ± 0.4802 in Leuprorelin groups, respectively.

Those for deep dyspareunia were -0.068 ± 0.3629 in placebo, -0.081 ± 0.4852 in TAK-385 10-mg, -0.096 ± 0.5660 in TAK-385 20-mg, -0.074 ± 0.4924 in TAK-385 40-mg, and -0.355 ± 0.5205 in Leuprorelin groups, respectively.

The changes from baseline in mean of M-B&B score for dysmenorrhea in placebo were smaller than those at any dose levels of TAK-385 throughout the treatment period. Those for pelvic pain in placebo were smaller only compared to 40 mg of TAK-385 in latter treatment period. The profiles of M-B&B score in TAK-385 40-mg group were similar to those in Leuprorelin group. However, there seemed to be no clear change from baseline in mean of M-B&B score for deep dyspareunia with the treatment of TAK-385.

Use of pain killers

The changes from baseline in proportion of days with usage of pain killer at the end of treatment period (mean ± SD) were -2.01 ± 10.375% in placebo, -6.56 ± 10.795% in TAK-385 10-mg, -6.25 ± 14.003% in TAK-385 20-mg, -10.09± 13.443% in TAK-385 40-mg, and -8.30 ± 12.692% in Leuprorelin groups. There seemed to be a lower proportion of days with usage of pain killer at any doses of TAK-385. The changes from baseline in proportion of days with usage of pain killer was slightly lower in the Leuprorelin group than in TAK-385 40-mg group, but a profile in each group was similar throughout the treatment period.

Loss of Blood and Status of Amenorrhea

The changes from baseline in mean score of amount of bleeding (a self-reporting amount scored with a range from 0 to 5) at the end of treatment period (mean ± SD) were -0.005 ± 0.7503 in placebo, -0.603 ± 1.1701 in TAK-385 10-mg, -1.233 ± 1.2472 in TAK-385 20-mg, -2.250 ± 0.7237 in TAK-385 40-mg, and -2.320 ± 0.7281 in Leuprorelin groups. There seemed to be a lower amount of bleeding in the higher doses levels of TAK-385 throughout the treatment period. The profile of change in TAK-385 40-mg group was similar to that in Leuprorelin group.

The proportion of subjects who achieved amenorrhea at the end of treatment period were 2.1%, 25.2%, 54.0%, 92.2%, and 97.5% in placebo, TAK-385 10-mg, TAK-385 20-mg, TAK-385 40-mg, and Leuprorelin groups, respectively. There seemed to be a higher proportion of subjects who achieved amenorrhea at higher dose levels of TAK-385. The profile of proportions in TAK-385 40-mg group was comparable to that in Leuprorelin group.

Quality of life (Endometriosis Health Profile-30 score)

The changes from baseline in EHP-30 score for pain at Week 12 (mean ± SD) were -5.58 ± 18.988 in placebo, -18.32 ± 19.758 in TAK-385 10-mg, -17.76 ± 20.355 in TAK-385 20-mg, -25.34 ± 20.865 in TAK-385 40-mg, and -23.15 ± 20.410 in Leuprorelin groups, respectively. There seemed to be lower EHP-30 scores at any dose levels of TAK-385 compared to placebo throughout the treatment period. The profile of EHP-30 scores in TAK-385 40-mg group was comparable to that in Leuprorelin group.

The changes from baseline in EHP-30 score for control & powerlessness were -8.20 ± 18.740 in placebo, -13.70 ± 18.709 in TAK-385 10-mg, -14.58 ± 23.593 in TAK-385 20-mg, -17.24 ± 22.478 in TAK-385 40-mg, and -19.58 ± 23.265 in Leuprorelin groups, respectively. There seemed to be lower EHP-30 scores at higher dose levels of TAK-385 in the latter treatment period.

In contrast, the changes from baseline in EHP-30 score in placebo, TAK-385 10-mg, TAK-385 20-mg, TAK-385 40-mg, and Leuprorelin groups were -6.27 ± 14.482, -8.29 ± 16.442, -8.88 ± 18.620, -10.35 ± 17.767, and -8.77 ± 17.253, respectively, for emotional well-being, -3.23 ± 14.591, -6.57 ± 10.290, -8.43 ± 16.950, -6.81 ± 15.189, and -6.75 ± 16.355 for social support, and -3.94 ± 16.421, -5.53 ± 11.562, -6.34 ± 14.895, -8.42 ± 16.184, and -6.14 ± 16.350 for self-image. There were larger changes in higher dose level of TAK-385.

2.4.1.2. Phase II study TAK-385/OCT-101 (12-week extension study of TAK-385/CCT-101)

TAK-385/OCT-101 was a long-term extension study to evaluate the safety and efficacy of TAK-385 when administered for 24 weeks (24 weeks from VISIT 3 of TAK-385/CCT-101) in subjects who participated in TAK-385/CCT-101. This was an open-label study, but study drug randomization information was broken after testing and observation at Week 24 of the last subject of this study (or when the last subject had withdrawn or been removed from the study, at the end of testing and observation of the subject who was participating in the study at that point).

The study consisted of a treatment period of 12 weeks and a follow-up period of 4 weeks. The total period of study participation, therefore, was 16 weeks (overall period starting from VISIT 1 of the TAK-385/CCT-101 study was 32 to 40 weeks, of which the treatment period was 24 weeks).
The primary endpoint was safety, including BMD, adverse events (AEs), vital signs, weight, 12-lead electrocardiogram (ECG), clinical laboratory tests, and biochemical bone metabolism markers (serum type I collagen cross-linked N-telopeptide [NTx] and bone-specific alkaline phosphatase [BAP]).

The secondary endpoint included the Visual analogue scale (VAS) score for pelvic pain and dyspareunia during the treatment period. Additional endpoints included Modified Biberoglu & Behrman (M-B&B) and Biberoglu & Behrman(B&B) score for pelvic pain and dyspareunia, use of pain killers, decrease in menstrual blood loss, QoL (Endometriosis Health Profile-30), plasma concentrations of unchanged TAK-385, blood concentrations of LH, FSH, E2 and progesterone and the biochemical endometriosis marker (CA125).

Efficacy Results

Secondary Endpoints

VAS score for pelvic pain during the treatment period
Whereas the mean of VAS scores for pelvic pain at baseline were around 15 mm in each treatment group, a decrease in the mean of VAS score (mean ± SD) was noted in time which was dose dependent. At the end of treatment period the mean VAS score was 12.387 ± 12.7540 mm for placebo, 7.746 ± 9.0900 mm for 10 mg, 6.557 ± 11.2902 mm for 20 mg, 3.335 ± 6.4059 mm for 40 mg and 2.629 ± 5.5783 mm in Leuprorelin group .

VAS score for dyspareunia during the treatment period
Whereas the mean of VAS scores for dyspareunia at baseline were about 8.8 to 12.5 mm in each treatment group, the mean of VAS score (mean ± SD) at the end of the treatment period was 11.318 ± 15.7393 mm in the placebo group, 6.218 ± 10.6280 mm in the 10 mg group, 6.363 ± 13.1847 mm in 20-mg group, 4.842 ± 9.1145 mm in 40-mg group, and 4.913 ± 10.6249 mm in Leuprorelin group.

VAS score for dysmenorrhea during the treatment period
Whereas the mean of baseline VAS scores for dysmenorrhea were about 27 to 30 mm in each treatment group, the mean of VAS score (mean ± SD) at the end of treatment period were 22.607 ± 17.5557 mm in placebo group, 12.857 ± 15.0429 mm in TAK-385 10-mg group, 7.878 ± 14.2406 mm in 20-mg group, and 0.918 ± 4.3438 mm in 40-mg group, and 0.174 ± 1.1623 mm in Leuprorelin group.

Additional endpoints

Additional endpoints in this study included Modified Biberoglu & Behrman (M-B&B) scores, Biberoglu & Behrman (B&B) scores, Use of pain killers, Loss of blood and status of amenorrhea, QOL) (Endometriosis Health Profile-30 [EHP-30]).
Overall, a dose related change from baseline values was noted for these endpoints with the effect of the TAK-385 40-mg group was comparable to that in Leuprorelin group.

Safety Results

Treatment emergent adverse events (TEAE) and treatment related TEAE

Treatment-emergent AEs (TEAEs) were defined as AEs whose date of onset occurred on or after the start of study drug administration.

The incidence of TEAEs in each group was 81.4% (79/97 subjects) in placebo group, 86.4% (89/103 subjects) in TAK-385 10-mg group, 96.0% (96/100 subjects) in TAK-385 20-mg group, 95.1% (98/103 subjects) in TAK-385 40-mg group, and 97.5% (79/81 subjects) in Leuprorelin group.

The incidence of drug-related TEAEs in each group was 39.2% (38/97 subjects) in placebo group, 66.0% (68/103 subjects) in TAK-385 10-mg group, 88.0% (88/100 subjects) in TAK-385 20-mg group, 88.3% (91/103 subjects) in TAK-385 40-mg group, and 90.1% (73/81 subjects) in Leuprorelin group. The incidences were higher in TAK-385 and Leuprorelin groups compared with placebo group and those in TAK-385 40-mg group were similar to those in Leuprorelin group.

Among drug-related TEAEs, those with an incidence of > 10% in any treatment group were hot flush, hyperhidrosis, metrorrhagia, menstruation irregular, menorrhagia, and oligomenorrhoea and most of TEAEs were deemed to be related to the pharmacological effect of TAK-385. Numbers of subjects with any TEAEs were slightly higher than those reported in the proceeding TAK-385/CCT-101 study. The major drug-related TEAEs, which being newly reported in the period of TAK-385/OCT-101 study (between Week 12 and 24 after study drug initiation), were bone density decreased and musculoskeletal stiffness, being the symptoms known to occur in relation to an estrogen deficiency.

Intensity

All TEAEs were mild or moderate in intensity with an exception of 2 severe events in placebo group (blood creatine phosphokinase increased and ovarian cyst ruptured).

Of the moderate TEAEs, those considered related to the study drug were reported in 3 subjects in placebo group, 1 subject in TAK-385 10-mg group, 7 subjects in TAK-385 20-mg group, 6 subjects in TAK-385 40-mg group, and 11 subjects in Leuprorelin group.

Table 5. Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term ≥5% in Any Treatment Group

System Organ Class Preferred Term	Number of Subjects (%) Placebo (N=97)	TAK-385 10mg (N=103)	TAK-385 20mg (N=100)	TAK-385 40mg (N=103)	Leuprorelin (N=81)
Subjects with Any TEAEs	38(39.2)	68(66.0)	88(88.0)	91(88.3)	73(90.1)
General disorders and administration site conditions	14(14.4)	6(5.8)	8(8.0)	14(13.6)	11(13.6)
Malaise	9(9.3)	2(1.9)	1(1.0)	5(4.9)	2(2.5)
Investigations	2(2.1)	2(1.9)	7(7.0)	18(17.5)	12(14.8)
Bone density decreased	1(1.0)	1(1.0)	2(2.0)	6(5.8)	4(4.9)
Musculoskeletal and connective tissue disorders	1(1.0)	-	5(5.0)	9(8.7)	9(11.1)
Musculoskeletal stiffness	-	-	4(4.0)	3(2.9)	5(6.2)
Nervous system disorders	8(8.2)	5(4.9)	10(10.0)	14(13.6)	12(14.8)
Headache	6(6.2)	3(2.9)	9(9.0)	8(7.8)	6(7.4)
Reproductive system and breast disorders	18(18.6)	52(50.5)	72(72.0)	54(52.4)	55(67.9)
Metrorrhagia	6(6.2)	28(27.2)	36(36.0)	30(29.1)	32(39.5)
Menstruation irregular	5(5.2)	20(19.4)	21(21.0)	7(6.8)	5(6.2)
Menorrhagia	5(5.2)	11(10.7)	16(16.0)	15(14.6)	9(11.1)
Oligomenorrhoea	2(2.1)	12(11.7)	12(12.0)	1(1.0)	-
Genital haemorrhage	2(2.1)	3(2.9)	5(5.0)	7(6.8)	8(9.9)
Skin and subcutaneous tissue disorders	1(1.0)	5(4.9)	14(14.0)	15(14.6)	13(16.0)
Hyperhidrosis	1(1.0)	4(3.9)	11(11.0)	10(9.7)	10(12.3)
Vascular disorders	8(8.2)	12(11.7)	23(23.0)	55(53.4)	38(46.9)
Hot flush	8(8.2)	12(11.7)	23(23.0)	55(53.4)	38(46.9)

TEAE leading to study drug discontinuation

In the period of TAK-385/OCT-101 study (from 12 weeks to 24 weeks after study drug initiation), TEAEs leading to discontinuation were: irritability/hot flush in 1 subject, anaemia in 1 subject, depression/palpitations/hot flush/headache/malaise/sleep disorder/feeling cold in 1 subject, narcolepsy in 1 subject (the same to SAE), and haemorrhagic ovarian cyst in 1 subject (the same to SAE) in placebo group, headache/intercostal neuralgia/back pain in 1 subject and hot flush in 1 subject in TAK-385 20-mg group, alanine aminotransferase increased in 1 subject (the same to SIAE) in TAK-385 40-mg group, and menopausal symptoms in 1 subject, oestrogen deficiency in 1 subject, palpitations in 1 subject, anxiety disorder in 1 subject, arthralgia in 1 subject, and dermatitis allergic in 1 subject in Leuprorelin group. Except for narcolepsy and haemorrhagic ovarian cyst in placebo group and dermatitis allergic in Leuprorelin group, all these TEAEs were considered related to the study drug.

Serious TEAE

Table 6. Summary of Serious TEAEs

System Organ Class Preferred Term	Number of Subjects (%) Placebo (N=97)	TAK-385 10mg (N=103)	TAK-385 20mg (N=100)	TAK-385 40mg (N=103)	Leuprorelin (N=81)
Subjects with Any Serious TEAEs	5(5.2)	-	2(2.0)	-	-
General disorders and administration site conditions	-	-	1(1.0)	-	-
Pseudocyst	-	-	1(1.0)	-	-
Investigations	-	-	1(1.0)	-	-
Liver function test abnormal	-	-	1(1.0)	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(1.0)	-	-	-	-
Langerhans' cell histiocytosis	1(1.0)	-	-	-	-
Nervous system disorders	1(1.0)	-	-	-	-
Narcolepsy	1(1.0)	-	-	-	-
Reproductive system and breast disorders	3(3.1)	-	-	-	-
Ovarian cyst ruptured	2(2.1)	-	-	-	-
Haemorrhagic ovarian cyst	1(1.0)	-	-	-	-

Seven serious TEAEs were reported. Of these, Langerhans' cell histiocytosis (n=1), narcolepsy (n=1), ovarian cyst ruptured (n=2), and haemorrhagic ovarian cyst (n=1) in placebo group and pseudocyst (n=1) in TAK-385 20-mg group, were considered not related to the study drug. A drug-related serious TEAE of liver function test abnormal (n=1) was reported in TAK-385 20-mg group.

No deaths were reported in this study.

Bone Mineral Density

The summary of bone mineral density is shown in the table below.

Table 7. Summary of Bone Mineral Density

Visit / Statistics	Placebo (N=97) Observed Value at Visit	Placebo (N=97) Percent Change from Baseline	TAK-385 10mg (N=103) Observed Value at Visit	TAK-385 10mg (N=103) Percent Change from Baseline	TAK-385 20mg (N=100) Observed Value at Visit	TAK-385 20mg (N=100) Percent Change from Baseline	TAK-385 40mg (N=103) Observed Value at Visit	TAK-385 40mg (N=103) Percent Change from Baseline	Leuprorelin (N=81) Observed Value at Visit	Leuprorelin (N=81) Percent Change from Baseline
Baseline										
N	97		103		100		103		81	
Mean	1.0519		1.0459		1.0257		1.0593		1.0600	
SD	0.14157		0.12503		0.13670		0.14940		0.14476	
Minimum	0.771		0.794		0.756		0.805		0.819	
Median	1.0460		1.0170		1.0010		1.0400		1.0440	
Maximum	1.443		1.432		1.465		1.569		1.416	
Week 12										
N	93	93	103	103	95	95	103	103	80	80
Mean	1.0490	-0.07	1.0364	-0.95	1.0147	-1.34	1.0366	-2.10	1.0373	-2.21
SD	0.13912	1.727	0.12955	1.875	0.13105	2.087	0.14413	2.218	0.14457	1.709
Minimum	0.775	-3.9	0.780	-6.1	0.754	-8.6	0.769	-8.4	0.791	-5.8
Median	1.0440	-0.10	1.0140	-1.10	0.9830	-1.30	1.0090	-2.30	1.0225	-2.05
Maximum	1.497	5.0	1.440	3.4	1.456	4.5	1.459	2.5	1.435	1.6
Week 24										
N	75	75	81	81	77	77	88	88	64	64
Mean	1.0483	-0.23	1.0305	-1.61	0.9977	-2.58	0.9979	-4.90	1.0091	-4.43
SD	0.13204	1.986	0.12859	2.338	0.12752	2.936	0.14045	2.912	0.14771	2.157
Minimum	0.758	-7.9	0.782	-7.4	0.728	-13.3	0.749	-11.3	0.756	-10.4
Median	1.0400	-0.10	1.0050	-1.40	0.9630	-2.50	0.9825	-4.85	0.9895	-4.20
Maximum	1.391	5.9	1.425	3.8	1.345	4.7	1.430	4.0	1.371	-0.8

(g/cm^2)

As for the TEAEs related to BMD, a total of 14 subjects with bone density decreased (1 subject each in placebo and TAK-385 10-mg groups, 2 subjects in TAK-385 20-mg group, 6 subjects in TAK-385 40-mg group, and 4 subjects in Leuprorelin group) were reported at Week 24, while those at Week 12 were 2 subjects (1 subject each in TAK-385 20-mg and 40-mg groups). All these TEAEs were considered related to the study drug. Except for 1 moderate event in Leuprorelin group, other TEAEs were mild in intensity. In addition, bone resorption test abnormal was observed in 1 subject in TAK-385 40-mg group, which being considered related to the study drug and mild in intensity.

Rationale for dose selection for the phase 3 clinical trials

Above studies examined 3 dose levels of relugolix monotherapy (10-, 20-, and 40-mg) versus placebo, and GnRH-agonist leuprorelin (3.75 mg monthly injection) as a therapeutic benchmark. Data from these studies demonstrated dose-dependent improvements, compared with placebo, in pain associated with endometriosis. Additionally, the effects of relugolix on endometriosis-associated pain and the safety profile observed at a 40-mg dose were shown to be similar to those observed with leuprorelin, with efficacy better than that observed with the 10- and 20-mg doses of relugolix, and significantly better than placebo. In these studies, the safety profile of relugolix also was characterized by a dose-dependent increase of vasomotor symptoms and BMD loss. A dose-dependent reduction in BMD was

observed with a mean percent change from baseline in BMD at lumbar spine of -4.90% after 24 weeks of treatment, similar to that (-4.43%) observed for leuprorelin, limiting the duration of treatment with relugolix as monotherapy. Although the 10- and 20-mg doses of relugolix were associated with a lower degree of BMD loss, these doses did not provide an adequate reduction in pelvic pain in a sufficient proportion of women to support continued evaluation in phase 3 studies and, based on the dual x-ray absorptiometry (DXA) data, were not expected to prevent BMD loss in the majority of women. Furthermore, these phase 2 studies also demonstrated dose-dependent reductions in systemic estradiol concentrations that were progressively less variable with higher relugolix doses. Additional exposure-response (efficacy) analysis that evaluated the relationship between relugolix exposure were supportive, see section 5.3.4. Based on efficacy data from these two phase 2 studies, a 40-mg dose of relugolix was selected for further evaluation in phase 3 development for the endometriosis indication.

2.4.2. Main studies

The main studies were two replicate, pivotal phase 3 studies (MVT-601-3101 and MVT-601-3102). As these studies were replicates, they are described together and differences, if any, are addressed.

Study title MVT-601-3101 (SPIRIT 1): An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain.

The first patient was screened 28 Sept 2017, the last Patient completed 9 Jun 2020.

A total of 1369 patients were screened, and 638 patients were randomized at 124 centers globally, including the following countries: North America (Canada and United States) and Rest of World (Argentina, Belgium, Bulgaria, Czech Republic, Finland, Hungary, Poland, Portugal, South Africa, Spain, and Ukraine).

Study title MVT-601-3102 (SPIRIT 2): An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain

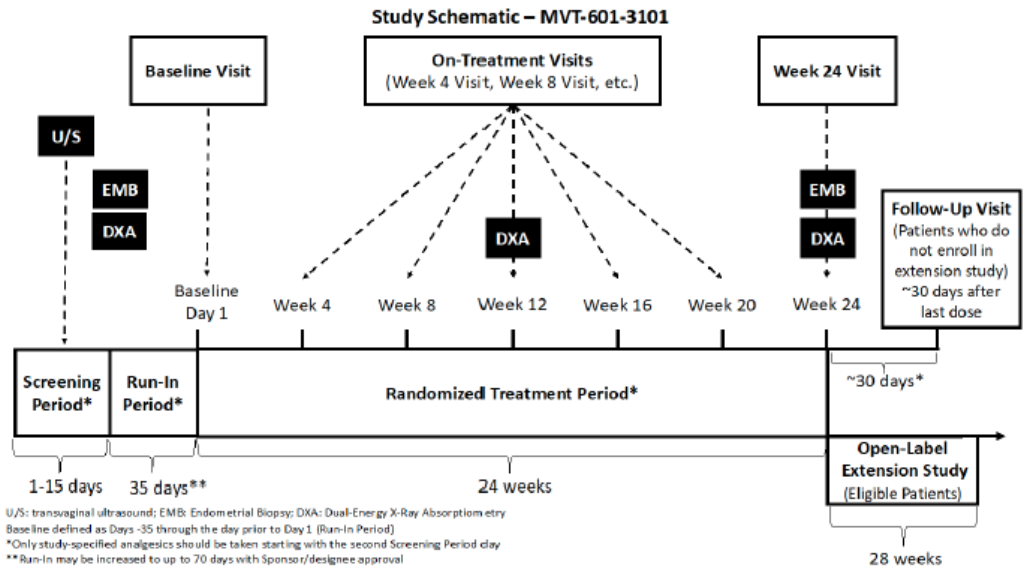
A total of 1281 patients were screened, and 623 patients were randomized at 95 centers globally, including the following countries: North America (United States [US]) and Rest of World (Australia, Brazil, Chile, Czech Republic, Georgia, Italy, New Zealand, Poland, Romania, and Sweden).

The first patient screened 21 Sept 2017, last patient completed 1 Apr 2020.

Methods

The study consisted of a screening period of 1-15 days, a run-in period of 35 days (single-blind, to exclude from the randomized study population patients who exhibited a robust placebo response), a randomized treatment period of 24 weeks (double-blind) and a safety follow-up period of approximately 30 days. Eligible patients could enrol in the open label extension study for up to 80 weeks. The study design is given in the following figure:

Figure 12. MVT-601-3101 and MVT-601-3102 study schematic



Abbreviations: DXA = dual-energy x-ray absorptiometry; EMB = endometrial biopsy; U/S = ultrasound.

Primary objectives

The study had two co-primary endpoints that separately evaluated the proportion of responders for dysmenorrhea and NMPP, the two most common symptoms of endometriosis.

Diagnosis

Transvaginal ultrasound (U/S) must have been performed to confirm the absence of any significant pathology that might have been responsible for the pelvic pain and was read locally. Diagnosis of endometrial biopsies (EMB) was confirmed by a central laboratory. Bone densitometry was assessed by dual-energy x-ray absorptiometry (DXA) and submitted for central reading.

Treatment arms

Randomization among the three treatment arms was 1:1:1 to receive relugolix 40 mg co-administered with E2 1 mg and NETA 0.5 mg for 24 weeks (Group A), relugolix monotherapy 40 mg for 12 weeks followed by co-administration with E2 1 mg and NETA 0.5 mg for 12 weeks (Group B), or placebo for 24 weeks (Group C).

Monotherapy for 12 weeks of relugolix 40 mg followed by 12 weeks of relugolix 40 mg co-administered with E2/NETA was included to provide an assessment of the requirement for E2/NETA to mitigate the adverse effects of relugolix monotherapy on BMD loss and vasomotor symptoms.

Placebo was selected as the comparator because it facilitates double-blinding and allows for a clearer characterization of the safety and efficacy profile of relugolix, a new chemical entity, than would be possible with an active comparator. Furthermore, there is no single standard-of-care treatment for endometriosis-associated pain.

Study duration

Patients who completed study MVT-601-3101 or MVT-601-3102, including those randomized to placebo, and who met other eligibility criteria were offered the opportunity to enroll in an up to 80-week open-label, long-term extension (LTE) study (MVT-601-3103) in which all patients receive

relugolix + E2/NETA. Patients who did not proceed to the LTE study were to attend a follow-up visit approximately 30 days after their last dose of study drug to undergo specific follow-up procedures.

Study participants

The study population was selected to include approximately 600 premenopausal women 18 to 50 years of age with endometriosis-associated pain.

Women should have a diagnosis of endometriosis and had, within 10 years prior to signing the ICF, surgical or direct visualization and/or histopathologic confirmation of endometriosis, for example, during a laparoscopy or laparotomy.

Eligible patients should have reported moderate, severe, or very severe pain during the most recent menses and for NMPP in the prior month at the screening visit and during the run-in period had dysmenorrhea pain score NRS score ≥ 4.0 on at least 2 days *and*

a) Had a mean NMPP NRS score ≥ 2.5, or

b) Had a mean NMPP NRS score ≥ 1.25 and NMPP NRS score ≥ 5.0 on ≥ 4 days.

Women with a baseline BMD z-score < −2.0 at spine, total hip, or femoral neck during the run-in period were not allowed in the study.

Patients who were receiving hormonal contraceptives were to have discontinued these 28 to 56 days prior to the start of the single-blind run-in period and nonhormonal contraception as described in the protocol consistently during the screening period, run-in period, randomized treatment period, and for 30 days following treatment discontinuation.

The in- and exclusion criteria were in detail:

Inclusion Criteria:

A patient was eligible for enrollment and randomization in this study only if all inclusion criteria were met at the time of the baseline Day 1 visit.

1. Had voluntarily signed and dated the informed consent form (ICF) prior to initiation of any screening or study-specific procedures;
2. Was a premenopausal female aged 18-50 years (inclusive) on the day of signing and dating the ICF;
3. By the patient's report, had had 2 consecutive regular menstrual cycles (ie, 21-35 days in duration) immediately prior to randomization. For patients who had washed off hormonal contraceptives, the 2 regular cycles must have been after the first (withdrawal) bleeding following discontinuation of contraceptives;
4. Had agreed to use only study-specified analgesic medications during the study and was not known to be intolerant to these;
5. Had a diagnosis of endometriosis and had, within 10 years prior to signing the ICF, surgical or direct visualization and/or histopathologic confirmation of endometriosis, for example, during a laparoscopy or laparotomy
6. During the screening visit, the patient had reported moderate, severe, or very severe pain during the most recent menses and for NMPP in the prior month;

7. During the run-in period Days R1-R35, had at least 24 days of completed eDiary scores;
8. During the run-in period Days R1-R35, had a dysmenorrhea NRS score ≥ 4.0 on at least 2 days and
    a) Had a mean NMPP NRS score ≥ 2.5, or
    b) Had a mean NMPP NRS score ≥ 1.25 and NMPP NRS score ≥ 5.0 on ≥ 4 days;

    For patients with fewer than three dysmenorrhea scores during Days R1-R35, dysmenorrhea scores from Days R36-R70 were to be included in the eligibility determination until a total of three dysmenorrhea scores from the run-in period were available.
9. Had menstruated for at least 3 days during the run-in period;
10. Was not expected to undergo gynaecological surgery or other surgical procedures for treatment of endometriosis (including ablation, shaving, or excision) during the study, including during the follow-up period, and the patient did not desire such treatment during this time frame;
11. Had a negative urine pregnancy test at the screening visit and on the baseline Day 1 visit;
12. Had agreed to use contraception during the study and for 30 days following the last dose of study drug. Specifically, had agreed to use nonhormonal contraception as described in the protocol consistently during the screening period, run-in period, randomized treatment period, and for 30 days following treatment discontinuation. However, the patient was not required to use the specified nonhormonal contraception if she:
    a) Had a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b) Had a bilateral tubal occlusion (including ligation and blockage methods such as EssureTM), at least 6 months prior to the screening visit (patients with Essure must have had prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome," in the investigator's opinion);
    c) Was not sexually active with men; periodic sexual relationship(s) with men required the use of nonhormonal contraception as noted above; or
    d) Practiced total abstinence from sexual intercourse as her preferred lifestyle. Periodic abstinence was not acceptable;
13. Had an adequate endometrial (aspiration) biopsy that was performed during the screening visit or run-in period, or one that was locally performed within 6 months prior to screening with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer);

    Note: Patients for whom polyps were detected on the biopsy but were either not evident on ultrasound or < 2.0 cm by ultrasound were eligible;

    Note: Endometrial biopsies that were performed or repeated during the run-in period and met criteria were acceptable;
14. If ≥ 39 years of age at the time of the screening visit, had a normal mammogram (Breast Imaging Reporting and Data System category 1 to 2 or equivalent) during the run-in period or within 6 months prior to the run-in period.

<u>Exclusion Criteria:</u>

1. Had a history of chronic pelvic pain that was not caused by endometriosis (eg, vaginismus, chronic pelvic infection, symptomatic hydrosalpinx, symptomatic dermoid, symptomatic corpus lutea, persistent symptomatic ovarian cyst, suspected ovarian torsion, or pelvic floor disorders);
2. Had four or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis;
3. During the run-in period, reported NMPP was "much better" on the PGIC for NMPP;
4. Had a transvaginal ultrasound during the screening or run-in period demonstrating pathology other than endometriosis that could be responsible for or contributing to the patient's chronic pelvic pain or a clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

   Note: Saline or gel contrast was not routinely required. Use of such contrast was required only when the endometrium could not be evaluated or when there were ambiguous and potentially exclusionary findings on the transvaginal ultrasound or endometrial biopsy (eg, suspected intrauterine masses, equivocal endometrial findings, etc.);

   Note: Transvaginal ultrasounds that were repeated during the run-in period and met criteria were acceptable;
5. Had any chronic pain or frequently recurring pain condition, other than endometriosis, that was treated with opioids or required analgesics for $\geq$ 7 days per month;
6. Had a surgical procedure for treatment of endometriosis within the 3 months prior to the screening visit;
7. Had a history of previous non-response of NMPP or dysmenorrhea to gonadotropin-releasing hormone (GnRH) receptor agonists, GnRH receptor antagonists, or depot medroxyprogesterone acetate based on patient's report or treating physician's assessment of chart documentation.

   Note: A partial response to these drugs was not exclusionary;
8. Had unexplained vaginal bleeding outside of the patient's regular menstrual period, defined as bleeding occurring > 4 days outside the patient's usual range of menses duration;
9. Had a weight that exceeded the weight limit of the DXA scanner or had a condition that precluded an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
10. Had a BMD z-score < −2.0 at spine, total hip, or femoral neck during the run-in period;
11. Had a gastrointestinal disorder affecting absorption or gastrointestinal motility;
12. Had used, was using, or was anticipated to use prohibited medications;
13. Patients receiving selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, or tricyclic antidepressants that had been recently started or undergone recent dose changes. Patients who had been on stable doses for at least 3 months and were anticipated to remain on stable doses during the study (including the run-in period) may have been enrolled;
14. Had a history of or currently had osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, 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;

15. Had a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat BMD loss;
16. Had a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic syndromes, etc.). Psoriasis not requiring or anticipated to require systemic therapy was permitted;
17. Had any contraindication to treatment with low-dose E2/NETA, including:
    a) Known, suspected, or history of breast cancer;
    b) Known or suspected estrogen-dependent neoplasia;
    c) Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the baseline Day 1 visit;
    d) History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e) Known anaphylactic reaction or angioedema or hypersensitivity to E2 or NETA;
    f) Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g) Migraine with aura;
    h) History of porphyria;
18. Had jaundice or known current active liver disease from any cause, including non-alcoholic fatty liver disease, hepatitis A (hepatitis A virus immunoglobulin M [IgM]), hepatitis B (hepatitis B virus surface antigen [HBsAg]), or hepatitis C (hepatitis C virus [HCV] antibody [Ab] positive, confirmed by HCV RNA);
19. On the most recently documented Papanicolaou test, had any of the following cervical pathology: high-grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, or atypical squamous cells favoring high-grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may have been included in the study if high-risk human papilloma virus testing was negative or if DNA testing for human papilloma virus 16 and 18 was negative;
20. Had any of the following clinical laboratory abnormalities during the screening or run-in period:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 × the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Estimated glomerular filtration rate (eGFR) < 60 mL/min/m2 using the Modification of Diet in Renal Disease method;
    c. Hypocalcemia (< lower limit of normal [LLN] or hypercalcemia (> ULN);
    d. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);
21. Had a clinically significant cardiovascular disease, including:

a) Prior history of myocardial infarction;

b) History of angina or significant coronary artery disease (ie, > 50% stenosis);

c) History of congestive heart failure;

d) History of clinically significant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, Mobitz II second degree or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);

e) QT interval by the Fridericia correction formula (QTcF) of > 470 msec on the screening visit or baseline Day 1 ECG;

f) Hypotension, as indicated by systolic blood pressure < 84 mm Hg on two repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mm Hg decrease in systolic blood pressure 1 minute or more after assuming an upright position;

g) Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg on two repeat measures at least 15 minutes apart during the screening period;

h) Bradycardia as indicated by a heart rate of < 45 bpm on the screening visit or baseline Day 1 ECG unless judged by the investigator to be due to physical fitness;

22. Was a participant in an investigational drug or device study within the 1 month prior to the screening visit;

23. Had a history of clinically significant condition(s) including, but not limited to, the following:

    a) Untreated thyroid dysfunction (patients with adequately treated hypothyroidism who were stable on medication were not excluded);

    b) History of malignancy within the past 5 years or ongoing malignancy other than curatively treated non-melanoma skin cancer or surgically cured Stage 0 in situ melanoma;

    c) Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria, who had been unstable or not well controlled, based on the investigator's or mental health professional's judgement, or whose history or stability could not be ascertained, or whose psychiatric drug regimen had changed during the 3 months prior to the screening visit or was expected to change during the study were not to be enrolled;

24. Was currently pregnant or lactating, or intended to become pregnant during the study period through 1 month after the last dose of study drug, or intended to donate ova during the study period or within 2 months after the last dose of study drug;

25. Had a contraindication or history of sensitivity to any of the study treatments or components thereof, including protocol-specified analgesic medications, or had a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicated study participation;

26. Had a prior (within 1 year of the screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients were to be questioned about their drug and alcohol use);
27. Had participated in a previous clinical study that included the use of relugolix;Was an immediate family member, was a study site employee, or was in a dependent relationship with a study site employee who was involved in the conduct of this study (eg, spouse, parent, child, or sibling);
28. Was inappropriate for participation in this study because of conditions that may have interfered with interpretation of study results or prevented the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor.

Removal of patients

Completion of the Week 24 visit defined completion of the study. Patients may have withdrawn consent to participate in the study and discontinued treatment at any time for any reason. Investigators or the medical monitor may have removed patients from therapy for reasons of safety and/or lack of compliance. Patients removed from study treatment for any reason were to undergo the assessments for the EOT visit (Week 24 visit) on the schedule of activities and were to attend a follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

If a patient failed to attend the clinic for a required study visit within the protocol-defined window, the site was to attempt to contact the patient and reschedule the missed visit as soon as possible. Only after at least three documented telephone calls and, if necessary, a certified letter was sent to the patient's last known mailing address, was the patient to be withdrawn from the study with a primary reason of "Lost to Follow-Up."

Contraception and Pregnancy Avoidance

Medication and devices containing hormones for contraception were excluded, and patients had to agree to use nonhormonal contraception throughout the study, including through 30 days following the last dose of study drug.

Urine pregnancy tests were to be performed at monthly intervals during the study (including just prior to receiving the first dose of study drug and at the 30-day safety follow-up visit), and patients were to receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who became pregnant during the study were to be withdrawn from the study and followed for pregnancy outcome.

Treatments

Run-in period

During the single-blind run-in period, all patients received a placebo tablet and a placebo capsule QD. Patients were kept blinded to the treatment.

Randomized treatment period

Women meeting all inclusion criteria at the end of the run-in period were randomized 1:1:1 to receive double blinded therapy once a day with:

- relugolix 40 mg (tablet), co-administered with E2 1 mg and NETA 0.5 mg (capsule);
- relugolix 40 mg (tablet) monotherapy with a placebo (tablet) for 12 weeks followed by relugolix 40 mg (tablet) co-administered with E2 1 mg and NETA 0.5 mg (capsule) for 12 weeks;
- placebo (tablet and capsule) for 24 weeks

Selection of dose

The dose of relugolix selected for phase 3 evaluation of treatment for endometriosis-associated pain was 40 mg QD. This dose was selected based on a combination of phase 1 and phase 2 efficacy data (TAK-385/CCT-101) and phase 2 BMD data (TAK-385/OCT-101), see section 5.4.2, subsection dose rationale.

Timing of dose

The study treatment was to be taken in the fasted state (except for water, tea, or coffee) in the morning, at least 1 hour before breakfast. If the dose was missed in the morning for any reason, the study treatment may have been taken later in the day, under fasted conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment was to be taken as close as possible to the same time of morning each day.

On selected clinic visit days, study drug was administered in the clinic (see Table 2) for the visits during which patients took study drug in the clinic rather than at home).

Prohibited medication
Broadly, there were four types of medications that were restricted or prohibited.

- Hormonal treatments with an effect on the gonadotropin-pituitary-gonadal axis (eg, estrogens, progestins, hormonal contraceptives, GnRH receptor agonists, and GnRH receptor antagonists)
- drugs with potential to affect BMD (eg, systemic corticosteroids, bisphosphonates)
- analgesic medications (other than the protocol-specified Tier 1 and Tier 2 analgesic medications), including certain classes of antidepressants that may be treatments for neuropathic pain
- p-glycoprotein inducers and inhibitors.

After signing the ICF, patients could enter a washout period for restricted medications to be washed out, if needed. During this period, patients were monitored for pain control and analgesics were to be adjusted as needed.

Rescue medication

Only study-specific Tier 1 and Tier 2 analgesic medications were to be taken starting with the second day of the screening visit (if the screening visit was conducted over more than 1 day), during the run-in period, and subsequently during randomized phase. Analgesic medications were to be taken for control of pain and not for prophylactic use. There were no protocol restrictions for analgesic use during the washout period through the first screening visit day.

Short-term use of non-study specified analgesics for the treatment of an intercurrent event (eg, injury or surgery) was allowed if required. Such events were to be reported as adverse events.

The quantity of opioids prescribed was based on the patient's expected usage until the next study visit. Prescriptions for Tier 1 and Tier 2 rescue analgesic medications was to be in accordance with their full prescribing information (ie, the local product labeling) and prescriptions for opioids were not to provide for any refills. Patients were to be counseled on the safe use of opioids.

Use of protocol-specified rescue analgesic medications and any other analgesics taken for any type of pain, were to be recorded by the patient in the e-Diary during the run-in period, treatment period, and follow-up period of the study.

Tier 1 medication for all patients was:

- Ibuprofen (200 mg dose strength, which could have been taken in multiples, as prescribed).

Each patient was to be prescribed one of the possible Tier 2 medications to be used throughout the study. Choice of available Tier 2 medications differed by country. All Tier 2 drugs that contained acetaminophen or paracetamol were fixed-dose combination products. Tier 2 medications included the following:

- tramadol (37.5 mg) / paracetamol (325 mg)
- tramadol (50 mg)
- codeine (30 mg)
- codeine (30 mg) / paracetamol (300 mg)
- codeine (30 mg) / paracetamol (500 mg)
- codeine 15 mg / paracetamol (500 mg)
- hydrocodone (5 mg) / acetaminophen 325 mg

Objectives and endpoints

All objectives and endpoints hold for both MVT-601-3101 and MVT-601-3102 unless otherwise stated.

Table 6. MVT-601-3101 and MVT-601-3102: Study Objectives and Endpoints

Objectives	**Endpoints**
Co-Primary Efficacy: The co-primary efficacy objectives and endpoints were based on comparisons between relugolix + E2/NETA and placebo	
To determine the benefit on dysmenorrhea	Proportion of patients who meet the dysmenorrhea responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary
To determine the benefit on NMPP	Proportion of patients who meet the NMPP responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary
Key Secondary Efficacy: Alpha-protected for hierarchical hypothesis testing of relugolix + E2/NETA versus placebo	

1.To determine the benefit on function measured by the EHP-30 pain domain	Change from baseline to Week 24 in the EHP-30 pain domain score
2.To determine the benefit on dysmenorrhea measured by the NRS	Change from baseline to Week 24/EOT in the mean dysmenorrhea NRS score
3.To determine the benefit on NMPP measured by the NRS	Change from baseline to Week 24/EOT in the mean NMPP NRS score
4.To determine the benefit on overall pelvic pain measured by the NRS	Change from baseline to Week 24/EOT in the mean overall pelvic pain NRS score
5. For MVT-601-3101: To determine the benefit on protocol-specified opioid use (Tier 2) for endometriosis-associated pain as recorded in the eDiary 5. For MVT-601-3102: To determine the benefit on dyspareunia measured by the NRS	Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain at Week 24/EOT Change from baseline to Week 24/EOT in the mean dyspareunia NRS score
6. For MVT-601-3101: To determine the benefit on dyspareunia measured by the NRS 6. For MVT-601-3102: To determine the benefit on protocol-specified opioid use (Tier 2) for endometriosis-associated pain as recorded in the eDiary	Change from baseline to Week 24/EOT in the mean dyspareunia NRS score Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain at Week 24/EOT
7. For MVT-601-3101: To determine the benefit on protocol- specified analgesic use (Tier 1 and Tier 2) for endometriosis-associated pain as recorded in the eDiary 7. For MVT-601-3102: To determine the benefit on protocol-specified analgesic use (Tier 1 and Tier 2)	Proportion of patients who are not using analgesics for endometriosis-associated pain at Week 24/EOT. Change from baseline to Week 24/EOT in protocol-specified analgesic use for endometriosis-associated pain based on mean pill count.
Other Secondary Efficacy (Not included in hierarchical hypothesis testing) [a] The additional secondary efficacy objectives and endpoints below are based on comparisons between relugolix + E2/NETA and placebo	
To determine the benefit of relugolix +E2/NETA compared with placebo on function measured by the EHP-30 pain domain	Proportion of patients who have a reduction of at least 20 points in the EHP-30 pain domain from baseline to Week 24
To determine dysmenorrhea responder rate	Percentage of dysmenorrhea responders by month
To determine NMPP responder rate	Percentage of NMPP responders by month
To determine change in dysmenorrhea measured by NRS	Mean change and percent change in dysmenorrhea NRS score by month
To determine change in NMPP measured by NRS	Mean change and percent change in NMPP NRS score by month
To determine change in overall pelvic pain measured by NRS	Mean change and percent change in overall NRS score by month
To determine change in dyspareunia measured by NRS	Mean change and percent change in dyspareunia NRS score by month

To determine change in protocol-specified ibuprofen (Tier 1) use	Mean change from baseline to Week 24/EOT in protocol-specified ibuprofen (Tier 1) pill count
To determine change in protocol-specified opioid (Tier 2) use	Mean change from baseline to Week 24/EOT in protocol-specified opioid (Tier 2) pill count
To determine the benefit on dysmenorrhea-related functional effects (sB&B)	Change from baseline to Week 24/EOT in the mean dysmenorrhea functional impairment on the sB&B scale Mean change and percent change from baseline to each month in dysmenorrhea score
To determine the benefit on NMPP-related functional effects (sB&B)	Change from baseline to Week 24/EOT in the mean NMPP functional impairment on the sB&B scale Mean change and percent change from baseline to each month in NMPP
To determine the benefit on effects on dyspareunia-related functional effects (sB&B scale)	Change from baseline to Week 24/EOT in the mean dyspareunia functional impairment on the sB&B scale Mean change and percent change from baseline for each month in dyspareunia score
To determine the benefit on the PGA for dysmenorrhea symptom severity	Change from baseline to Week 24 on the PGA of dysmenorrhea symptom severity Proportion of patients with improvement, no change, or worsening from baseline to Week 24
To determine the benefit on the PGA for NMPP symptom severity	Change from baseline to Week 24 on the PGA for NMPP symptom severity Proportion of patients with improvement, no change, or worsening from baseline to Week 24
To determine the benefit on the PGA for pain severity	Change from baseline to Week 24 on the PGA for pain severity Proportion of patients with improvement, no change, or worsening from baseline to Week 24
To determine the benefit on the PGA for functional impairment	Change from baseline to Week 24 on the PGA for functional impairment Proportion of patients with improvement, no change, or worsening from baseline to Week 24
To determine the benefit on the PGIC for dysmenorrhea	Proportion of patients who are “better” or “much better” on the PGIC for dysmenorrhea at Week 24
To determine the benefit on the PGIC for NMPP	Proportion of patients who are “better” or “much better” on the PGIC for NMPP at Week 24
To determine the benefit on the PGIC for dyspareunia	Proportion of patients who are “better” or “much better” on the PGIC for dyspareunia at Week 24
To determine the benefit on endometriosis-associated quality of life (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains of the EHP-30)	Change from baseline to Week 24 in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image)
Endometriosis-associated quality of life (EHP-30 total score)	Change from baseline to Week 24 in the EHP-30 scale total score
Effects of endometriosis on work (EHP Work domain)	Change from baseline to Week 24 in the EHP Work domain score
Quality of life as assessed by the EQ-5D-5L scale	Categorical change from baseline to Week 24 for each of the EQ-5D-5L scale terms Change from baseline to Week 24 in EQ-5D-5L visual analogue scale score

Secondary Efficacy Objectives and Endpoints Based on Comparisons Between Relugolix + Delayed E2/NETA and Placebo (Not included in hierarchical hypothesis testing) [a]	
To determine the benefit on dysmenorrhea measured by the NRS	Proportion of patients who meet the dysmenorrhea responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary
To determine the benefit on NMPP measured by the NRS	Proportion of patients who meet the NMPP responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary
To determine the benefit on function measured by the EHP-30 Pain Domain	Change from baseline at Week 24 in the EHP-30 Pain Domain score. Proportion of patients who meet the definition of responder, achieving a reduction of at least 20 points from baseline at Week 24 based on EHP-30 Pain Domain scores
Safety	
To determine the safety of 24 weeks of relugolix + E2/NETA or relugolix + delayed E2/NETA	Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, ECGs, and BMD by DXA, and EMBs (EMBs only for MVT-601-3101)
To determine the percent change from baseline to Week 12 in BMD at the lumbar spine (L1-L4) in relugolix + E2/NETA compared with relugolix + delayed E2/NETA	Percent change from baseline to Week 12 in BMD at the lumbar spine (L1-L4) as assessed by DXA (for MVT-601-3102 only: [b])
To determine the change in BMD after 24 weeks of treatment with relugolix + E2/NETA or relugolix + delayed E2/NETA	Percent change from baseline to Week 24 in BMD at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA
To determine the incidence of vasomotor symptoms with relugolix + E2/NETA compared with relugolix + delayed E2/NETA through Week 12	Incidence of vasomotor symptoms at Week 12
Pharmacokinetic and Pharmacodynamic	
Only for MVT-601-3101: To evaluate plasma concentrations of relugolix and estradiol at Week 4 in patients treated with relugolix +E2/NETA or relugolix delayed E2/NETA	Week 4 relugolix and estradiol predose plasma concentrations
To evaluate the pharmacodynamic effects of 24 weeks of relugolix + E2/NETA	Change from baseline to Week 24 in LH, FSH, estradiol, and progesterone predose serum concentrations

Abbreviations: BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; DYS = dysmenorrhea; E2 = estradiol; eDiary = electronic diary; ECG = electrocardiogram; EHP = Endometriosis Health Profile; EMB = endometrial biopsy; EOT = End-of-Treatment; EQ-5D-5L = European Quality of Life Five-Domain Five- Level; FSH = follicle-stimulating hormone; LH = luteinizing hormone; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = numerical rating scale; PGA = Patient Global Assessment; PGIC = Patient Global Impression of Change; sB&B = subject modified Biberoglu and Behrman.

[a] These secondary endpoints were assessed comparing the relugolix + E2/NETA group with the placebo group; comparisons between the relugolix + E2/NETA group and the relugolix + delayed E2/NETA group, and between the relugolix + delayed E2/NETA group and the placebo group were made descriptively, unless otherwise specified.

[b] These safety endpoints were assessed comparing the relugolix + E2/NETA group with the relugolix + delayed E2/NETA group. They were not included in the hierarchical hypothesis testing of secondary endpoints.

Sample size

For the assessment of the superiority of relugolix versus placebo in the percentage of responders for each individual co-primary endpoint (dysmenorrhea and NMPP), a sample size of approximately 200

patients in the relugolix + E2/NETA group versus 200 patients in the placebo group provided at least 95% power at the 2-sided significance level of 0.05 to detect an absolute treatment difference of 20% between the relugolix + E2/NETA group and the placebo group, assuming a dropout rate of 20%. This provided an overall power of at least 90% for the study to detect an absolute treatment difference of 20% for both co-primary endpoints simultaneously.

The responder rate for the placebo group was assumed to be between 30% to 35%. With an additional 200 patients in the relugolix + delayed E2/NETA group, the total sample size for the study was planned to be approximately 600 patients (randomized 1:1:1). The sample size and power calculation were based on the chi-squared test.

Randomisation

Randomization was conducted centrally and stratified by geographic region and duration of endometriosis, as follows:

- Geographic region: North America versus Rest of World;
- Years since endometriosis diagnosis: < 5 or ≥ 5 years.

Blinding (masking)

During the single-blind run-in period, only patients were blinded. During the double-blind randomized treatment and follow-up periods, all patients, investigators, and sponsor staff or representatives involved in the conduct of the study were blinded to treatment assignment. Patients received one of the double-blind oral study treatments, which were co-packaged. Each patient was instructed to take 1 tablet and 1 capsule per day. The relugolix placebo tablet was manufactured to match the relugolix tablet in size, shape, and color. The E2/NETA placebo capsule was designed to match the over-encapsulated E2/NETA active product in size, shape, and color.

Statistical methods

Estimand

The estimand that the studies target was prepared (*post-hoc*) by the MAH and is provided in Table 7. The strategies for each intercurrent event, a composite strategy for early discontinuation and a hypothetical strategy for missing NRS scores are further described below.

Table 7 Estimand for endometriosis pivotal studies MVT-601-3101 and MVT-601-3102

Co-primary Objectives	Estimand Description (Including Co-Endpoints)
The co primary efficacy objectives and endpoints are based on comparisons between relugolix + E2/NETA and placebo	
• To determine the benefit on dysmenorrhea (DYS) • To determine the benefit on non-menstrual pelvic pain (NMPP)	• **Co-Primary Endpoint**: Proportion of patients who meet the DYS responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in DYS NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary • **Co-Primary Endpoint**: Proportion of patients who meet the NMPP responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary Estimand descriptions: • **Target population:** population of premenopausal women with endometriosis-associated pain. • **Treatment**: relugolix+E2/NETA or placebo • **Intercurrent events**: the following intercurrent events could impact the assessment of co-primary endpoints: - Early discontinuation of treatment (< 5 weeks of treatment) - Missing NRS scores reported in e-Diary (1 or 0 days with DYS Scores or < 14 days with NMPP scores) • **Population-level summary**: treatment effect of relugolix+E2/NETA compared with placebo was quantified by difference (95%CI) in proportion of DYS responders (NMPP responders) and p-value for treatment comparison between relugolix+E2/NETA and placebo

Analysis Populations

Efficacy analyses were performed using the modified Intent-to-Treat (mITT) Population, unless otherwise specified. The mITT Population was defined as all randomized patients who received any amount of study drug (relugolix/placebo or E2/NETA/placebo). Efficacy analyses were performed by treatment group as randomized.

The Per-Protocol Population was defined as all members of the mITT Population who did not have any of a pre-specified subset of important protocol deviations. The Per-Protocol Population was used for sensitivity analysis of the primary efficacy endpoint. The Per-Protocol Population and the associated subset of important protocol deviations were identified prior to unblinding the trial.

Safety analyses were performed using the Safety Population, unless otherwise specified. The Safety Population was defined as all randomized patients who received any amount of study drug. Safety data were analyzed by treatment group according to the actual treatment received.

Exclusion of Site 3015 from Efficacy and Safety Analyses.

Audit findings and subsequent investigations raised significant concerns about data integrity at Site 3015 that rendered the data unreliable. Therefore, data for the 6 patients randomized at this site were excluded from all efficacy and safety analyses.

Co-Primary Efficacy Analyses

The study had two co-primary efficacy endpoints comparing the relugolix + E2/NETA group and placebo. The co-primary efficacy endpoints were:

- Proportion of patients who meet the dysmenorrhea responder criteria at the Week 24/EOT pain assessment period (defined as the last 35 calendar days immediately prior to and including the date of last dose of randomized study drug)
- Proportion of patients who meet the NMPP responder criteria at the Week 24/EOT pain assessment period.

A dysmenorrhea responder at Week 24/EOT was defined as a patient with data that satisfied each of the following:

- Had a reduction in average dysmenorrhea NRS pain score from baseline of at least 2.8 points or had a Week 24/EOT score $\leq$ 0.1 if the baseline dysmenorrhea pain score was less than 2.8
- Did not have an increase in the use of rescue analgesic medications for endometriosis associated pain compared with baseline use

An NMPP responder at Week 24/EOT was defined as a patient with data that satisfied each of the following:

- Had a reduction in average NMPP NRS pain score from baseline of at least 2.1 points or had a Week 24/EOT score $\leq$ 0.1 if the baseline NMPP NRS pain score was less than 2.1
- Did not have an increase in the use of rescue analgesic medications for endometriosis associated pain compared with baseline use.

The reduction from baseline in dysmenorrhea or NMPP pain scores at Week 24/EOT was calculated as the absolute difference between the respective average pain score at Week 24/EOT and the average pain score at baseline. According to the description provided above, patients who had an average baseline dysmenorrhea or NMPP score smaller than the corresponding meaningful change threshold may still have been classified as a responder if their average pain score at Week 24/EOT was no more than 0.1. This condition was strict and could only have been met when nearly all daily pain scores from the assessment period were 0, with the very few remaining daily pain score(s) being minimal.

The meaningful change thresholds for the co-primary endpoints were determined by an independent, external expert (Clinical Outcomes Solutions) before the finalization of SAP v1.0. The determination of each threshold was based primarily on anchor-based analyses (utilizing the anchor-based cumulative distribution function/probability density function method considering the PGA for dysmenorrhea and NMPP, respectively) using pooled blinded data from studies MVT-601-3101 and MVT-601-3102 (approximately 200 patients from each study). Results from a patient exit interview substudy (MVT-601-038) were also available and considered as supportive information in the threshold determinations.

A logistic regression model was used to compare relugolix +E2/NETA with placebo for each pain measure (dysmenorrhea or NMPP). The responder status (responder versus non-responder) was the

dependent variable, treatment was the main effect, baseline pain score (dysmenorrhea or NMPP) and stratification factors were the covariates.

The Type I error rate for the primary analysis of each pain measure was controlled at the 2-sided 0.05 significance level. The trial was positive if and only if both co-primary endpoints were met, eg, the p-value for each hypothesis test was < 0.05. The point estimate and 2-sided 95% CI for the difference in the proportions of responders for each co-primary endpoint was calculated between the relugolix +E2/NETA and the placebo groups.

Missing data

Missing data handling rules were implemented for deriving responder status at Week 24/EOT (last 35 days of treatment) for the primary analysis of the co-primary endpoints. Elements considered included duration of treatment exposure and compliance with pain score entry on daily eDiary (ie, number of days with NRS entries on eDiary required for dysmenorrhea and NMPP). Patients who completed < 5 weeks of treatment were considered non-responders for both dysmenorrhea and NMPP. For patients who completed at least 5 weeks of treatment, responder status for dysmenorrhea and NMPP was derived considering ≥ 2 days of NRS scores for dysmenorrhea and ≥ 14 days of NRS scores for NMPP reported in the eDiary taking protocol-specified analgesic use into consideration. Detailed missing data handling rules and definition of protocol-specified analgesic use were pre-specified.

Table 8. Missing Data Handling Rules for Average Dysmenorrhea Score at Week 24/ End of Treatment

Treatment Exposure	Number of Days with DYS Scores Reported in eDiary	Menstruation Status per eCRF	Average DYS Score Status	Responder Status[a]
< 5 weeks	n/a	n/a	n/a	Non-responder
≥ 5 weeks	≥ 2 days	n/a	Observed	Based on observed change from baseline and analgesic use
	1 day	No more than 1 menstruation day reported	Observed	Based on observed change from baseline and analgesic use
		More than 1 menstruation day reported	Missing (to be imputed from mixed-effects model)	Based on imputed change from baseline and analgesic use
	0 days	No menstruation days reported	Assigned as 0	Based on change from baseline and analgesic use
		At least 1 menstruation day reported	Missing (to be imputed from mixed-effects model)	Based on imputed change from baseline and analgesic use

Abbreviations: eCRF = electronic case report form; eDiary = electronic diary; n/a = not applicable.

[a] Determined by comparing the observed (or imputed) change from baseline to the responder threshold and by examination of change from baseline in analgesic use.

Table 9. Missing Data Handling Rules for Average Non-Menstrual Pelvic Pain Score at Week 24/End of Treatment

Treatment Exposure	Number of Days with NMPP Scores Reported in eDiary	Average NMPP Score Status	Responder Status[a]
< 5 weeks	n/a	n/a	Non-responder
≥ 5 weeks	≥ 14 days	Observed	Based on observed change from baseline and analgesic use
	< 14 days	Missing (to be imputed from mixed-effects model)	Based on imputed change from baseline and analgesic use

Abbreviations: eDiary = electronic diary; n/a = not applicable; NMPP = non-menstrual pelvic pain.

[a] Determined by comparing the observed (or imputed) change from baseline to the responder threshold and by examination of change from baseline in analgesic use.

For the primary analysis, patients with missing pain scores at Week 24/EOT will be identified for DYS and NMPP separately, per the missing data handling rules described above. For imputing missing data for the primary analysis of each co-primary endpoint, a mixed-effects model approach will be used separately to derive predicted average pain scores. A mixed-effects model with repeated measures of average pain scores at multiple time points (Weeks 4, 8, 12, 16, 20, and 24) will be fitted to predict change in average pain scores from baseline (as a dependent variable) through the fixed-effects associated with covariates (ie, stratification factors of years since endometriosis diagnosis at baseline and geographic region, visit, treatment, baseline average NRS score, and visit by treatment interaction) and random effects (from the individual patients). In this model, an unstructured variance-covariance matrix is assumed for each patient.

Sensitivity analyses

To assess the robustness of the primary analyses, the following sensitivity analyses of the co-primary endpoints will be performed.

1. A patient's responder status will be defined as follows:
    - A patient will be considered a non-responder if
        - she discontinues study drug during the first 12 weeks due to an adverse event or lack of efficacy, OR
        - she discontinues study drug during the first 5 weeks for any reason.
    - All other patients will have their responder status assigned using data from the Week 24/EOT pain assessment period in the same way as in the primary analysis.
2. The co-primary endpoints will be analyzed for the Completers population. The Completers Population is defined as patients in the mITT population who completed 24 weeks of study treatment.
3. The co-primary endpoints will be analyzed for the Per-Protocol population.
4. A multiple imputation approach (Rubin 1987; von Hippel 2018) will be used to impute missing or incomplete Week 24/EOT pain scores. In this method, an arbitrary missing pattern will be

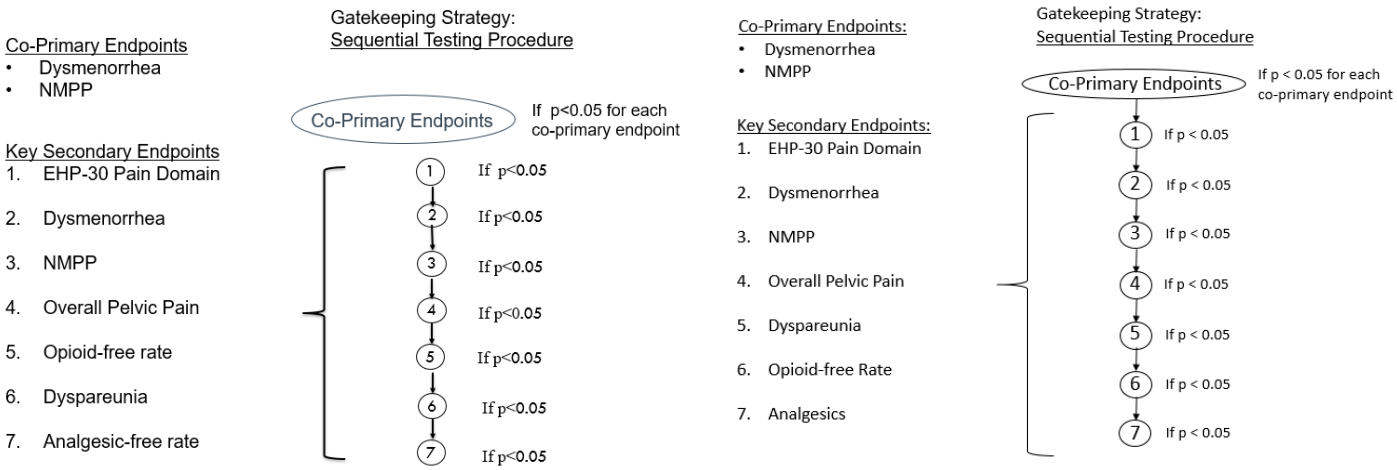
assumed using Markov Chain Monte Carlo imputation to generate a monotone missing patternfor the observed pain scores. Imputation will be performed separately by randomized treatment group (Sullivan et al, 2018), given the distinct bleeding patterns among the three treatment groups.

5. The co-primary endpoints will be analyzed using the observed data, ie, without imputation of any missing data.

Secondary efficacy analysis

Secondary efficacy variables included 7 key secondary endpoints with alpha-protection (see Figure Figure) and a number of other secondary endpoints. The treatment effect of relugolix + E2/NETA compared with placebo was tested for the alpha-protected secondary endpoints using a gate-keeping procedure.

Figure 13. Fixed Seqence Testing Procedure for the Co-Primary and Key Secondary Endpoints for SPIRIT 1 (left) and SPIRIT 2 (right).



The treatment comparison for key secondary endpoints assessing change from baseline to Week 24/EOT (endpoints one through four and endpoint six for SPIRIT 1, and endpoints one through five and endpoint seven for SPIRIT 2) will be performed using a mixed-effects model with treatment, visit, randomization stratification factors, and treatment-by-visit interaction included as fixed effects and assuming an unstructured covariance matrix. Based on this model, the least squares means at Week 24/EOT will be compared between the relugolix + E2/NETA and placebo groups and summarized along with the corresponding 95% CIs and p-value. The treatment comparison for the key secondary endpoints five and seven for SPIRIT 1, and for the key secondary endpoint six for SPIRIT 2, will be based on a stratified Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors and baseline opioid use (Use vs. No Use). Descriptive statistics will also be provided by treatment group and visit. Analgesics are defined as Tier 1 and/or Tier 2 analgesic medications.

Other secondary efficacy analyses

Analysis methods previously described for primary and secondary efficacy endpoint analyses will be used for the analysis of these endpoints. Mixed models were used to describe the change from baseline to week 24 for continuous endpoints. Stratified Cochran-Mantel-Haenszel test were used for evaluating binary endpoints/ proportions.

Multiplicity

Analyses of the co-primary endpoint and the ranked key secondary efficacy endpoints were performed at an overall alpha level of 0.05 (2-sided) comparing the relugolix + E2/NETA group with the placebo group. A test was deemed statistically significant if the 2-sided p-value rounded to 4 decimal places was < 0.05. A fixed sequence testing procedure was applied to maintain the family-wise Type I error rate.

Safety analysis:

Bone mineral density

Corrected BMD data will be used for analysis as determined by the central radiology laboratory in the three prespecified anatomical locations: lumbar spine (L1–L4), total hip, and femoral neck.

Bone mineral density at baseline, Week 12, and Week 24 visits will be summarized descriptively by treatment group and each anatomical location. Percentage changes from baseline along with 95% CIs of mean percentage changes will also be summarized by treatment group and anatomical location. Mean percentage change from baseline with its corresponding 95% CI will be plotted by visit, treatment group, and anatomical location.

To support the inclusion of E2/NETA in the treatment regimen, the safety endpoint of mean percent change from Baseline in BMD at the lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3101 and MVT-601-3102) with a formal comparison of the relugolix + E2/NETA group versus the relugolix + delayed E2/NETA group.

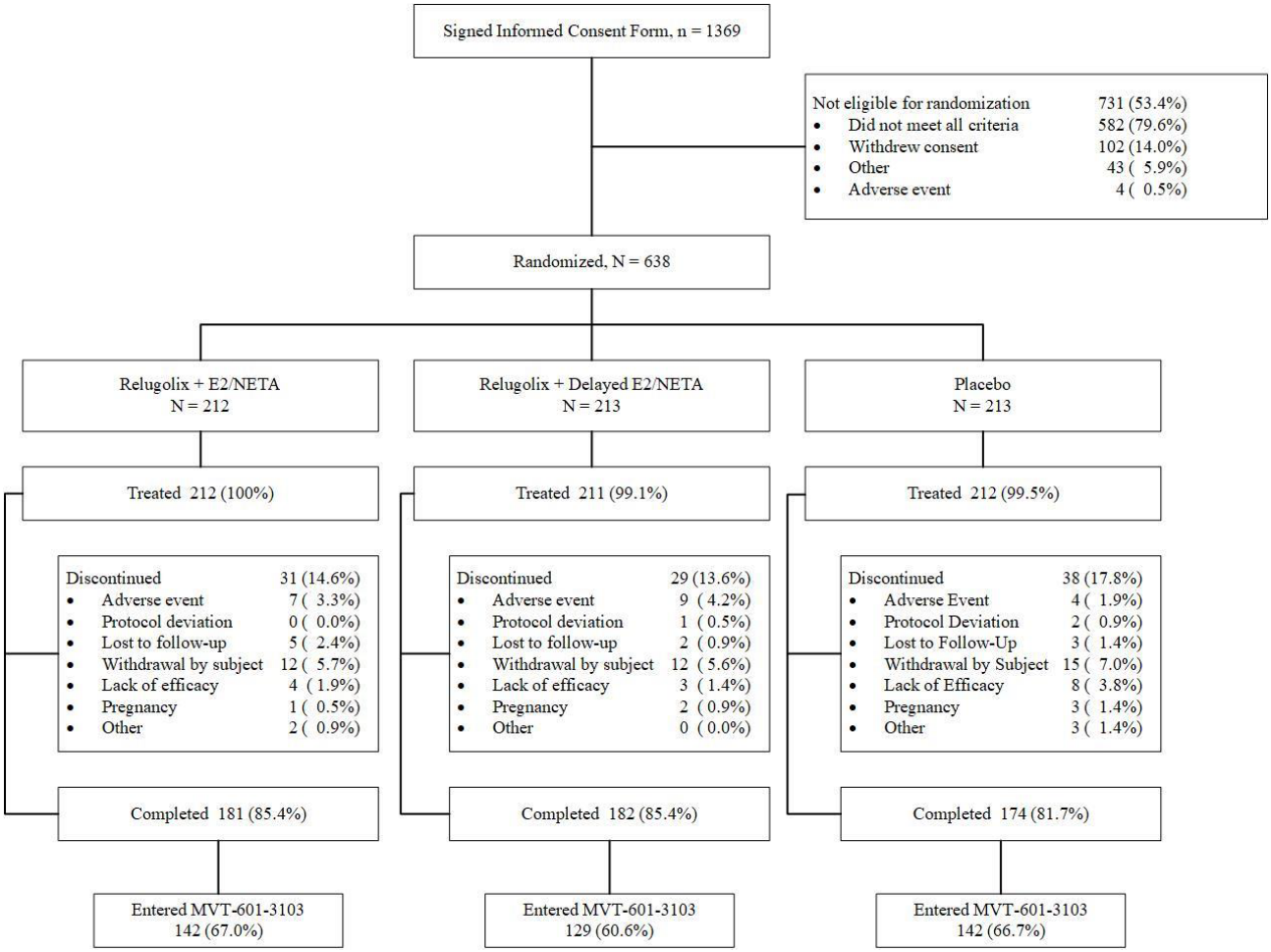
To account for participants whose BMD assessment may have been obtained outside of the protocol-specified window (Week 12 ± 3 weeks, Week 24 ± 3 and 4 weeks), a sensitivity analysis by visit will be conducted that includes all women who underwent DXA at both time points, regardless of whether the image was procured during the pre-specified time window.

A mixed-effects model with repeated measures will be used to describe treatment effect on BMD at 12 and 24 weeks. The model will have treatment group, age at baseline, visit, baseline BMD value, stratification factors (geographic region and time since initial surgical diagnosis of endometriosis), race (African American versus Other), BMI at baseline, and treatment-by-visit as fixed effects using an unstructured variance-covariance matrix. Least square means on each anatomical location will be presented and plotted at each visit with associated 95% CIs.

Results MVT-601-3101 – SPIRIT 1

Participant flow

Figure 14. MVT-601-3101: Patient Disposition



The proportion of patients who discontinued the study early was generally similar across treatment groups: 31 (14.6%) patients in the relugolix + E2/NETA group, 29 (13.6%) patients in the relugolix + delayed E2/NETA group, and 38 (17.8%) patients in the placebo group. The most common reasons for early discontinuations included the following: withdrawal by patient, adverse events, lack of efficacy, and lost to follow-up.

Protocol deviations

Table 10. MVT-601-3101: Summary of Important Protocol Deviations (mITT Population)

Protocol Deviation Category Subcategory	Relugolix+E2/NETA (N = 212)	Relugolix+Delayed E2/NETA (N = 211)	Placebo (N = 212)
Any Important Protocol Deviation, n (%)	64 (30.2%)	59 (28.0%)	59 (27.8%)
Key Study Procedures not Performed	52 (24.5%)	47 (22.3%)	40 (18.9%)
Bone Densitometry Scan not Performed	19 (9.0%)	13 (6.2%)	20 (9.4%)
Endometrial Biopsy not Performed	15 (7.1%)	6 (2.8%)	18 (8.5%)
EHP-30 not Completed	13 (6.1%)	9 (4.3%)	9 (4.2%)
Missed Key Study Procedure	11 (5.2%)	16 (7.6%)	4 (1.9%)
Laboratory Tests not Performed for at Least 2 Consecutive Visits	3 (1.4%)	2 (0.9%)	2 (0.9%)
Entire Study Visit Missed	3 (1.4%)	2 (0.9%)	1 (0.5%)
Transvaginal Ultrasound not Performed	0	1 (0.5%)	0

Restricted Medications	12 (5.7%)	6 (2.8%)	8 (3.8%)
Received Prohibited Concomitant Medication	12 (5.7%)	6 (2.8%)	8 (3.8%)
Study Drug	8 (3.8%)	5 (2.4%)	8 (3.8%)
Dispensed Incorrect or Expired Study Drug or Kit	8 (3.8%)	3 (1.4%)	5 (2.4%)
Overall Treatment Compliance < 75%	0	2 (0.9%)	3 (1.4%)
Key Eligibility Criteria	3 (1.4%)	3 (1.4%)	7 (3.3%)
Did not Satisfy Key Entry Criteria	3 (1.4%)	3 (1.4%)	7 (3.3%)
Informed Consent	1 (0.5%)	2 (0.9%)	3 (1.4%)
Delayed in Re-Consent	1 (0.5%)	2 (0.9%)	3 (1.4%)
Other	0	0	1 (0.5%)
Other Deviation Deemed Important Regarding Efficacy or Safety	0	0	1 (0.5%)
Safety	0	0	1 (0.5%)
Failed to Adhere to Safety Measures or Reporting	0	0	1 (0.5%)

Abbreviations: E2 = estradiol; mITT = modified intent-to-treat (Population); n = number of patients in subset; N = number of patients; NETA = norethindrone acetate. Percentages were based on the total number of patients in each treatment group or total.
Source: Table 8.1.3.1

The most common important protocol deviations were related to missed key procedures, most often the Week 24 endometrial biopsy (the sum of subcategories of "endometrial biopsy not performed" and "missed key study procedure" in Table 10). Reasons for missed biopsy most often were an inadequate first biopsy and refusal by the patient to undergo a second biopsy. The next most common procedure missed was a DXA scan in 6.2% to 9.4% of patients across the three groups. Reasons for missed DXA scans varied, but included logistical reasons (scheduling), broken devices, refusal by patient at the ET visit, and COVID-19 related concerns. Subsequent to database lock, 2 patients for whom an important protocol deviation had been reported were discovered to have had only a minor deviation because a key procedure (the EHP-30 in both cases) previously reported as missed had not been missed.

Restricted medication important protocol deviations were reported for 26 patients. These were reported with similar frequency across treatment groups (range: 2.8% to 5.7% of patients). Most of these deviations (20 patients) were related to taking a P-gp inhibitor (generally, a restricted antibiotic) for > 3 days following randomization. An additional 12 patients received > 4 days of a non-protocol-specified analgesic medication during the run-in period (6 patients in the relugolix + E2/NETA group; 2 patients in the relugolix + delayed E2/NETA group; and 4 patients in the placebo group). One patient took progesterone (relugolix + E2/NETA group).

Recruitment

A total of 1369 patients signed the ICF, 1105 patients entered the single-blind run-in period, and 638 patients were randomized at 124 centers globally, including centers in North America (Canada and United States), and Rest of World (Argentina, Belgium, Bulgaria, Czech Republic, Finland, Hungary, Poland, Portugal, South Africa, Spain, and Ukraine).

Overall, 80.9% of patients were enrolled from the Rest of World and 19.1% of patients were enrolled from North America.

The date first patient screened was 28 September 2017, the date last patient completed was 09 June 2020.

Conduct of the study

The original study protocol for study MVT-601-3101, dated 12 June 2017, was amended once, dated 12 March 2018.

The main purpose of the amendment was to incorporate additional Patient Global Assessment anchors for dysmenorrhea and pelvic pain. Modifications were also made to the Screening Visit and Run-In Windows and modifications or clarifications to study eligibility, as well as study procedures or tests.

The original SAP was developed for the two replicate studies MVT-601-3101 and MVT-601-3102 and was finalized on 12 Mar 2020. After unblinding of study MVT-601-3102, the SAP was amended (SAP v1.1) and finalized on 15 May 2020, prior to database lock of this study (17 Jun 2020).

The changes made were in the hierarchical testing order for the fifth and sixth secondary endpoints and replacement of the seventh secondary endpoints in this study:

- The fifth secondary endpoint was the proportion of patients not using opioids;
- The sixth secondary endpoint was the change in dyspareunia NRS score;
- The seventh secondary endpoint was the proportion of patients not using analgesics, which replaced the seventh endpoint (change in average daily pill count of analgesics) in study MVT-601-3102.

The main purpose of the amendment was to increase the probability of success for MVT-601-3101 based on the external data from MVT-601-3102. The data from MVT-601-3102 showed the majority of patients took only a few pills on some days and did not take any pills on the majority of the days over the pain assessment period (either at baseline or Week 24/EOT), making the distribution of average daily pill counts of analgesics heavily skewed towards 0 to 1. This observation suggested that average daily pill count would not be a sensitive measure for assessing treatment effect. A binary endpoint (proportion of patients not using analgesics) is of more clinical interest to quantify the treatment response; and therefore, was proposed as the seventh key endpoint for this study.

A second amendment in the SAP was on 23 Jul 2020 (SAP v1.2) to include the Psychometric Analysis Plan in the appendices. This was an administrative amendment.

- **Responder definition primary outcome - meaningful change threshold (MCT)**

Pooled blinded data from approximately the first third of patients enrolled in each of the MVT-601-3101 and MVT-601 3102 studies (n = 200 of 600 planned per study) were included in the threshold determination analysis (TDA) set used to determine the responder thresholds.

Uncollapsed changes on the PGA for dysmenorrhea anchor were used to determine the MCT for the endpoint of dysmenorrhea NRS (Table 11) . Examination of the mean change scores for the dysmenorrhea NRS from Baseline to Week 24/EOT for each change category of the anchor revealed that they monotonically increased between the +1 (worsening) and -4 (improvement) categories. A slight disorder was observed for the remaining worsening categories (ie, +2, +4), likely due to the

small sample sizes associated with these categories. For the derivation of the MCT for the dysmenorrhea NRS, first the lowest improvement category on the anchor with a SES ≥ 0.5 and a significant P-value was identified. The 1-category improvement group attained a significant within-group improvement (P-value < 0.0001) with a large SES (-1.25) according to Cohen's guidance.4 Comparison of the 95% CIs for the no change category (-2.53, -1.21) and the 1-category improvement (-2.88, -2.01) revealed that they overlapped. Since the 2 CIs overlapped, it was prudent to consider a slightly more conservative MCT (ie, more negative change). One option was -2.8 points, since this fell within the 1-category improvement CI, but outside the no change group CI.

An alternative option would have been to use a 2-category improvement. A visual inspection of the CDF and PDF curves (Figure 15) showsseparation between the 1-category improvement and the no change curves, although some overlap existed below approximately -3.5 points, affecting approximately 20% of patients. Therefore, utilizing a 2-category improvement on the anchor to define the MCT was deemed too conservative and would result in misclassifying a large percentage of patients, who indicated they improved according to the PGA anchor, as non-responders.

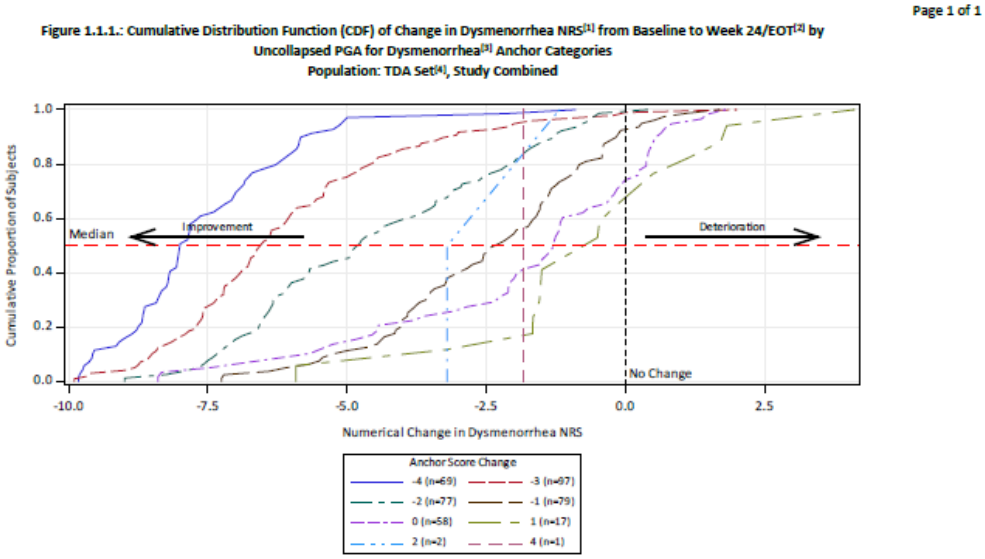
Table 11. Within Groups (Uncollapsed) Anchor-Based Meaningful Change Derivation for the dysmenorrhea NRS[1] at Week 24/EOT[2], using PGA for Dysmenorrhea[3] as an Anchor (TDA Set[4], Study Combined)

Table 2: Within Groups (Uncollapsed) Anchor-Based Meaningful Change Derivation for the Dysmenorrhea NRS[1] at Week 24/EOT[2], using PGA for Dysmenorrhea[3] as an Anchor (TDA Set[4], Study Combined)

Change in PGA for Dysmenorrhea	Correlation[5]	Correlation[6] At Baseline	N	Mean Change (SD)	Median Change	Min , Max	95% CI	*P*-value[7]	Standardized Effect Size of Change[8]
-4	0.709	0.455	69	-7.5 (1.66)	-8.0	-10, -1	(-7.93, -7.13)	< 0.0001	-4.54
-3			97	-6.1 (2.22)	-6.5	-10, 2	(-6.50, -5.60)	< 0.0001	-2.72
-2			77	-4.5 (2.30)	-4.8	-9, 0	(-5.01, -3.96)	< 0.0001	-1.95
-1			79	-2.4 (1.96)	-2.3	-7, 2	(-2.88, -2.01)	< 0.0001	-1.25
0			58	-1.9 (2.52)	-1.3	-8, 2	(-2.53, -1.21)	< 0.0001	-0.74
1			17	-0.5 (2.22)	-0.5	-6, 4	(-1.69, 0.59)	0.3232	-0.25
2			2	-2.2 (1.43)	-2.2	-3, -1	(-15.01, 10.63)	0.2748	-1.54
4			1	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: CI = confidence interval, EOT = end of treatment, max = maximum, min = minimum, N/A = not applicable, NRS = Numeric Rating Scale, PGA = Patient Global Assessment, TDA = threshold determination analysis.
[1]Dysmenorrhea scores are mean NRS pain scores recorded on days when the patient indicated she was menstruating as reported in the daily eDiary.
[2]The Week 24/EOT pain assessment period was defined as the last 35 calendar days immediately prior to and including the day of the last dose of randomized study drug treatment. Data were used for patients who either completed the study through Week 24 or early terminated at Week 12 or later.
[3]The PGA for dysmenorrhea asks patients who had a menstrual period in the past 4 weeks, "In the past 4 weeks, how would you rate your pelvic pain on days you had your period?", to rate their pelvic pain using a 5-point ordinal scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.
[4]This analysis set consisted of patients who had observed scores (ie, non-missing responses) in both dysmenorrhea NRS and PGA for dysmenorrhea for at least one visit (Week 12 or later). The latest observed pair of dysmenorrhea NRS and PGA for dysmenorrhea were included in the analysis set.
[5]Polyserial correlation coefficient was calculated between the categorized change from Baseline in the PGA for dysmenorrhea and the change from Baseline on the dysmenorrhea NRS.
[6]Polyserial correlation coefficient was calculated between Baseline PGA for dysmenorrhea and Baseline dysmenorrhea NRS.
[7]The *P*-value for each individual change group was derived from a paired (within samples) t-test assessing the difference over time.
[8]Standardized effect sizes were calculated as the mean divided by the standard deviation. They were judged as: small = 0.20, moderate = 0.50, and large = 0.80.
Source: Appendix C, Table 1.1.1

Figure 15. Cumulative Distribution Function (CDF) of Change in Dysmenorrhea NRS[1] from Baseline to Week 24/EOT[2] by Uncollapsed PGA for Dysmenorrhea[3] Anchor Categories Population: TDA Set[4], Study Combined



Abbreviations: NRS = Numeric rating scale, EOT = End of treatment, PGA = Patient Global Assessment, TDA = Threshold Determination Analysis.
[1] Dysmenorrhea scores are mean NRS pain scores recorded on days when the patient indicates she is menstruating as reported in the daily eDiary.
[2] The Week 24/EOT pain assessment period was defined as the last 35 calendar days immediately prior to and including the day of the last dose of randomized study drug treatment. Data were used for patients who either completed the study through Week 24 or early terminated at Week 12 or later.
[3] The PGA for dysmenorrhea asks patients who had a menstrual period in the past 4 weeks, "In the past 4 weeks, how would you rate your pelvic pain on days you had your period?", to rate their pelvic pain using a 5-point ordinal scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.
[4] This analysis set consists of patients who have observed scores (ie, non-missing responses) in both dysmenorrhea NRS and PGA for dysmenorrhea for at least one visit (Week 12 or later). The latest observed pair of dysmenorrhea NRS and PGA for dysmenorrhea will be included in the analysis set.
Analysis datasets: ADTHRES_COMBINED.

Uncollapsed changes on the PGA for NMPP anchor were used to determine the MCT for the NMPP NRS endpoint (Table 12). Examination of the mean change scores for the NMPP NRS from Baseline to Week 24/EOT for each anchor change category revealed that they monotonically increased between the +1 (worsening) and -4 (improvement) categories. A slight disorder was observed for the remaining worsening category (ie, +2), likely due to the associated small sample size.

Similar to the dysmenorrhea NRS, the 1-category improvement on the PGA attained a significant within-group improvement (P-value < 0.0001) with a large SES (-1.18).[4] Comparison between the 95% CIs for the no change category (-1.55, -0.78), and the 1-category improvement (-2.76, -2.07) revealed that they did not overlap. Therefore, one option is to set the MCT to -2.1 points, since it falls within the CI for the 1-category improvement and would not unduly inflate the proportion of patients erroneously classified as non-responders.

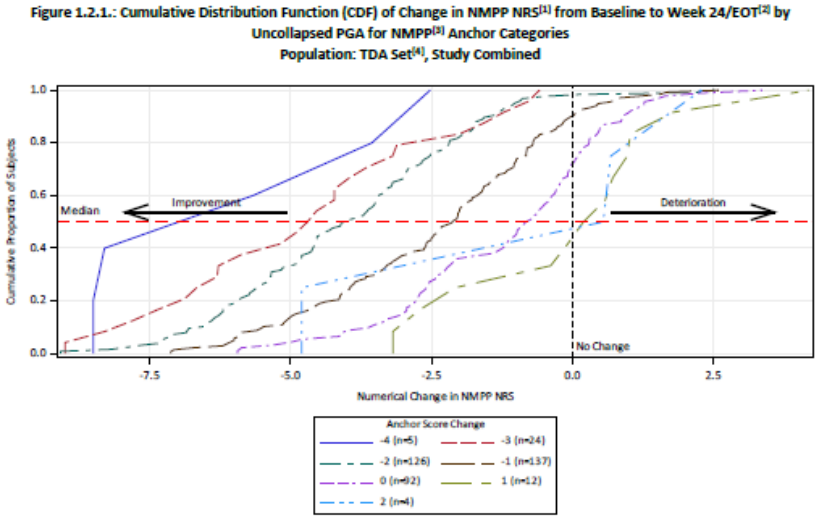
A visual inspection of the CDF and PDF curves (Figure 16) revealed clear separation between the 1-category improvement and the no change curves, thereby lending further support for this MCT value. It is important to note that utilizing a 2-category improvement to define the MCT would result in misclassifying a large percentage of patients, who indicated that they experienced less pelvic pain at Week 24/EOT than at Baseline based on the NMPP PGA, as non-responders.

Table 8. Within Groups (Uncollapsed) Anchor-Based Meaningful Change Derivation for the NMPP NRS[1] at Week 24/EOT[2], using PGA for NMPP[3] as an Anchor (TDA Set[4], Study Combined)

Change in PGA for NMPP	Correlation[5]	Correlation[6] At Baseline	N	Mean Change (SD)	Median Change	Min , Max	95% CI	*P*-value[7]	Standardized Effect Size of Change[8]
-4	0.558	0.331	5	-5.7 (2.71)	-5.7	-9, -3	(-9.07, -2.35)	0.0092	-2.11
-3			24	-4.7 (2.39)	-4.6	-9, -1	(-5.69, -3.67)	< 0.0001	-1.95
-2			126	-4.0 (2.09)	-4.0	-9, 3	(-4.36, -3.63)	< 0.0001	-1.91
-1			137	-2.4 (2.04)	-2.1	-7, 3	(-2.76, -2.07)	< 0.0001	-1.18
0			92	-1.2 (1.85)	-0.8	-6, 3	(-1.55, -0.78)	< 0.0001	-0.63
1			12	0.1 (2.03)	0.4	-3, 4	(-1.21, 1.38)	0.8849	0.04
2			4	-0.3 (3.09)	0.6	-5, 2	(-5.24, 4.59)	0.8479	-0.10

Abbreviations: CI = confidence interval, EOT = end of treatment, max = maximum, min = minimum, NMPP = non-menstrual Pelvic Pain, NRS = Numeric Rating Scale, PGA = Patient Global Assessment, TDA = threshold determination analysis.
[1]Non-menstrual pelvic pain scores are mean NRS pain scores recorded on days when the patient indicated she was not menstruating as reported in the daily eDiary.
[2]The Week 24/EOT pain assessment period was defined as the last 35 calendar days immediately prior to and including the day of the last dose of randomized study drug treatment. Data were used for patients who either completed the study through Week 24 or early terminated at Week 12 or later.
[3]The PGA for dysmenorrhea asks patients who had a menstrual period in the past 4 weeks, "In the past 4 weeks, how would you rate your pelvic pain on days you had your period?", to rate their pelvic pain using a 5-point ordinal scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.
[4]This analysis set consisted of patients who had observed scores (ie, non-missing responses) in both NMPP NRS and PGA for NMPP for at least one visit (Week 12 or later). The latest observed pair of NMPP NRS and PGA for NMPP was included in the analysis set.
[5]Polyserial correlation coefficient was calculated between the categorized change from Baseline in the PGA for NMPP and the change from Baseline on the NMPP NRS.
[6]Polyserial correlation coefficient was calculated between Baseline PGA for NMPP and Baseline NMPP NRS.
[7]The *P*-value for each individual change group was derived from a paired (within samples) t-test assessing the difference over time.
[8]Standardized effect sizes were calculated as the mean divided by the standard deviation. They were judged as: small = 0.20, moderate = 0.50, and large = 0.80.
Source: Appendix C, Table 1.2.1

Figure 16. Cumulative Distribution Function (CDF) of Change in NMPP NRS[1] from Baseline to Week 24/EOT[2] by Uncollapsed PGA for NMPP[3] Anchor Categories Population: TDA Set[4], Study Combined



Abbreviations: NRS = Numeric rating scale, EOT = End of treatment, PGA = Patient Global Assessment, TDA = Threshold Determination Analysis, NMPP = Non-menstrual Pelvic Pain.
[1] Non-menstrual pelvic pain scores are mean NRS pain scores recorded on days when the patient indicates she is not menstruating as reported in the daily eDiary.
[2] The Week 24/EOT pain assessment period was defined as the last 35 calendar days immediately prior to and including the day of the last dose of randomized study drug treatment. Data were used for patients who either completed the study through Week 24 or early terminated at Week 12 or later.
[3] The PGA for dysmenorrhea asks patients who had a menstrual period in the past 4 weeks, "In the past 4 weeks, how would you rate your pelvic pain on days you had your period?", to rate their pelvic pain using a 5-point ordinal scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.
[4] This analysis set consists of patients who have observed scores (ie, non-missing responses) in both NMPP NRS and PGA for NMPP for at least one visit (Week 12 or later). The latest observed pair of NMPP NRS and PGA for NMPP will be included in the analysis set.
Analysis datasets: ADTHRES_COMBINED.

Baseline data

Overall, demographic characteristics were generally similar across treatment groups. The mean (SD) age for all patients was 34.2 (6.52) years, with the mean age similar across treatment groups.

The predominant racial representation in the study was White (581 [91.5%] patients), consistent with the generally described epidemiology of endometriosis, although recent studies suggest that there may

be an ascertainment bias due to differences in the odds of diagnosis of endometriosis by race and ethnicity - higher in White and Asian women and lower in Black or African American and Hispanic women (Bougie et al. 2019).

Table 13. MVT-601-3101: Summary of Patient Demographics (mITT Population)

	Relugolix+ E2/NETA (N = 212)	Relugolix+ Delayed E2/NETA (N = 211)	Placebo (N = 212)
Age (years)			
Mean (SD)	33.9 (6.30)	34.3 (6.72)	34.2 (6.56)
Age Category, n (%)			
< 35 years	108 (50.9%)	109 (51.7%)	106 (50.0%)
≥ 35 years	104 (49.1%)	102 (48.3%)	106 (50.0%)
Geographic Region, n (%)			
North America	40 (18.9%)	41 (19.4%)	40 (18.9%)
Rest of World	172 (81.1%)	170 (80.6%)	172 (81.1%)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.5%)	0
Asian	0	2 (0.9%)	0
Black or African American	13 (6.1%)	10 (4.7%)	12 (5.7%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	194 (91.5%)	194 (91.9%)	193 (91.0%)
Other	1 (0.5%)	4 (1.9%)	4 (1.9%)
Multiple	4 (1.9%)	0	3 (1.4%)
Not Reported	0	0	0
Ethnicity, n (%)			
Not Hispanic or Latino	198 (93.4%)	192 (91.0%)	195 (92.0%)
Hispanic or Latino	13 (6.1%)	17 (8.1%)	17 (8.0%)
Not Reported	1 (0.5%)	2 (0.9%)	0

Abbreviations: E2 = estradiol; mITT = modified intent-to-treat (Population); N = number of patients; n = number of patients in subset; NETA = norethindrone acetate. Source: Table 8.1.4.1

Table 14. MVT-601-3101: Summary of Disease-Specific Baseline Characteristics and Bone Mineral Density (mITT Population)

	Relugolix+E2/NETA (N = 212)	Relugolix+Delayed E2/NETA (N = 211)	Placebo (N = 212)
Time Since Surgical Diagnosis of Endometriosis (years)			

n	212	211	212
Mean (SD)	3.8 (3.20)	4.4 (4.08)	3.8 (3.27)
Median	3.0	3.1	3.3
Min, Max	0.1, 16.0	0.1, 21.5	0.1, 15.4
< 5	151 (71.2%)	135 (64.0%)	148 (69.8%)
≥ 5	61 (28.8%)	76 (36.0%)	64 (30.2%)
Dysmenorrhea NRS score at Baseline			
n	212	211	212
Mean (SD)	7.2 (1.70)	7.0 (1.78)	7.1 (1.66)
Median	7.4	7.0	7.3
Min, Max	1.5, 10.0	1.6, 10.0	1.6, 10.0
< 7	84 (39.6%)	97 (46.0%)	90 (42.5%)
≥ 7	128 (60.4%)	114 (54.0%)	122 (57.5%)
< 4	8 (3.8%)	12 (5.7%)	8 (3.8%)
4 to < 7	76 (35.8%)	85 (40.3%)	82 (38.7%)
7 to 10	128 (60.4%)	114 (54.0%)	122 (57.5%)
NMPP NRS Score at Baseline			
n	212	211	212
Mean (SD)	5.9 (1.96)	5.6 (2.03)	5.8 (1.81)
Median	6.0	5.8	6.0
Min, Max	1.8, 9.8	1.4, 9.9	1.6, 10.0
< 4	43 (20.3%)	53 (25.1%)	43 (20.3%)
≥ 4	169 (79.7%)	158 (74.9%)	169 (79.7%)
< 4	43 (20.3%)	53 (25.1%)	43 (20.3%)
4 to < 7	98 (46.2%)	96 (45.5%)	108 (50.9%)
7 to 10	71 (33.5%)	62 (29.4%)	61 (28.8%)
Dyspareunia NRS Score at Baseline			
n [1]	174	173	165
Mean (SD)	5.7 (2.33)	5.3 (2.41)	5.7 (2.30)
Median	6.0	5.2	6.0
Min, Max	0.4, 10.0	0.1, 10.0	0.3, 10.0
Median	6.0	5.2	6.0
Min, Max	0.4, 10.0	0.1, 10.0	0.3, 10.0
EHP-30 Pain Domain at Baseline			
n	208	208	208
Mean (SD)	58.3 (16.65)	55.5 (16.77)	55.5 (16.03)
Median	61.4	56.8	54.5
Min, Max	20.5, 100.0	0.0, 100.0	6.8, 97.7
0 to < 25	7 (3.4%)	6 (2.9%)	5 (2.4%)
25 to < 50	53 (25.5%)	64 (30.8%)	62 (29.8%)
50 to < 75	114 (54.8%)	113 (54.3%)	119 (57.2%)
75 to 100	34 (16.3%)	25 (12.0%)	22 (10.6%)

PGA Dysmenorrhea [1]			
n	188	186	183
Absent [2]	2 (1.1%)	0	3 (1.6%)
Mild	2 (1.1%)	6 (3.2%)	0
Moderate	19 (10.1%)	19 (10.2%)	34 (18.6%)
Severe	90 (47.9%)	85 (45.7%)	77 (42.1%)
Very Severe	75 (39.9%)	76 (40.9%)	69 (37.7%)
PGA NMPP [1]			
n	188	186	183
Absent	0	1 (0.5%)	0
Mild	14 (7.4%)	17 (9.1%)	16 (8.7%)
Moderate	94 (50.0%)	79 (42.5%)	95 (51.9%)
Severe	70 (37.2%)	73 (39.2%)	61 (33.3%)
Very Severe	10 (5.3%)	16 (8.6%)	11 (6.0%)
PGA Function			
n	211	210	210
Not at All	0	1 (0.5%)	1 (0.5%)
Minimally	12 (5.7%)	14 (6.7%)	17 (8.1%)
Moderately	104 (49.3%)	102 (48.6%)	105 (50.0%)
Significantly	76 (36.0%)	77 (36.7%)	77 (36.7%)
Very Significantly	19 (9.0%)	16 (7.6%)	10 (4.8%)
PGA Pain			
n	208	209	207
Absent	11 (5.3%)	13 (6.2%)	11 (5.3%)
Mild	30 (14.4%)	52 (24.9%)	44 (21.3%)
Moderate	99 (47.6%)	84 (40.2%)	107 (51.7%)
Severe	56 (26.9%)	48 (23.0%)	35 (16.9%)
Very Severe	12 (5.8%)	12 (5.7%)	10 (4.8%)
BMD (g/cm^2) Lumbar L1-L4			
n	212	211	211
Mean (SD)	1.143 (0.1512)	1.138 (0.1550)	1.129 (0.1462)
Median	1.123	1.125	1.115
Min, Max	0.825, 1.698	0.832, 1.818	0.853, 1.670
BMD (g/cm^2) Total Hip			
n	212	211	211
Mean (SD)	0.971 (0.1227)	0.971 (0.1263)	0.971 (0.1183)
Median	0.962	0.968	0.964
Min, Max	0.713, 1.400	0.719, 1.365	0.714, 1.393
BMD (g/cm^2) Femoral Neck			

n	212	211	211
Mean (SD)	0.925 (0.1431)	0.931 (0.1466)	0.922 (0.1450)
Median	0.922	0.915	0.914
Min, Max	0.584, 1.480	0.630, 1.448	0.607, 1.331

Abbreviations: BMD = bone mineral density; E2 = estradiol; EHP-30 = Endometriosis Health Profile 30-item Questionnaire; Max = maximum; Min = minimum; mITT = modified intent-to-treat (Population); N = number of patients; n = number of patients in subset; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale; PGA = Patient Global Assessment; SD = standard deviation. [1] The PGAs for dysmenorrhea and NMPP were implemented under the protocol amendment of 12 Mar 2018. [2] Includes patients who answered "No" to the question, "In the past 4 weeks, did you have your period?"

The median time since surgical diagnosis of endometriosis in the study population was 3.0 years. Overall, disease-specific baseline characteristics were consistent with a population of women with endometriosis having moderate or severe pain. On a 10-point NRS scale, the median baseline dysmenorrhea score was 7.3 and the median NMPP score was 5.9.

At screening, only women who reported moderate, severe, or very severe dysmenorrhea during their most recent menses, and moderate, severe, or very severe NMPP during the past month on the EAPS (Endometriosis-Associated Pain Severity) questions could enter the run-in period. At baseline, which was defined as the mean of all run-in period scores on menses days, 28 (4.4%) patients had a dysmenorrhea score < 4 despite meeting the eligibility requirements (inclusion criterion 8) for having a run-in period.

While all patients had to have moderate NMPP by the EAPS at screening to enroll into the study, 139 (21.9%) patients had a mean NRS score < 4 at baseline, which was calculated based on run-in period scores.

The baseline patient global assessment (PGA) of dysmenorrhea was severe or very severe for 472 (84.7%) patients with baseline scores, and the baseline PGA of NMPP was severe or very severe for 241 (43.3%) patients with baseline scores. On the PGA for function, 586 (92.9%) patients reported that their daily activities had been moderately, significantly, or very significantly limited by endometriosis in the prior 4 weeks.

In general, as presented in Table 15, disease-specific baseline characteristics and BMD were comparable across treatment groups.

Table 15. MVT-601-3101: Summary of Medical History Reported for ⩾ 5% of Patients

Preferred Term	Relugolix+ E2/NETA (N = 212)	Relugolix+Delayed E2/NETA (N = 211)	Placebo (N = 212)
No. of Patients Reporting at Least One Medical History	174 (82.1%)	171 (81.0%)	166 (78.3%)
Caesarean Section	28 (13.2%)	34 (16.1%)	32 (15.1%)
Appendicectomy	19 (9.0%)	28 (13.3%)	21 (9.9%)
Headache	17 (8.0%)	26 (12.3%)	22 (10.4%)
Anxiety	15 (7.1%)	21 (10.0%)	17 (8.0%)
Myopia	17 (8.0%)	18 (8.5%)	17 (8.0%)
Depression	15 (7.1%)	16 (7.6%)	20 (9.4%)
Drug Hypersensitivity	16 (7.5%)	18 (8.5%)	17 (8.0%)
Seasonal Allergy	17 (8.0%)	16 (7.6%)	14 (6.6%)
Tonsillectomy	13 (6.1%)	16 (7.6%)	12 (5.7%)
Hypothyroidism	13 (6.1%)	11 (5.2%)	16 (7.5%)

Uterine Leiomyoma	16 (7.5%)	12 (5.7%)	11 (5.2%)
Ovarian Cyst	12 (5.7%)	16 (7.6%)	9 (4.2%)
Asthma	17 (8.0%)	8 (3.8%)	11 (5.2%)
Migraine	5 (2.4%)	15 (7.1%)	10 (4.7%)
Hypertension	8 (3.8%)	13 (6.2%)	7 (3.3%)
Gastroesophageal Reflux Disease	8 (3.8%)	11 (5.2%)	7 (3.3%)
Obesity	6 (2.8%)	7 (3.3%)	12 (5.7%)

Abbreviations: E2 = estradiol; N = number of patients; NETA = norethindrone acetate. Percentages were based on the total number of patients in each treatment group or total. Patients with multiple events for a given preferred term were counted only once for each preferred term. Events were sorted by preferred term and decreasing frequency overall. MedDRA (version 22.0).

Consistent with a patient population having chronic pain, anxiety and depression were two of the most common reported as medical history across all treatment groups, and a total of 105 (16.5%) patients had medical history consistent with psychiatric disorders. History of anxiety and depression was similarly frequent across treatment groups, but anxiety was reported with the highest frequency in the relugolix + delayed E2/NETA group and depression was reported with the highest frequency in the placebo group.

- **Pain medication**

Prior to the study period

The most frequently reported prior medications by anatomical therapeutic chemical classification level 3 term included the following: anti-inflammatory and anti-rheumatic products, nonsteroids (623 [98.1%] patients: 207 [97.6%] patients in the relugolix + E2/NETA group, 207 [98.1%] patients in the relugolix + delayed E2/NETA group; and 209 [98.6%] patients in the placebo group), and opioids (252 [39.7%] patients: 82 [38.7%] patients in the relugolix + E2/NETA group, 83 [39.3%] patients in the relugolix + delayed E2/NETA group, and 87 [41.0%] patients in the placebo group). Additionally, drugs within "other analgesics and antipyretics" were used by 90 (14.2%) patients.

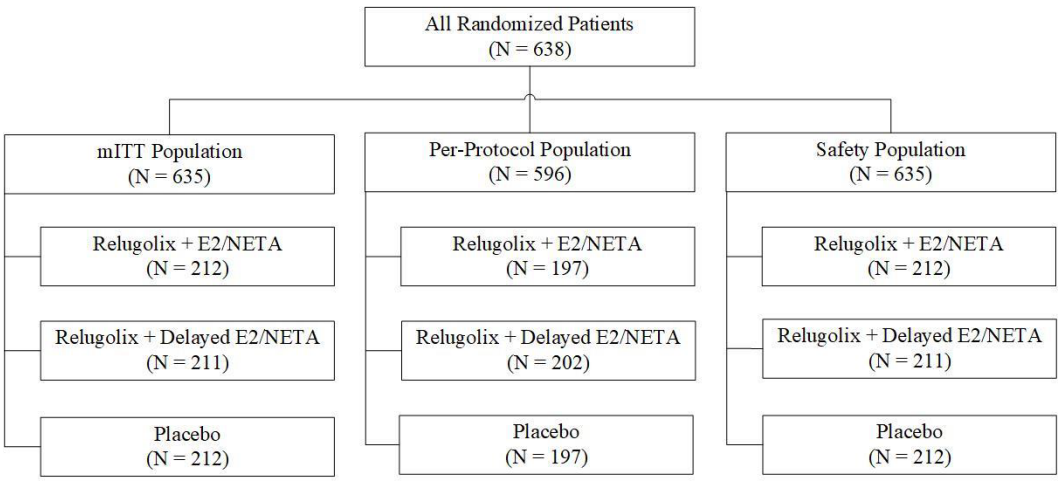
During the run-in period (i.e. baseline)

During the run-in (i.e., baseline) period, 189 (89.2%) patients in the relugolix + E2/NETA group, 186 (88.2%) patients in the relugolix + delayed E2/NETA group, and 183 (86.3%) patients in the placebo group used a protocol-specified Tier 1 analgesic (ibuprofen) for pelvic pain. The number and percentage of patients who used a protocol-specified Tier 2 analgesic (opioid or opioid combination) was 64 (30.2%) patients in the relugolix + E2/NETA group, 65 (30.8%) patients in the relugolix + delayed E2/NETA group, and 56 (26.4%) patients in the placebo group. Finally, both Tier 1 and Tier 2 medications were taken for pelvic pain during the run-in period by 61 (28.8%) patients in the relugolix + E2/NETA group, 62 (29.4%) patients in the relugolix + delayed E2/NETA group, and 46 (21.7%) patients in the placebo groups.

Numbers analysed

The number of patients included in each analysis set is presented in Figure 17.

Figure 17. MVT-601-3101: Number of Patients in Each Analysis Population by Treatment Group (All Randomized Patients)



Abbreviations: E2 = estradiol; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate. Three patients were excluded due to not receiving any treatment after randomization.

The mITT Population and Safety Population were identical, both defined as all randomized patients who received any amount of study drug and differentiated only in the handling of patients (if any) who did not receive the randomized treatment assigned.

The proportion of patients included in the Per-Protocol Population was similar across treatment groups, ranging from 92.5% in the placebo group to 94.8% in the relugolix + delayed E2/NETA group.

Outcomes and estimation

Primary Efficacy endpoints Analyses

The study had two co-primary efficacy endpoints, i.e. proportion of responders in dysmenorrhea NRS scores and responders in NMPP NRS scores, both of which compared the relugolix + E2/NETA group with the placebo group at the Week 24/EOT pain assessment period in the mITT.

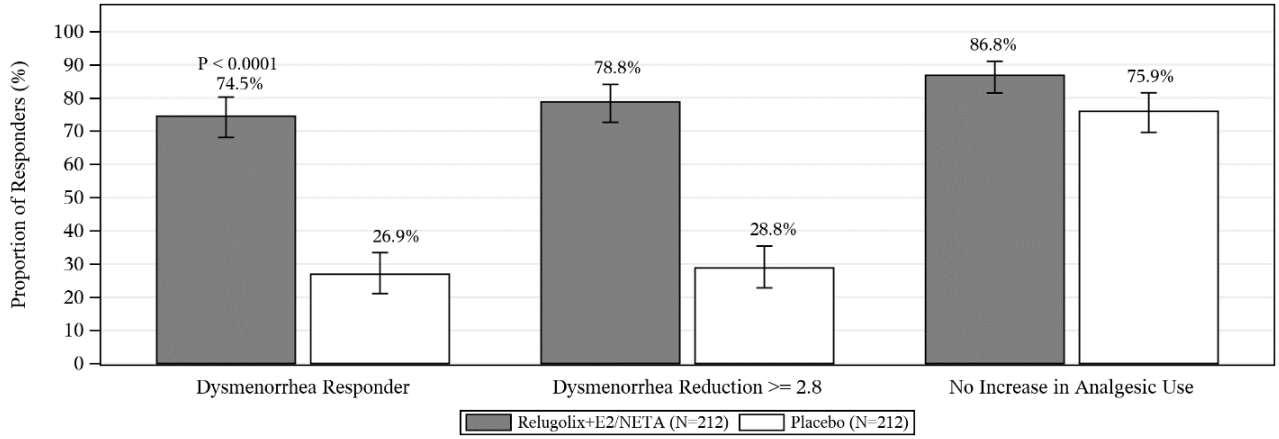
Dysmenorrhea Responder analysis

Table 16. MVT-601-3101: Co-Primary Efficacy Analysis, Proportion of Patients Classified as Dysmenorrhea Responders at Week 24/EOT (mITT Population)

	Relugolix+E2/NETA (N = 212)	Placebo (N = 212)
Number (%) of responders [1]	158 (74.5%)	57 (26.9%)
(95% CI) [2]	(68.11%, 80.25%)	(21.04%, 33.39%)
Difference from placebo (95% CI) [3]	47.6% (39.27%, 56.01%)	
P-value [4]	< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end of treatment; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate. Percentage was based on the number of patients in the mITT Population for each treatment group.
[1] Responders were patients whose NRS score for dysmenorrhea declined from baseline to Week 24/EOT by at least 2.8 points or the patient had a Week 24/EOT score ⩽ 0.1 if the baseline dysmenorrhea pain score was < 2.8, and the patient did not have increased use of study-specified analgesics for pelvic pain at Week 24/EOT relative to baseline.
[2] Based on exact binomial 95% CI (Clopper-Pearson).
[3] Difference in responder proportions of relugolix + E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution.
[4] P-value for treatment effect from the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ⩾ 5 years) and geographic region (North America, Rest of World) as covariates.

Figure 18. MVT-601-3101: Co-Primary Efficacy Endpoint, Proportion of Dysmenorrhea Responders at Week 24/EOT (mITT Population)



Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end of treatment; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate; NRS = Numerical Rating Scale. Responders were patients whose NRS score for dysmenorrhea declined from baseline to Week 24/EOT by at least 2.8 points or the patient had a Week 24/EOT score ⩽ 0.1 if the baseline dysmenorrhea pain score was < 2.8, and the patient did not have increased use of study specified analgesics for pelvic pain at Week 24/EOT relative to baseline. P-value for treatment effect was based on the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ⩾ 5 years) and geographic region (North America, Rest of World) as covariates. Error bars represent 95% CI. Source: Figure 8.2.1.1.

For the co-primary efficacy endpoint of dysmenorrhea responders, 158 (74.5%) patients in the relugolix + E2/NETA group and 57 (26.9%) patients in the placebo group achieved a decline in the dysmenorrhea NRS score by ⩾ 2.8 points without an increase in analgesic use. The between-group difference of 47.6% (95% CI: 39.27%, 56.01%) in favour of the relugolix + E2/NETA group was statistically significant (p < 0.0001) (Table 16).

Both components of the responder definition favoured the relugolix + E2/NETA group compared with placebo. An NRS score reduction of ⩾ 2.8 points was achieved by 78.8% of patients in the relugolix + E2/NETA group and 28.8% of patients in the placebo group (between-group difference of 50.0% [95% CI: 41.79%, 58.21%]). No increase in analgesic use was reported for 86.8% of patients in the relugolix + E2/NETA group or 75.9% of patients in the placebo group (between-group difference of 10.8% [95% CI: 3.51%, 18.19%]).

Nonmenstrual Pelvic Pain (NMPP) Responder Analysis

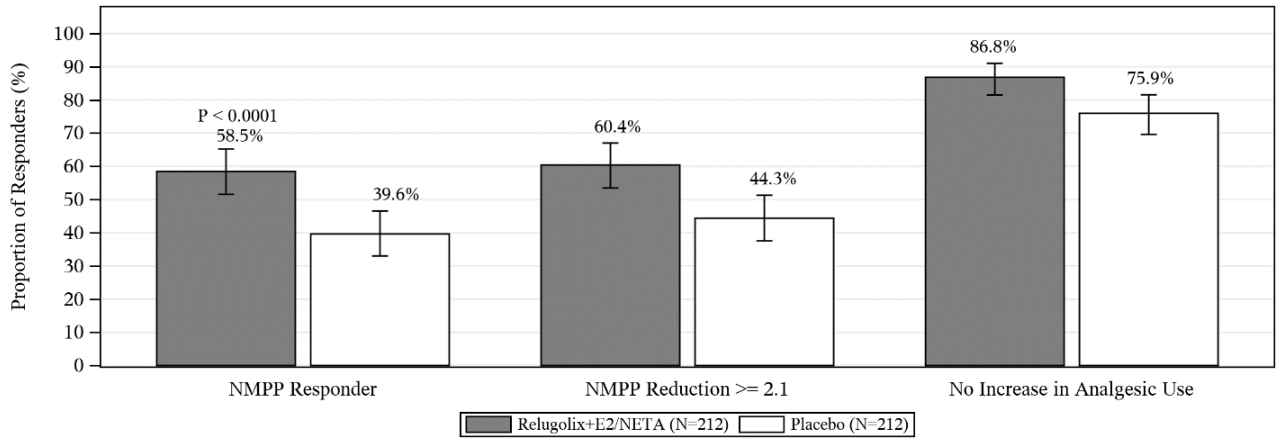
Table 17. MVT-601-3101: Co-Primary Efficacy Analysis, Proportion of Patients Classified as Nonmenstrual Pelvic Pain Responders at Week 24/EOT (mITT Population)

	Relugolix+E2/NETA (N = 212)	Placebo (N = 212)
Number (%) of responders [1]	124 (58.5%)	84 (39.6%)
(95% CI) [2]	(51.54%, 65.20%)	(32.99%, 46.55%)
Difference from placebo (95% CI) [3]	18.9% (9.52%, 28.21%)	
P-value [4]	< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end of treatment; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale. Percentage was based on the number of patients in the mITT Population for each treatment group.

[1] Responders were patients whose NRS score for NMPP declined from baseline to Week 24/EOT by at least 2.1 points or the patient had a Week 24/EOT score ⩽ 0.1 if the baseline NMPP score was < 2.1, and the patient did not have increased use of study specified analgesics for pelvic pain at Week 24/EOT relative to baseline.
[2] Based on exact binomial 95% CI (Clopper-Pearson).
[3] Difference in responder proportions of relugolix + E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution.
[4] P-value for treatment effect from the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ⩾ 5 years) and geographic region (North America, Rest of World) as covariates.

Figure 19. MVT-601-3101: Co-Primary Efficacy Endpoint, Proportion of Nonmenstrual Pelvic Pain Responders at Week 24/EOT (mITT Population)



Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end of treatment; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale. Responders were patients whose NRS score for NMPP declined from baseline to Week 24/EOT by at least 2.1 points or the patient had a Week 24/EOT score ⩽ 0.1 if the baseline NMPP score was < 2.1, and the patient did not have increased use of study specified analgesics for pelvic pain at Week 24/EOT relative to baseline.
P-value for treatment effect was based on the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ⩾ 5 years) and geographic region (North America, Rest of World) as covariates. Error bars represent 95% CI.

For the co-primary efficacy endpoint of NMPP responders, 124 (58.5%) patients in the relugolix + E2/NETA group and 84 (39.6%) patients in the placebo group achieved a decline in the NMPP NRS by ⩾ 2.1 points without an increase in analgesic use. The between-group difference of 18.9% (95% CI: 9.52%, 28.21%) in favour of the relugolix + E2/NETA group was statistically significant (p < 0.0001).

Both components of the responder definition favoured the relugolix + E2/NETA group compared with placebo. An NRS score reduction of ⩾ 2.1 points was achieved by 60.4% of patients in the relugolix + E2/NETA group and 44.3% of patients in the placebo group (between-group difference 16.0% [95% CI: 6.65%, 25.42%]). No increase in analgesic use was reported for 86.8% of patients in the relugolix + E2/NETA group and 75.9% in the placebo group (between-group difference 10.8% [95% CI: 3.51%, 8.19%]).

Sensitivity analysis

To test the robustness of the primary analysis, five sensitivity analyses were conducted. All five sensitivity analyses for both co-primary endpoints were consistent with the primary analysis for each endpoint. In each of these analyses, a significantly higher proportion of patients in the relugolix + E2/NETA group met the definition for responder than patients in the placebo group (Table 18 and Table 19).

Table 18. MVT-601-3101: Results of the Sensitivity Analysis for the Co-Primary Endpoint (Dysmenorrhea Responders)

Sensitivity Analysis	Relugolix+ E2/NETA	Placebo	Difference (95% CI)[1] p-value[2]
Patients who discontinued treatment prior to Week 12 due to adverse event or lack of efficacy and patients who discontinued study drug during the first 5 weeks for any reason as nonresponders, mITT Population	157 (74.1%)	56 (26.4%)	47.6% (39.27%, 56.01%) < 0.0001
24-Week Completers Population	147 (81.2%)	52 (29.9%)	51.3% (42.46%, 60.20%) < 0.0001
Per-Protocol Population	151 (76.6%)	55 (27.9%)	48.7% (40.12%, 57.34%) < 0.0001
Multiple imputation for handling missing average pain score, mITT Population [3]	74.5%	27.2%	47.3% (38.93%, 55.73%) < 0.0001
Observed data without using imputation, mITT Population	157 (74.1%)	58 (27.4%)	46.7% (38.28%, 55.11%) < 0.0001

Abbreviations: CI = confidence interval; E2 = estradiol; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate. Percentage was based on the number of patients for each treatment group in the analysis populations used for individual sensitivity analyses. [1] Difference in responder proportions of relugolix + E2/NETA minus placebo and its 95% CI were based on the approximation to the normal distribution. [2] P-value for treatment effect from the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ⩾ 5 years) and geographic region (North America, Rest of World) as covariates. [3] 100 imputed datasets were produced, and the estimates were combined by Rubin's rule.

Table 19. MVT-601-3101: Results of the Sensitivity Analysis for the Co-Primary Endpoint (Nonmenstrual Pelvic Pain Responders)

Sensitivity Analysis	Relugolix+ E2/NETA	Placebo	Difference (95% CI)[1] p-value[2]
Patients who discontinued treatment prior to Week 12 due to adverse event or lack of efficacy and patients who discontinued study drug during the first 5 weeks for any reason as nonresponders, mITT population	124 (58.5%)	83 (39.2%)	19.3% (10.00%, 28.68%) < 0.0001
24-Week Completers Population	118 (65.2%)	79 (45.4%)	19.8% (9.65%, 29.93%) 0.0002

Per-Protocol Population	118 (59.9%)	80 (40.6%)	19.3% (9.60%, 28.98%) 0.0001
Multiple imputation for handling missing average pain score, mITT Population [3]	58.0%	39.2%	18.8% (9.42%, 28.26%) 0.0001
Observed data without using imputation, mITT Population	123 (58.0%)	83 (39.2%)	18.9% (9.52%, 28.21%) < 0.0001

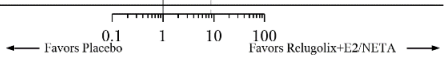
Abbreviations: CI = confidence interval; E2 = estradiol; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain. Percentage was based on the number of patients for each treatment group in the analysis populations used for individual sensitivity analyses. [1] Difference in responder proportions of relugolix + E2/NETA minus placebo and its 95% CI were based on the approximation to the normal distribution.
[2] P-value for treatment effect from the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ⩾ 5 years) and geographic region (North America, Rest of World) as covariates.
[3] 100 imputed datasets were produced, and the estimates were combined by Rubin's rule.

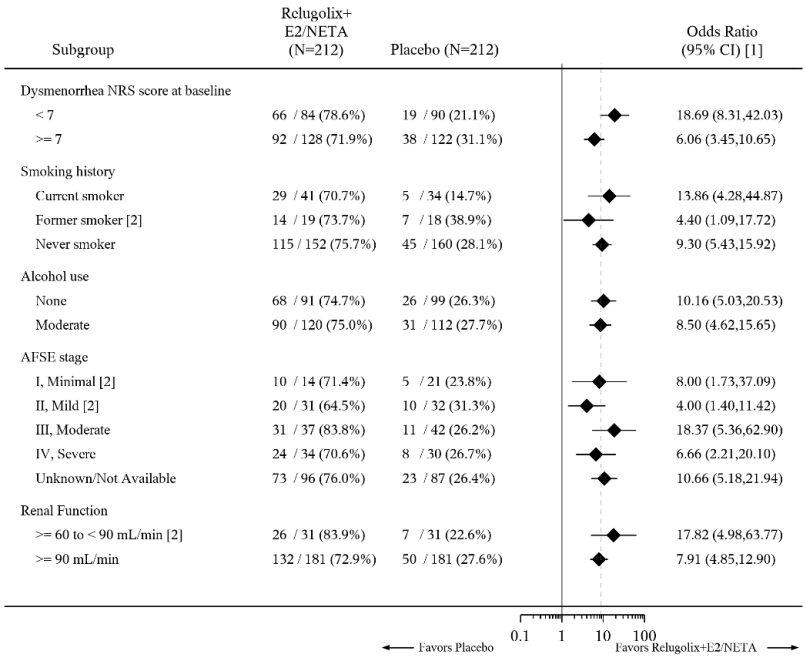
Ancillary analyses

Subgroup analyses were conducted for the co-primary efficacy endpoints by geographic region, time since surgical diagnosis of endometriosis, AFS endometriosis stage, age, race, BMI, smoking status, dysmenorrhea NRS score at baseline, NMPP NRS score at baseline, and renal function based on the Cockcroft-Gault formula for calculated creatinine clearance.

Table 20. MVT-601-3101: Proportion of Patients Classified as Dysmenorrhea Responders at Week 24/EOT, Subgroup Analyses (mITT Population)

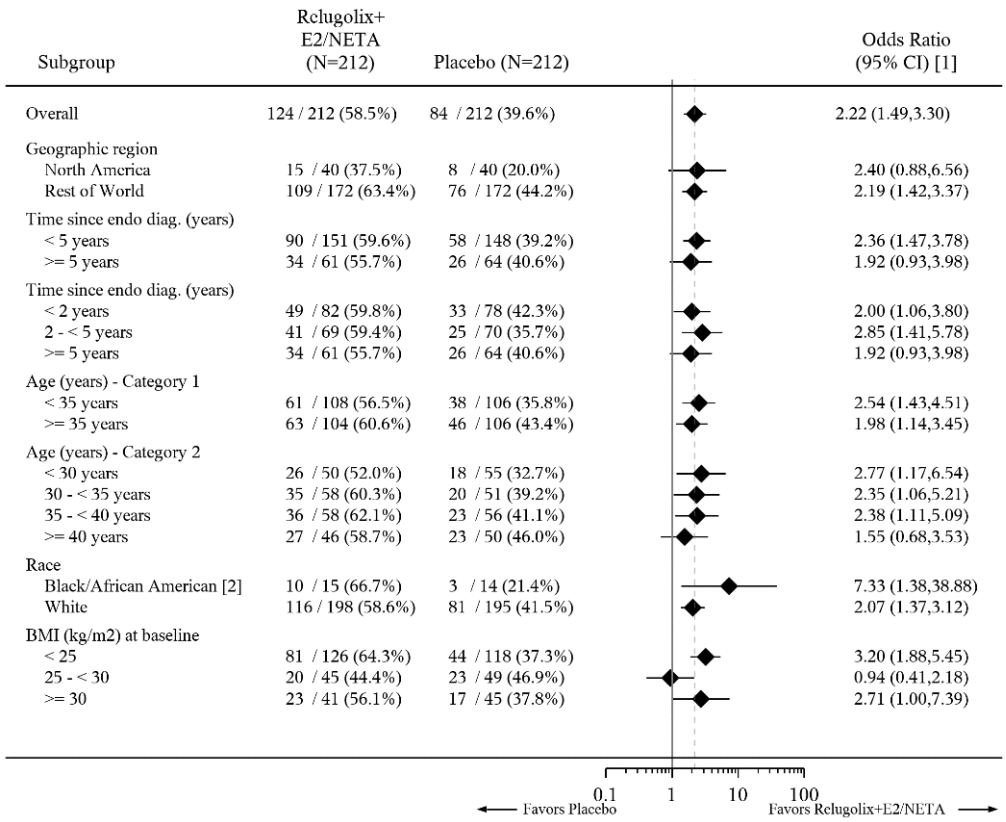
Subgroup	Relugolix+ E2/NETA (N=212)	Placebo (N=212)	Odds Ratio (95% CI) [1]
Overall	158 / 212 (74.5%)	57 / 212 (26.9%)	8.78 (5.59,13.81)
Geographic region			
North America	22 / 40 (55.0%)	5 / 40 (12.5%)	8.72 (2.81,27.06)
Rest of World	136 / 172 (79.1%)	52 / 172 (30.2%)	8.80 (5.37,14.41)
Time since endo diag. (years)			
< 5 years	117 / 151 (77.5%)	43 / 148 (29.1%)	9.09 (5.30,15.60)
>= 5 years	41 / 61 (67.2%)	14 / 64 (21.9%)	8.09 (3.53,18.54)
Time since endo diag. (years)			
< 2 years	66 / 82 (80.5%)	24 / 78 (30.8%)	9.61 (4.57,20.23)
2 - < 5 years	51 / 69 (73.9%)	19 / 70 (27.1%)	8.60 (3.91,18.91)
>= 5 years	41 / 61 (67.2%)	14 / 64 (21.9%)	8.09 (3.53,18.54)
Age (years) - Category 1			
< 35 years	77 / 108 (71.3%)	27 / 106 (25.5%)	8.70 (4.55,16.65)
>= 35 years	81 / 104 (77.9%)	30 / 106 (28.3%)	9.49 (4.97,18.11)
Age (years) - Category 2			
< 30 years	35 / 50 (70.0%)	12 / 55 (21.8%)	11.72 (4.24,32.40)
30 - < 35 years	42 / 58 (72.4%)	15 / 51 (29.4%)	6.54 (2.76,15.50)
35 - < 40 years	45 / 58 (77.6%)	14 / 56 (25.0%)	13.87 (5.27,36.49)
>= 40 years	36 / 46 (78.3%)	16 / 50 (32.0%)	7.20 (2.84,18.22)
Race			
Black/African American [2]	11 / 15 (73.3%)	2 / 14 (14.3%)	16.50 (2.51,108.59)
White	148 / 198 (74.7%)	55 / 195 (28.2%)	8.45 (5.28,13.53)
BMI (kg/m2) at baseline			
< 25	103 / 126 (81.7%)	35 / 118 (29.7%)	10.97 (5.96,20.17)
25 - < 30	30 / 45 (66.7%)	16 / 49 (32.7%)	5.00 (1.98,12.64)
>= 30	25 / 41 (61.0%)	6 / 45 (13.3%)	14.35 (4.28,48.16)

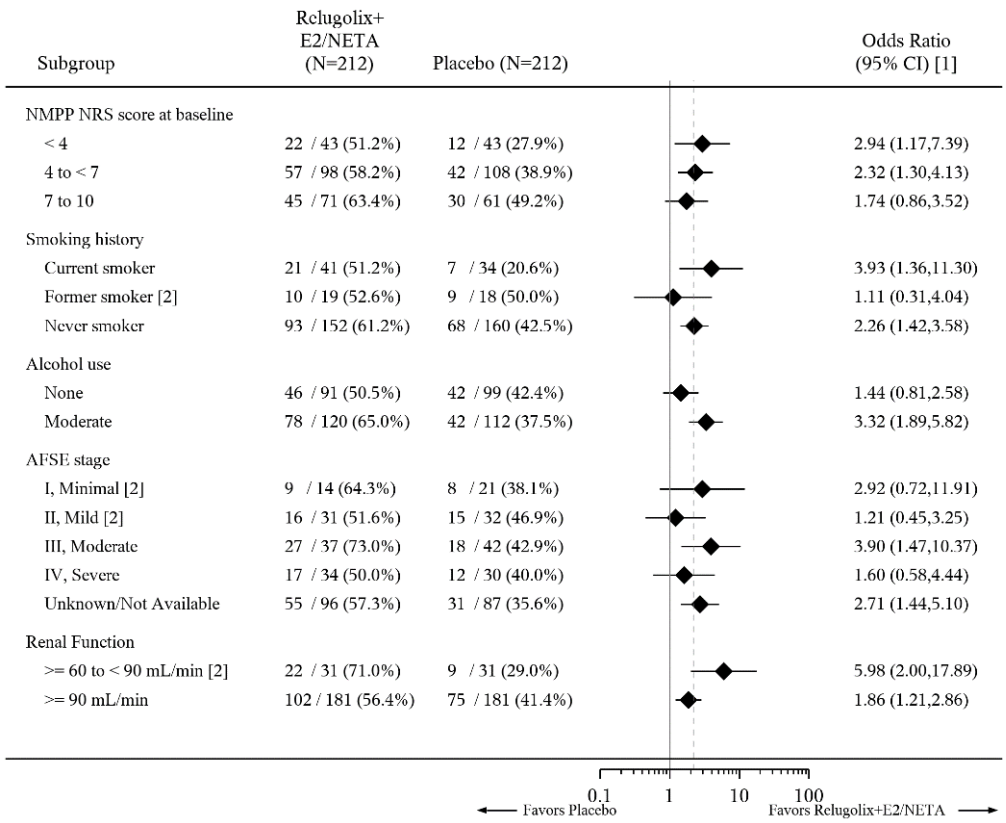




Abbreviations: AFSE = American Fertility Society of Endometriosis; BMI = body mass index; CI = confidence interval; diag = diagnosis; E2 = estradiol; endo = endometriosis; EOT = end of treatment; mITT = modified intent to-treat (Population); N = number of patients; NETA = norethindrone acetate; NRS = Numerical Rating Scale.
[1] Odds ratio based on logistic regression with treatment group, time since initial surgical diagnosis of endometriosis (< 5 years, ⩾ 5 years), and geographic region (North America, Rest of World) as covariates with odds ratio > 1 favoring relugolix + E2/NETA over placebo. [2] Odds ratio based on logistic regression with treatment group as the only covariate with odds ratio > 1 favoring relugolix + E2/NETA over placebo. Error bars represent 95% CI.

Table 21. MVT-601-3101: Proportion of Patients Classified as Nonmenstrual Pelvic Pain Responders at Week 24/EOT, Subgroup Analyses (mITT Population)


Subgroup
Relugolix+ E2/NETA (N=212)
Placebo (N=212)
Odds Ratio (95% CI) [1]
Overall 124 / 212 (58.5%) 84 / 212 (39.6%) 2.22 (1.49,3.30)
Geographic region
North America 15 / 40 (37.5%) 8 / 40 (20.0%) 2.40 (0.88,6.56)
Rest of World 109 / 172 (63.4%) 76 / 172 (44.2%) 2.19 (1.42,3.37)
Time since endo diag. (years)
< 5 years 90 / 151 (59.6%) 58 / 148 (39.2%) 2.36 (1.47,3.78)
>= 5 years 34 / 61 (55.7%) 26 / 64 (40.6%) 1.92 (0.93,3.98)
Time since endo diag. (years)
< 2 years 49 / 82 (59.8%) 33 / 78 (42.3%) 2.00 (1.06,3.80)
2 - < 5 years 41 / 69 (59.4%) 25 / 70 (35.7%) 2.85 (1.41,5.78)
>= 5 years 34 / 61 (55.7%) 26 / 64 (40.6%) 1.92 (0.93,3.98)
Age (years) - Category 1
< 35 years 61 / 108 (56.5%) 38 / 106 (35.8%) 2.54 (1.43,4.51)
>= 35 years 63 / 104 (60.6%) 46 / 106 (43.4%) 1.98 (1.14,3.45)
Age (years) - Category 2
< 30 years 26 / 50 (52.0%) 18 / 55 (32.7%) 2.77 (1.17,6.54)
30 - < 35 years 35 / 58 (60.3%) 20 / 51 (39.2%) 2.35 (1.06,5.21)
35 - < 40 years 36 / 58 (62.1%) 23 / 56 (41.1%) 2.38 (1.11,5.09)
>= 40 years 27 / 46 (58.7%) 23 / 50 (46.0%) 1.55 (0.68,3.53)
Race
Black/African American [2] 10 / 15 (66.7%) 3 / 14 (21.4%) 7.33 (1.38,38.88)
White 116 / 198 (58.6%) 81 / 195 (41.5%) 2.07 (1.37,3.12)
BMI (kg/m2) at baseline
< 25 81 / 126 (64.3%) 44 / 118 (37.3%) 3.20 (1.88,5.45)
25 - < 30 20 / 45 (44.4%) 23 / 49 (46.9%) 0.94 (0.41,2.18)
>= 30 23 / 41 (56.1%) 17 / 45 (37.8%) 2.71 (1.00,7.39)
0.1
1
10
100
Favors Placebo
Favors Relugolix+E2/NETA


Subgroup
Relugolix+ E2/NETA (N=212)
Placebo (N=212)
Odds Ratio (95% CI) [1]
NMPP NRS score at baseline
< 4 22 / 43 (51.2%) 12 / 43 (27.9%) 2.94 (1.17,7.39)
4 to < 7 57 / 98 (58.2%) 42 / 108 (38.9%) 2.32 (1.30,4.13)
7 to 10 45 / 71 (63.4%) 30 / 61 (49.2%) 1.74 (0.86,3.52)
Smoking history
Current smoker 21 / 41 (51.2%) 7 / 34 (20.6%) 3.93 (1.36,11.30)
Former smoker [2] 10 / 19 (52.6%) 9 / 18 (50.0%) 1.11 (0.31,4.04)
Never smoker 93 / 152 (61.2%) 68 / 160 (42.5%) 2.26 (1.42,3.58)
Alcohol use
None 46 / 91 (50.5%) 42 / 99 (42.4%) 1.44 (0.81,2.58)
Moderate 78 / 120 (65.0%) 42 / 112 (37.5%) 3.32 (1.89,5.82)
AFSE stage
I, Minimal [2] 9 / 14 (64.3%) 8 / 21 (38.1%) 2.92 (0.72,11.91)
II, Mild [2] 16 / 31 (51.6%) 15 / 32 (46.9%) 1.21 (0.45,3.25)
III, Moderate 27 / 37 (73.0%) 18 / 42 (42.9%) 3.90 (1.47,10.37)
IV, Severe 17 / 34 (50.0%) 12 / 30 (40.0%) 1.60 (0.58,4.44)
Unknown/Not Available 55 / 96 (57.3%) 31 / 87 (35.6%) 2.71 (1.44,5.10)
Renal Function
>= 60 to < 90 mL/min [2] 22 / 31 (71.0%) 9 / 31 (29.0%) 5.98 (2.00,17.89)
>= 90 mL/min 102 / 181 (56.4%) 75 / 181 (41.4%) 1.86 (1.21,2.86)
0.1
1
10
100
Favors Placebo
Favors Relugolix+E2/NETA

Abbreviations: AFSE = American Fertility Society of Endometriosis; BMI = body mass index; CI = confidence interval; diag = diagnosis; E2 = estradiol; endo = endometriosis; EOT = end of treatment; mITT = modified intent to- treat (Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale.
[1] Odds ratio based on logistic regression with treatment group, time since initial surgical diagnosis of endometriosis (< 5 years, ⩾ 5 years), and geographic region (North America, Rest of World) as covariates with odds ratio > 1 favoring relugolix + E2/NETA over placebo.
[2] Odds ratio based on logistic regression with treatment group as the only covariate with odds ratio > 1 favoring relugolix + E2/NETA over placebo. Error bars represent 95% CI.

Consistent with the findings for the overall population, treatment differences with regard to the co-primary endpoints were consistent across nearly all subgroups as demonstrated by the odds ratio point estimate consistently favouring relugolix + E2/NETA over placebo on the dysmenorrhea and NMPP co-primary endpoints. For NMPP, the middle category (ie, 25 to < 30) of BMI had an odds ratio close to 1, but lower (ie, < 25) and higher (ie, ≥ 30) categories favoured relugolix + E2/NETA over placebo. Given the lack of a trend and the relatively small sample of this subgroup, this finding was likely related to chance.

Key secondary efficacy endpoints

There were seven key secondary efficacy endpoints in this study that were hierarchically tested after both co-primary endpoints were met.

Table 22. MVT-601-3101: Alpha-Protected Key Secondary Efficacy Endpoints (mITT Population)

	Relugolix+ E2/NETA (N = 212)	Placebo (N = 212)	Difference (95% CI) p-value
1. Change from baseline to Week 24 in the EHP-30 Pain Domain score, LS Mean (SE)[1]	-33.8 (1.83)	-18.7 (1.83)	-15.1 (2.33) (-19.7, -10.5) < 0.0001
2. Change from baseline to Week 24/EOT in the mean dysmenorrhea NRS score, LS Mean (SE)[1]	-5.1 (0.19)	-1.8 (0.19)	-3.3 (0.26) (-3.8, -2.8) < 0.0001
3. Change from baseline to Week 24/EOT in the mean NMPP NRS score, LS Mean (SE)[1]	-2.9 (0.18)	-2.0 (0.18)	-0.9 (0.24) (-1.4, -0.4) 0.0002
4. Change from baseline to Week 24/EOT in the mean overall pelvic pain NRS score, LS Mean (SE)[1]	-3.1 (0.17)	-1.9 (0.17)	-1.1 (0.24) (-1.6, -0.7) < 0.0001
5. Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain at Week 24/EOT, n (%)[2]	182 (85.8%)	162 (76.4%)	9.4% (2.0%, 16.8%)

			0.0005
6. Change from baseline to Week 24/EOT in the mean dyspareunia NRS score, LS Mean (SE)[1]	-2.4 (0.21)	-1.7 (0.22)	-0.7 (0.29) (-1.3, -0.1) 0.0149
7. Proportion of patients who are not using analgesics for endometriosis-associated pain at Week 24/EOT, n (%)[3]	119 (56.1%)	65 (30.7%)	25.5% (16.4%, 34.6%) < 0.0001

Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end of treatment; LS = least squares; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale; SE = standard error.
[1] LS means and p-value for test of difference between relugolix + E2/NETA and placebo, relugolix + delayed E2/NETA and placebo were based on mixed-effects model with treatment, baseline value, visit, geographic region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years), and treatment-by-visit interaction included as fixed effects; visit was also included in the model as random effect within each patient, and an unstructured covariance matrix was assumed.
[2] Difference in responder proportions of relugolix + E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution. P-value was based on Cochran-Mantel-Haenszel test stratified by baseline opioid use, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years), and geographic region (North America, Rest of World).
[3] Difference in responder proportions of relugolix + E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution. P-value was based on Cochran-Mantel-Haenszel test stratified by baseline analgesic use, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years), and geographic region (North America, Rest of World).

These key secondary endpoints extend the findings of the co-primary endpoints by showing benefits of treatment with relugolix + E2/NETA on common types of pain experienced by women with endometriosis (dysmenorrhea, NMPP, overall pelvic pain, and dyspareunia). Importantly, reduction in pain occurred without an increase in analgesic use – in fact, analgesic use declined and a significantly higher percentage of patients in the relugolix + E2/NETA group (versus placebo) were opioid-free and analgesic-free at the end of treatment. Finally, the effective treatment of endometriosis-associated pain with relugolix + E2/NETA resulted in improved daily functioning that included activities such as standing, sitting, walking, sleeping, and performing jobs around the house.

Other Secondary Endpoints

Responder rate by month

The majority of patients in the relugolix + E2/NETA group met the responder definition for dysmenorrhea (a decline in the dysmenorrhea NRS by ⩾ 2.8 points without an increase in analgesic use) within 8 weeks of initiating treatment. The majority of patients in the relugolix + E2/NETA group met the responder definition for NMPP (a decline in the NMPP NRS by ⩾ 2.1 points without an increase in analgesic use) within 16 weeks of initiating treatment. In contrast, the percentage of patients in the placebo group who met the responder definitions for dysmenorrhea and NMPP did not reach 50.0% at any timepoint.

Change in Tier 1 and 2 use and average analgesic pill count

The mean (SD) Tier 1 use decreased by 65.2%, from 29.3 (36.0) to 10.1 (40.7) in the relugolix + E/2NETA group compared to 51.4%, from 28.3 (39.7) to 11.0 (21.98) in the placebo group.

The mean (SD) Tier 2 use decreased from baseline to 24 Week/EOT by 41.1% (from 3.4 (9.93) to 2 (7.84)) in the relugolix combination treatment. In the placebo group this was 5.12% (from 3.9 (10.01) to 3.7 (19.38)).

The average daily pill count (both Tier 1 and 2) changed by -0.5 (56.3% reduction) in the relugolix +E2/NETA group and by -0.4 (34.5% reduction) in the placebo group (p=0.4094).

Other secondary endpoints

Other pre-specified secondary efficacy endpoints included PGA of dysmenorrhea and NMPP, and PGIC for dysmenorrhea, NMPP, and dyspareunia. Numerically higher percentages of patients in the relugolix + E2/NETA group (vs. placebo) reported improvement on the PGA categories. The proportion of patients reporting 'better' or 'much better' on the PGIC was higher in the relugolix + E2/NETA group compared to placebo (statistically significant for dysmenorrhea, NMPP and dyspareunia). This suggests that the observed changes in NRS pain scores for dysmenorrhea, NMPP, and dyspareunia were noticeable and meaningful to patients.

Women participating in this study had substantial physical limitations related to their endometriosis. A number of other secondary endpoints were included to evaluate the effects of treatment with relugolix + E2/NETA on function. Moreover, the improvement in pain and function observed in the relugolix + E2/NETA group correlated with greater ability to work as assessed by the EHP Work Module.

The effects of relugolix + E2/NETA on aspects of endometriosis in addition to pain and function were also evaluated as secondary endpoints using various (non-pain) domains of the EHP-30. On all of these domains, patients in the relugolix + E2/NETA group reported significantly greater improvements (vs. placebo) in additional facets of endometriosis-associated quality of life, including emotional well-being, self-image, sense of power and control, and feelings of perception of others (nominal $p < 0.001$ for all domains at Week 24/EOT).

Secondary Efficacy Objectives and Endpoints Based on Comparisons Between Relugolix + Delayed E2/NETA and Placebo

Dysmenorrhea Responder analysis

In addition to the co-primary efficacy analyses comparing the relugolix + E2/NETA group with the placebo group, an analysis was also performed comparing the relugolix + delayed E2/NETA group with the placebo group. In the relugolix + delayed E2/NETA group, 151 (71.6%) patients met the responder criteria for dysmenorrhea at Week 24/EOT, results which were consistent with findings from the relugolix + E2/NETA group.

Nonmenstrual Pelvic Pain Responder Analysis

In addition to the co-primary efficacy analyses comparing the relugolix + E2/NETA group with the placebo group, an analysis was performed comparing the relugolix + delayed E2/NETA group with the placebo group. In the relugolix + delayed E2/NETA group, 122 (57.8%) patients met the responder criteria for NMPP at Week 24/EOT, results which were consistent with findings from the relugolix + E2/NETA group.

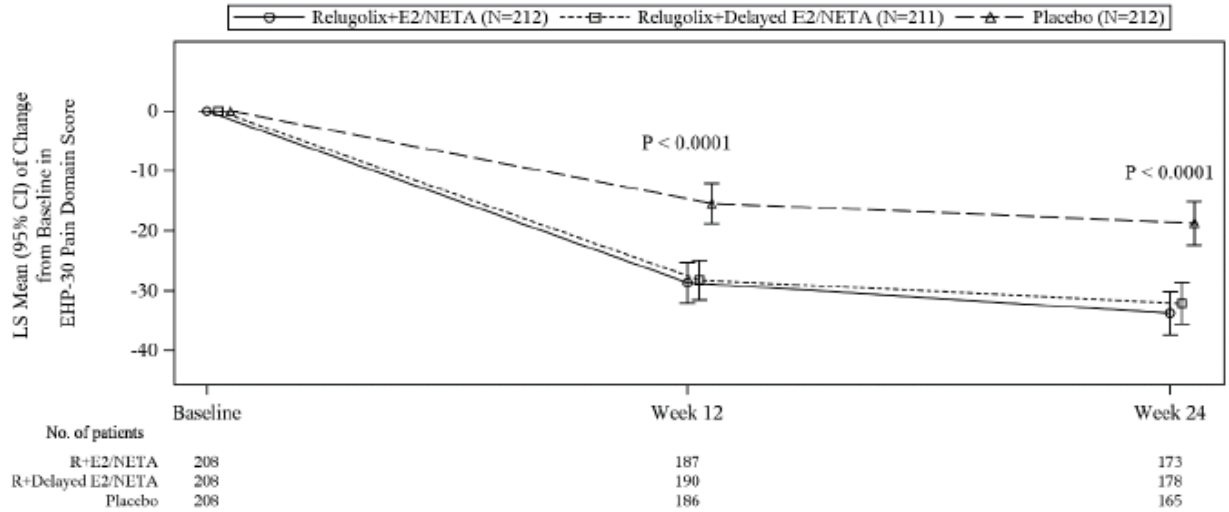
To determine the benefit on function measured by the EHP-30 pain domain

Change from baseline at Week 24 in the EHP-30 pain domain score

The baseline EHP-30 Pain Domain mean (SD) score was 58.3 (16.65) in the relugolix + E2/NETA group and 55.5 (16.03) in the placebo group. There was a statistically significant improvement in the EHP-30 Pain Domain score for the relugolix + E2/NETA group compared with the placebo group at Week 24, LS mean (standard error [SE]) change from baseline: −33.8 (1.83) versus −18.7 (1.83), $p < 0.0001$.

Results for the relugolix + delayed E2/NETA group were consistent with that of the relugolix + E2/NETA group (Figure 20)).

Figure 6. MVT-601-3101: Change from Baseline in Endometriosis Health Profile-30 Pain Domain Score by Visit (mITT Population)



Abbreviations: CI = confidence interval; E2 = estradiol; EHP-30 = Endometriosis Health Profile 30-item Questionnaire; LS = least squares; mITT = modified intent-to-treat (Population); N = number of patients; NETA = norethindrone acetate; R = relugolix.

LS means and p-value for test of difference between relugolix + E2/NETA and placebo were based on mixed-effects model with treatment, baseline value, visit, geographic region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years), and treatment-by-visit interaction included as fixed effects; visit was also included in the model as random effect within each patient, and an unstructured covariance matrix was assumed.

Error bars represent 95% CI.

Proportion of patients who meet the definition of responder, achieving a reduction of at least 20 points from baseline at Week 24 based on EHP-30 pain domain scores

In the relugolix + E2/NETA group, 76.3% of patients had a meaningful improvement (i.e., reduction of at least 20 points) in the EHP-30 Pain Domain score at Week 24 compared with 48.5% in the placebo group. The between-group difference was 27.8% (95% CI: 17.90%, 37.73%), favouring relugolix + E2/NETA (nominal p < 0.0001).

Results for the relugolix + delayed E2/NETA group were consistent with that of the relugolix + E2/NETA group (Table 23)).

Table 23. MVT-601-3101: Proportion of Patients Classified as Responders Based on Reduction in EHP-30 Pain Domain Score by Visit (mITT Population)

	Relugolix+E2/NETA (N = 212)	Relugolix+Delayed E2/NETA (N = 211)	Placebo (N = 212)
Number of evaluable patients	187	190	186
Number (%) of EHP-30 pain domain responders [1]	126 (67.4%)	118 (62.1%)	74 (39.8%)
(95% CI) [2] at Week 12	(60.16%, 74.04%)	(54.80%, 69.03%)	(32.70%, 47.20%)
Difference from placebo (95% CI) [3]	27.6% (17.87%, 37.32%)		
P-value [4]	< 0.0001		
Number of evaluable patients	173	178	165
Number (%) of EHP-30 pain domain responders [1]	132 (76.3%)	127 (71.3%)	80 (48.5%)
(95% CI) [2] at Week 24	(69.25%, 82.42%)	(64.11%, 77.86%)	(40.64%, 56.38%)
Difference from placebo (95% CI) [3]	27.8% (17.90%, 37.73%)		
P-value [4]	< 0.0001		

The database lock date was 17 Jun 2020.
Abbreviations: CI = confidence interval; E2 = estradiol; EHP-30 = Endometriosis Health Profile 30-item Questionnaire; LS = least squares; mITT = modified intent-to-treat; N = number of patients in the treatment group; NETA = norethindrone acetate.
Evaluable patients include those who have observed data at both baseline and the relevant post-baseline timepoint.
[1] Responders are patients with a reduction of at least 20 points in the EHP-30 Pain Domain at visit.
[2] Based on exact binomial 95% CI (Clopper-Pearson).
[3] Difference in responder proportions of relugolix + E2/NETA minus placebo, or relugolix + delayed E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution.
[4] P-value is based on Cochran-Mantel-Haenszel test stratified by time since initial surgical diagnosis of endometriosis (< 5 years, >= 5 years) and geographic region (North America, Rest of World).

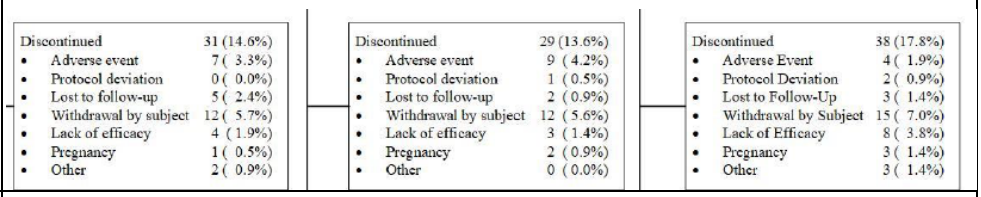
Summary of main efficacy results MVT-601-3101

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 24. Summary of efficacy for trial MVT-601-3101

Title: SPIRIT 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain		
Study identifier	Protocol number: MVT-601-3101, EudraCT number: 2017-001588-19, NCT number NCT03204318	
Design	Randomized, Double-Blind, Placebo-Controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 35 days 30 days safety follow-up
Hypothesis	Superiority	
Treatments groups	Relugolix + E2/NETA group	**treatment**: Oral relugolix 40 mg tablets co-administered with over-encapsulated low-dose E2 (1 mg) and NETA (0.5 mg) QD; **duration** 24 weeks; **number randomized**: 212
	Relugolix + delayed E2/NETA group	**treatment**: Oral relugolix 40 mg tablets co-administered with a placebo capsule designed to match the over-encapsulated low-dose E2 (1 mg) and NETA (0.5 mg) (12 weeks of monotherapy) followed by oral relugolix 40 mg tablets QD co-administered with over-encapsulated low-dose E2 (1 mg) and NETA (0.5 mg) QD (12 weeks of combination therapy); **duration** 12 weeks of monotherapy and 12 weeks of combination therapy – total 24 weeks; **number randomized**: 213
	Placebo group	**treatment**: Placebo tablets designed to match relugolix, co-administered with a placebo capsule designed to match the over-encapsulated E2/NETA. **duration**:24 weeks; **number randomized**: 213

Endpoints and definitions	<Co->Primary endpoint 1	Dysmenorrhea Responder rate	Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 24 Or End Of Treatment (EOT). A responder was defined as a woman who achieved a pre-defined reduction in dysmenorrhea NRS scores of at least 2.8 points without increased use of analgesics.	
	<Co->Primary endpoint 2	NMPP Responder rate	Percentage Of Participants Who Meet The Non-Menstrual Pelvic Pain (NMPP) Responder Criteria At Week 24 Or EOT. A responder was defined as a woman who achieved a predefined reduction in nonmenstrual NRS scores of at least 2.1 points without increased use of analgesics.	
	<Key secondary>	Change in EHP-30 Pain	Change from baseline to Week 24 in the Endometriosis Health Profile (EHP)-30 pain domain Score.	
	<Key secondary>	Change in dysmenorrhea	Change from baseline to Week 24/EOT in the mean dysmenorrhea NRS score.	
	<Key secondary>	Change in NMPP NRS	Change from baseline to Week 24/EOT in the mean NMPP NRS score.	
	<Key secondary>	Change in Pelvic Pain NRS	Change from baseline to Week 24/EOT in the mean overall pelvic pain NRS score.	
	<Key secondary>	No Opioid use	Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain at Week 24/EOT.	
	<Key secondary>	Change in dyspareunia NRS	Change from baseline to Week 24/EOT in the mean dyspareunia NRS score.	
	<Key secondary>	No Analgesic use	Proportion of patients who are not using analgesics for endometriosis-associated pain at Week 24/EOT.	
	<Secondary> Safety	Percent change in BMD at W12	Percent change from baseline to Week 12 in bone mineral density (BMD) at the lumbar spine (L1-L4)	
	<Secondary> Safety	Percent change in BMD at W24	Percent change from baseline to Week 24 in BMD at the lumbar spine (L1-L4), femoral neck, and total hip	
	<Secondary> Safety	Vasomotor W12	Incidence of vasomotor symptoms at Week 12	
Database lock	17 June 2020			
Results and Analysis				
Analysis description	**Co-Primary Analysis – pre-specified**			
Analysis population and time point description	Modified Intent to treat (mITT) population (defined as all randomized patients who received any amount of study drug (relugolix/placebo or E2/NETA/placebo).) time point: Week 24			
Descriptive statistics and estimate variability	Treatment group	Relugolix+E2/NETA *{as per above terminology}*	Placebo *{as per above terminology}*	
	Number of subject	212	212	
	Dysmenorrhea Responder rate; n (%)	158 (74.5%)	57 (26.9%)	
	Exact binomial 95% Confidence Interval	68.11%, 80.25%	21.04%, 33.39%	
	NMPP Responder rate n (%)	124 (58.5%)	84 (39.6%)	
	Exact binomial 95% Confidence Interval	51.54%, 65.20%	32.99%, 46.55%	
Effect estimate per comparison	<Co->Primary endpoint Dysmenorrhea Responder rate	Comparison groups	Relugolix+E2/NETA vs. Placebo	
		Difference in responder proportions of relugolix + E2/NETA minus placebo %.	47.6%	

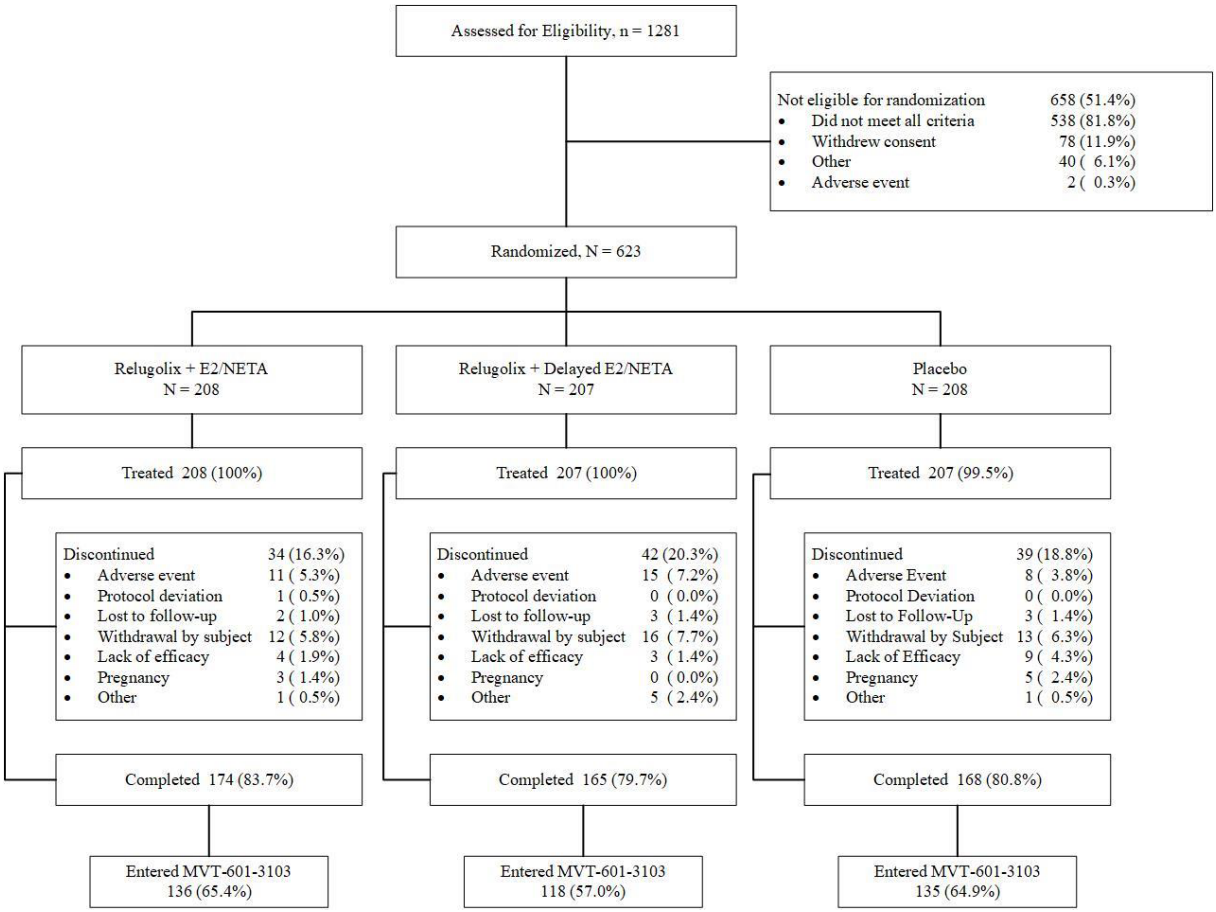
		95% Confidence Interval	39.27%, 56.01%
		P-value	< 0.0001
	<Co->Primary > NMPP Responder rate	Comparison groups	Relugolix+E2/NETA vs. Placebo
		Difference in responder proportions of relugolix + E2/NETA minus placebo %.	18.9%
		95% Confidence Interval	9.52%, 28.21%
		P-value	< 0.0001
Notes	The study was considered positive if treatment effects for both co-primary endpoints were statistically significant with 2-sided p-values < 0.05. To test the robustness of the primary analysis, five sensitivity analyses were conducted. All of the analyses were prespecified prior to data unblinding. These analyses explored the effects of discontinuations due to adverse events, lack of efficacy, or any reason within the first 5 weeks of treatment [1]; use of alternative analysis populations (completers [2] and per-protocol [3]); and different methods of handling missing data (multiple imputation [4] and without imputation [5]). The numbers of such early terminators were small and relatively balanced across the three arms (12 patients in the relugolix + E2/NETA group, 6 patients in the relugolix + delayed E2/NETA group, and 7 patients in the placebo group). Reasons for patients drop-outs  Discontinued 31 (14.6%) • Adverse event 7 (3.3%) • Protocol deviation 0 (0.0%) • Lost to follow-up 5 (2.4%) • Withdrawal by subject 12 (5.7%) • Lack of efficacy 4 (1.9%) • Pregnancy 1 (0.5%) • Other 2 (0.9%) Discontinued 29 (13.6%) • Adverse event 9 (4.2%) • Protocol deviation 1 (0.5%) • Lost to follow-up 2 (0.9%) • Withdrawal by subject 12 (5.6%) • Lack of efficacy 3 (1.4%) • Pregnancy 2 (0.9%) • Other 0 (0.0%) Discontinued 38 (17.8%) • Adverse Event 4 (1.9%) • Protocol Deviation 2 (0.9%) • Lost to Follow-Up 3 (1.4%) • Withdrawal by Subject 15 (7.0%) • Lack of Efficacy 8 (3.8%) • Pregnancy 3 (1.4%) • Other 3 (1.4%)		
Analysis description	**Secondary analysis – key secondary endpoints – pre-specified:**		
Analysis population and time point description	Modified Intent to treat (mITT) population (defined as all randomized patients who received any amount of study drug (relugolix/placebo or E2/NETA/placebo). time point: Week 24		
Descriptive statistics and estimate variability	Treatment group	Relugolix+E2/NETA	Placebo
	Number of subject	212	212
	Change in EHP-30 Pain, LS Mean (SE)	-33.8 (1.83)	-18.7 (1.83)
	Change in dysmenorrhea NRS, LS Mean (SE)	-5.1 (0.19)	-1.8 (0.19)
	Change in NMPP NRS, LS Mean (SE)	-2.9 (0.18)	-2.0 (0.18)
	Change in Pelvic Pain NRS, LS Mean (SE)	-3.1 (0.17)	-1.9 (0.17)
	No Opioid use , n (%)	182 (85.8%)	162 (76.4%)
	Change in dyspareunia NRS, LS Mean (SE)	-2.4 (0.21)	-1.7 (0.22)
	No Analgesic use, n (%)	119 (56.1%)	65 (30.7%)
Effect estimate per comparison	1. Key secondary endpoint: change in EHP-30 Pain	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-15.1 (2.33)
		95% Confidence Interval	-19.7, -10.5

		P-value	< 0.0001
	2. Key secondary endpoint: change in dysmenorrhea NRS	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-3.3 (0.26)
		95% Confidence Interval	-3.8, -2.8
		P-value	< 0.0001
	3. Key secondary endpoint: change in NMPP NRS	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-0.9 (0.24)
		95% Confidence Interval	-1.4, -0.4
		P-value	0.0002
	4. Key secondary endpoint: change in pelvic pain NRS	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-1.1 (0.24)
		95% Confidence Interval	-1.6, -0.7
		P-value	< 0.0001
	5. Key secondary endpoint: no Opioid use	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in responder proportions of relugolix + E2/NETA minus placebo in %.	9.4%
		95% CI	2.0%, 16.8%
		P-value	0.0005
	6. Key secondary endpoint: change in dyspareunia NRS	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-0.7 (0.29)
		95% Confidence Interval	-1.3, -0.1
		P-value	0.0149
	7. Key secondary endpoint: no Analgesic use	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in responder proportions of relugolix + E2/NETA minus placebo in %.	25.5%
		95% CI	16.4%, 34.6%
		P-value	< 0.0001
Notes	Secondary efficacy variables included 7 key secondary endpoints with alpha-protection and a number of other secondary endpoints. The treatment effect of relugolix + E2/NETA compared with placebo was tested for the 7 key secondary endpoints sequentially in the order change in EHP-30 pain (#1) to analgesic use (#7).		
Analysis description	**Secondary analysis – safety endpoints – pre-specified:**		
Analysis population and time point description	Safety population (defined as all randomized patients who received any amount of study drug) Time point: Week 12 (all) and Week 24 (BMD only)		

Descriptive statistics and estimate variability	Treatment group	Relugolix+E2/NETA	Relugolix+Delayed E2/NETA	Placebo
	Number of subject	177	181	172
	Percent change in BMD at W12, LS Mean Percent Change from Baseline (95% Confidence Interval)	-0.52 (-0.99, -0.05)	-1.69 (-2.16, -1.21)	0.29 (-0.18, 0.77)
	Number of subject	164	174	161
	Percent change in BMD at W24 LS Mean Percent Change from Baseline (95% Confidence Interval)	-0.70 (-1.20, -0.20)	-1.99 (-2.49, -1.48)	0.21 (-0.30, 0.71)
	Number of subject	212	211	212
	Vasomotor W12, n (%)	22 (10.4%)	73 (34.6%)	23 (10.8%)
Effect estimate per comparison	Secondary endpoint Percent change in BMD at W12	Comparison groups	Relugolix+E2/NETA vs. Placebo	
		Difference of LS means for relugolix + E2/NETA minus placebo (SE)	-0.81	
		95% Confidence Interval.	-1.27, -0.35	
		P-value	NA	
	Secondary endpoint Percent change in BMD at W12	Comparison groups	Relugolix + delayed E2/NETA vs. Placebo	
		Difference of LS means for relugolix + delayed E2/NETA minus placebo (SE)	-1.98	
		95% Confidence Interval.	-2.44, -1.52	
		P-value	NA	
	Secondary endpoint Percent change in BMD at W24	Comparison groups	Relugolix+E2/NETA vs.Placebo	
		Difference of LS means for relugolix + E2/NETA minus placebo (SE)	-0.90	
		95% Confidence Interval.	-1.42, -0.38	
		P-value	NA	
	Secondary endpoint Percent change in BMD at W24	Comparison groups	Relugolix + delayed E2/NETA vs. Placebo	
		Difference of LS means for relugolix + delayed E2/NETA minus placebo (SE)	-2.19	
		95% Confidence Interval.	-2.71, -1.68	
		P-value	NA	

Results MVT-601-3102 – SPIRIT 2

Participant flow



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

Protocol deviations

The most common important protocol deviations are reported in Table 25

Table 25. MVT-601-3102: Summary of Important Protocol Deviations (mITT Population)

Protocol Deviation Category Subcategory	Relugolix + E2/NETA (N = 206)	Relugolix + Delayed E2/NETA (N=206)	Placebo (N = 204)
Any Important Protocol Deviation, n (%)	39 (18.9%)	41 (19.9%)	28 (13.7%)

Informed Consent	1 (0.5%)	1 (0.5%)	0
Delay in re-consent	1 (0.5%)	1 (0.5%)	0
Key Eligibility Criteria	3 (1.5%)	0	3 (1.5%)
Did not satisfy key entry criteria	2 (1.0%)	0	3 (1.5%)
NRS scores during run-in did not satisfy entry criteria	1 (0.5%)	0	0
Key Study Procedures Not Performed	18 (8.7%)	19 (9.2%)	15 (7.4%)
Bone densitometry scan not performed	8 (3.9%)	10 (4.9%)	8 (3.9%)
EHP-30 not completed	6 (2.9%)	8 (3.9%)	7 (3.4%)
Entire study visit missed	2 (1.0%)	3 (1.5%)	1 (0.5%)
Laboratory tests not performed for at least 2 consecutive visits	2 (1.0%)	0	0
Key study procedure not adhered to	1 (0.5%)	0	0
Other	4 (1.9%)	2 (1.0%)	3 (1.5%)
Other deviation deemed important regarding efficacy or safety	4 (1.9%)	2 (1.0%)	3 (1.5%)
Restricted Medications	8 (3.9%)	6 (2.9%)	8 (3.9%)
Received prohibited concomitant medication	8 (3.9%)	6 (2.9%)	8 (3.9%)
Safety	3 (1.5%)	2 (1.0%)	1 (0.5%)
Failed to adhere to safety measures or reporting	3 (1.5%)	2 (1.0%)	1 (0.5%)
Study Drug	8 (3.9%)	14 (6.8%)	4 (2.0%)
Overall treatment compliance < 75%	4 (1.9%)	8 (3.9%)	2 (1.0%)
Dispensed incorrect or expired study drug or kit	4 (1.9%)	6 (2.9%)	2 (1.0%)
Withdrawal Criteria	1 (0.5%)	0	0
Met withdrawal criteria but not withdrawn	1 (0.5%)	0	0

Abbreviations: E2 = estradiol; mITT = modified Intent-to-Treat (Population); n = number of patients in subset; N = number of patients; NETA = norethindrone acetate.
Note: Percentages were based on the total number of patients in each treatment group or total.

Recruitment

A total of 1281 patients signed the ICF, 1069 patients entered the single-blind run-in period, and 623 patients were randomized at 95 centers globally, including centers in North America (US), Australia, Brazil, Chile, Czech Republic, Georgia, Italy, New Zealand, Poland, Romania, and Sweden.
Overall, 75.1% of patients were enrolled from the Rest of World and 24.9% of patients were enrolled from North America.

The date first patient screened was 21 September 2017, the date last patient completed was 01 April 2020.

Conduct of the study

The original study Protocol (dated 12 Jun 2017), was amendment once, dated 12 Mar 2018.

The main purpose of the protocol amendment was to incorporate additional PGA anchor questions for dysmenorrhea and pelvic pain. Modifications were also made to the screening visit and run-in windows, and modifications or clarifications were made to study eligibility as well as study procedures or tests.

Baseline data

Overall, demographic characteristics were generally similar across treatment groups. The mean (SD) age for all patients was 33.7 (6.66) years with the mean age being similar across treatment groups.

The predominant racial representation in the study was White (557 [90.4%] patients), consistent with the generally described epidemiology of endometriosis, although recent studies suggest that there may be an ascertainment bias due to differences in the odds of diagnosis of endometriosis by race and ethnicity - higher in White and Asian women and lower in Black and Hispanic women) (Bougie et al. 2019).

There were similar numbers of White patients randomized to each treatment group.

Table 9. MVT-601-3102: Summary of Patient Demographics (mITT Population)

	Relugolix + E2/NETA (N = 206)	Relugolix + Delayed E2/NETA (N=206)	Placebo (N = 204)
Age (years)			
Mean (SD)	33.8 (6.73)	33.7 (6.79)	33.6 (6.49)
Age Category, n (%)			
< 35 years	115 (55.8%)	111 (53.9%)	110 (53.9%)
≥ 35 years	91 (44.2%)	95 (46.1%)	94 (46.1%)
Geographic Region, n (%)			
North America	50 (24.3%)	50 (24.3%)	49 (24.0%)
Rest of World	156 (75.7%)	156 (75.7%)	155 (76.0%)
Race, n (%)			
American Indian or Alaska Native	1 (0.5%)	0	1 (0.5%)
Asian	0	0	0
Black or African American	14 (6.8%)	10 (4.9%)	12 (5.9%)
Native Hawaiian or Other Pacific Islander	0	2 (1.0%)	1 (0.5%)
White	186 (90.3%)	188 (91.3%)	183 (89.7%)
Other	3 (1.5%)	2 (1.0%)	5 (2.5%)
Multiple	2 (1.0%)	4 (1.9%)	2 (1.0%)
Not Reported	0	0	0
Ethnicity, n (%)			
Not Hispanic or Latino	175 (85.0%)	170 (82.5%)	167 (81.9%)
Hispanic or Latino	30 (14.6%)	36 (17.5%)	36 (17.6%)

Abbreviations: E2 = estradiol; mITT = modified Intent-to-Treat (Population); n = number of patients in subset; N = number of patients; NETA = norethindrone acetate.

Table 27. MVT-601-3102: Summary of Disease-Specific Baseline Characteristics and Bone Mineral Density (mITT Population)

	Relugolix + E2/NETA (N = 206)	Relugolix + Delayed E2/NETA (N=206)	Placebo (N = 204)
Time Since Surgical Diagnosis of Endometriosis (years)			
n	206	206	204
Mean (SD)	4.1 (3.46)	4.2 (3.52)	3.8 (3.02)
Median	3.4	3.3	3.2
Min, Max	0.1, 19.3	0.1, 21.0	0.1, 15.4
< 5	137 (66.5%)	135 (65.5%)	143 (70.1%)
≥ 5	69 (33.5%)	71 (34.5%)	61 (29.9%)
Dysmenorrhea NRS score at Baseline			
n	206	206	204
Mean (SD)	7.1 (1.57)	6.9 (1.51)	7.0 (1.57)
Median	7.0	7.0	7.0
Min, Max	2.2, 10.0	2.7, 10.0	2.6, 10.0
< 7	92 (44.7%)	97 (47.1%)	96 (47.1%)
≥ 7	114 (55.3%)	109 (52.9%)	108 (52.9%)
< 4	9 (4.4%)	8 (3.9%)	4 (2.0%)
4 to < 7	83 (40.3%)	89 (43.2%)	92 (45.1%)
7 to 10	114 (55.3%)	109 (52.9%)	108 (52.9%)
NMPP NRS Score at Baseline			
n	206	206	204
Mean (SD)	5.8 (1.94)	5.5 (1.93)	5.5 (1.94)
Median	5.9	5.8	5.8
Min, Max	1.7, 9.7	1.6, 10.0	1.5, 9.7
< 4	42 (20.4%)	55 (26.7%)	45 (22.1%)
≥ 4	164 (79.6%)	151 (73.3%)	159 (77.9%)
< 4	42 (20.4%)	55 (26.7%)	45 (22.1%)
4 to < 7	112 (54.4%)	108 (52.4%)	114 (55.9%)
7 to 10	52 (25.2%)	43 (20.9%)	45 (22.1%)
Dyspareunia NRS Score at Baseline			
n	173	167	162
Mean (SD)	5.5 (2.32)	5.4 (2.14)	5.3 (2.29)
Median	6.0	5.5	5.5
Min, Max	0.1, 10.0	0.5, 10.0	0.2, 10.0
EHP-30 Pain Domain at Baseline			
n	203	206	204
Mean (SD)	56.2 (17.12)	55.5 (15.20)	55.0 (16.17)
Median	59.1	54.5	56.8
Min, Max	0.0, 100.0	2.3, 100.0	4.5, 95.5

0 to < 25	9 (4.4%)	6 (2.9%)	7 (3.4%)
25 to < 50	53 (26.1%)	56 (27.2%)	67 (32.8%)
50 to < 75	113 (55.7%)	125 (60.7%)	113 (55.4%)
75 to 100	28 (13.8%)	19 (9.2%)	17 (8.3%)
PGA Dysmenorrhea [1]			
n	177	169	174
Absent [2]	3(1.7%)	1 (0.6%)	1 (0.6%)
Mild	1 (0.6%)	2 (1.2%)	2 (1.1%)
Moderate	33 (18.6%)	37 (21.9%)	36 (20.7%)
Severe	75 (42.4%)	85 (50.3%)	74 (42.5%)
Very Severe	65 (36.7%)	44 (26.0%)	61 (35.1%)
PGA NMPP [1]			
n	176	170	173
Absent	0	1 (0.6%)	0
Mild	8 (4.5%)	12 (7.1%)	13 (7.5%)
Moderate	92 (52.3%)	91 (53.5%)	87 (50.3%)
Severe	65 (36.9%)	59 (34.7%)	63 (36.4%)
Very Severe	11 (6.3%)	7 (4.1%)	10 (5.8%)
PGA Function			
n	205	203	202
Not at All	3 (1.5%)	2 (1.0%)	1 (0.5%)
Minimally	13 (6.3%)	8 (3.9%)	16 (7.9%)
Moderately	102 (49.8%)	103 (50.7%)	92 (45.5%)
Significantly	69 (33.7%)	78 (38.4%)	81 (40.1%)
Very Significantly	18 (8.8%)	12 (5.9%)	12 (5.9%)
PGA Pain			
n	203	205	203
Absent	10 (4.9%)	16 (7.8%)	17 (8.4%)
Mild	48 (23.6%)	47 (22.9%)	47 (23.2%)
Moderate	93 (45.8%)	90 (43.9%)	85 (41.9%)
Severe	41 (20.2%)	45 (22.0%)	46 (22.7%)
Very Severe	11 (5.4%)	7 (3.4%)	8 (3.9%)
Bone Mineral Density (g/cm^2) Lumbar L1-L4			
n	206	206	204
Mean (SD)	1.158 (0.1584)	1.154 (0.1554)	1.167 (0.1508)
Median	1.150	1.142	1.161
Min, Max	0.838, 1.606	0.879, 1.650	0.840, 1.583

Bone Mineral Density (g/cm^2) Total Hip			
n	206	206	204
Mean (SD)	0.989 (0.1401)	0.980 (0.1315)	0.988 (0.1285)
Median	0.978	0.968	0.972
Min, Max	0.738, 1.400	0.708, 1.408	0.700, 1.399
Bone Mineral Density (g/cm^2) Femoral Neck			
n 206	206	206	204
Mean (SD)	0.944 (0.1572)	0.936 (0.1566)	0.951 (0.1612)
Median	0.946	0.929	0.939
Min, Max	0.602, 1.372	0.591, 1.373	0.595, 1.496

Abbreviations: E2 = estradiol; EHP-30 = Endometriosis Health Profile 30-item Questionnaire; Max = maximum; Min = minimum; mITT = modified intent-to-treat (Population); n = number of patients in subset; N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale; PGA = Patient Global Assessment; SD = standard deviation. [1] The PGAs for dysmenorrhea and NMPP were implemented under the protocol amendment of 12 Mar 2018. [2] Includes patients who answered "No" to the question, "In the past 4 weeks, did you have your period?"

Table 10. MVT-601-3101: Summary of Medical History Reported for ⩾ 5% of Patients

Preferred Term	Relugolix + E2/NETA (N = 206)	Relugolix + Delayed E2/NETA (N=206)	Placebo (N = 204)
No. of Patients Reporting at Least One Medical History	164 (79.6%)	167 (81.1%)	165 (80.9%)
Anxiety	25 (12.1%)	23 (11.2%)	19 (9.3%)
Headache	16 (7.8%)	18 (8.7%)	27 (13.2%)
Depression	19 (9.2%)	22 (10.7%)	15 (7.4%)
Ovarian cyst	18 (8.7%)	18 (8.7%)	19 (9.3%)
Caesarean section	15 (7.3%)	18 (8.7%)	17 (8.3%)
Drug hypersensitivity	15 (7.3%)	18 (8.7%)	15 (7.4%)
Appendicectomy	11 (5.3%)	16 (7.8%)	19 (9.3%)
Asthma	14 (6.8%)	14 (6.8%)	16 (7.8%)
Uterine leiomyoma	15 (7.3%)	14 (6.8%)	12 (5.9%)
Anaemia	12 (5.8%)	20 (9.7%)	8 (3.9%)
Seasonal allergy	8 (3.9%)	16 (7.8%)	14 (6.9%)
Hypothyroidism	9 (4.4%)	16 (7.8%)	11 (5.4%)
Migraine	12 (5.8%)	11 (5.3%)	12 (5.9%)
Osteopenia	10 (4.9%)	13 (6.3%)	9 (4.4%)
Hypertension	8 (3.9%)	10 (4.9%)	13 (6.4%)
Ovarian cystectomy	9 (4.4%)	11 (5.3%)	6 (2.9%)
Insomnia	11 (5.3%)	7 (3.4%)	6 (2.9%)

- **Pain medication**

Prior to the study period

The most frequently reported prior medications by anatomical therapeutic chemical classification level 3 term included the following: anti-inflammatory and anti-rheumatic products (601 [97.6%] patients overall; 200 [97.1%] patients in the relugolix + E2/NETA group; 200 [97.1%] patients in the relugolix + delayed E2/NETA group; and 201 [98.5%] patients in the placebo group), and opioids (418 [67.9%] patients overall; 136 [66.0%] patients in the relugolix + E2/NETA group; 147 [71.4%] patients in the relugolix + delayed E2/NETA group; and 135 [66.2%] patients in the placebo group). Additionally, drugs within "other analgesics and antipyretics" were used by 97 (15.7%) patients overall.

During the run-in period (i.e. baseline)

During the run-in (ie, baseline) period, 186 (90.3%) patients in the relugolix + E2/NETA group, 186 (90.3%) patients in the relugolix + delayed E2/NETA group, and 184 (90.2%) patients in the placebo group used a protocol-specified Tier 1 analgesic (ibuprofen) for pelvic pain. A protocol-specified Tier 2 analgesic (opioid or opioid combination) was used by 100 (48.5%) patients in the relugolix + E2/NETA group, 101 (49.0%) patients in the relugolix + delayed E2/NETA group, and 95 (46.6%) patients in the placebo group. Finally, both Tier 1 and Tier 2 medication were taken for pelvic pain during the run-in period by 89 (43.2%) patients in the relugolix + E2/NETA group, 92 (44.7%) patients in the relugolix + delayed E2/NETA group, and 87 (42.6%) patients in the placebo group.

Outcomes and estimation

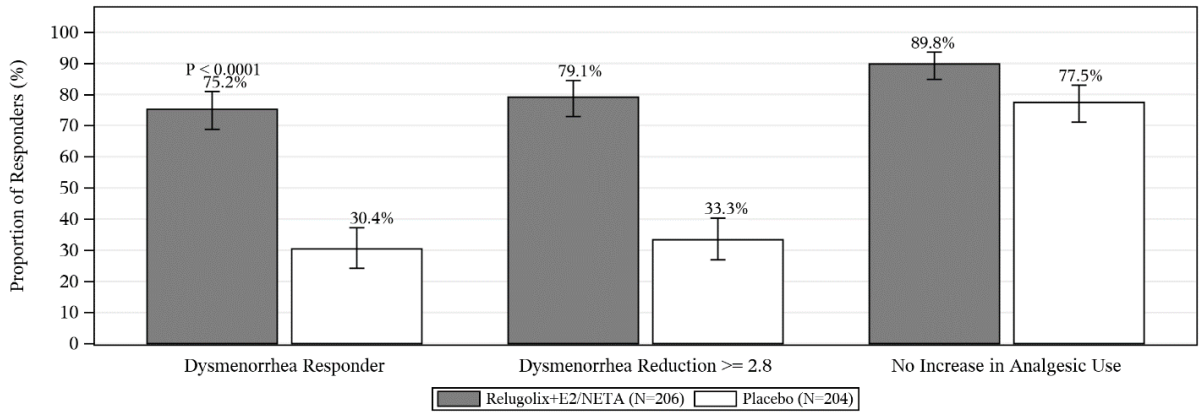
First co-primary endpoint: Dysmenorrhea Responder analysis

Table 11. MVT-601-3102: Co-Primary Efficacy Analysis, Proportion of Patients Classified as Dysmenorrhea Responders at Week 24/EOT (mITT Population)

	Relugolix +E2/NETA (N = 206)	Placebo (N = 204)
Number (%) of responders [1]	155 (75.2%)	62 (30.4%)
(95% CI) [2]	(68.77%, 80.98%)	(24.16%, 37.20%)
Difference from placebo (95% CI) [3]	44.9% (36.21%, 53.49%)	
P-value [4]	< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; EOT = End-of-Treatment; mITT = modified Intent-to-Treat (Population); N = number of patients; NETA = norethindrone acetate; NRS = numerical rating scale. Percentage was based on the number of patients in the mITT Population for each treatment group. [1] Responders were patients with a reduction of at least 2.8 points on the NRS for dysmenorrhea and no increase in analgesic use at Week 24/EOT. [2] Based on exact binomial 95% CI (Clopper-Pearson).
[3] Difference in responder proportions of relugolix + E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution. [4] P-value for treatment effect from the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years) and geographic region (North America, Rest of World) as covariates.

Figure 7. MVT-601-3102: Co-Primary Efficacy Endpoint, Proportion of Dysmenorrhea Responders at Week 24/EOT (mITT Population)



Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end-of-treatment; mITT = modified Intent-to-Treat (Population); N = number of patients; NETA = norethindrone acetate; NRS = Numerical Rating Scale.
A dysmenorrhea responder at Week 24/EOT was a patient who had a reduction of at least 2.8 points in average dysmenorrhea NRS score from baseline and no increase in analgesic use.
P-value for treatment effect was based on the logistic regression model which includes treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years) and geographic region (North America, Rest of World) as covariates. Error bars represent 95% CI.

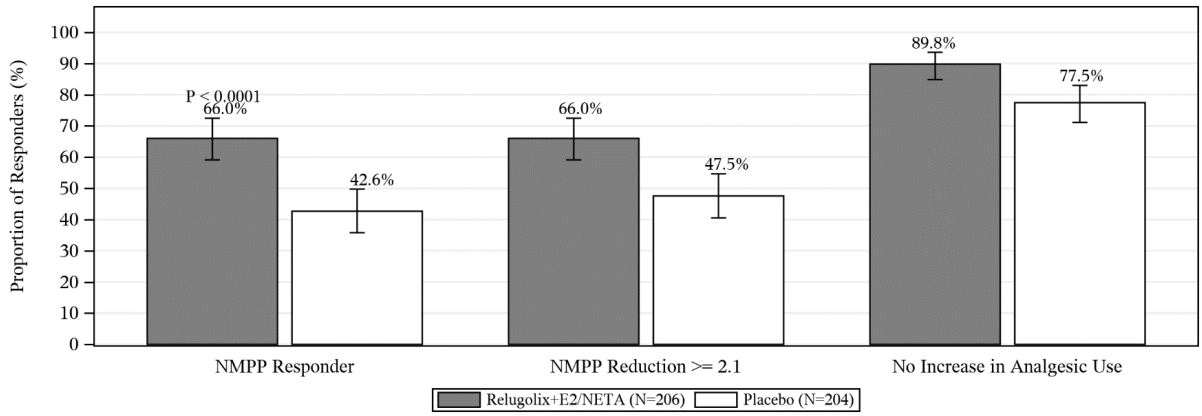
Second co-primary endpoint Nonmenstrual Pelvic Pain Responder Analysis

Table 30. MVT-601-3102: Co-Primary Efficacy Analysis, Proportion of Patients Classified as Nonmenstrual Pelvic Pain Responders at Week 24/EOT (mITT Population)

	Relugolix +E2/NETA (N = 206)	Placebo (N = 204)
Number (%) of responders [1]	136 (66.0%)	87 (42.6%)
(95% CI) [2]	(59.11%, 72.46%)	(35.77%, 49.74%)
Difference from placebo (95% CI) [3]	23.4% (14.00%, 32.75%)	
P-value [4]	< 0.0001	

Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end-of-treatment; mITT = modified Intent-to-Treat (Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale.
Percentage was based on the number of patients in the mITT population for each treatment group.
[1] Responders were patients with a reduction of at least 2.1 points on the NRS for NMPP and no increase in analgesic use at Week 24/EOT. [2] Based on exact binomial 95% CI (Clopper-Pearson).
[3] Difference in responder proportions of relugolix + E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution. [4] P-value for treatment effect from the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years) and geographic region (North America, Rest of World) as covariates.

Figure 22. MVT-601-3101: Co-Primary Efficacy Endpoint, Proportion of Nonmenstrual Pelvic Pain Responders at Week 24/EOT (mITT Population)

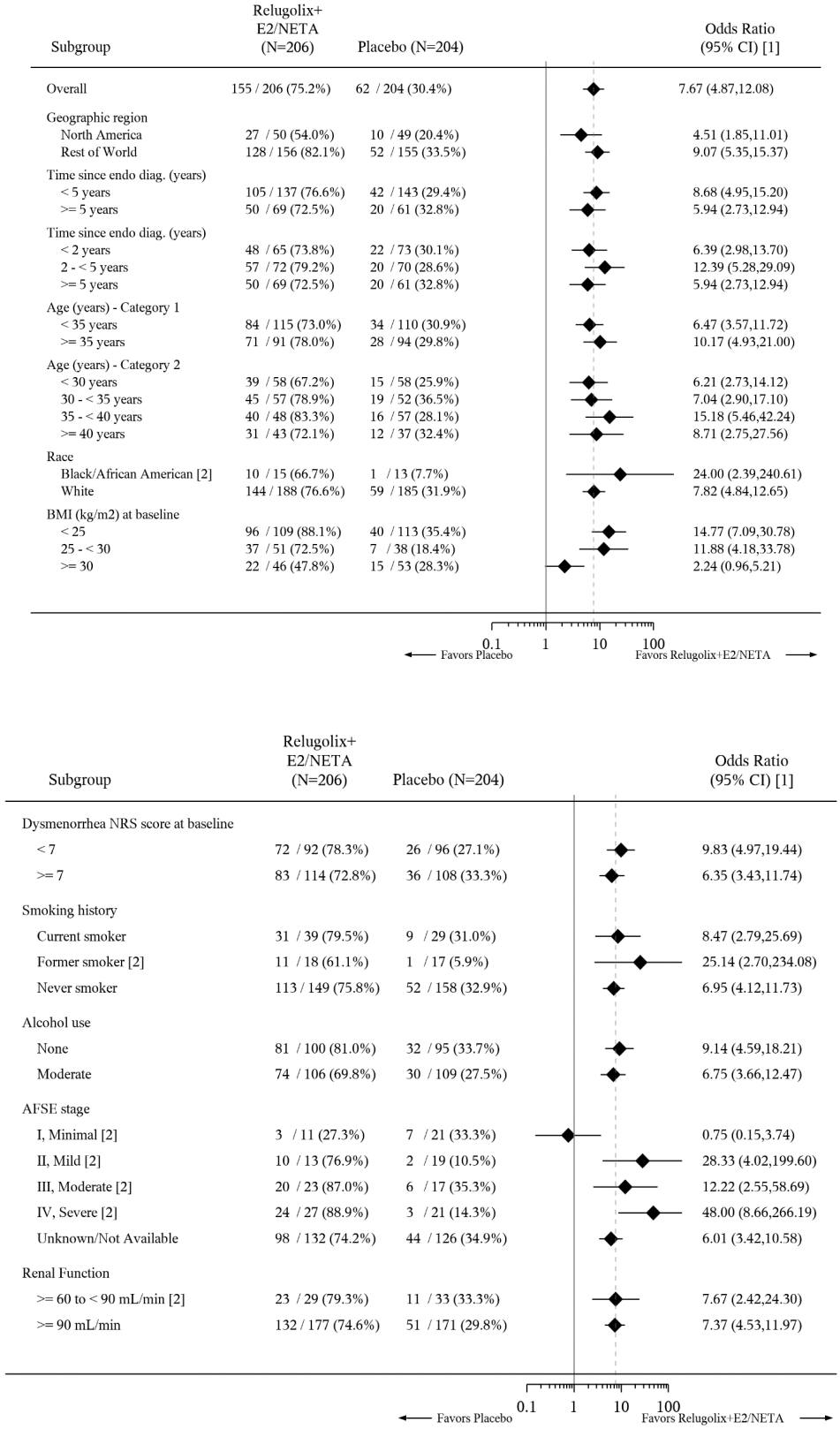


Abbreviations: CI = confidence interval; E2 = estradiol; EOT = End-of-Treatment; mITT = modified Intent-to-Treat Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale.
An NMPP responder at Week 24/EOT was a patient who had a reduction of at least 2.1 points in average NMPP NRS score from baseline and no increase in analgesic use.
P-value for treatment effect was based on the logistic regression model which included treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years) and geographic region (North America, Rest of World) as covariates. Error bars represent 95% CI.

Ancillary analyses

Subgroup analyses were conducted for the co-primary efficacy endpoints by geographic region, time since surgical diagnosis of endometriosis, AFS endometriosis stage, age, race, BMI, smoking status, dysmenorrhea NRS score at baseline, NMPP NRS score at baseline, and renal function based on the Cockcroft-Gault formula for calculated creatinine clearance.

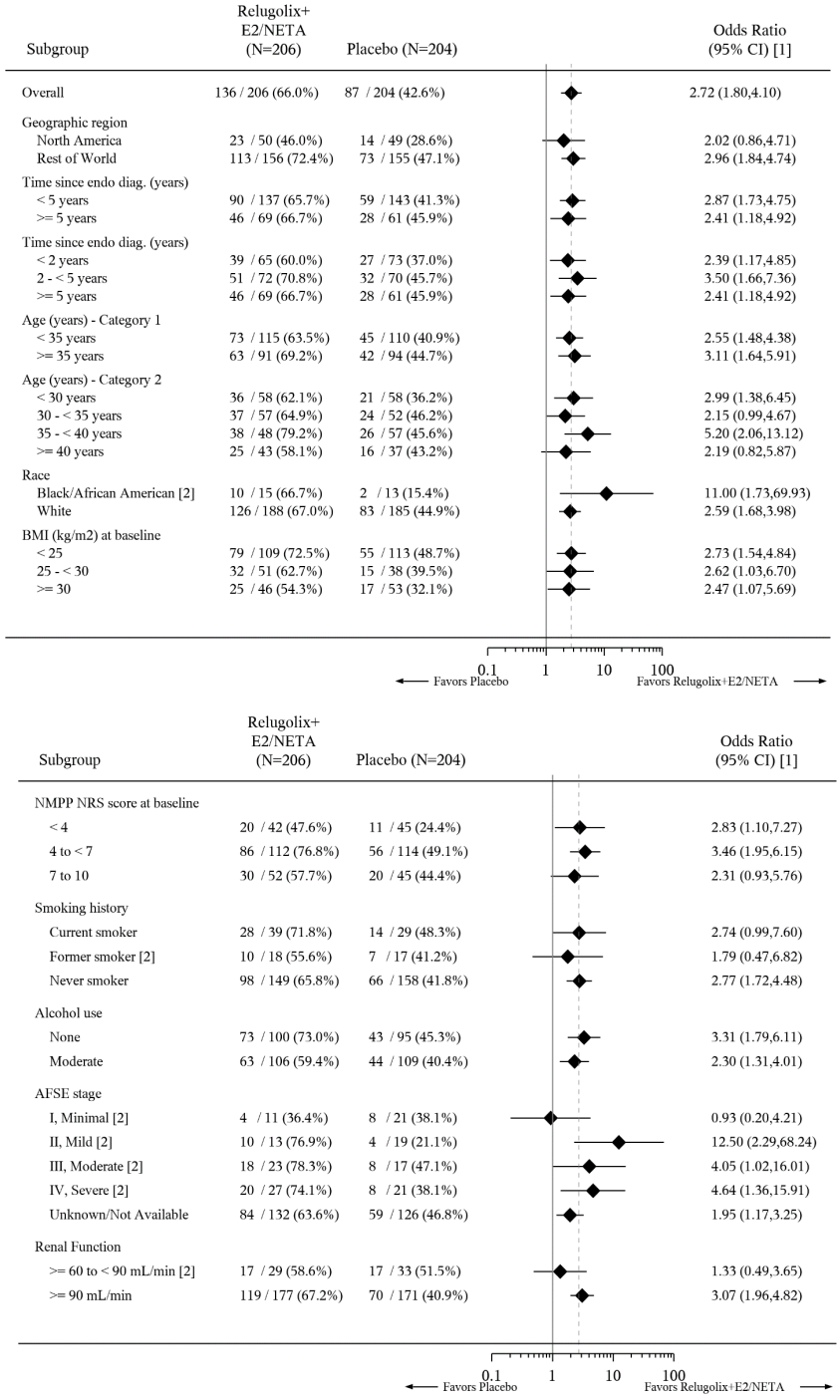
Figure 23. MVT-601-3102: Proportion of Patients Classified as Dysmenorrhea Responders at Week 24/EOT, Subgroup Analyses (mITT Population)



Abbreviations: AFSE = American Fertility Society of Endometriosis; BMI = body mass index; CI = confidence interval; diag = diagnosis; E2 = estradiol; endo = endometriosis; EOT = End-of-Treatment; mITT = modified intentto- treat (Population); N = number of patients; NETA = norethindrone acetate; NRS = Numerical Rating Scale. [1] Odds ratio based on logistic regression with

treatment group, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years), and geographic region (North America, Rest of World) as covariates with odds ratio > 1 favoring relugolix + E2/NETA over placebo. [2] Odds ratio based on logistic regression with treatment group as the only covariate with odds ratio > 1 favoring relugolix + E2/NETA over placebo. Error bars represent 95% CI.

Figure 24. MVT-601-3102: Proportion of Patients Classified as Nonmenstrual Pelvic Pain Responders at Week 24/EOT, Subgroup Analyses (mITT Population)



Abbreviations: AFSE = American Fertility Society of Endometriosis; BMI = body mass index; CI = confidence interval; diag = diagnosis; E2 = estradiol; endo = endometriosis; EOT = end of treatment; mITT = modified intentto- treat (Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale.
[1] Odds ratio based on logistic regression with treatment group, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years), and geographic region (North America, Rest of World) as covariates with odds ratio > 1 favoring relugolix + E2/NETA over

placebo. [2] Odds ratio based on logistic regression with treatment group as the only covariate with odds ratio > 1 favoring relugolix + E2/NETA over placebo. Error bars represent 95% CI.

Consistent with the findings for the overall population, treatment differences with regard to the co-primary endpoints were consistent across nearly all subgroups as demonstrated by the odds ratio point estimate consistently favoring relugolix + E2/NETA over placebo on the dysmenorrhea and NMPP co-primary endpoints.

Together, these data provide support for the efficacy of relugolix + E2/NETA across age groups, race, BMI, level of pain at baseline, disease duration, renal function, smoking status, and geography.

Key secondary efficacy endpoints

There were seven key secondary efficacy endpoints in this study that were hierarchically tested after both co-primary endpoints were met.

Table 31 Key secondary efficacy endpoints

Endpoint Definition	Relugolix+ E2/NETA (N=206)	Placebo (N=204)	Difference (95% CI) p-value
1. Change from baseline to Week 24 in the EHP-30 Pain Domain score, LS Mean (SE)[1]	-32.2 (1.68)	-19.9 (1.69)	-12.3(2.25) (-16.7, -7.9) < 0.0001
2. Change from baseline to Week 24/EOT in the mean dysmenorrhea NRS score, LS Mean (SE)[1]	-5.1 (0.19)	-2.0 (0.19)	-3.2 (0.26) (-3.7, -2.7) < 0.0001
3. Change from baseline to Week 24/EOT in the mean NMPP NRS score, LS Mean (SE)[1]	-2.7 (0.17)	-2.0 (0.17)	-0.7 (0.23) (-1.2, -0.3) 0.0012
4. Change from baseline to Week 24/EOT in the mean overall pelvic pain NRS score, LS Mean (SE)[1]	-2.9 (0.16)	-2.0 (0.17)	-0.9 (0.22) (-1.4, -0.5) < 0.0001
5. Change from baseline to Week 24/EOT in the mean dyspareunia NRS score, LS Mean (SE)[1]	-2.4 (0.19)	-1.9 (0.19)	-0.5 (0.26) (-1.0, -0.0) 0.0371
6. Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain at Week 24/EOT, n (%)[2]	169 (82.0%)	135 (66.2%)	15.9% (7.5%, 24.2%) < 0.0001
7. Change from baseline to Week 24/EOT in protocol-specified analgesic use for endometriosis-associated pain based on mean pill count, LS Mean (SE)[1]	-0.5 (0.06)	-0.4 (0.06)	-0.1 (0.07) (-0.3, 0.0) 0.1141

Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end-of-treatment; LS = least square; mITT = modified Intent-to-Treat (Population); N = number of patients; NETA = norethindrone acetate; NMPP = nonmenstrual pelvic pain; NRS = Numerical Rating Scale. [1] LS means and p-value for test of difference between relugolix + E2/NETA and placebo, relugolix + delayed E2/NETA and placebo were based on mixed-effects model with treatment, baseline value, visit, geographic region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5, ≥ 5 years), and treatment-by-visit interaction included as fixed effects; visit was also included in the model as random effect within each patient, and an unstructured covariance matrix was ssumed.

[2] Difference in responder proportions of relugolix + E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution. P-value was based on Cochran-Mantel-Haenszel test stratified by baseline opioid use, time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years), and geographic region (North America, Rest of World).

The study met 6 of the 7 key secondary endpoints. These key secondary endpoints extend the findings of the co-primary endpoints by showing benefits of treatment with relugolix + E2/NETA on common types of pain experienced by women with endometriosis (dysmenorrhea, NMPP, overall pelvic pain, and dyspareunia). Importantly, reduction in pain occurred without an increase in analgesic use – in fact, opioid use declined and a significantly higher percentage of patients in the relugolix + E2/NETA group (versus placebo) were opioid-free at EOT. Finally, the effective treatment of endometriosis-associated pain with relugolix + E2/NETA resulted in improved daily functioning that included activities such as standing, sitting, walking, sleeping, and performing jobs around the house.

Other Secondary Endpoints

Responder rate by month

The majority of patients in the relugolix + E2/NETA group met the responder definition for dysmenorrhea (a decline in the dysmenorrhea NRS by $\geqslant$ 2.8 points without an increase in analgesic use) within 8 weeks of initiating treatment. The majority of patients in the relugolix + E2/NETA group met the responder definition for NMPP (a decline in the NMPP NRS by $\geqslant$ 2.1 points without an increase in analgesic use) within 12 weeks of initiating treatment. In contrast, the percentage of patients in the placebo group who met the responder definitions for dysmenorrhea and NMPP did not reach 50.0% at any timepoint.

Change in Tier 1 and 2 use and average analgesic pill count

Tier 1 use decreased by 53.6%, from 24.0 (30.6) to 9.3 (24.8) in the relugolix + E/2NETA group compared to 29.9%, from 26.8 (39.9) to 13.4 (30.2) in the placebo group.

The mean (SD) Tier 2 used decreased from baseline to 24 Week/EOT by 75.7% (from 5.4 (13.0) to 1.4 (4.6)) in the relugolix combination treatment. In the placebo group this was 42.2% (from 5.8 (12.5) to 3.4 (12.5)).

Other secondary endpoints

Other pre-specified secondary efficacy endpoints were the same as in study 3101 and included PGA of dysmenorrhea and NMPP, PGIC for dysmenorrhea, NMPP, dyspareunia, and EHP-30.

Secondary Efficacy Objectives and Endpoints Based on Comparisons Between Relugolix + Delayed E2/NETA and Placebo

Dysmenorrhea Responder analysis

In addition to the co-primary efficacy analyses comparing the relugolix + E2/NETA group with the placebo group, an analysis was performed comparing the relugolix + delayed E2/NETA group with the placebo group. In the relugolix + delayed E2/NETA group, 150 (72.8%) patients met the responder criteria for dysmenorrhea at Week 24/EOT, results which were consistent with findings from the relugolix + E2/NETA group.

Nonmenstrual Pelvic Pain Responder Analysis

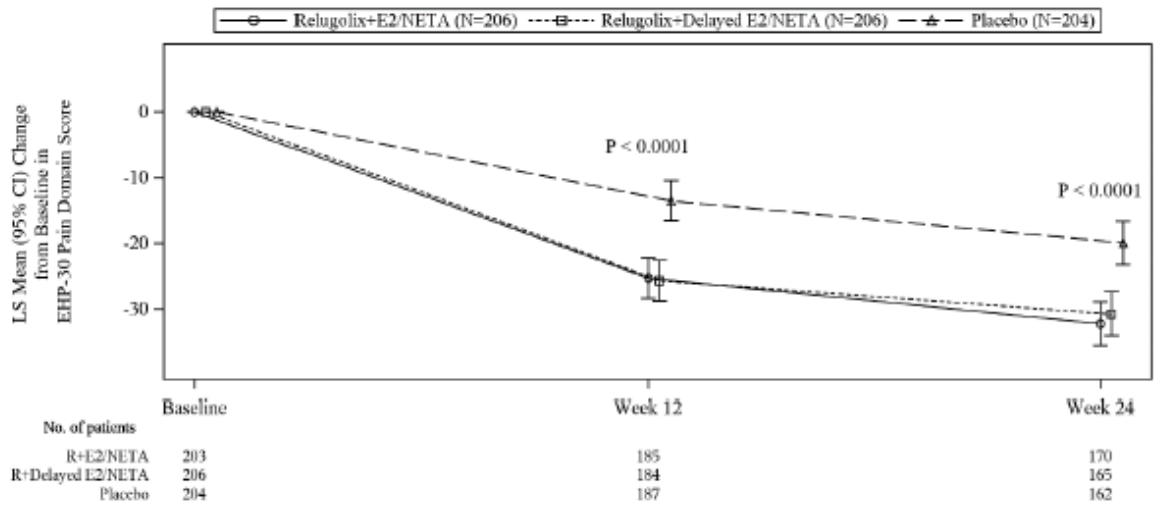
In addition to the co-primary efficacy analyses comparing the relugolix + E2/NETA group with the placebo group, an analysis was performed comparing the relugolix + delayed E2/NETA group with the placebo group. In the relugolix + delayed E2/NETA group, 109 (52.9%) patients met the responder criteria for NMPP at Week 24/EOT, results which were consistent with findings from the relugolix + E2/NETA group.

To determine the benefit on function measured by the EHP-30 pain domain

Change from baseline at Week 24 in the EHP-30 pain domain score

The baseline EHP-30 Pain Domain mean (SD) score was 56.2 (17.12) in the relugolix + E2/NETA group and 55.0 (16.17) in the placebo group. There was a statistically significant improvement in the EHP-30 Pain Domain score for the relugolix + E2/NETA group compared with the placebo group at Week 24, LS mean (standard error [SE]) change from baseline: −32.2 (1.68) versus −19.9 (1.69) ($p < 0.0001$) (Table 25).
Results for the relugolix + delayed E2/NETA group were consistent with those for the relugolix + E2/NETA group (Figure 25)).

Figure 25. MVT-601-3102: Change from Baseline in Endometriosis Health Profile-30 Pain Domain Score by Visit (mITT Population)



Abbreviations: CI = confidence interval; E2 = estradiol; EHP 30 = Endometriosis Health Profile 30-Item Questionnaire; mITT = modified Intent-to-Treat (Population); N = number of patients; NETA = norethindrone acetate.

Least squares means and p-value for test of difference between relugolix + E2/NETA and placebo were based on mixed-effects model with treatment, baseline value, visit, geographic region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5, ≥ 5 years), and treatment-by-visit interaction included as fixed effects; visit was also included in the model as random effect within each patient, and an unstructured covariance matrix was assumed.

Error bars represent 95% CI. Nominal p-value at Week 12

Proportion of patients who meet the definition of responder, achieving a reduction of at least 20 points from baseline at Week 24 based on EHP-30 pain domain scores

In the relugolix + E2/NETA group, 72.9% of patients had a meaningful improvement (ie, reduction of at least 20 points) in the EHP-30 Pain Domain score at Week 24 compared with 52.5% in the placebo group. The between-group difference was 20.5% (95% CI: 10.29%, 30.66%), favoring relugolix + E2/NETA (nominal p = 0.0002).

The results for the relugolix + delayed E2/NETA group were consistent with those observed in the relugolix + E2/NETA group (Table 32).

Table 32. MVT-601-3102: Proportion of Patients Classified as Responders Based on Reduction in EHP-30 Pain Domain Score by Visit (mITT Population)

	Relugolix+E2/NETA (N = 206)	Relugolix+Delayed E2/NETA (N = 206)	Placebo (N = 204)
Number of evaluable patients	185	184	187
Number (%) of EHP-30 pain domain responders [1]	118 (63.8%)	119 (64.7%)	70 (37.4%)
(95% CI) [2] at Week 12	(56.41%, 70.71%)	(57.30%, 71.56%)	(30.48%, 44.79%)
Difference from placebo (95% CI) [3]	26.4% (16.55%, 36.15%)		
P-value [4]	< 0.0001		
Number of evaluable patients	170	165	162
Number (%) of EHP-30 pain domain responders [1]	124 (72.9%)	121 (73.3%)	85 (52.5%)
(95% CI) [2] at Week 24	(65.61%, 79.46%)	(65.90%, 79.91%)	(44.49%, 60.36%)
Difference from placebo (95% CI) [3]	20.5% (10.29%, 30.66%)		
P-value [4]	0.0002		

The database lock date was 15 Apr 2020.
Abbreviations: CI = confidence interval; E2 = estradiol; EHP-30 = Endometriosis Health Profile 30-item Questionnaire; LS = least squares; mITT = modified intent-to-treat; N = number of patients in the treatment group; NETA = norethindrone acetate.
Evaluable patients include those who have observed data at both baseline and the relevant post-baseline timepoint.
[1] Responders are patients with a reduction of at least 20 points in the EHP-30 Pain Domain at visit.
[2] Based on exact binomial 95% CI (Clopper-Pearson).
[3] Difference in responder proportions of relugolix + E2/NETA minus placebo, or relugolix + delayed E2/NETA minus placebo. 95% CI based on the approximation to the normal distribution.
[4] P-value is based on Cochran-Mantel-Haenszel test stratified by time since initial surgical diagnosis of endometriosis (< 5 years, >= 5 years) and geographic region (North America, Rest of World).

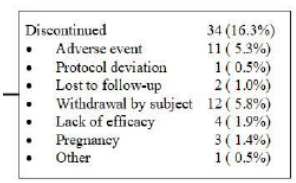
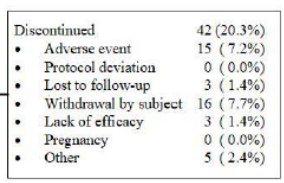
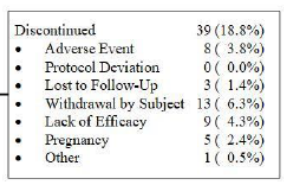
Summary of main efficacy results MVT-601-3102

The following table 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 33. Summary of efficacy for trial MVT-601-3102

Title: SPIRIT 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain		
Study identifier	Protocol number: MVT-601-3102, EudraCT number: 2017-001632-19, NCT number NCT03204331	
Design	Randomized, Double-Blind, Placebo-Controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 35 days 30 days safety follow-up
Hypothesis	Superiority	
Treatments groups	Relugolix + E2/NETA group	**treatment**: Oral relugolix 40 mg tablets co-administered with over-encapsulated low-dose E2 (1 mg) and NETA (0.5 mg) QD; **duration** 24 weeks; **number randomized**: 208

	Relugolix + delayed E2/NETA group		**treatment**: Oral relugolix 40 mg tablets co-administered with a placebo capsule designed to match the over-encapsulated low-dose E2 (1 mg) and NETA (0.5 mg) QD (12 weeks of monotherapy) followed by oral relugolix 40 mg tablets QD co-administered with over-encapsulated low-dose E2 (1 mg) and NETA (0.5 mg) QD (12 weeks of combination therapy); **duration** 12 weeks of monotherapy and 12 weeks of combination therapy – total 24 weeks; **number randomized**: 207
	Placebo group		**treatment**: Placebo tablets designed to match relugolix, co-administered with a placebo capsule designed to match the over-encapsulated E2/NETA QD. **duration**:24 weeks; **number randomized**: 208
Endpoints and definitions	<Co->Primary endpoint 1	Dysmenorrhea Responder rate	Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 24 Or End Of Treatment (EOT). A responder was defined as a woman who achieved a pre-defined reduction in dysmenorrhea NRS scores of at least 2.8 points without increased use of analgesics.
	<Co->Primary endpoint 2	NMPP Responder rate	Percentage Of Participants Who Meet The Non-Menstrual Pelvic Pain (NMPP) Responder Criteria At Week 24 Or EOT. A responder was defined as a woman who achieved a predefined reduction in nonmenstrual NRS scores of at least 2.1 points without increased use of analgesics.
	<Key secondary>	Change in EHP-30 Pain	Change from baseline to Week 24 in the EHP-30 pain domain Score.
	<Key secondary>	Change in dysmenorrhea NRS	Change from baseline to Week 24/EOT in the mean dysmenorrhea NRS score.
	<Key secondary>	Change in NMPP NRS	Change from baseline to Week 24/EOT in the mean NMPP NRS score.
	<Key secondary>	Change in Pelvic Pain NRS	Change from baseline to Week 24/EOT in the mean overall pelvic pain NRS score.
	<Key secondary>	Change in dyspareunia NRS	Change from baseline to Week 24/EOT in the mean dyspareunia NRS score.
	<Key secondary>	No Opioid use	Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain at Week 24/EOT.
	<Key secondary>	No Analgesic use	Change from baseline to Week 24/EOT in protocol-specified analgesic use for endometriosis-associated pain based on mean pill count
	<Secondary> Safety	Percent change in BMD at W12	Percent change from baseline to Week 12 in BMD at the lumbar spine (L1-L4)
	<Secondary> Safety	Percent change in BMD at W24	Percent change from baseline to Week 24 in BMD at the lumbar spine (L1-L4), femoral neck, and total hip
	<Secondary> Safety	Vasomotor W12	Incidence of vasomotor symptoms at Week 12
Database lock	15 April 2020		
Results and Analysis			
Analysis description	**Co-Primary Analysis – pre-specified**		

Analysis population and time point description	Modified Intent to treat (mITT) population (defined as all randomized patients who received any amount of study drug (relugolix/placebo or E2/NETA/placebo).) time point: Week 24		
Descriptive statistics and estimate variability	Treatment group	Relugolix+E2/NETA	Placebo
	Number of subject	206	204
	Dysmenorrhea Responder rate, n (%)	155 (75.2%)	62 (30.4%)
	Exact binomial 95% Confidence Interval	68.77%, 80.98%	24.16%, 37.20%
	NMPP Responder rate, n (%)	136 (66.0%)	87 (42.6%)
	Exact binomial 95% Confidence Interval	59.11%, 72.46%	35.77%, 49.74%
Effect estimate per comparison	<Co->Primary endpoint Dysmenorrhea Responder rate	Comparison groups	Relugolix+E2/NETA vs. Placebo
		Difference in responder proportions of relugolix + E2/NETA minus placebo %.	44.9%
		95% Confidence Interval	36.21%, 53.49%
		P-value	< 0.0001
	<Co->Primary > NMPP Responder rate	Comparison groups	Relugolix+E2/NETA vs. Placebo
		Difference in responder proportions of relugolix + E2/NETA minus placebo.	23.4%
		95% Confidence Interval	14.00%, 32.75%)
		P-value	< 0.0001
Notes	The study was considered positive if treatment effects for both co-primary endpoints were statistically significant with 2-sided p-values < 0.05. To test the robustness of the primary analysis, five sensitivity analyses were conducted. All of the analyses were prespecified prior to data unblinding. These analyses explored the effects of discontinuations due to adverse events, lack of efficacy, or any reason within the first 5 weeks of treatment [1]; use of alternative analysis populations (completers [2] and per-protocol [3]); and different methods of handling missing data (multiple imputation [4] and without imputation [5]). Reasons for patients drop-outs  Discontinued 34 (16.3%) • Adverse event 11 (5.3%) • Protocol deviation 1 (0.5%) • Lost to follow-up 2 (1.0%) • Withdrawal by subject 12 (5.8%) • Lack of efficacy 4 (1.9%) • Pregnancy 3 (1.4%) • Other 1 (0.5%)  Discontinued 42 (20.3%) • Adverse event 15 (7.2%) • Protocol deviation 0 (0.0%) • Lost to follow-up 3 (1.4%) • Withdrawal by subject 16 (7.7%) • Lack of efficacy 3 (1.4%) • Pregnancy 0 (0.0%) • Other 5 (2.4%)  Discontinued 39 (18.8%) • Adverse Event 8 (3.8%) • Protocol Deviation 0 (0.0%) • Lost to Follow-Up 3 (1.4%) • Withdrawal by Subject 13 (6.3%) • Lack of Efficacy 9 (4.3%) • Pregnancy 5 (2.4%) • Other 1 (0.5%)		
Analysis description	**Secondary analysis – key secondary endpoints – pre-specified: >**		
Analysis population and time point description	Modified Intent to treat (mITT) population (defined as all randomized patients who received any amount of study drug (relugolix/placebo or E2/NETA/placebo). time point: Week 24		
	Treatment group	Relugolix+E2/NETA	Placebo

Descriptive statistics and estimate variability	Number of subject	206	204
	Change in EHP-30 Pain, LS Mean (SE)	-32.2 (1.68)	-19.9 (1.69)
	Change in dysmenorrhea NRS, LS Mean (SE)	-5.1 (0.19)	-2.0 (0.19)
	Change in NMPP NRS, LS Mean (SE)	-2.7 (0.17)	-2.0 (0.17)
	Change in pelvic Pain NRS, LS Mean (SE)	-2.9 (0.16)	-2.0 (0.17)
	Change in dyspareunia NRS, LS Mean (SE)	-2.4 (0.19)	-1.9 (0.19)
	No Opioid use, n (%)	169 (82.0%)	135 (66.2%)
	No Analgesic use , LS Mean (SE)	-0.5 (0.06)	-0.4 (0.06)

Effect estimate per comparison	1. Key secondary endpoint: change in EHP-30 Pain	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-12.3 (2.25)
		95% Confidence Interval	-16.7, -7.9
		P-value	< 0.0001
	2. Key secondary endpoint: change in dysmenorrhea NRS	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-3.2 (0.26)
		95% Confidence Interval	(-3.7, -2.7)
		P-value	< 0.0001
	3. Key secondary endpoint: change in NMPP NRS	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-0.7 (0.23)
		95% Confidence Interval	-1.2, -0.3
		P-value	0.0012
	4. Key secondary endpoint: change in pelvic pain NRS	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-0.9 (0.22)
		95% Confidence Interval	-1.4, -0.5
		P-value	< 0.0001
	5. Key secondary endpoint: change in dyspareunia NRS	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in Least Square means between groups (SE)	-0.5 (0.26)
		95% Confidence Interval	-1.0, -0.0
		P-value	0.0371

	6. Key secondary endpoint: no opioid use	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in responder proportions of relugolix + E2/NETA minus placebo in %.	15.9%
		95% CI based on the approximation to the normal distribution.	7.5%, 24.2%
		P-value	< 0.0001
	7. Key secondary endpoint: no Analgesic use	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference in responder proportions of relugolix + E2/NETA minus placebo in %.	-0.1 (0.07)
		95% CI based on the approximation to the normal distribution.	-0.3, 0.0
		P-value	0.1141

Notes	A number of additional analyses (listed in the CSR) were conducted post-hoc based on emerging data and clinical relevance to the study objectives.			
Analysis description	**Secondary analysis – Other: safety endpoints – pre-specified:**			
Analysis population and time point description	Safety population (defined as all randomized patients who received any amount of study drug.) Time point: Week 12 (all) and Week 24 (BMD only)			
Descriptive statistics and estimate variability	Treatment group	Relugolix+E2/NETA	Relugolix+Delayed E2/NETA	Placebo
	Number of subject	172	166	166
	Percent change in BMD at W12 LS Mean Percent Change from Baseline (95% Confidence Interval)	-0.47 (-0. 90, -0.05)	-1.87 (-2.31, -1.43)	-0.14 (-0.57, 0.29)
	Number of subject	168	163	156
	Percent change in BMD at W24 LS Mean Percent Change from Baseline (95% Confidence Interval	-0.78 (-1.23, -0.32)	-1.92 (-2.39, -1.45)	0.02 (-0.45, 0.48)
	Number of subject	206	206	204
	Vasomotor W12, n (%))	33 (16.0%)	72 (35.0%)	7 (3.4%)

Effect estimate per comparison	Secondary endpoint Percent change in BMD at W12	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference of LS means for relugolix + E2/NETA minus placebo (SE)	-0.33
		95% Confidence Interval.	-0.75, 0.10
		P-value	NA

	Secondary endpoint Percent change in BMD at W12	Comparison groups	Relugolix + delayed E2/NETA vs. Placebo
		Difference of LS means for relugolix + delayed E2/NETA minus placebo (SE)	-1.72
		95% Confidence Interval.	-2.15, -1.29
		P-value	NA
	Secondary endpoint Percent change in BMD at W24	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference of LS means for relugolix + E2/NETA minus placebo (SE)	-0.79
		95% Confidence Interval.	-1.28, -0.30
		P-value	NA
	Secondary endpoint Percent change in BMD at W24	Comparison groups	Relugolix+E2/ NETA vs. Placebo
		Difference of LS means for relugolix + delayed E2/NETA minus placebo (SE)	-1.93
		95% Confidence Interval.	-2.43, -1.44
		P-value	NA

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

Studies MVT-601-3101 and MVT-601-3102 Pooled

Subgroup analyses were conducted for the co-primary efficacy endpoints by geographic region, time since surgical diagnosis of endometriosis (the two stratification factors at randomization), age, race, ethnicity, BMI, dysmenorrhea NRS score at baseline, NMPP NRS score at baseline, smoking status, alcohol use, and renal function based on the Cockcroft-Gault formula for calculated CLCR.

Consistent with the findings observed in the individual studies, treatment differences with regard to the co-primary endpoints were consistent across nearly all subgroups with a higher proportion of patients in the relugolix + E2/NETA group meeting the definition for responder than patients in the placebo group, as indicated by the point estimate of the odds ratio being greater than 1, favouring relugolix + E2/NETA over placebo. Additionally, for all the subgroups, except for the small subgroup of patients with BMI 25 to < 30 with NMPP and former smokers, the lower bound of the 95% CI for the odds ratios also was above 1, favouring relugolix + E2/NETA over placebo. Notably, while the numbers of patients in the predefined category for race of Black/African American (5.7% of the pooled population) versus Not Black/African American and ethnicity of Hispanic or Latino (12.0% of the pooled population) versus Not Hispanic or Latino were limited, the observed treatment effect of relugolix + E2/NETA compared with placebo was favourable for these subgroups (ie, 95% CIs for odds ratio excluding 1), which is consistent with the positive results observed on the overall mITT population.

2.4.3. MVT-601-3103 - Long-term efficacy study (52 and 104 weeks)

MVT-601-3103 (SPIRIT EXTENSION): An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain.

Study period: first patient enrolled 22 May 2018, Last 30-day safety follow-up completed 26 Jan 2022.

A total of 802 patients were enrolled at 171 centers globally, including the following: North America (United States [US]) and Rest of World (Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, Czech Republic, Finland, Georgia, Hungary, Italy, New Zealand, Poland, Portugal, Romania, South Africa, Spain, and Ukraine

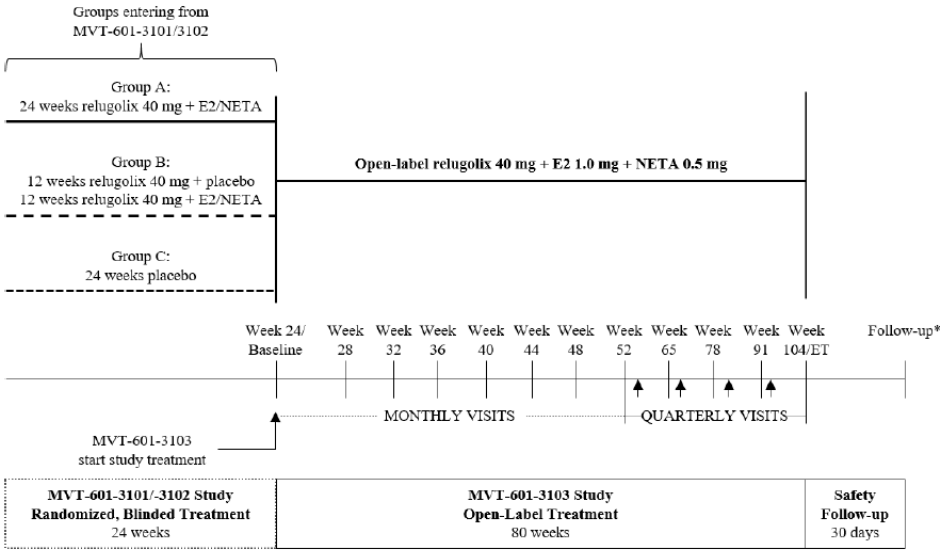
Methods

MVT-601-3103 was a multinational, phase 3, open-label, single-arm, long-term efficacy and safety study that enrolled eligible patients who completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled pivotal (also referred to as "parent") studies (MVT-601-3101 or MVT-601-3102). All patients were to receive open-label oral relugolix 40 mg QD co-administered with low-dose E2 (1 mg) and NETA (0.5 mg) for up to 80 weeks.

Design

Eligible patients were required to complete participation in one of the pivotal studies and consented to participate in this extension study. Baseline procedures for this study were conducted at the same time as the Week 24 visit for the pivotal study (referred to as the "Week 24/Baseline visit"). The administration of the first dose of study drug for MVT-601-3103 defined enrollment into this study. Thereafter, study participants were to take the open-label study treatment (relugolix combination therapy) orally QD for 80 weeks.

Figure 26. MVT-601-3103: Study Schematic



E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg; eDiary = electronic diary; ET = Early Termination.
* The Follow-up visit is schedule approximately 30 days after the last dose of study drug.
↑ Indicates telephone contact to review concomitant medication, evaluation of adverse events, and a review of eDiary and study medication compliance. To be conducted at Week 57, Week 71, Week 85, and Week 98.

Primary objectives

The primary efficacy objectives were to evaluate the long-term efficacy of relugolix 40 mg once daily (QD) co-administered with low-dose estradiol (E2) and norethindrone acetate (NETA) on endometriosis-associated pain at 52 weeks and 104 weeks, among patients who previously completed a 24-week treatment period in one of the pivotal studies (MVT-601-3101 or MVT-601-3102).

Treatment arms

In this extension study, all patients are to receive the following open-label oral study treatment.

Study duration

Patients who completed study MVT-601-3101 or MVT-601-3102 (24 weeks), including those randomized to placebo, and who met other eligibility criteria were offered the opportunity to enrol in an up to 80-week open-label, long-term extension (LTE) study (MVT-601-3103) in which all patients receive relugolix + E2/NETA. This results in an exposure time up to Relugolix + E2/NETA of

- 104 weeks for patients in the parent study on Relugolix + E2/NETA (Group A)
- 92 weeks plus 12 weeks relugolix monotherapy for patients in the parent study on Relugolix + delayed E2/NETA (group B)
- 80 weeks for patients in de placebo group in the parent study (Group C)

Study participants

Approximately 800 patients were planned for enrollment.

Patients were to have received their last dose of study drug in the pivotal study (MVT-601-3101 or MVT-601-3102) on the day prior to the Week 24/Baseline visit and were to receive their first dose of

study drug for this extension study in the clinic after they were determined to be eligible for this extension study.

The in- and exclusion criteria were in line with those from the pivotal studies MVT-601-3101 and MVT-601-3102. Below, only the additional or adjusted in- and exclusion criteria compared to the pivotal are presented:

Additional inclusion criteria

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;

Furthermore, the following non hormonal contraception method was added: Had a non-hormonal intrauterine device placed in the uterus

Additional exclusion Criteria:

1. Had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. Had a Z-score < −2.0 or had a ≥ 7% decrease in BMD from the parent study baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of BMD;
3. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 × the upper limit of normal (ULN), or
   b. Bilirubin (total bilirubin) > 1.5 × ULN (or > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
4. Had a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor):
   a. 90 or lower and 5 or more points lower at the Week 24/Baseline visit relative to the parent study baseline visit, or
   b. The presenting visual acuity score had decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study baseline visit;

   Note: Visual acuity score must have been obtained with corrective lenses, if applicable.
5. Met a withdrawal criterion in the parent study.

Removal of patients

Patients with endometrial hyperplasia, endometrial carcinoma, and those with BMD loss ≥ 7% compared with the pivotal study baseline at the lumbar spine, total hip, or femoral neck are to be withdrawn from study drug treatment and followed per instructions in the pivotal and/or extension study protocol. Additionally, patients with malignant breast lesion(s) or breast carcinoma or certain elevation of liver tests or who become pregnant are to be withdrawn from study drug treatment.

Patients removed from therapy for any reason are to undergo the assessments for the ET visit (see the Week 104 visit on the schedule of activities, Table 2) and are to have a follow-up visit to assess safety

approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

Contraception and Pregnancy Avoidance

As applied in the pivotal studies.

Study treatment

In this extension study, all patients were to receive the following open-label oral study treatment:

- 80 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of E2 1 mg and NETA 0.5 mg.

Dose selection

In this extension study, all patients were to receive the same dose of relugolix (40 mg), E2 (1 mg), and NETA (0.5 mg) as used in the relugolix + E2/NETA group of the pivotal studies in order to assess the long-term safety and efficacy of this combination.

Timing of dose

The study drug was to be taken in the fasted state (except for water, tea, or coffee) in the morning, at least 1 hour before breakfast. If the dose was missed in the morning for any reason, the study drug could be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study drug was to be taken as close as possible to the same time of morning each day.

Prohibited and rescue medication
These are completely the same as for the pivotal studies.

Objectives and endpoints

Table 12. MVT-601-3103: Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary Efficacy	
To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	To be assessed Week 52: • Proportion of patients who meet the dysmenorrhea responder criteria at the Week 52 pain assessment period, achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily electronic diary (eDiary). • Proportion of patients who meet the NMPP responder criteria at the Week 52 pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary

To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	To be assessed at Week 104: • Proportion of patients who meet the dysmenorrhea responder criteria at the Week 104/EOT pain assessment period, achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary. • Proportion of patients who meet the NMPP responder criteria at the Week 104/EOT pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary
Secondary Efficacy (To be assessed at Week 52 and Week 104, unless otherwise specified)	
To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102), on the following	To be assessed on the following
• Function, as measured by the Endometriosis Health Profile Questionnaire (EHP-30) Pain Domain	• Change from the pivotal phase 3 study Baseline in the EHP-30 Pain Domain scores • Proportion of patients who have a reduction of at least 20 points in the EHP-30 Pain Domain scores from the pivotal phase 3 study Baseline
• Dysmenorrhea, as measured by the Numerical Rating Scale (NRS) for dysmenorrhea	• Change and percent change from the pivotal phase 3 study Baseline in the mean dysmenorrhea NRS score
• Patient Global Impression of Change (PGIC) for dysmenorrhea	• Proportion of patients who are “better” or “much better” on the PGIC for dysmenorrhea (at Week 52 only)
• Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP	• Change and percent change from the pivotal phase 3 study Baseline in the mean NMPP NRS score
• Overall pelvic pain, as measured by the NRS for overall pelvic pain	• Change and percent change from the pivotal phase 3 study Baseline in the mean overall pelvic pain NRS score
• Analgesic use	• Proportion of patients not using opioids (Week 104)[1]; • Proportion of patients not using analgesics (Week 104)[1]
• PGIC for NMPP	• Proportion of patients who are “better” or “much better” on the PGIC for NMPP (at Week 52 only)
• Dyspareunia, as measured by the NRS	• Change and percent change from the pivotal phase 3 study Baseline in the mean dyspareunia NRS scores
• PGIC for dyspareunia	• Proportion of patients who are” better” or “much better” on the PGIC for dyspareunia (at Week 52 only)

• Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B])	• Change and percent change from the pivotal phase 3 study Baseline in the mean dyspareunia functional impairment on the sB&B scale
• Patient Global Assessment (PGA) for pain	• Change from the pivotal phase 3 study Baseline in severity scores on the PGA for pain; • Proportion of Patients with Improvement, Worsening, No change from baseline;
• PGA for function	• Change from the pivotal phase 3 study Baseline in function impairment on the PGA for function; • Proportion of Patients with Improvement, Worsening, No Change from Baseline
• Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social • Support, Emotional Well-Being, and Self-Image domains	• Change from the pivotal phase 3 study in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image)
• Dysmenorrhea-related functional effects (sB&B)	• Change and percent change from the pivotal phase 3 study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B)
• NMPP-related functional effects (sB&B)	• Change and percent change from the pivotal phase 3 study Baseline pain assessment period in NMPP related functional effects (sB&B)
Safety	
• To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102), including: o Adverse events o Changes in bone mineral density (BMD)	To be assessed at Week 52 and Week 104 • Incidence of adverse events • Percent change from the pivotal phase 3 study Baseline to Week 52 or Week 104 in BMD at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA) To be assessed at 6-months and 12-months posttreatment: Percent change from the pivotal phase 3 study Baseline in BMD at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA.
Pharmacodynamic	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT601-3102), on estradiol	• Change from pivotal phase 3 study Baseline to Week 52 in pre-dose concentrations of serum estradiol • Change from pivotal phase 3 study Baseline to Week 104 in pre-dose concentrations of serum estradiol
Exploratory Efficacy	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), patient-reported quality of life outcomes (European Quality of Life Five Dimension Five-Level Scale [EQ-5D-5L]) for up to 104 weeks among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102)	To be assessed at Week 52 and Week 104 • Change from pivotal phase 3 study Baseline in the EHP-30 scale total score • Change from pivotal phase 3 study Baseline in the EHP Work Domain score. • Change from pivotal phase 3 study Baseline in the EQ-5D-5L

Abbreviations: DXA = dual-energy x-ray absorptiometry; E2 = estradiol; eDiary = electronic diary; EHP = Endometriosis Health profile; EOT = end-of-treatment; EQ-5D-5L = European Quality of Life Five-Domain Five-Level; NETA = norethindrone acetate;

NMPP = nonmenstrual pelvic pain; NRS = numerical rating scale; PGA = Patient Global Assessment; PGIC = Patient Global Impression of Change; QD = once daily; sB&B = Subject Modified Biberoglu and Behrman.
[1] These endpoints were analyzed at Week 104/EOT.

Co-primary efficacy endpoints

Dysmenorrhea: Proportion of patients who meet the dysmenorrhea responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary.

NMPP: Proportion of patients who meet the NMPP responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary.

Numerical Rating Scale (NRS) score

For an explanation on the NRS score.

Sample size

Because this was an extension study, the sample size was determined by the number of patients who completed pivotal study MVT-601-3101 or MVT-601-3102 and who were eligible and willing to participate in the extension study. It was estimated that this study would enroll approximately 800 patients (67% of the total number of patients enrolled in the pivotal studies).

Statistical methods

Analysis Populations

The Week 52 efficacy analyses for the Week 52 CSR included efficacy data for up to 52 weeks of treatment on the Extension Study Population. These Week 52 safety analyses included safety data for up to 52 weeks and post-treatment safety follow-up data as available at the time of the 52-Week database lock. The final analysis presented in this CSR includes efficacy data through the 30-day PTFU in the Extension Study Population as well as menses status follow-up through approximately 4 months post-treatment.

The Extension Study Population is defined as all patients who enrolled into MVT-601-3103 and received any amount of open-label study drug in MVT-601-3103. Efficacy analyses were performed by treatment group as randomized in the pivotal phase 3 study.

The Extension Safety Population was defined as all enrolled patients who received any amount of open-label study drug in MVT-601-3103, consistent with analysis in the pivotal phase 3 pivotal studies. Safety data were analyzed by pivotal phase 3 study treatment group according to the actual treatment received (not the randomized treatment in the pivotal phase 3 study).

Exclusion of Site 3015 from Efficacy and Safety Analyses.

Due to the results of an audit which found evidence of data integrity issues at Site 3015 (in Study MVT-601-3102), the data for 3 patients enrolled into the long term extension study at that site were excluded from all efficacy and safety analyses. The data for these 3 patients is presented in the disposition table and listing, and in the listing of patients excluded from efficacy and safety analyses.

Efficacy Analyses

Efficacy analyses were conducted using the Extension Study Population by pivotal phase 3 study treatment group. No formal treatment comparisons will be performed for this extension study. As there are no inferential statistics for these analyses, there was no need for multiplicity adjustment.

The pivotal study baseline will be used as the reference point for this extension study for the analyses of change from baseline.

For the final analyses, efficacy outputs include all data up to Week 104. Study visits include each monthly visit from Week 4 to Week 52 and each quarterly visit after Week 52.

Primary Efficacy Analyses

The primary endpoints are referred to as responder rates and derived on the basis of reduction of pain score and no increase in use of analgesic medications as recorded in a daily eDiary.

The primary efficacy endpoints of the study for the final analyses are for Week 52 and Week 104/EOT.

The primary efficacy endpoints of the study for the Week 52 and Week 104/EOT analyses were as for the pivotal studies.

The responder rate and two-sided 95% CI was presented by pivotal phase 3 study treatment group. No treatment comparisons were performed for this extension study.

Missing data

For the primary efficacy analysis, both primary endpoints will incorporate the missing data handling rules at Week 52, Week 104/EOT as follows: For patients missing eDiary for all visits in the extension study, their Baseline/Week 24 responder status from the pivotal phase 3 study will be carried over as their responder status to Week 52, Week 104/EOT.

- For patients who have any pain score entries in eDiary in the extension study, responder status for DYS and NMPP will be derived in the same way as for patients with at least 5 weeks of study treatment in the pivotal studies (see above).

Secondary Efficacy Analyses

All secondary efficacy measures over the course of both the pivotal phase 3 pivotal studies and the extension study are presented by the pivotal study treatment group using descriptive statistics. No treatment comparisons will be performed for this extension study.

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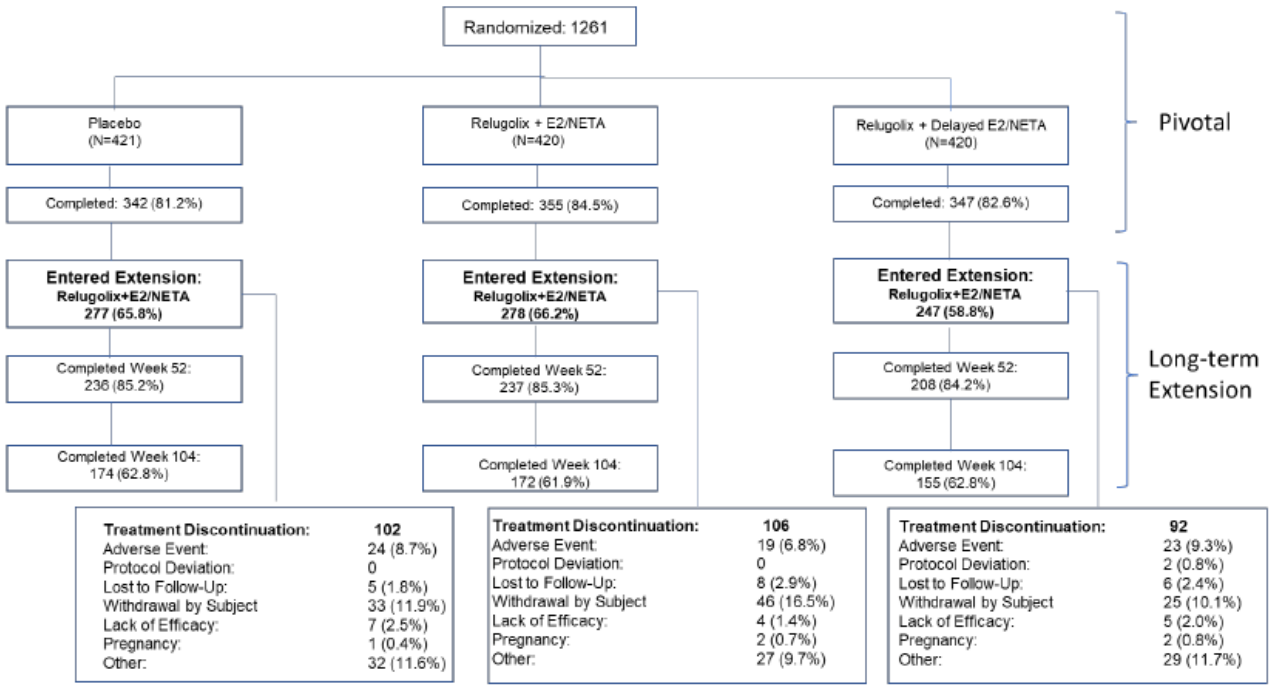
Participant flow

Figure 8. MVT-601-3103: Patient Disposition



A total 799 of the 802 patients enrolled in the study were included in the efficacy and safety analyses; 3 patients were excluded due to GCP noncompliance at one site (3015).

The percentage of the 799 patients who completed the pivotal studies, continued into the extension study, and included in the safety and efficacy analyses was generally similar across treatment groups (Figure 27)

Of 242 patients who completed the pivotal studies and did not enroll in this LTE, 16 patients (across both pivotal studies) were not eligible because they met the BMD loss exclusion criterion (2 in the relugolix + E2/NETA group, 13 in the relugolix + delayed E2/NETA group, and 1 in the placebo group). An additional 10 patients across both pivotal studies (5 in the relugolix + E2/NETA group, 4 in the relugolix + delayed E2/NETA group, and 1 in the placebo group) met the Z-score < -2.0 at any anatomic location exclusion criterion but did not meet BMD percentage decline criterion. In accordance with the eligibility criteria for study MVT-601-3103, no patient was enrolled with a Week 24 Z-score < 2.0 or ≥ 7% decline in BMD at any anatomical site.

Of the 802 patients who were enrolled in this LTE study, 681 patients (84.9%) completed 52 weeks of treatment and 501 patients (62.5%) of patients completed 104 weeks of treatment. The percentages of patients completing 52 weeks and 104 weeks of treatment were similar across the 3 treatment groups.

A total of 300 patients discontinued from the study early; the reasons for discontinuation were most commonly due to withdrawal by subject (104 patients [13.0%]) or due to other reasons (88 patients [11.0%]). Discontinuations due to adverse events were reported in 66 patients (8.2%). The reasons for discontinuing from the study were similar across the 3 treatment groups.

Protocol deviations

Table 35. MVT-601-3103: Summary of Important Protocol Deviations (mITT Population)

Protocol Deviation Category Subcategory	Relugolix+E2/NETA (N = 277)	Relugolix+Delayed E2/NETA (N = 247)	Placebo (N = 275)
Any Important Protocol Deviation n (%)	151 (54.5%)	128 (51.8%)	157 (57.1%)
Key Study Procedures Not Performed	116 (41.9%)	92 (37.2%)	116 (42.2%)
DXA Not Performed	45 (16.2%)	30 (12.1%)	42 (15.3%)
Endometrial Biopsy Not Done	40 (14.4%)	16 (6.5%)	31 (11.3%)
EHP-30 Pain Domain Not Completed At Week 52, Week 104, Or Early Termination Visit	26 (9.4%)	19 (7.7%)	16 (5.8%)
Endometrial Biopsy Specimen Inadequate, TVU Not Done	8(2.9%)	18 (7.3%)	18 (6.5%)
Mammogram Not Performed	14(5.1%)	13 (5.3%)	11 (4.0%)
Missed Week 52, Week 104, Or Early Termination Visit	13 (4.7%)	9 (3.6%)	14 (5.1%)
Safety Laboratory Test Not Performed For Two Or More Consecutive Visits	5 (1.8%)	11 (4.5%)	11 (4.0%)
TVU Shows Endometrial Thickness Is > 5mm. Repeat Endometrial Biopsy Not Done	6(2.2%)	4 (1.6%)	5 (1.8%)
Restricted Medications [1]	21 (7.6%)	19 (7.7%)	26 (9.5%)
Informed Consent [2]	17 (6.1%)	14 (5.7%)	16 (5.8%)
Study Drug	6 (2.2%)	8 (3.2%)	9 (3.3%)
Withdrawal Criteria [3]	8 (2.9%)	5 (2.0%)	6 (2.2%)
Withdrawal Criteria	8 (2.9%)	5 (2.0%)	6 (2.2%)
Safety	2 (0.7%)	7 (2.8%)	8 (2.9%)
Failure To Report Serious Adverse Events or Adverse Events of Clinical Interest	2 (0.7%)	7 (2.8%)	8 (2.9%)
Key Eligibility Criteria	2 (0.7%)	7 (2.8%)	2 (0.7%)
Excluded Device or Procedure	0	0	1 (0.4%)
Other [4]	27 (9.7%)	27 (10.9%)	23 (8.4%)

Date of database lock was 23 Feb 2022. Abbreviations: E2 = estradiol; TVU = transvaginal ultrasound; DXA = dual X-ray absorptiometry; n = number of patients; N = number of patients (MVT-601-3103) in the pivotal study (MVT-601-3101, MVT-601-3102) treatment group; NETA = norethindrone acetate. Events are sorted by decreasing frequency of category under relugolix + E2/NETA treatment in the pivotal study (MVT-601-3101, MVT-601-3102). Percentages are based on the total number of patients in each pivotal study (MVT-601-3101, MVT-601-3102) treatment group. At each level of summarization, patients are counted once only. [1] The category restricted medications was used for deviations related to the use of restricted medications [2] The category informed consent was used for deviations related timely re-consenting of patients when informed consent forms were updated. Informed consent deviations related to the original consent were reported as eligibility criteria deviations. [3] The category "withdrawal criteria" was used for deviations related to patients not being withdrawn from treatment in a reasonable timeframe once a withdrawal criterion was identified [4] The category "other" was used for deviations deemed important but for which there was not an existing important deviation category.

The most common important protocol deviations in the LTE study were related to key study procedures not performed. The frequency of individual missed key study procedures was generally similar across

treatment groups. The most common missed procedures were one or more DXA scan not performed (14.6%)

Recruitment
A total of 802 patients were enrolled at 171 centers globally, including the following: North America (United States [US]) and Rest of World (Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, Czech Republic, Finland, Georgia, Hungary, Italy, New Zealand, Poland, Portugal, Romania, South Africa, Spain, and Ukraine). A total of 799 patients were included in the efficacy and safety analyses; 3 patients were excluded due to GCP noncompliance (Site 3015).

The date first patient enrolled was 22 May 2018, the date last patient completed was 26 Jan 2022.

Conduct of the study

The original study Protocol (dated 06 Nov 2017), was amended 5 times:

The main purpose of protocol amendment 1 (20 Mar 2018) was to align the protocol with changes made to the pivotal study protocols (MVT-601-3101 amendment 1 and MVT-601-3102 amendment 1) such as the addition of the list of the allowed Tier 2 medications, addition of procedural details on short-term non-study specified analgesics for intercurrent events, changes to study vendor for safety reporting, updating to the most recent information on study drug storage requirements, etc.

The main purpose of protocol amendment 2 (11 Dec 2018) was to extend the study from 52 weeks of treatment to 104 weeks of treatment, inclusive of the 24 weeks of treatment in the pivotal study and to include an endometrial biopsy at Week 52 and an optional endometrial biopsy at Week 104/ EOT.

The main purpose of protocol amendment 3 (1 Jul 2020) was to include a mammogram at Week 52 or Week 104/EOT for women ≥ 40 years of age. Additionally, mitigation plans were included to ensure the safety of patients and minimize the risks to the integrity of the study for patients who remained enrolled during and after March 2020 due to national and local restrictions on movement, and for patient safety related to the global COVID-19 pandemic (see COVID19 Risk Management Plan, Appendix 16.1.12). Due to an administrative error within the document, this amendment was not sent to study sites, and amendment 3.1 (25 Aug 2020) directly superseded amendment 3.0.

The main purpose of protocol Amendment 4 (1 Jul 20201 was to add BMD PTFU for all study patients who were, at the time, within 14 month since their last dose of relugolix + E2/NETA, independent of BMD change during the study.

Baseline data

In general, demographics were consistent across the three treatment groups. The age range spanned 18 years to 50 years, 12.5% of patients were Hispanic or Latino, and 7.6% represented non-Whites.

Table 13. MVT-601-3103: Summary of Patient Demographics (Extension Study Population)

	Relugolix + E2/NETA (N=277)	Relugolix + Delayed E2/NETA (N=247)	Placebo (275)
Age (years)			
Mean (SD)	34.1 (6.55)	35.1 (6.49)	34.3 (6.48)

Age Category n (%)			
< 35 years	142 (51.3%)	114 (46.2%)	136 (49.5%)
>= 35 years	135 (48.7%)	133 (53.8%)	139 (50.5%)
Geographic Region n (%)			
North America	48 (17.3%)	46 (18.6%)	56 (20.4%)
Rest of World	229 (82.7%)	201 (81.4%)	219 (79.6%)
Race n (%)			
American Indian or Alaska Native	1 (0.4%)	1 (0.4%)	0
Asian	0	1 (0.4%)	0
Black or African American	17 (6.1%)	7 (2.8%)	13 (4.7%)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.4%)
White	254 (91.7%)	236 (95.5%)	248 (90.2%)

Date of database lock was 23 Feb 2022. Abbreviations: E2 = estradiol; N = number of patients (MVT-601-3103) in the pivotal study (MVT-601-3101, MVT-601-3102) treatment group; n = number of patients included in summary statistics; NETA = norethindrone acetate; SD = standard deviation.

Population analyzed

The number of patients included in each analysis set is presented in Table 37.

Table 37. MVT-601-3103: Number of Patients in Each Analysis Population by Treatment Group (All Patients Enrolled in the Extension Study)

	Relugolix+E2/NETA (N = 278)	Relugolix+Delayed E2/NETA (N = 247)	Placebo (N = 277)	Total (N = 02)
Extension Study Population	277 (99.6%)	247 (100.0%)	275 (99.3%)	799 (99.6%)
Extension Safety Population	277 (99.6%)	247 (100.0%)	275 (99.3%)	799 (99.6%)

Outcomes and estimation

A patient was defined as a responder for the dysmenorrhea primary endpoints if the NRS score for dysmenorrhea declined from baseline to the endpoint timepoint (Week 52 or Week 104/EOT) by at least 2.8 points without increased use of protocol-specified analgesics for pelvic pain at the endpoint timepoint (Week 52 or Week 104/EOT) relative to baseline. A patient was defined as a responder for the NMPP primary endpoints if the NRS score for NMPP declined from baseline to the endpoint timepoint (Week 52 or Week 104/EOT) by at least 2.1 points without increased use of protocol-specified analgesics for pelvic pain at the endpoint timepoint (Week 52 or Week 104/EOT) relative to baseline.

Dysmenorrhea Responder analysis

Table 38. MVT-601-3103: Primary Efficacy Analysis, Proportion of Patients Classified as Dysmenorrhea Responders at Week 52 and Week 104/EOT (Extension Study Population)

	Relugolix+Delayed	Placebo

	Relugolix+E2/NETA (N = 277)	E2/NETA (N = 247)	(N = 275)
Number (%) of responders [1] at Week 52	235 (84.8%)	203 (82.2%)	208 (75.6%)
(95% CI) [2]	(80.06%, 88.85%)	(76.83%, 86.75%)	(70.12%, 80.59%)
Number (%) of patients with a reduction of at least 2.8 points from baseline in mean dysmenorrhea NRS score at Week 52	250 (90.3%)	211 (85.4%)	216 (78.5%)
(95% CI) [2]	(86.14%, 93.48%)	(80.40%, 89.58%)	(73.22%, 83.25%)
Number (%) of patients with no increase in analgesic use from baseline at Week 52	259 (93.5%)	232 (93.9%)	256 (93.1%)
(95% CI) [2]	(89.92%, 96.10%)	(90.18%, 96.56%)	(89.42%, 95.79%)
Number (%) of responders [1] at Week 104/EOT	235 (84.8%)	205 (83.0%)	221 (80.4%)
(95% CI) [2]	(80.06%, 88.85%)	(77.72%, 87.46%)	(75.17%, 84.89%)
Number (%) of patients with a reduction of at least 2.8 points from baseline in mean dysmenorrhea NRS score at Week 104/EOT	246 (88.8%)	211 (85.4%)	227 (82.5%)
(95% CI) [2]	(84.49%, 92.27%)	(80.40%, 89.58%)	(77.53%, 86.84%)
Number (%) of patients with no increase in analgesic use from baseline at Week 104/EOT	264 (95.3%)	231 (93.5%)	265 (96.4%)
(95% CI) [2]	(92.11%, 97.48%)	(89.69%, 96.25%)	(93.41%, 98.24%)

Date of database lock was 23 Feb 2022.
Abbreviations: CI = confidence interval; E2 = estradiol; EOT = end of treatment; N = number of patients (MVT-601-3103) in the pivotal study (MVT-601-3101, MVT-601-3102) treatment group; NETA = norethindrone acetate; NRS = numerical rating scale. Percentage is based on the number of patients in the extension study population for each pivotal study (MVT-601-3101, MVT-601-3102) treatment group. [1] Responders are patients with a reduction of at least 2.8 points from baseline in mean dysmenorrhea NRS score and no increase from baseline in analgesic use. [2] Based on exact binomial 95% CI (Clopper-Pearson).

Nonmenstrual Pelvic Pain Responder Analysis

Table 39. MVT-601-3103: Primary Efficacy Analysis, Proportion of Patients Classified as Nonmenstrual Pelvic Pain Responders at Week 52 and Week 104/EOT (Extension Study Population)

	Relugolix+E2/NETA (N = 277)	Relugolix+Delayed E2/NETA (N = 247)	Placebo (N = 275)
Number (%) of responders [1] at Week 52	204 (73.6%)	174 (70.4%)	187 (68.0%)
(95% CI) [2]	(68.04%, 78.74%)	(64.33%, 76.06%)	(62.13%, 73.47%)
Number (%) of patients with a reduction of at least 2.1 points from baseline in mean NMPP NRS score at Week 52	210 (75.8%)	180 (72.9%)	191 (69.5%)
(95% CI) [2]	(70.33%, 80.74%)	(66.87%, 78.32%)	(63.64%, 74.84%)

Number (%) of patients with no increase in analgesic use from baseline at Week 52	259 (93.5%)	232 (93.9%)	256 (93.1%)
(95% CI) [2]	(89.92%, 96.10%)	(90.18%, 96.56%)	(89.42%, 95.79%)
Number (%) of responders [1] at Week 104/EOT	210 (75.8%)	177 (71.7%)	201 (73.1%)
(95% CI) [2]	(70.33%, 80.74%)	(65.60%, 77.19%)	(67.44%, 78.24%)
Number (%) of patients with a reduction of at least 2.1 points from baseline in mean NMPP NRS score at Week 104/EOT	215 (77.6%)	185 (74.9%)	206 (74.9%)
(95% CI) [2]	(72.25%, 82.39%)	(69.01%, 80.18%)	(69.35%, 79.92%)
Number (%) of patients with no increase in analgesic use from baseline at Week 104/EOT	264 (95.3%)	231 (93.5%)	265 (96.4%)
(95% CI) [2]	(92.11%, 97.48%)	(89.69%, 96.25%)	(93.41%, 98.24%)

Efficacy analyses in subgroups

For all subgroups, the relugolix + E2/NETA group, for both primary endpoints (dysmenorrhea and NMPP) showed consistent point estimates and confidence intervals for the subgroups, overlapping with those of the overall population.

Table 14. MVT-601-3103: Proportion of Patients Classified as Dysmenorrhea Responders at Week 104/EOT, Subgroup Analyses, Relugolix + E2/NETA Group

Subgroups	Category	Number of Evaluable patients	Number (%) of Responders [1]	95% CI [2]
Overall		277	235 (84.8%)	(80.06%, 88.85%)
Geographic region	North America	48	35 (72.9%)	(58.15%, 84.72%)
	Rest of World	229	200 (87.3%)	(82.32%, 91.35%)
Age (years)	< 35 years	142	114 (80.3%)	(72.78%, 86.48%)
	>= 35 years	135	121 (89.6%)	(83.21%, 94.21%)
Race	Black/African American	18	14 (77.8%)	(52.36%, 93.59%)
	White	258	220 (85.3%)	(80.35%, 89.36%)
BMI (kg/m^2) at baseline	< 25	161	142 (88.2%)	(82.19%, 92.74%)
	25 - < 30	65	56 (86.2%)	(75.34%, 93.47%)
	>= 30	51	37 (72.5%)	(58.26%, 84.11%)

Date of database lock was 23 Feb 2022. Abbreviations: BMI = body mass index; CI = confidence interval; E2 = estradiol; EOT = end of treatment; N = number of patients (MVT-601-3103) in the pivotal study (MVT-601-3101, MVT-601-3102) treatment group; NETA = norethindrone acetate. Percentage is based on the number of patients in the extension study population for each pivotal study (MVT-601-3101, MVT-601-3102) treatment group. [1] Responders are patients with a reduction of at least 2.8 points from baseline in mean dysmenorrhea NRS score and no increase from baseline in analgesic use. [2] Based on exact binomial 95% CI (Clopper-Pearson).

Table 41. MVT-601-3103: Proportion of Patients Classified as Nonmenstrual Pelvic Pain Responders at Week 104/EOT, Subgroup Analyses, Relugolix + E2/NETA Group

Subgroups	Category	Number of Evaluable patients	Number (%) of Responders [1]	95% CI [2]

Overall		277	210 (75.8%)	(70.33%, 80.74%)
Geographic region	North America	48	33 (68.8%)	(53.75%, 81.34%)
	Rest of World	229	177 (77.3%)	(71.31%, 82.55%)
Age (years)	< 35 years	142	108 (76.1%)	(68.18%, 82.81%)
	>= 35 years	135	102 (75.6%)	(67.42%, 82.54%)
Race	Black/African American	18	14 (77.8%)	(52.36%, 93.59%)
	White	258	196 (76.0%)	(70.28%, 81.05%)
BMI (kg/m^2) at baseline	< 25	161	125 (77.6%)	(70.41%, 83.82%)
	25 - < 30	65	49 (75.4%)	(63.13%, 85.23%)
	>= 30	51	36 (70.6%)	(56.17%, 82.51%)

Date of database lock was 23 Feb 2022. Abbreviations: BMI = body mass index; CI = confidence interval; E2 = estradiol; EOT = end of treatment; NETA = norethindrone acetate. [1] Responders are patients with a reduction of at least 2.1 points from baseline in mean NMPP NRS score and no increase from baseline in analgesic use. [2] Based on exact binomial 95% CI (Clopper-Pearson).

Secondary Efficacy Analyses

Secondary endpoints in this study included endpoints that were analogous to the key secondary endpoints for the pivotal studies.

The results supported that at 104 weeks, the magnitude of effect in the (former) relugolix + E2/NETA group is comparable or higher compared to Week 24, suggesting maintenance/ further improvement in NRS scores, EHP-30 pain domain and proportion of patients not using opioids/ analgesics.

2.4.4. Supportive study

TAK-385-3A, active controlled, 24 weeks

In this double-blind, active controlled phase 3 study, the efficacy, safety and pharmacodynamics of relugolix 40 mg monotherapy once daily for 24 weeks was compared with leuprorelin (subcutaneously once every 4 weeks at 3.75 or 1.88 mg) in patients with endometriosis.

The primary efficacy endpoint was "*Change from baseline in maximum of VAS score for endometriosis associated pelvic pain at the end of the treatment period (28 days)*". The change (mean ± SD) and the least squares means were-52.2 ± 24.7 and-52.6 in TAK-385, and -57.9 ± 21.7 and-57.5 in leuprorelin, respectively. With baseline as a covariate, the covariate-adjusted treatment difference was 4.9 and the upper of 95% CI was 8.7. Therefore, it was verified that TAK-385 was noninferior to leuprorelin because the upper of the 95% CI prespecified was <10.0. The efficacy of TAK-385 was verified. In addition, there were no new clinically relevant safety concerns, and TAK-385 was well tolerated, similar to the safety information in the package insert (uterine fibroids indication) for RELUMINA® Tablets 40mg.

2.4.5. Discussion on clinical efficacy

Design and conduct of clinical studies

Main efficacy studies (MVT-601-3101 and MVT-601-3102)

The two main studies were replicate pivotal phase 3 multi-national randomized, double-blind, placebo-controlled studies with relugolix combined therapy with E2/NETA (as separate tablets) (MVT-601-3101 and MVT-601-3102) conducted in the US (25%), Europe (60%) and rest of world (15%). The studies consisted of a screening visit, a run-in period (single-blind, 35 days), a randomized treatment period (double-blind, 24 weeks), and a safety follow-up period (approximately 30 days). The study also contained 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 of relugolix monotherapy with relugolix +E2/NETA. Both studies were adequate and well-designed.

All eligible women who completed the 24-week studies were offered the opportunity to enroll in an open-label efficacy and safety extension study (MVT-601-3103) of another 80 weeks (in total up to 104 weeks of active treatment).

Participants

In both studies, in total 1261 women participated (638 and 623, respectively). The study population consisted of premenopausal women, aged 18 to 50 years (mean 34 years) with moderate-to-severe pain associated with endometriosis at screening (diagnosed within 10 years before the trial by surgical or direct visualization and/or histopathologic confirmation of endometriosis). Diagnosis by transvaginal ultrasound or MRI allowed was not allowed.

For both pivotal studies together, 83.2% of the women had previous surgical interventions for endometriosis treatment and prior medication use for endometriosis was nearly universal at study entry (98.6%), nearly all patients (92.6%) used analgesics for pelvic pain, including 29.1% of patients in MVT-601-3101 and 48.4% of patients in MVT-601-3102 who used opioids. The most frequently reported previous pharmacotherapies for endometriosis included dienogest (19.4%), estrogen-progestin oral contraceptive (15.2%) and GnRH agonists (7.6%). Eight percent of the studied population did not have previous surgical or medical treatment before inclusion in the study, which is described in section 5.1 of the SmPC. The population enrolled in the pivotal phase 3 endometriosis studies with relugolix combination therapy is consistent with the standard of care for endometriosis in treatment guidelines. Administration of relugolix + E2/NETA as part of clinical trial participation represented de facto second-line treatment in the management of their disease. Product labelling reflects that Ryeqo is indicated for patients who have had prior management for endometriosis.

Before inclusion, patients had to have at least two cycles with moderate to severe pain (during the screening period and during the run-in period). This has been described in section 5.1 of the SmPC.

The inclusion criterion on moderate to severe pain score and NRS score are suitable to evaluate the selected co-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. The patient population was adequately selected to reflect the population of women with endometriosis.

Contraception

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 co-primary endpoints were:

- The proportion of patients who meet the dysmenorrhea responder criteria at the Week 24/EOT pain assessment period (The Week 24/EOT assessment period is defined as the 35 days up to and including the date of last dose of randomized study treatment, which should occur on the day prior to the Week 24/EOT visit), achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary
- The proportion of patients who meet the dysmenorrhea responder criteria at the Week 24/EOT pain assessment period (last 35 days of the specific period), achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary

in the relugolix + E2/NETA group vs. the placebo group.

Pain assessment was performed by the NRS score. The NRS score is one of the most commonly used and clinically accepted validated methods for measuring pain. Separate measures of dysmenorrhea and NMPP NRS are supported since treatment can lead to amenorrhoea. NRS is a verbal numeric scale, where the patient grades their own pain on a scale between 0 and 10. Both, the VAS (used in dose-finding stud) and the NRS are validated tools for measuring pain, and the terms are often used as equivalents.

Although the progestogen dienogest is also registered for treatment of endometriosis based on demonstrated reduction in pain scores for long-term use in the EU, the choice of a placebo group as comparator is considered accepted, as it also allows for a comparison of effects on bone mineral density versus placebo.

The additional arm of relugolix + delayed E2/NETA group, i.e relugolix monotherapy for 12 weeks followed by relugolix + E2/NETA for 12 weeks, was included to assess the efficacy of the addition of E2/NETA to relugolix in mitigating the adverse effects of the hypoestrogenic state (BMD loss (at 12 and 24 weeks) and vasomotor symptoms (at 12 weeks)) brought on by relugolix monotherapy.

Key secondary efficacy endpoints

There were seven predefined key secondary endpoints. The seven key secondary analysis consisted of the comparison between relugolix + E2/NETA group and the placebo group (hierarchical hypothesis tested).

These were related to the improvement on pain domain (EHP-30), dysmenorrhea, NMPP, overall pelvic pain and dyspareunia (NRS score), proportion of patients not using opioids and proportion of women not using analgesics (MVT-601-3101)/ change in mean analgesic pill count (MVT-601-3102). Measures chosen for assessment either are well established methods for evaluation of such endpoints or were validated to measure those outcomes. All hierarchical endpoints focused on pain which is acceptable as this is the main symptom. As all these endpoints relate to pain, a high degree of concordance is to be expected, thus explaining the large number of endpoints to be tested hierarchically.

Statistical methods

The randomization and blinding procedures are considered acceptable.

The sample size was based on detecting a 20% difference in responder rates between relugolix + E2/NETA and placebo for each co-primary endpoint, the responder rate for placebo was assumed to be 30-35%. The assumptions are reasonable, and the calculation is acceptable.

The primary analysis population is the mITT (defined as all randomized patients who received any amount of study drug (relugolix/placebo or E2/NETA/placebo) and the co-primary and secondary endpoint analyses are considered adequate and are acceptable.

The analysis of the primary endpoints uses a logistic regression model including baseline values and stratification factors. This is considered a standard method for dichotomous endpoints and is acceptable. Missing data for the primary endpoints was imputed based on the number of available days and menstruation status, imputing estimated change in scores under a missing at random (MAR) assumption. Sensitivity analyses were performed to test different missing data imputations (multiple imputation, observed cases). This can be acceptable as the amount of missing data is small and balanced.

Continuous secondary endpoints are tested using a mixed-effects model, dichotomous secondary endpoints are analysed using the Cochran-Mantel-Haenszel test. Both are considered appropriate for the type of endpoint. Multiplicity for the primary endpoints was handled by testing them as co-primary endpoints, secondary endpoints were tested according to a fixed sequence procedure, protecting the overall type I error rate.

The responder thresholds for the co-primary endpoints were determined at -2.8 points for dysmenorrhea and -2.1 points for NMPP. These thresholds were based on pooled blinded data of 1/3rd of the patients in MVT-601-3101 and MVT-601 and supported by the exit interviews collected in substudy MVT-601-038. Using cumulative distribution curves and probability density functions with patient global assessment as anchor is an acceptable method to define clinically meaningful thresholds. It was performed on blinded data, by an independent and external statistician and using a predefined analysis plan. However, the thresholds were not based on external data and are thus not considered to be formally validated and should be interpreted with caution.

Efficacy data and additional analyses

Primary efficacy analysis

Efficacy relugolix + E2/NETA versus placebo at Week 24

The co-primary efficacy endpoints were the **proportion of women** in the relugolix + E2/NETA group versus the placebo group who meet the dysmenorrhea/NMPP responder criteria at the Week 24/EOT pain assessment period, achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8/2.1 points, respectively and no increase in use of analgesic medications as recorded in a daily eDiary.

Both studies MVT-601-3101 and MVT-601-3102 the proportion of women in the relugolix + E2/NETA met both co-primary efficacy endpoints, in being statistically significantly superior compared with placebo. The results were consistent between the studies:

- For dysmenorrhea, the proportion of responders was 74.5% and 75.1%, respectively, which met the responders criteria in the relugolix combinations treatment group compared to 26.9% and 30.5% in the placebo group, respectively. The observed between group differences were 47.6% and 44.9%.

- For NMPP, the proportion of responders was 58.5% and 65.9%, respectively, which met the responders criteria in the relugolix combinations treatment group compared to 39.6% and 42.5% in the placebo group, respectively. The observed between group differences were 18.9% and 23.4%.

These difference in responder rate for dysmenorrhea and for NMPP are both statistically significant and can be considered clinically relevant (at least 20%). Sensitivity analyses of the primary endpoints all supported the observed treatment effect.

Secondary efficacy objectives - Relugolix + Delayed E2/NETA vs Placebo 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-601-3101, the proportion of responders for dysmenorrhea was 71.6% in the relugolix + delayed E2/NETA group. The observed difference with the placebo group was 44.7% in favour of the relugolix + delayed E2/NETA group. In study MVT-601-3102, the proportion of responders for dysmenorrhea was 72.8% in the relugolix + delayed E2/NETA group with an observed difference to the placebo of 42.4% in favour of the relugolix + delayed E2/NETA group which was statistically significant.

For NMPP, in MVT-601-3101, the proportion of responders in the relugolix + delayed E2/NETA group was 57.8% compared to 39.6% in the placebo group (between group difference 18.2%). In MVT-601-3102, the proportion of responders was respectively 52.9% and 42.5% (between group difference 10.3%).

These results are considered to confirm the treatment effect as captured in primary analysis, showing that the addition of E2/NETA did not result in a decrease in efficacy.

Key secondary efficacy endpoints

The seven key secondary endpoint outcomes are in support of the primary endpoint:

Results on the key secondary endpoints at Week 24:

The change in **EHP-30 pain domain (quality of life)** was in both studies statistically significantly greater in the relugolix + E2/NETA groups versus placebo (-33.8 and -32.2 vs -18.7 and -19.9).

The **changes in dysmenorrhea, NMPP, pelvic pain and dyspareunia** were a reduction of -5.1, -2.8, -3, -2.4 (mean of the two study point estimates), respectively in the relugolix + E2/NETA groups compared to -1.9, -2, -1.95 and -1.8 for placebo. The differences were all statistically significant.

The **proportion of patients not using opioids** was 85.8% in the relugolix combination treatment vs 66.2% in the placebo group in MVT-601-3101, and 82% vs. 66.2% in MVT-601-3102. For both studies, this difference between the active treatment group and placebo was statistically significant.

In MVT-601-3101, the 7th secondary endpoint was changed into **proportion of patients not using analgesics**. This was 56.1% in the relugolix+E2/NETA group compared to 30.7% in the placebo group ($p<0.0001$). In MVT-601-3102, the 7th secondary endpoint was **the change in mean analgesic pill**

count. The mean change in the relugolix +E2/NETA was -0.5 compared to -0.4 in the placebo group (p=0.1141).

Ancillary analyses (subgroup analyses) of the co-primary efficacy endpoints

Subgroup analyses were conducted for the co-primary efficacy endpoints by geographic region, time since surgical diagnosis of endometriosis (the two stratification factors at randomization), AFS endometriosis stage, age, race, ethnicity, BMI, dysmenorrhea NRS score at baseline, NMPP NRS score at baseline, and renal function based on the Cockcroft-Gault formula for calculated creatinine clearance.

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. Although relatively limited, there seemed a trend of a slightly reduced effect in patients with a higher BMI. According to the Applicant this might be due to chance.

Efficacy during open-label long term use up to 104 weeks

A total of 802 patients were enrolled in this open label long-term extension study, this was 63.6% of the patients randomized in the pivotal studies and 76.8% of those who completed the pivotal studies. A total of 62.5% (501 patients) completed the long-term extension study.

Efficacy primary endpoint

At the end of the open label long-term extension study (Week 104), 235 of 277 patients (84.8%) in the (former) relugolix + E2/NETA group met the primary endpoint for dysmenorrhea: a reduction of at least 2.8 points from baseline in mean dysmenorrhea NRS score and no increase from baseline in analgesic use. The proportion of responders increased during the first 24 Weeks, with a responder proportion of 62.8% at 8 weeks, and maintained during the long-term study period at levels between 82.7% and 84.8% in those patients who received relugolix + E2/NETA for the entire period of 104 weeks.

For NMPP (a reduction of at least 2.1 points from baseline in mean dysmenorrhea NRS score and no increase from baseline in analgesic use), the proportion of responders at 104 weeks was 210 out of 277 patients (75.8%) in the (former) relugolix + E2/NETA group. The proportion of responders increased during the first 16 weeks to 54.2% and to 66.4% at 24 Weeks. This increased to 75.8% after 52 weeks and remained at this level during treatment up to 104 weeks in those patients who received relugolix + E2/NETA for the entire period of 104 weeks.

Efficacy key secondary endpoints

At the end of the long-term study, patients in the (former) relugolix+E2/NETA group had received 104 weeks of relugolix combination therapy. The key secondary outcomes were as follows, the data at 24 Weeks are presented as pooled data from MVT-601-3101 and MVT-601-3102:

- EHP-30 pain domain: the change in LS mean was -41.3 at 104 weeks compared to -33.0 at 24 weeks, showing durability (and even slight increase) of the effect of relugolix.
- Dysmenorrhea NRS score: the change in LS mean at 104 weeks was -5.9, compared to -5.1 at 24 weeks, showing maintenance of the effect.
- NMPP NRS score: the effect on the NRS score for NMPP was slightly increased after 104 weeks (-4.0) compared to -2.8 at 24 weeks.

- Overall pelvic pain NRS score: change from baseline was -4.2 at 104 compared to -3.0 at 24 weeks
- Dyspareunia NRS score: also the change in NRS score for dyspareunia was higher after 104 weeks of treatment (-3.5) compared to 24 weeks (-2.4).
- Proportion of patients not using opioids; the proportion of patients not using opioids remained about the same (91% at 104 vs. 83.9% at 24 Weeks).
- Proportion of patients not using analgesics: the proportion of patients not using analgesics increased from 55.2% at 24 weeks to 75.1% after 104 weeks.

All key secondary endpoints show that treatment with relugolix + E2/NETA was associated with sustained improvements in endometriosis-associated pain for the duration of 104 weeks of treatment in those patients who received relugolix + E2/NETA for the entire period of 104 weeks. For patients who transitioned from placebo to relugolix combination therapy, results at Week 104 (i.e. after 80 weeks of relugolix + E2/NETA treatment) were similar to those of the relugolix combination therapy groups.

Other secondary endpoints

Secondary efficacy endpoints in supporting studies of efficacy included improvement in the EHP-30 (including the EHP-30 Pain Domain), dysmenorrhea, NMPP, overall pelvic pain, and dyspareunia. Additionally, onset of effect and change in protocol-specified rescue analgesic medications - tier 1 (ibuprofen) and tier 2 use (opioids) has been evaluated.

The improvements noted in PRO quality of life analyses (sB&B, EHP-30, PGA, and PGIC) are supportive of the noted improvement in the co-primary endpoints based on the NRS score.

Onset of effect

In the in the relugolix+E2/NETA treatment group, 16-19% met the responder criteria for dysmenorrhea after 4 weeks of treatment, and > 50% at 8 weeks. For NMPP, 14-22% met the responder criteria at 4 weeks and after 12-16 weeks this was ≥50%. For both endpoints, a proportion >50% was never reached in the placebo group.

Change in protocol-specified rescue analgesic medications - tier 1 (ibuprofen) and tier 2 use (opioids)

The mean (SD) number of Tier 1 (ibuprofen) decreased from baseline to 24 weeks/ EOT by 65% (mean (SD) decreased from 29.3 (36.0) to 10.1 (40.7) pills) in MVT-601-3101 and by 53.6% (from 24 to 9.3) in MVT-601-3102 for the relugolix combination treatment. For the placebo group this decrease was 51.4% (from 28.3 (39.7) to 11.0 (21.98) in MVT-601-3101 and 29.9% (from 26.8 (39.9) to 13.4 (30.2) in MVT-601-3102.

Tier 2 (opioids) use decreased from baseline to 24 weeks/EOT by 41% (mean (SD) decreased from 3.4 (9.9) to 2 (7.8) pills) and 75.7% (from 5.4 (13.0) to 1.4 (4.6)) in MVT-601-3101 and MVT-601-3102, respectively. For the placebo groups this decrease was 5.1% (from 3.9 (10.0) to 3.7 (19.4)) and 42.2% (from 5.8 (12.5) to 3.4 (12.5)), respectively. It is noted that there are quite some differences in the decrease in opioid use, both in the placebo as in the active treatment group, between the two replicate pivotal studies. The applicant explains that European women compared to North American and Latin American women, in general, take less opioids, which is acknowledged. The applicant also states that in MVT-601-3101 more European patients were included compared to MVT-601-3102, which is acknowledged as well.

Comparison of the effect in the dose-response study vs. the pivotal studies

The results of the co-primary endpoints in the pivotal phase 3 studies cannot be compared to the 3-armed phase II dose-response study (relugolix monotherapy (3 different doses) vs. placebo and leuprorelin). Although NRS and VAS are often used as if there are interchangeable, studies have shown strong similarities between those two scales, direct interchange is difficult. However, in all three studies strong reduction on dysmenorrhea was noted after 12 weeks (percent reduction in pain score of 79.3% and 80.3% in the phase 3 studies and 93.2% in the TAK-385/CCT-101 dose-finding study). Similarly in all 3 studies overall pelvic pain score was reduced at week 12, with 68.2% reduction in the TAK-385 40 mg group and 44.2% and 52.6% in the pivotal phase 3 studies.

Noteworthy is that for all these endpoints, the baseline measures in the dose-response study were considerably lower than in the pivotal studies.

Supportive studies

Patient reported outcome study (interview) – MVT-601-038

MVT-601 038, a substudy to MVT-601-3101 and MVT-601-3102, 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. Next to pain meaningful improvements, impact was measured by the EHP-30 scale to evaluate the burden of endometriosis from a patients' perspective and the relation between function and pain.

The study results suggest that these women could distinguish a clinically meaningful change in their symptomatology and supports the changes set for dysmenorrhea, NMPP and EHP-30. A limitation of the study was that the population (N=40, only from the US) was very small compared to the total number of subjects from MVT-601-3101 + MVT-601-3101 (samples were respectively N=537 and N=507, total US sample was 20% of this).

2.4.6. Conclusions on the clinical efficacy

Efficacy of relugolix + E2/NETA in patients with moderate to severe pain associated with endometriosis is shown to be superior to placebo in terms of a statistically and clinically relevant higher proportion of patients who met the responder criteria for reduction in dysmenorrhea and NMPP over a treatment period of 24 weeks as demonstrated in 2 very similarly designed phase 3 studies. The co-primary endpoints are supported by results of key secondary endpoints showing a clinically meaningful reduction in difficulties in daily activities (EHP-30 pain domain), NRS scores for dysmenorrhea, NMPP, dyspareunia and overall pelvic pain, and importantly, higher proportions of patients not using opioids and/ or analgesics compared to placebo. Results in the relugolix+ delayed E2/NETA groups are comparable to those in the relugolix + E2/NETA group.
The effect of relugolix+E2/NETA remained over the long-term open-label extension treatment period of 80 weeks (total duration of combination treatment up to 104 weeks) for the primary endpoints and the key secondary endpoints. A total of 84.8% of the patients in the relugolix+E2/NETA group met the responder criteria at week 104/EOT for dysmenorrhea and 75.8% for NMPP.

2.5. Clinical safety

Introduction

In the relugolix clinical development program on endometriosis, safety was evaluated based on the assessment of:

- Adverse events,
- Adverse events of clinical interest (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] $\geq 3 \times$ upper limit of normal [ULN], total bilirubin >2x ULN) clinical laboratory tests,
- Bone mineral density (BMD) measurements by dual-energy x-ray absorptiometry (DXA)
- Endometrial biopsies.
- 12 lead electrocardiogram (ECG) parameters,
- Vital sign measurements, 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-601-3101 and MVT-601-3102) along with supportive information from a long-term extension study (MVT-601-3103).

Since the initial aim of the endometriosis clinical development program was to develop relugolix as monotherapy in women for the short-term management of pain associated with endometriosis, single and multiple rising dose studies with relugolix monotherapy were conducted to establish initial safety and tolerability, and to inform dose selection. These results were reported in detail in the initial MAA for Ryeqo for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Three phase 2 studies were subsequently conducted in support of endometriosis and uterine fibroids.

The focus in this Safety section is on relugolix combination therapy in women with endometriosis. Two pooled safety populations, based on phase 3 studies in women with moderate to severe pain associated with endometriosis, are presented. In addition, a third population, based on completers of the pivotal phase 3 relugolix combination therapy studies who participated in an open-label extension study, see overview of the total safety base in the table below.

Table 42. Grouping of Studies and Treatments in the Integrated Safety Analysis Sets

Integrated Safety Analysis Set	Pooling Rationale	Studies Included	Treatment Groups Displayed in Outputs
Population 1 Endometriosis 24Week Combination Therapy Safety Population	This population of 1,251 women is the primary population used to assess the safety and tolerability of relugolix combination therapy (versus placebo) in women with pain associated with endometriosis.	MVT-601-3101 MVT-601-3102	relugolix + E2/NETA relugolix + delayed E2/NETA placebo

Population 2 Endometriosis LongTerm Combination Therapy Safety Population	This population of 1,251 women with up to 52 weeks on treatment is used to assess the long-term safety and tolerability of relugolix combination therapy in women with pain associated with endometriosis. It includes women from both the pivotal studies (up to Week 24) and those who enrolled in the open-label extension (through up to an additional 28 weeks of treatment) to provide a comprehensive denominator.	MVT-601-3101 MVT-601-3102 MVT-601-3103	relugolix + E2/NETA relugolix + delayed E2/NETA placebo
Population 3 Extension Safety Population	This population of 799 women with up to 104 weeks on treatment is used to assess additional safety and tolerability of relugolix combination therapy in women with pain associated with endometriosis. The population includes only women who competed the pivotal studies and enrolled in the open-label extension through two years of treatment.	MVT-601-3103	relugolix + E2/NETA relugolix + delayed E2/NETA placebo

Safety populations

Population 1: Endometriosis placebo-controlled 24-Week Combination Therapy Safety Population

In this population, safety data from the two replicate phase 3 studies MVT-601-3101 and MVT-601-3102, are pooled. This population, consisting of 1,251 patients, is considered the primary safety population and the basis of the safety profile of relugolix combination therapy in women with moderate to severe pain associated with endometriosis.

Population 2: Endometriosis Long-Term Combination Therapy Safety Population through Week 52

In this population, data from the two replicate phase 3, randomized, placebo controlled pivotal studies, MVT-601-3101 and MVT-601-3102, are pooled with Week 52 data from the long-term extension study for these pivotal studies. The population includes 799 patients from the pivotal studies who enrolled in the long-term extension study. Inclusion of patients from the pivotal studies and 28 weeks of the open-label extension permits inclusion of events from the first 52 weeks of treatment and does not censor events from patients who early terminated participation from either the pivotal or extension study. This analytical approach permits a conservative approach to risk assessment during the treatment period.

The data from this Endometriosis Long-Term Combination Therapy population through Week 52 also are presented as pooled data for all patients exposed to relugolix combination therapy at any time. These analyses provide a larger pool of data that starts for each patient when relugolix combination therapy was initiated. Adverse events with onset on or after Day 1 in relugolix + E2/NETA group; after the last dose of relugolix monotherapy in the relugolix + delayed E2/NETA group; and on or after the

first dose date of MVT-601-3103 study medication in the placebo group will be counted as adverse events occurring in the "Any relugolix + E2/NETA" (combination therapy) group.

Population 3: Extension Safety Population through Week 104

The Extension Safety Population includes those patients who had completed one of two pivotal studies, MVT-601-3101 or MVT-601-3102 (representing 24 weeks of treatment) and had enrolled into the extension study MVT-601-3103 (representing an additional 80 weeks of treatment). Thus, those patients that completed participation in the extension study represent up to 104 weeks of exposure to relugolix combination therapy. These data were summarized in the MVT-601-3103 CSR dated 21 July 2022. Data from Week 52 to Week 104 for these patients have not been included in the integrated analysis of the Endometriosis Long-Term Safety Population (Population 2) because their interval exposure to treatment was not associated with a change in the understanding of the safety profile. Therefore, data up to 104 weeks of treatment from MVT-601-3103 were not pooled with the two pivotal studies (MVT-601-3101 and MVT-601-3102) and are included separately, as appropriate, in this safety assessment.

Patient exposure

The overall extent of exposure to relugolix alone or in combination with E2 and NETA (relugolix combination therapy) in the clinical development program supporting this application is presented below:

Table 43. Number of Subjects Treated with Relugolix in Completed Trials (Safety Population)

Relugolix Treatment Group	Number of Subjects with ≥ 1 Dose	Number of Subjects with ≥ 6 Months	Number of Subjects with ≥ 12 Months	Number of Subjects with ≥ 18 Months	Number of Subjects with ≥ 24 Months
Any relugolix	4587	2652	1569	714	441
Any relugolix ≥ 40 mg	4116	2494	1569	714	441
Any relugolix monotherapy	3229	1210	620	76	49
1 mg	20				
5 mg	20				
10 mg	189	81			
20 mg	242	77			
40 mg	1361	157			
60 mg	86				
80 mg	132	63	57	42	28
120 mg	1066	832	563	34	21
160 mg	25				
180 mg	12				
360 mg	76				
Relugolix 40 mg (12 Weeks) followed by relugolix + E2/NETA	589	530	322	198	180
Relugolix 40 mg + E2/NETA	1381	912	627	440	212

Abbreviation: E2/NETA = estradiol/norethisterone acetate.
All studies for which study drug dosing was completed as of 25 May 2022 are included.
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; ≥ 48 weeks as ≥ 12 months; ≥ 72 weeks as ≥ 18 months; ≥ 96 weeks as ≥ 24 months.
Both co-administration and fixed dose combination of relugolix 40 mg and E2/NETA are included in 'relugolix 40 mg + E2/NETA.'
This table includes exposure from the following studies: For phase 1 (TAK-385-101, -102, -106, -1009, -1010, -1011, CPH-001, -010, C27001, C27005, TB-AK160108, MVT-601-1001, -1002, -1003, -1004, -036, -039, -40, -041, -042, -043, -044, -045, -046, -054 -055, -057), for phase 2 (TAK-385/CCT-001, CCT-101, OCT-101, C27002, C27003), for phase 3 (MVT-601-3001, -3002, -3003, -035, CCT-002, TAK-385-3008, MVT-601-3201, MVT-601-3101, -3102, -3103).
For the number of subjects with ≥ 1 dose, 612 participants across 5 studies (MVT-601-039, MVT-601-3001, MVT-601-3002, MVT-601-3101, MVT-601-3102) received ≥ 1 dose of 40 mg relugolix and ≥ 1 dose of relugolix 40 mg with E2/NETA and are thus included in both the monotherapy and combination therapy rows and Total.

Endometriosis 24-Week Combination Therapy Safety Population (population 1)

The extent of exposure to study drug in the Endometriosis 24-Week Combination Therapy Safety Population is presented in Table 44.

Table 15. Extent of Exposure: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Treatment duration (weeks)			
n	418	417	416
Mean (SD)	22.9 (6.17)	22.8 (5.89)	22.8 (6.00)
Median	24.7	24.9	24.7
Min, Max	0.1,29.1	0.7,30.0	0.1,28.9
Treatment duration category (weeks)			
≤ 4	14 (3.3%)	11 (2.6%)	11 (2.6%)
> 4 to ≤ 12	24 (5.7%)	28 (6.7%)	27 (6.5%)
> 12 to ≤ 24	98 (23.4%)	100 (24.0%)	102 (24.5%)
> 24 to ≤ 28	277 (66.3%)	275 (65.9%)	272 (65.4%)
> 28	5 (1.2%)	3 (0.7%)	4 (1.0%)

Abbreviations: E2 = estradiol; Max = maximum; Min = minimum; NETA = norethisterone acetate; SD = standard deviation. Treatment duration in weeks is calculated as (date of last dose – date of first dose + 1) / 7. Source: ISS Table 3.1.1, Module 5.3.5.3.

Population 2: Endometriosis Long-Term Combination Therapy Safety Population through Week 52

A summary of the extent of exposure for patients in the Endometriosis Long-Term Combination Therapy Safety Population is presented in Table . Because the Week 52 analysis visit window was up to 411 days (58.7 weeks), exposures included study drug taken up to the end of the analysis window (411 days).

Table 45. Extent of Exposure: Endometriosis Long-Term Combination Therapy Safety Population through Week 52 (MVT-601-3101, MVT-601-3102, MVT-601-3103)

Category	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)	Total (N = 1251)
Treatment duration (weeks)				
n	418	417	416	1251
Mean (SD)	40.41 (17.201)	38.42 (17.282)	40.16 (17.456)	39.66 (17.322)
Median	52.00	50.00	51.93	51.71
Min, Max	0.1, 60.0	0.7, 60.3	0.1, 60.3	0.1, 60.3
Treatment duration category (weeks), n (%)				
≤ 4	14 (3.3%)	11 (2.6%)	11 (2.6%)	36 (2.9%)
> 4 to ≤ 12	24 (5.7%)	28 (6.7%)	27 (6.5%)	79 (6.3%)
> 12 to ≤ 24	39 (9.3%)	51 (12.2%)	51 (12.3%)	141 (11.3%)
> 24 to ≤ 36	78 (18.7%)	92 (22.1%)	71 (17.1%)	241 (19.3%)
> 36 to ≤ 52	62 (14.8%)	61 (14.6%)	59 (14.2%)	182 (14.5%)
> 52	201 (48.1%)	174 (41.7%)	197 (47.4%)	572 (45.7%)

Treatment duration in extension study (weeks)a				
n	277	247	275	799
Mean (SD)	26.38 (5.698)	26.20 (6.134)	26.21 (6.674)	26.26 (6.175)
Median	28.00	28.00	28.00	28.00
Min, Max	2.1,33.6	1.4,36.4	0.1,36.3	0.1,36.4
Treatment duration category in extension study (weeks),[a] n (%)				
≤ 6	5 (1.8%)	5 (2.0%)	12 (4.4%)	22 (2.8%)
> 6 to ≤ 12	14 (5.1%)	13 (5.3%)	8 (2.9%)	35 (4.4%)
> 12 to ≤ 28	130 (46.9%)	108 (43.7%)	120 (43.6%)	358 (44.8%)
> 28	128 (46.2%)	121 (49.0%)	135 (49.1%)	384 (48.1%)
Treatment duration in combination therapy (weeks)				
n	418	373	275	1066
Mean (SD)	40.41 (17.201)	30.06 (14.431)	26.21 (6.674)	33.12 (15.378)
Median	52.00	39.86	28.00	29.43
Min, Max	0.1,60.0	0.1,49.0	0.1,36.3	0.1,60.0
Treatment duration category in combination therapy (weeks), n (%)				
≤ 4	14 (3.3%)	10 (2.7%)	9 (3.3%)	33 (3.1%)
> 4 to ≤ 12	24 (5.7%)	49 (13.1%)	11 (4.0%)	84 (7.9%)
> 12 to ≤ 24	39 (9.3%)	79 (21.2%)	19 (6.9%)	137 (12.9%)
> 24 to ≤ 36	78 (18.7%)	24 (6.4%)	235 (85.5%)	337 (31.6%)
> 36 to ≤ 52	62 (14.8%)	211 (56.6%)	1 (0.4%)	274 (25.7%)
>52	201 (48.1%)	0	0	201 (18.9%)

Abbreviations: E2 = estradiol; n = number of patients included in summary statistics; N = number of patients in the treatment group; NETA = norethisterone 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-601-3103), 2 treatment durations will be calculated separately based on 2 dates of first dose, one for the date of the first dose in the pivotal study, one for the date of first dose in the extension study. The date of last dose is the date of last dose in extension study. a Only applies for patients enrolled in extension study.

Population 3: Extension Safety Population through Week 104

A cumulative summary of exposure to relugolix + E2/NETA throughout the 104-week treatment period in the extension study population is presented in Table 46

Table 46. MVT-601-3103: Summary of Exposure to Relugolix + E2/NETA (Extension Safety Population)

	Mean (SD)[1]	<=6 Weeks	>6 to <=12 Weeks	>12 to <=24 Weeks	>24 to <=36 Weeks	>36 to <=52 Weeks
Relugolix + E2/NETA (N = 277)	87.0 (26.28)	0	0	0	14 (5.1%)	28 (10.1%)
Relugolix + delayed E2/NETA (N = 247)	75.0 (26.84)	0	0	12 (4.9%)	24 (9.7%)	31 (12.6%)
Placebo (N = 275)	63.2 (25.96)	12 (4.4%)	8 (2.9%)	18 (6.5%)	19 (6.9%)	17 (6.2%)

	>52 to <=65 weeks	>65 to <=78 weeks	>78 to <=91 weeks	>91 to <=104 weeks	>104 weeks
Relugolix + E2/NETA (N = 277)	30 (10.8%)	18 (6.5%)	9 (3.2%)	39 (14.1%)	139 (50.2%)
Relugolix + delayed E2/NETA (N = 247)	7 (2.8%)	12 (4.9%)	15 (6.1%)	146 (59.1%)	0
Placebo (N = 275)	16 (5.8%)	11 (4.0%)	174 (63.3%)	0	0

Date of database lock was 23 Feb 2022. Abbreviations: E2 = estradiol; N = number of patients (MVT-601-3103) in pivotal study (MVT-601-3101, MVT-601-3102) the treatment group; NETA = norethisterone acetate; R = relugolix; SD = standard deviation. Treatment duration is calculated as (last dose date of any study drug – first dose date of study drug + 1) / 7.
[1] The mean column depicts mean (SD) weeks of exposure.

Demographics

Demographics and other baseline characteristics of the Endometriosis 24-Week Combination Therapy Safety Population (Studies MVT-601-3101 and MVT-601-3102) are provided in Table 47. Patients in the pooled safety population 2 and the cumulative extension safety population 3 participated in MVT-601-3101 and MVT-601-3102, therefore demographics and baseline characteristics are the same as for Endometriosis 24-Week Combination Therapy Safety Population.

A high percentage of patients (83.2%) had undergone prior surgical interventions for endometriosis treatment. Baseline use of analgesics for pelvic pain was nearly universal (89.0% of patients) and 38.4% of patients used opioids at baseline.

Table 47. Demographics and Other Baseline Characteristics: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)	Total (N = 1251)
Age (years)				
n	418	417	416	1251
Mean (SD)	33.9 (6.50)	34.0 (6.75)	33.9 (6.52)	33.9 (6.59)

Age Category n (%)				
n	418	417	416	1251
< 35 years	223 (53.3%)	220 (52.8%)	216 (51.9%)	659 (52.7%)
≥ 35 years	195 (46.7%)	197 (47.2%)	200 (48.1%)	592 (47.3%)
Geographic Region n (%)				
n	418	417	416	1251
North America	90 (21.5%)	91 (21.8%)	89 (21.4%)	270 (21.6%)
Rest of World	328 (78.5%)	326 (78.2%)	327 (78.6%)	981 (78.4%)
Age category (years)				
n	418	417	416	1251
< 30 years	108 (25.8%)	108 (25.9%)	113 (27.2%)	329 (26.3%)
30 - < 35 years	115 (27.5%)	112 (26.9%)	103 (24.8%)	330 (26.4%)
35 - < 40 years	106 (25.4%)	101 (24.2%)	113 (27.2%)	320 (25.6%)
≥ 40 years	89 (21.3%)	96 (23.0%)	87 (20.9%)	272 (21.7%)
Body mass index (kg/m^2)				
n	418	417	416	1251
Mean (SD)	25.9 (6.22)	26.0 (6.01)	25.9 (6.22)	25.9 (6.15)
Median	24.2	25.0	24.1	24.4
Min, Max	17.1, 55.7	14.5, 62.8	17.2, 58.6	14.5, 62.8
Body mass index (kg/m^2)				
n	418	417	416	1251
< 18.5	9 (2.2%)	13 (3.1%)	18 (4.3%)	40 (3.2%)
18.5 to < 25	226 (54.1%)	192 (46.0%)	213 (51.2%)	631 (50.4%)
25 to < 30	96 (23.0%)	121 (29.0%)	87 (20.9%)	304 (24.3%)
≥ 30	87 (20.8%)	91 (21.8%)	98 (23.6%)	276 (22.1%)
Race n (%)	418	417	416	1251
n				
American Indian or Alaska Native	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)
Asian	0	2 (0.5%)	0	2 (0.2%)
Black or African American	27 (6.5%)	20 (4.8%)	24 (5.8%)	71 (5.7%)
Native Hawaiian or Other Pacific Islander	0	2 (0.5%)	1 (0.2%)	3 (0.2%)
White	380 (90.9%)	382 (91.6%)	376 (90.4%)	1138 (91.0%)
Other	4 (1.0%)	6 (1.4%)	9 (2.2%)	19 (1.5%)
Multiple	6 (1.4%)	4 (1.0%)	5 (1.2%)	15 (1.2%)
Not Reported	0	0	0	0
Ethnicity n (%)	418	417	416	1251
n				
Not Hispanic or Latino	373 (89.2%)	362 (86.8%)	362 (87.0%)	1097 (87.7%)
Hispanic or Latino	43 (10.3%)	53 (12.7%)	53 (12.7%)	149 (11.9%)
Not Reported	2 (0.5%)	2 (0.5%)	1 (0.2%)	5 (0.4%)
Time since surgical diagnosis of endometriosis (years)				
n	418	417	416	1251

Median	3.2	3.2	3.2	3.2
Min, Max	0.1, 19.3	0.1, 21.5	0.1, 15.4	0.1, 21.5
Dysmenorrhea NRS score at Baseline				
n	418	417	416	1251
Median	7.2	7.0	7.1	7.1
Min, Max	1.5, 10.0	1.6, 10.0	1.6, 10.0	1.5, 10.0
NMPP NRS score at Baseline				
n	418	417	416	1251
Median	6.0	5.8	5.9	5.9
Min, Max	1.7, 9.8	1.4, 10.0	1.5, 10.0	1.4, 10.0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients included in summary statistics; NETA = norethisterone acetate; SD = standard deviation.

Adverse events

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

The overall incidence of adverse events was higher in the relugolix + E2/NETA group relative to the placebo group (75.8% vs. 70.4%). Incidence was highest (79.4%) in the relugolix + delayed E2/NETA group. Treatment discontinuations due to an adverse event were reported with higher frequency in the relugolix + E2/NETA group (4.5%) relative to the placebo group (2.9%) and highest in the relugolix + delayed E2/NETA group (5.8%).

Adverse events assessed as related to study drug by the investigator were reported at higher frequencies in the relugolix + E2/NETA group compared with the placebo group, with the highest frequency of events in the relugolix + delayed E2/NETA group. These findings were consistent across the two pivotal studies.

Endometriosis Long-Term Combination Therapy (population 2)

The overall incidence of adverse events was generally similar across all three treatment groups with numerically higher incidences in the relugolix + delayed E2/NETA or placebo groups relative to the relugolix + E2/NETA group in the categories of adverse events leading to treatment discontinuation, treatment interruption, related to study drug, and serious adverse events. In the relugolix + E2/NETA group, in which patients were exposed for up to 52 weeks of treatment with relugolix combination therapy, fewer events across all categories of adverse events were accrued over the additional 28 weeks of exposure, relative to those reported over the initial 24 weeks. The adverse event profile over 52 weeks 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.

Extension Safety Population through Week 104 (Population 3)

The overall incidence of adverse events in the extension safety population was generally similar across all three treatment groups with numerically higher incidences in the relugolix + delayed E2/NETA or placebo groups relative to the relugolix + E2/NETA group in the categories of adverse events leading to treatment discontinuation, treatment interruption, related to study drug, and serious adverse events. In the relugolix + E2/NETA group, cumulatively over the 104-week treatment period, in which patients were exposed for up to 104 weeks of treatment with relugolix combination therapy, fewer events across all categories of adverse events were accrued over the additional 80 weeks of exposure,

relative to those reported over the initial 24 weeks. The adverse event profile over 104 weeks 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.

Common adverse events

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

A summary of adverse events reported in at least 2% of patients in any treatment group for the Endometriosis 24-Week Combination Therapy Safety Population is presented in Table 48.

Table 48. Summary of Adverse Events Reported in at Least 2% of Patients in Any Treatment Group by Preferred Term: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102 Pooled)

Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Patients with ≥ 1 adverse event, n (%)	317 (75.8%)	331 (79.4%)	293 (70.4%)
Headache	138 (33.0%)	146 (35.0%)	110 (26.4%)
Hot flush	50 (12.0%)	143 (34.3%)	28 (6.7%)
Nasopharyngitis	42 (10.0%)	24 (5.8%)	29 (7.0%)
Nausea	25 (6.0%)	18 (4.3%)	17 (4.1%)
Toothache	23 (5.5%)	10 (2.4%)	10 (2.4%)
Back pain	20 (4.8%)	19 (4.6%)	12 (2.9%)
Bone density decreased	16 (3.8%)	21 (5.0%)	9 (2.2%)
Libido decreased	16 (3.8%)	15 (3.6%)	5 (1.2%)
Urinary tract infection	15 (3.6%)	19 (4.6%)	11 (2.6%)
Arthralgia	15 (3.6%)	19 (4.6%)	9 (2.2%)
Influenza	14 (3.3%)	14 (3.4%)	10 (2.4%)
Fatigue	13 (3.1%)	11 (2.6%)	10 (2.4%)
Dizziness	13 (3.1%)	9 (2.2%)	5 (1.2%)
Metrorrhagia	13 (3.1%)	3 (0.7%)	6 (1.4%)
Upper respiratory tract infection	12 (2.9%)	13 (3.1%)	13 (3.1%)
Mood swings	10 (2.4%)	12 (2.9%)	9 (2.2%)
Diarrhoea	10 (2.4%)	12 (2.9%)	8 (1.9%)
Depression	10 (2.4%)	4 (1.0%)	7 (1.7%)
Vulvovaginal dryness	9 (2.2%)	15 (3.6%)	2 (0.5%)
Alopecia	9 (2.2%)	9 (2.2%)	15 (3.6%)
Acne	9 (2.2%)	8 (1.9%)	24 (5.8%)
Oedema peripheral	9 (2.2%)	3 (0.7%)	4 (1.0%)
Insomnia	8 (1.9%)	13 (3.1%)	9 (2.2%)
Migraine	8 (1.9%)	13 (3.1%)	6 (1.4%)
Hyperhidrosis	8 (1.9%)	10 (2.4%)	5 (1.2%)
Sinusitis	7 (1.7%)	9 (2.2%)	9 (2.2%)
Weight increased	6 (1.4%)	9 (2.2%)	7 (1.7%)
Bronchitis	6 (1.4%)	9 (2.2%)	4 (1.0%)
Anaemia	6 (1.4%)	3 (0.7%)	10 (2.4%)

Vomiting	5 (1.2%)	10 (2.4%)	4 (1.0%)
Vitamin D decreased	5 (1.2%)	8 (1.9%)	18 (4.3%)
Cystitis	2 (0.5%)	9 (2.2%)	6 (1.4%)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate. 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 group, followed by the relugolix + delayed E2/NETA group, followed by the placebo group. MedDRA version 22.0.

The review of the adverse event profile of the Endometriosis 24-Week Combination Therapy Safety Population in women was informed by the adverse drug reactions for other approved products, including GnRH agonists and antagonists (eg, leuprorelin, elagolix (approved in US, but not in EU) with and without E2/NETA, and relugolix combination therapy), and for E2/NETA.

In the Endometriosis 24-Week Combination Therapy Safety Population, adverse events reported in at least 2% of patients in the relugolix + E2/NETA group compared with the placebo group, respectively, are: headache (33.0% vs. 26.4%), hot flush (12.0% vs. 6.7%), metrorrhagia (3.1% vs. 1.4), back pain (4.8% vs. 2.9%), libido decreased (3.8% vs. 1.2%), arthralgia (3.6% vs. 2.2%), hyperhidrosis (1.9% vs. 1.2%), vulvovaginal dryness (2.2% vs. 0.5%), and toothache (5.5% vs. 2.4%).

Adverse events associated with a hypoestrogenic state including hot flush, hyperhidrosis, and vulvovaginal dryness were reported at a greater frequency in the relugolix + E2/NETA group than in the placebo group; however, such events were reported at a lower rate than in the relugolix + delayed E2/NETA group, which supports the value of combination therapy in enhancing tolerability.

Summary of Overall Incidence of Common Adverse Events

Endometriosis Long-Term Combination Therapy (population 2)

In patients receiving relugolix + E2/NETA for up to 52 weeks, the majority of adverse events were reported in < 5% of patients. A comparison of the frequency of common adverse events during the first 24-weeks of treatment in the relugolix + E2/NETA group to those reported cumulatively through Week 52 of treatment in this group showed no evidence of a time-dependent incremental increase in events (ie, more than what would be expected given the longer follow-up). Events reported in patients previously on placebo and subsequently on relugolix + E2/NETA for 6 months help to highlight those events that are likely to be causally related to relugolix + E2/NETA (libido decreased and metrorrhagia) and those events (for which frequency is not disproportionately increased) that are less likely to be causally related (eg, headache, back pain, arthralgia).

Extension Safety Population through Week 104 (Population 3)

Evaluation of trends through up to 104 weeks of treatment did not suggest a disproportionate increase in events relative to that observed with shorter duration of treatment up to 24 weeks during the randomized placebo-controlled period.

Treatment-related adverse events

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

In the Endometriosis 24-Week Combination Therapy Safety Population, the incidence of drug-related adverse events was higher in the relugolix + E2/NETA group (47.4%) compared with the placebo group (37.5%). The incidence of most drug-related adverse events was small and similar between treatment groups. Adverse events of hot flush related to study drug, not unexpectedly, were reported with a notably higher frequency in the relugolix + delayed E2/NETA group compared with the relugolix + E2/NETA group and the placebo group. The most frequently reported drug-related adverse event in

any treatment group (≥ 5% in any treatment group) was hot flush, reported in 11.7%, 33.6%, and 6.5% of patients in the relugolix + E2/NETA, relugolix + delayed E2/NETA, and placebo groups, respectively. In addition, headache was reported most frequently in 17.0%and 13.5% of patients in the relugolix + E2/NETA and placebo groups, respectively.

Endometriosis Long-Term Combination Therapy (population 2)

Adverse events related to the study drug in patients treated with relugolix + E2/NETA for up to 52 weeks were, most commonly, headache (20.1%), hot flush (13.4%), and bone density decreased (5.7%). The frequency of these events did not disproportionally increase with long term treatment compared with the first 24 weeks of treatment in the pivotal studies where the incidences of these related events was 17.0% (headache), 11.7% (hot flush), and 3.8% (bone density decreased). Bone mineral density-related adverse events were reported predominantly by a single site, contrary to adverse event reporting guidelines and, thus, reporting was not systematic. As such, the frequency of these adverse events is not interpretable.

All other related adverse events during long-term treatment with relugolix + E2/NETA were reported with a frequency < 5%. The incidence of drug-related events during treatment with relugolix + E2/NETA across all treatment groups was consistent with the above observations.

Extension Safety Population through Week 104 (Population 3)

In the relugolix + E2/NETA group, adverse events assessed by the investigator as related to study drug were reported for 172 patients (62.1%). Over the 104-week treatment in the pivotal phase 3 studies and the LTE study, the most frequently reported adverse events assessed as related to study drug included headache (71 patients [25.6%]), hot flush (38 patients [13.7%]) and bone density decrease (25 patients [9.0%]). Of the patients with a reported related event of headache over the course of the 104-week treatment, the event was first reported during the LTE study in 12 patients (4.3%). Of the patients with a reported related event of hot flush over the course of the 104-week treatment, the event was first reported during the LTE study in 7 patients (2.5%). Of the patients with a reported related event of bone density decreased over the course of the 104-week treatment, the event was first reported during the LTE study in 9 patients (3.2%).

Summary of Drug-Related Adverse Events

Adverse events related to the study drug in patients treated with relugolix + E2/NETA for up to 52 weeks were, most commonly, headache (20.1%), hot flush (13.4%), and bone density decreased (5.7%). The types of adverse events most commonly reported as related were similar across the first 24 weeks of treatment and cumulatively through Week 52 of treatment in the relugolix combination studies and their frequency did not disproportionally increase with long term treatment compared with the first 24 weeks of treatment in the pivotal studies. One of the most common related adverse events are known adverse effects of hypoestrogenism (hot flush). Through 104 weeks, there was no pattern or trend suggesting an increased frequency in events related to relugolix + E2/NETA with the longer duration of exposure in MVT-601-3103.

Adverse drug-reactions

Adverse drug reactions associated with relugolix combination therapy were assessed by review of adverse events observed at a frequency of **≥ 3% for relugolix combination therapy and at greater frequency than placebo** (based on the observed frequencies of adverse events at higher incidence than placebo in the context of sample size), with consideration of other supporting data inclusive of medical judgment. Certain adverse drug reactions were identified at a frequency < 3%

based on considerations including frequency relative to placebo, biological plausibility, temporality, and medical judgment. Table 49 summarizes adverse events reported that were identified as adverse drug reactions using the ICH E2A definition. The 3% threshold was selected based on the observed frequencies of adverse events at higher incidence than placebo in the context of the sample size.

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Table 49. Adverse Drug Reactions: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

Adverse Reaction	Relugolix + E2/NETA (N = 418) %	Placebo (N = 416) %
Headache	33.0	26.4
Hot flush, hyperhidrosis, or night sweats	12.9	7.2
Abnormal uterine bleeding [1]	6.7	4.6
Back pain	4.8	2.9
Libido decreased [2]	4.1	1.2
Arthralgia	3.6	2.2

Abbreviations: E2 = estradiol; NETA = norethisterone acetate.
[1] Includes menorrhagia, metrorrhagia, vaginal haemorrhage, uterine haemorrhage, polymenorrhoea, and menstruation irregular.
[2] Includes libido decreased and libido disorder.

The adverse drug reactions included in tabular format in section 4.8 of the SmPC are presenting the pooled numbers of AEs, which were assessed by investigators as study drug related observed in both indications and considered as ADRs. The studies included are MVT-601-3001 and MVT-601-3002 (Uterine fibroids) and MVT-601-3101 and MVT-601-3102 (endometriosis).

2.5.1.1. Description of Selected Adverse Events

In the Endometriosis 24-Week Combination Therapy Safety Population, adverse events reported in at least 2% of patients in the relugolix + E2/NETA group compared with the placebo group, respectively, are described in greater detail below.

Headache

Headache was the most commonly reported AE and was reported at a higher frequency in the relugolix + E2/NETA group (33.0% [138 patients]) than that reported in the placebo group (26.4% [110 patients]). Headaches were typically grade 1 or 2 in severity and rarely (≤ 0.5% in either group) resulted in study drug discontinuation. Grade 3 headaches were reported for 1.7% of patients (7 patients) in the relugolix + E2/NETA group and 0.5% of patients (2 patients) in the placebo group. In approximately half of patients with at least one AE of headache, the event was considered related to study drug by the investigator (17.0% [71 patients] in the relugolix + E2/NETA group and 13.5% [56 patients] in the placebo group)

Hot flush and hyperhidrosis

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

A summary of all adverse events consistent with vasomotor symptoms in the Endometriosis 24-Week Combination Therapy Safety Population by PT is presented in the table below.

The predefined statistical comparison of the incidence of vasomotor symptoms reported by Week 12 between the relugolix + E2/NETA group and the relugolix + delayed E2/NETA groups is provided in the table below:

Table 50. Vasomotor Symptoms by Preferred Term: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Patients with ≥ 1 adverse event of vasomotor symptom n (%)	55 (13.2%)	145 (34.8%)	30 (7.2%)
Hot flush	50 (12.0%)	143 (34.3%)	28 (6.7%)
Hyperhidrosis	8 (1.9%)	10 (2.4%)	5 (1.2%)
Night sweats	5 (1.2%)	6 (1.4%)	0
Flushing	1 (0.2%)	0	0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate. 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 in the relugolix + E2/NETA group, followed by the relugolix + delayed E2/NETA group, followed by the placebo group. Vasomotor symptoms includes preferred terms of hyperhidrosis, feeling hot, hot flush, night sweats, and flushing. MedDRA version 22.0.

Table 51. Summary of Incidence Rate of Vasomotor Symptoms by Week 12: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)
Incidence rate of vasomotor symptoms		
n (%)	40 (9.57%)	135 (32.37%)
(95% CI)[a]	(6.92%, 12.80%)	(27.90%, 37.10%)
Treatment comparison – Relugolix+E2/NETA versus Relugolix+Delayed E2/NETA		
Relative risk (95% CI)b	0.30 (0.21,0.41)	
P-value[c]	< 0.0001	

Abbreviations: E2 = estradiol; CI = confidence interval; N = number of patients in the treatment group; NETA = norethisterone acetate. Vasomotor symptom includes preferred terms of hyperhidrosis, feeling hot, hot flush, night sweats, and flushing. a Based on exact binomial 95% CI (Clopper-Pearson). b relugolix + E2/NETA over relugolix + delayed E2/NETA. c P-value is based on Fisher's exact test.

In the pooled Endometriosis 24-Week Combination Therapy Safety Population, vasomotor symptom events were reported with the lowest frequency in the placebo group (7.2%) and higher frequency in the relugolix + E2/NETA group (13.2%). The highest frequency, as expected, was in the relugolix + delayed E2/NETA group (34.8%, 145 patients).

Treatment with relugolix combination therapy significantly reduced the incidence of vasomotor symptoms by 70% (relative risk of 0.3 [95% CI: 0.21, 0.41]; $p < 0.0001$) relative to relugolix monotherapy ($p < 0.0001$), demonstrating the benefit of the combination therapy in mitigating vasomotor symptoms.

Endometriosis Long-Term Combination Therapy (population 2)

A summary of all adverse events consistent with vasomotor symptoms in the Endometriosis Long-Term Combination Therapy Safety Population by PT is presented in Table 52

Table52. Vasomotor Symptoms by Preferred Term: Endometriosis Long-Term Combination Therapy Safety Population through Week 52 (MVT-601-3101, MVT-601-3102, and MVT-601-3103)

Preferred Term	Relugolix + E2/NETA (N=418)	Relugolix + Delayed E2/NETA (N=417)	Placebo (N=416)	Any Relugolix+ E2/NETA (N=1066)
Patients with ≥ 1 AE of vasomotor symptoms n (%)	64 (15.3%)	154 (36.9%)	45 (10.8%)	110 (10.3%)
Hot flush	58 (13.9%)	151 (36.2%)	42 (10.1%)	101 (9.5%)
Hyperhidrosis	10 (2.4%)	11 (2.6%)	6 (1.4%)	13 (1.2%)
Night sweats	6 (1.4%)	7 (1.7%)	1 (0.2%)	8 (0.8%)
Flushing	1 (0.2%)	0	0	1 (< 0.1%)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate. Patients with multiple events for a given preferred term are counted only once for each preferred term. Any Relugolix + E2/NETA summarizes any adverse events reported in the treatment period of relugolix + E2/NETA Events are sorted by decreasing frequency of categories in the any relugolix + E2/NETA group, followed by relugolix + E2/NETA group, followed by the relugolix + delayed E2/NETA group, followed by the placebo group. Vasomotor symptoms includes preferred terms of hyperhidrosis, feeling hot, hot flush, night sweats, and flushing. MedDRA version 22.0.

The incidence of vasomotor symptoms in the pooled Endometriosis Long-Term Combination Therapy Safety Population showed little incremental increase in these symptoms with continued long-term treatment with relugolix + E2/NETA through Week 52. The incidence of vasomotor symptoms in the relugolix + E2/NETA group in the pivotal studies was 13.2% (55 patients) (Table 69) compared with 15.3% (64 patients) (Table 71) through 52 weeks of treatment. Similarly, the comparable incidences in the relugolix + delayed E2/NETA group were 34.8% and 36.2%. In the placebo group, in which patients received relugolix + E2/NETA during the long-term extension study, the incidence of vasomotor symptoms increased minimally in comparison with the pivotal studies (10.8% versus 7.2%). When examined by time interval, the onset of vasomotor symptoms in patients treated with relugolix + E2/NETA was most common in the first 28 days (3.4%) and second 28 days (Days 29 to 56) (2.3%) of treatment.

Endometriosis Extension Safety Population through Week 104 (population 3)

The incidence of vasomotor symptoms in the Extension Safety Population are presented cumulatively through Week 104 and with new onset during the LTE study in Table .

Table 53. MVT-601-3103: Summary of Vasomotor Symptoms by Preferred Term through Week 104 (Extension Safety Population)

	Relugolix + E2/NETA (N = 277)		Relugolix + Delayed E2/NETA (N = 247)		Placebo (N = 275)	
Preferred Term	**Cumulative**	**LTE**	**Cumulative**	**LTE**	**Cumulative**	**LTE**
Patients with at least one AE of vasomotor symptoms n (%)	46 (16.6%)	12 (4.3%)	107 (43.3%)	10 (4.0%)	43 (15.6%)	23 (8.4%)
Hot flush	41 (14.8%)	9 (3.2%)	106 (42.9%)	8 (3.2%)	40 (14.5%)	22 (8.0%)
Hyperhidrosis	9 (3.2%)	3 (1.1%)	9 (3.6%)	1 (0.4%)	5 (1.8%)	1 (0.4%)

Night sweats	4 (1.4%)	1 (0.4%)	5 (2.0%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Flushing	1 (0.4%)	0	0	0	0	0

Date of database lock was 23 Feb 2022. Abbreviations: AE = adverse event; E2 = estradiol; LTE = Long-Term Extension (study); N = number of patients (MVT-601-3103) in the pivotal study (MVT-601-3101, MVT-601-3102) treatment group; n = number of patients with AE of interest; NETA = norethisterone acetate. Percentages are based on the total number of patients in each pivotal study (MVT-601-3101, MVT-601-3102) 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 in the pivotal study (MVT-601-3101, MVT-601-3102) under Cumulative column. Vasomotor symptoms include preferred terms of Hyperhidrosis, Feeling hot, Hot flush, Night sweats and Flushing. MedDRA (version 22.0).

In the relugolix + E2/NETA group, the cumulative incidence of vasomotor adverse events was 16.6% (46 patients). The incidence of vasomotor adverse events declined with long-term treatment with relugolix + E2/NETA.

Metrorrhagia / change in bleeding pattern

The core safety information for relugolix combination therapy includes a warning and precaution about potential changes in bleeding pattern that may occur with treatment including amenorrhea or a reduction in the amount, intensity, or duration of menstrual bleeding, which may delay the ability to recognize pregnancy.

Changes in bleeding pattern were assessed in the relugolix combination therapy studies from the daily electronic diary (eDiary) in which patients entered their menstruation status each day. When menstruating, they also recorded the intensity of bleeding as spotting, light, moderate, heavy, or very heavy.

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Bleeding pattern

Bleeding profile categories are presented in Table . Observed bleeding profiles during the first 90 days showing that more patients in the relugolix + E2/NETA group (15.2%) compared with the placebo group (2.7%) had frequent bleeding indicating > 5 days of bleeding/spotting during the 90-day bleeding profile period and that more patients in the relugolix + E2/NETA group (53.5% of patients) had an infrequent bleeding profile (1-2 bleeding/spotting episodes during the 90-day period) compared with the placebo group (6.7%).

From days 91 to end of treatment (EOT), the most common bleeding profile among patients in the relugolix + E2/NETA group (58.1%) was no bleeding during the entire 90-day period. In contrast, the most common profile in the placebo group was normal bleeding (65% of patients).

Table 54. Summary of Bleeding Profile Categories: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

Period **Bleeding Profile Category**	**Relugolix + E2/NETA (N = 418)**	**Relugolix + Delayed E2/NETA (N = 417)**	**Placebo (N = 416)**
Study Treatment Days 1-90			
n	376	374	374
No bleeding	15 (4.0%)	41 (11.0%)	3 (0. 8%)

Prolonged bleeding	13 (3.5%)	7 (1.9%)	6 (1.6%)
Irregular bleeding	62 (16.5%)	39 (10.4%)	42 (11.2%)
Frequent bleeding	57 (15.2%)	3 (0.8%)	10 (2.7%)
Infrequent bleeding	201 (53.5%)	251 (67.1%)	25 (6.7%)
Normal bleeding	28 (7.4%)	33 (8.8%)	288 (77.0%)
Study Treatment Days 91 to EOT			
n	358	349	346
No bleeding	208 (58.1%)	157 (45.0%)	5 (1.4%)
Prolonged bleeding	5 (1.4%)	17 (4.9%)	5 (1.4%)
Irregular bleeding	37 (10.3%)	47 (13.5%)	64 (18.5%)
Frequent bleeding	35 (9.8%)	42 (12.0%)	11 (3.2%)
Infrequent bleeding	56 (15.6%)	61 (17.5%)	36 (10.4%)
Normal bleeding	17 (4.7%)	25 (7.2%)	225 (65.0%)

Bleeding intensity

Bleeding intensity was ascertained in patients who still reported bleeding. At Week 24, for example, 95 patients in the relugolix + E2/NETA group and 282 patients in the placebo group reported bleeding. Among those still reporting bleeding at each post-baseline timepoint, the intensity of bleeding was lower in the relugolix + E2/NETA group compared with the placebo group.
These findings are consistent with the effects of reduced and stable concentrations of estrogen and progesterone/progestin in the relugolix group, even among those who did not achieve amenorrhea.

Bleeding days

During the run-in period, the distribution of days with no bleeding, spotting, light, moderate, heavy, and extremely heavy bleeding was similar in all three treatment groups. In the relugolix + E2/NETA group the number of days with no bleeding increased steadily while days with moderate, heavy, and extremely heavy bleeding declined steadily during the 24-week treatment period. During the 28-day interval prior to Week 24, the number of days of moderate bleeding or heavy bleeding was 0.5 and there were no days of extremely heavy bleeding. The average number of days with spotting was 0.9. In the placebo group, by comparison, at Week 24, the number days of moderate bleeding or heavy bleeding days was 2.0 and there were 0.3 days of extremely heavy bleeding. The average number of days with spotting was 1.4.

Adverse event related to uterine bleeding

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Table 55. Uterine Bleeding-Related Events: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

Visit Days in Bleeding Intensity Category	Relugolix + E2/NETA (N=418)	Relugolix + Delayed E2/NETA (N=417)	Placebo (N=416)
Patients with ≥ 1 adverse event of bleeding events[a], n (%)	28 (6.7%)	23 (5.5%)	19 (4.6%)
Metrorrhagia	13 (3.1%)	3 (0.7%)	6 (1.4%)
Vaginal haemorrhage	8 (1.9%)	8 (1.9%)	4 (1.0%)
Menorrhagia	4 (1.0%)	7 (1.7%)	7 (1.7%)
Menstruation irregular	3 (0.7%)	2 (0.5%)	1 (0.2%)
Uterine haemorrhage	2 (0.5%)	2 (0.5%)	1 (0.2%)
Polymenorrhoea	1 (0.2%)	0	0
Menometrorrhagia	0	1 (0.2%)	0

Abbreviations: E2 = estradiol; N = number of patients in the pivotal study treatment group; n = number of patients with adverse event; NETA = norethisterone acetate.
Percentages are based on the total number of patients in each pivotal study treatment group.
Events are sorted by decreasing frequency of preferred term in the relugolix + E2/NETA group.
Includes preferred term of Menorrhagia, Metrorrhagia, Menstruation irregular, Uterine haemorrhage, Vaginal haemorrhage, Menometrorrhagia, Polymenorrhoea.
a This SMQ was initially developed for the uterine fibroid program and thus the same terms were used for the analyses for the endometriosis studies to allow pooling of data. The term of dysfunctional uterine bleeding was additionally reported in the endometriosis studies in one patient in study MVT-601-3101 (relugolix + delayed E2/NETA) and one patient in study MVT-601-3102 (relugolix + E2/NETA) and are not included in the above table.
MedDRA version 22.0.

In the Endometriosis 24-Week Combination Therapy Safety Population, the overall incidence of uterine bleeding adverse events was similar in both treatment groups (6.7% and 4.6% in the relugolix + E2/NETA and placebo groups, respectively).

Bleeding intensity

Bleeding intensity was ascertained in patients who still reported bleeding. At Week 24, for example, 95 patients in the relugolix + E2/NETA group and 282 patients in the placebo group reported bleeding. Among those still reporting bleeding at each post-baseline timepoint, the intensity of bleeding was lower in the relugolix + E2/NETA group compared with the placebo group.
These findings are consistent with the effects of reduced and stable concentrations of estrogen and progesterone/progestin in the relugolix group, even among those who did not achieve amenorrhea.

Bleeding days

During the run-in period, the distribution of days with no bleeding, spotting, light, moderate, heavy, and extremely heavy bleeding was similar in all three treatment groups. In the relugolix + E2/NETA group the number of days with no bleeding increased steadily while days with moderate, heavy, and

extremely heavy bleeding declined steadily during the 24-week treatment period. During the 28-day interval prior to Week 24, the number of days of moderate bleeding or heavy bleeding was 0.5 and there were no days of extremely heavy bleeding. The average number of days with spotting was 0.9. In the placebo group, by comparison, at Week 24, the number days of moderate bleeding or heavy bleeding days was 2.0 and there were 0.3 days of extremely heavy bleeding. The average number of days with spotting was 1.4.

Adverse event related to uterine bleeding

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Table Metrorrhagia was reported for 13 (3.1%) patients in the relugolix + E2/NETA group and 6 (1.4%) patients in the placebo group. All uterine bleeding-related events were grade 1 or 2 in severity. Consistent with bleeding pattern data showing a low percentage of patients with prolonged or frequent bleeding while on treatment relugolix arm, the incidence of adverse events of menorrhagia was low with relugolix + E2/NETA (1.0%) and comparable to placebo (1.7%).

Endometriosis Long-Term Combination Therapy (population 2)

The incidence of uterine bleeding events in the relugolix + E2/NETA group increased minimally with long-term treatment through Week 52 (7.9% [33 patients] \compared with that observed during the pivotal studies (6.7% [28 patients]) . A similar finding was observed in the relugolix + delayed E2/NETA group (7.0% and 5.5%, respectively). In the placebo group, the percentage of uterine bleeding events increased from 4.6% during the pivotal studies to 10.3% cumulatively, likely reflecting both the change in treatment to relugolix + E2/NETA and longer duration of follow-up.

Extension Safety Population through Week 104 (Population 3)

A summary of adverse events within a custom MedDRA SMQ "uterine bleeding-related events" for the Extension Safety Population is presented in Table 56.

Table 56. Summary of Uterine Bleeding Adverse Events by Preferred Term through Week 104 (Extension Safety Population)

Preferred Term	Relugolix + E2/NETA (N = 277)	Relugolix + Delayed E2/NETA (N = 247)	Placebo (N = 275)	Total (N = 799)
No. of patients with at least one AE n (%)	23 (8.3%)	26 (10.5%)	46 (16.7%)	95 (11.9%)
Metrorrhagia	14 (5.1%)	8 (3.2%)	20 (7.3%)	42 (5.3%)
Menorrhagia	5 (1.8%)	8 (3.2%)	16 (5.8%)	29 (3.6%)
Menstruation irregular	4 (1.4%)	2 (0.8%)	10 (3.6%)	16 (2.0%)
Vaginal haemorrhage	3 (1.1%)	7 (2.8%)	3 (1.1%)	13 (1.6%)
Menometrorrhagia	0	1 (0.4%)	0	1 (0.1%)
Polymenorrhoea	0	1 (0.4%)	1 (0.4%)	2 (0.3%)
Uterine haemorrhage	0	2 (0.8%)	1 (0.4%)	3 (0.4%)

Date of database lock was 23 Feb 2022. Abbreviations: AE = adverse event; E2 = estradiol; N = number of patients (MVT-601-3103) in the pivotal study (MVT-601-3101, MVT-601-3102) treatment group; n = number of patients with AE of interest; NETA = norethisterone acetate. Percentages are based on the total number of patients in each pivotal study (MVT-601-3101, MVT-601-

3102) treatment group or total. Patients with multiple events for a given preferred term are counted only once for each preferred term. Event of uterine bleeding includes MedDRA preferred terms: menorrhagia, metrorrhagia, menstruation irregular, vaginal haemorrhage, menometrorrhagia, polymenorrhoea, and uterine haemorrhage. MedDRA (version 22.0).

In the relugolix + E2/NETA group, cumulatively, 23 patients (8.3%) had uterine bleeding-related events and all events were nonserious. Of these 23 patients, 6 patients had events with an onset on or prior to Day 30 and 9 patients had events with an onset on or prior to Day 60.

In the relugolix + delayed E2/NETA group, cumulatively, 26 patients (10.5%) had uterine bleeding-related events and all events were nonserious. Bleeding-related events were first reported during the LTE study in 11 patients (4.5%).

In the placebo group, cumulatively, 46 patients (16.7%) had uterine bleeding-related events and all but one event which was associated with uterine fibroids, were nonserious. Bleeding-related events were first reported during the LTE study in the 32 (11.6%) patients. The majority of the events reported during the LTE (25 of 32 patients) had an onset within 60 days following the Week 24 visit target date.

Amenorrhea

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Amenorrhea, based on the patient's daily menstruation status as reported in the eDiary, was defined as the lack of bleeding for at least 56 consecutive days after starting randomized study treatment.

In the relugolix + E2/NETA group, the rate of women achieving amenorrhea during the preceding 56-day interval increased during the study starting at Week 12 and reaching a level above 60% starting at Week 20 whereas there was no change over time in the placebo group where amenorrhea rates were < 2% at all time intervals.

By Week 24, sustained amenorrhea (defined as lack of bleeding for at least 56 days that continued until the last dose of randomized treatment), was observed in 56.7% and 1.9% of patients in the relugolix + E2/NETA group and placebo group, respectively.

Endometriosis Long-Term Combination Therapy (population 2)

At Week 24 and Week 52, respectively, the proportion of patients with amenorrhea was 61.5% (188 patients) (95% CI: 62.0, 73.3) and 76.6% (180 patients) (95% CI: 70.7, 81.9).

Extension Safety Population through Week 104 (Population 3)

At Week 104, of patients remaining on treatment, 82.3% (107/130) of patients in the relugolix + E2/NETA group, 74.1% (86/116) of patients in the relugolix + delayed E2/NETA group, and 76.2% (96/126) of patients were amenorrheic during the preceding 28-day interval. The percentages were similar at Week 104/EOT in the relugolix + E2/NETA and relugolix + delayed E2/NETA groups and lower in the placebo group (76.9%, 72.9%, and 68.0%, respectively) (Table 8.4.7.1.3, MVT-601-3103 104-week CSR).

Resumption of menstruation

Menstruation status was evaluated at the 30-day PTFU after patients prematurely discontinued or completed study drug treatment in the LTE study. Patients without an explanation (eg, surgery, drug treatment) for absence of menses during this time period were to be contacted by telephone

approximately 3 months after the follow-up visit to ascertain resumption of menses or reasons for non-resumption (eg, surgery, drug treatment, pregnancy, etc.).

The median time to resumption of menses was 33.0 days, 32.0 days, and 32.0 days in the relugolix + E2/NETA group, relugolix + delayed E2/NETA group, and placebo group, respectively. These median resumption times were similar to those reported for patients discontinuing treatment at or prior to Week 52 (33.0, 32.0, and 31.0 days, respectively), showing that longer duration of treatment with relugolix + E2/NETA, up to 104 weeks, does not prolong time to return of menses. Over 90% of patients resumed menses within 2 months of stopping the study drug.

Back pain

Back pain was reported at a numerically higher frequency in the relugolix + E2/NETA group (4.8% [20 patients]) compared with the placebo group (2.9% [12 patients]). None of the events were serious, resulted in study drug discontinuation, or study drug interruption. Most of these events were of grade 1 or 2 severity. Nearly all of these events were considered unrelated to the study drug by the investigator. In the relugolix + E2/NETA group, there was no pattern in terms of the timing of the onset of back pain.

Back pain is one of the most common symptoms reported by women with endometriosis and is sometimes described as a manifestation of pelvic pain ("pelvic pain spreading towards the back") (Fauconnier et al. 2013; Maddern et al. 2020). The relationship between estrogen and back pain is not clearly established.

Given that back pain is part of the symptom complex of endometriosis and the significant efficacy of relugolix + E2/NETA in reducing pelvic pain when rigorously and quantitatively assessed (Module 2.7.3 EM), the small numerical imbalance in adverse event reporting may be a spurious finding.

Libido decreased

Libido decreased was reported at a numerically higher frequency in the relugolix + E2/NETA group (3.8% [16 patients]) compared with the placebo group (1.2% [5 patients]). None of the events were serious (ISS Table 4.19.1, Module 5.3.5.3). One event in the relugolix + E2/NETA group (grade 2 in severity) resulted in treatment discontinuation. The onset of this event in the relugolix + E2/NETA group was predominantly in the first 12 weeks of treatment (14 patients) with few patients reporting new events of libido decreased beyond this time point through Week 52.

Vulvovaginal dryness

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Vulvovaginal dryness was reported at a numerically higher frequency in the relugolix + E2/NETA group (2.2% [9 patients]) and relugolix + delayed E2/NETA group (3.6% [15 patients]) compared with the placebo group (0.5% [2 patients]). None of the events were serious, one event in the relugolix + delayed E2/NETA group resulted in study drug discontinuation, none of the events resulted in study drug interruption, and none were grade 3 or higher. In the relugolix + E2/NETA group, the majority of these events had an onset during the first 12 weeks of treatment (9 patients) and none were reported after Week 24. While vulvovaginal dryness is a hypoestrogenic effect, among patients receiving relugolix + E2/NETA, the incidence of this event was low (2.2%), self-limited in the majority, and not treatment-limiting.

Extension Safety Population through Week 104 (Population 3)

Cumulatively, during the pivotal and LTE studies, for the (former) Relugolix+E2/NETA group, vulvovaginal dryness was reported for 25 patients (9.0%) and 15 patients (5.4%). Of these, 24 (8.7%) and 14 (5.1%) were considered treatment related.

Arthralgia

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Arthralgia was reported at a numerically higher frequency in the relugolix + E2/NETA group (3.6% [15 patients]) compared with the placebo group (2.2% [9 patients]). None of the events were serious or resulted in study drug interruption. Arthralgia resulted in study drug discontinuation in 1 patient in the placebo group. Most of these events were of grade 1 or 2 severity.

Arthralgia was considered related to the study drug by the investigator for 2.2% (9 patients) in the relugolix + E2/NETA group and in 1.0% (4 patients) in the placebo group. In the relugolix + E2/NETA group, there was no pattern in terms of the timing of the onset of arthralgia.

Hypoestroegenemia, through its effect on inflammatory cytokines, has been hypothesized to be a mechanism of the well-described arthralgia associated with aromatase inhibitors used in the treatment of breast cancer (Niravath 2013).

Extension Safety Population through Week 104 (Population 3)

Cumulatively, during the pivotal and LTE studies, arthralgia was reported for 20 patients (7.2%) and 9 patients (3.2%). Of these, 10 and 4 were considered study treatment related adverse events.

Toothache

Toothache was reported at a numerically higher frequency in the relugolix + E2/NETA group (5.5% [23 patients]) than in the placebo group (2.4% [10 patients]). None of the events was serious or resulted in study drug interruption. With the exception of 1 patient in the relugolix + E2/NETA group whose toothache started on Day 7 and resolved on Day 35, without treatment and without change in study drug dosing, none of the events were considered related to study drug or resulted in study drug discontinuation. These observations, lack of biological plausibility, and the lack of a signal for toothache events (1.6% [4 patients] in the relugolix + E2/NETA group and 0.4% [1 patient]) in the uterine fibroid pivotal phase 3 studies (ISS Table 4.3.1, UF ISS, marketing application for Ryeqo for the management of symptoms associated with uterine fibroids), suggest that the imbalance may have been a spurious finding.

Vaginal Infections

Vaginal infection adverse events (vaginal infection, vulvovaginal mycotic infection, vulvovaginal candidiasis, bacterial vaginosis, and vaginal discharge) were reported with similar frequency across both treatment groups: 2.9% (12 patients) in the relugolix + E2/NETA group and 2.4% (10 patients) in the placebo group.

2.5.1.2. Safety parameters of interest

Effect on Bone Mineral Density

- ***Adverse Events Related to Bone Mineral Density and Fractures***

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

A summary of all adverse events potentially related to loss of bone mass reported in the Endometriosis 24-Week Combination Therapy Safety Population by PT is presented in Table 57Table 57. Bone density was formally evaluated with DXA scanning in all patients at protocol-specified time points. Bone mineral density-related adverse events were reported predominantly by a single site, contrary to adverse event reporting guidelines and, thus, reporting was not systematic. As such, the frequency of these adverse events is not interpretable.

Table 57. Adverse Event Category - Loss of Bone Mineral Density or Fractures by Decreasing Frequency of Preferred Term: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Patients with ≥ 1 adverse event of loss of bone mineral density or fractures, n (%)	18 (4.3%)	24 (5.8%)	13 (3.1%)
Bone density decreased	16 (3.8%)	21 (5.0%)	9 (2.2%)
Osteopenia	1 (0.2%)	4 (1.0%)	1 (0.2%)
Traumatic fracture	1 (0.2%)	0	0
Foot fracture	0	1 (0.2%)	1 (0.2%)
Clavicle fracture	0	1 (0.2%)	0
Hand fracture	0	0	2 (0.5%)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate; SMQ = Standardised MedDRA Query. 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". MedDRA version 22.0.

Bone fractures were reported in 6 patients in total across all 3 treatment groups (1 in the relugolix + E2/NETA group, 2 in the relugolix + delayed E2/NETA group and 3 in the placebo group). An increase in fractures was not expected in the relugolix + E2/NETA group compared with the placebo group and was not observed.

Endometriosis Long-Term Combination Therapy (population 2)

A summary of all adverse events potentially related to loss of bone mass reported in the Endometriosis Long-Term Combination Therapy Safety Population (studies MVT-601-3101, MVT-601-3102, and MVT-601-3103) is presented in Table 58.

Table 58. Adverse Event Category - Loss of Bone Mineral Density by Decreasing Frequency of Preferred Term: Endometriosis Long-Term Combination Therapy Safety Population through Week 52 (MVT-601-3101, MVT-601-3102, MVT-601-3103)

Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Patients with ≥ 1 adverse event of loss of bone mineral density, n (%)	26 (6.2%)	36 (8.6%)	21 (5.0%)
Bone density decreased	24 (5.7%)	28 (6.7%)	17 (4.1%)
Osteopenia	1 (0.2%)	8 (1.9%)	2 (0.5%)

Fibula fracture	1 (0.2%)	2 (0.5%)	0
Traumatic fracture	1 (0.2%)	0	0
Tibia fracture	0	2 (0.5%)	0
Foot fracture	0	1 (0.2%)	1 (0.2%)
Clavicle fracture	0	1 (0.2%)	0
Hand fracture	0	0	2 (0.5%)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate; SMQ = Standardised MedDRA Query. Treatment groups were as received in studies MVT-601-3101 and MVT-601-3102. 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.

There were no new fracture events in patients who had been randomized at pivotal study baseline to relugolix + E2/NETA or placebo. Four new fracture events were reported for two patients in MVT-601-3103, both of whom had been randomized at pivotal study baseline to relugolix + delayed E2/NETA.

Extension Safety Population through Week 104 (Population 3)

In the Extension Safety Population, bone health events through 104 weeks were reported for 10.1% (28 patients) in the relugolix + E2/NETA group with 1 fracture event that occurred during the run-in period, one during the pivotal phase 3 study MVT-601-3102 that resolved during MVT-601-3103, and a new event that occurred during MVT-601-3103. The corresponding numbers in the placebo group were 7.6% (21 patients) with bone events and 3 fracture events during the pivotal phase 3 studies and none during the 80 weeks of MVT-601-3103. In the relugolix + delayed E2/NETA group, bone health events were reported for 15.0% (37 patients) among which were 2 fracture events during the pivotal studies and 4 fracture events in two patients, which occurred during MVT-601-3103.

- Percent Change from Baseline in Bone Mineral Density

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Data for least squares (LS) mean percent changes in BMD as measured at the lumbar spine and total hip have been pooled for the pivotal phase 3 studies (MVT-601-3101 and MVT-601-3102) and a summary is presented in 2.7.4 – Table 33 and Figure 28.

- *Lumbar Spine Bone Mineral Density*

To evaluate the effect of relugolix + E2/NETA compared with relugolix monotherapy on BMD, the LS mean percent change from baseline to Week 12 in BMD at the lumbar spine in the relugolix + E2/NETA group was compared with that of the relugolix + delayed E2/NETA group. The between-group difference at Week 12 was 1.28% (95% CI: 0.97%, 1.59%), which was statistically significant ($p < 0.0001$), favoring the relugolix + E2/NETA group. This finding further demonstrated the value of using relugolix in combination with E2/NETA from the start of treatment to minimize bone loss associated with relugolix monotherapy and is consistent with what was observed in the individual pivotal studies.

- *Total Hip Bone Mineral Density*

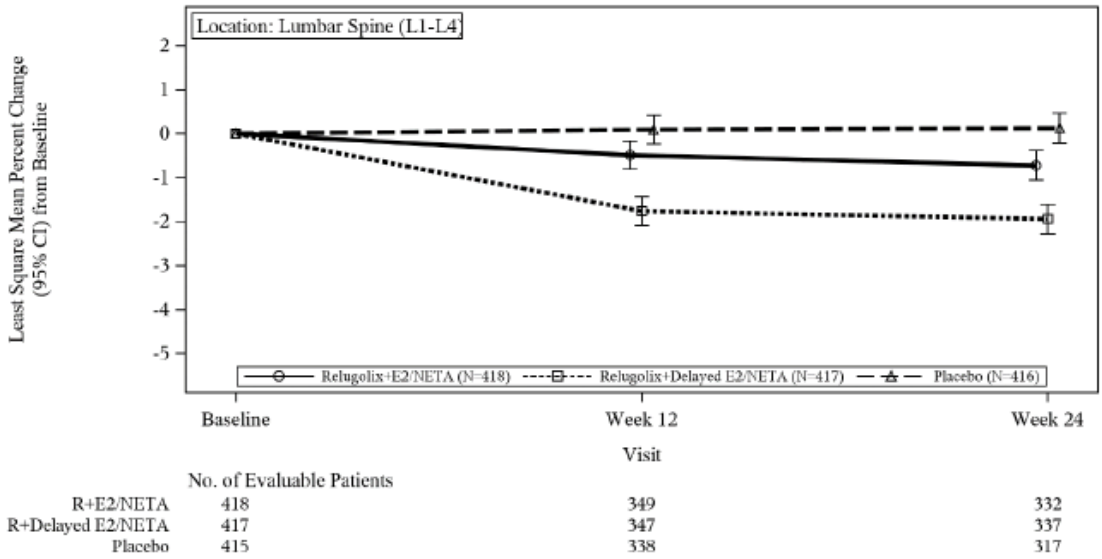
To evaluate the effect of relugolix + E2/NETA compared with relugolix monotherapy on BMD, the LS mean percent change from baseline to Week 12 in BMD at the total hip in the relugolix + E2/NETA group was compared with that of the relugolix + delayed E2/NETA group. The between-group difference at Week 12 was 0.59% (95% CI: 0.32%, 0.86%), which was statistically significant (p <

0.0001), favoring the relugolix + E2/NETA group. This finding further demonstrated the value of using relugolix in combination with E2/NETA to minimize bone loss associated with relugolix monotherapy and is consistent with what was observed in the individual pivotal studies.

Figure 28 presents longitudinal percent change from baseline in lumbar spine and total hip BMD for pooled studies MVT-601-3101 and MVT-601-3102.

Figure 28. Least Square Mean Percent Change from Baseline to Week 12 and Week 24 in Bone Mineral Density at the Lumbar Spine (L1-L4): Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

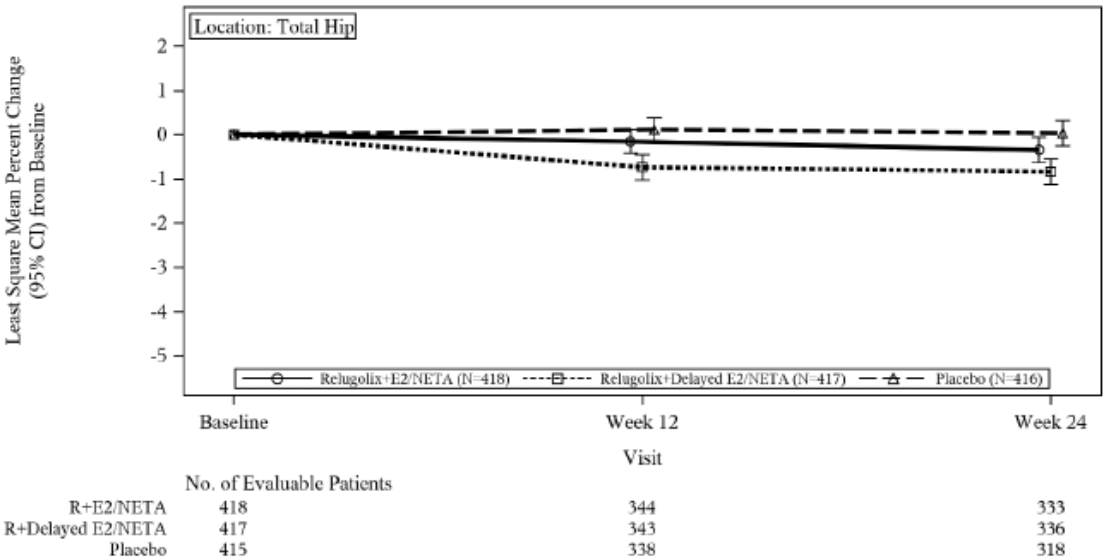
Panel A: Lumbar Spine (L1-L4)



No. of Evaluable Patients

R+E2/NETA	418	349	332
R+Delayed E2/NETA	417	347	337
Placebo	415	338	317

Panel B: Total Hip



No. of Evaluable Patients

R+E2/NETA	418	344	333
R+Delayed E2/NETA	417	343	336
Placebo	415	338	318

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; NETA = norethisterone acetate.
Least square means and corresponding 95% CIs are based on a mixed-effect model with repeated measures. The model has treatment group, age at baseline, visit, baseline bone mineral density value, stratification factors (geographic region and time since initial endometriosis diagnosis), race group, body mass index at baseline and treatment-by-visit interaction as fixed effects using unstructured variance-covariance matrix. Baseline values used are from the pivotal studies, MVT-601-3101 or MVT-601-3102.

- *Lumbar Spine Bone Mineral Density*

Least-squares mean percent changes from baseline to Week 12 and Week 24 in BMD at the lumbar spine (L1-L4) differed between the relugolix + E2/NETA and placebo groups in pooled MVT-601-3101 and MVT-601-3102 data (Week 12: -0.49% vs. 0.09%; Week 24: -0.72% vs. 0.12%). The relugolix +

E2/NETA within group change in BMD between Week 12 and Week 24 was −0.19 (95% CI: −0.42, 0.05) with the 95% CIs including 0 (ISS Table 8.5.1.6, Module 5.3.5.3), suggesting that BMD stabilized between Week 12 and Week 24.

However, the percent change for relugolix + E2/NETA was < 1% at both timepoints and is not considered clinically meaningful. The decline in BMD likely reflects adaptation to the new steady state of E2 concentrations associated with relugolix combination therapy.

For the relugolix + delayed E2/NETA group at Week 12 and Week 24, the LS mean percent changes from baseline at the lumbar spine were -1.76 % (95% CI: -2.09%, -1.44%) and -1.94% (95% CI: -2.29%, -1.60%), respectively. These data reflect a decline in BMD with relugolix monotherapy followed by stabilization with transition to relugolix + E2/NETA at Week 12.

- *Total Hip Bone Mineral Density*

Least-squares mean percent changes from baseline to Week 12 and Week 24 in BMD at the total hip differed between the relugolix + E2/NETA and placebo groups in pooled MVT-601-3101 and MVT-601-3102 (Week 12: -0.15% vs. 0.11%; Week 24: -0.34% vs. 0.03%). The relugolix + E2/NETA within-group decline in BMD between Week 12 and Week 24 was −0.14 (95% CI: -0.34, 0.06), with the 95% CI including 0, suggesting that BMD stabilized between Week 12 and Week 24.

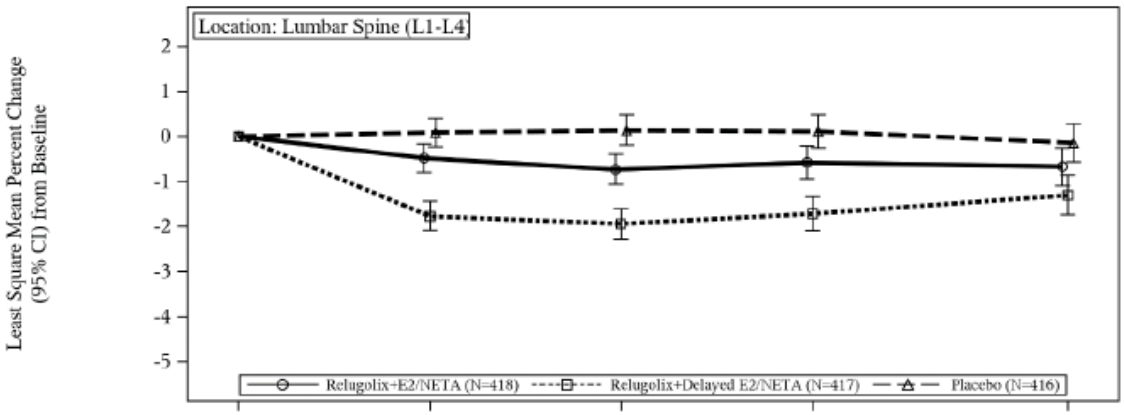
However, the percent change for relugolix + E2/NETA was < 1% and is not considered clinically meaningful.

Endometriosis Long-Term Combination Therapy (population 2)

A summary of percent change in BMD as measured at the lumbar spine, total hip, and femoral neck from pooled pivotal study MVT-601-3101 and MVT-601-3102 baseline to Week 52 is presented in Figure 29.

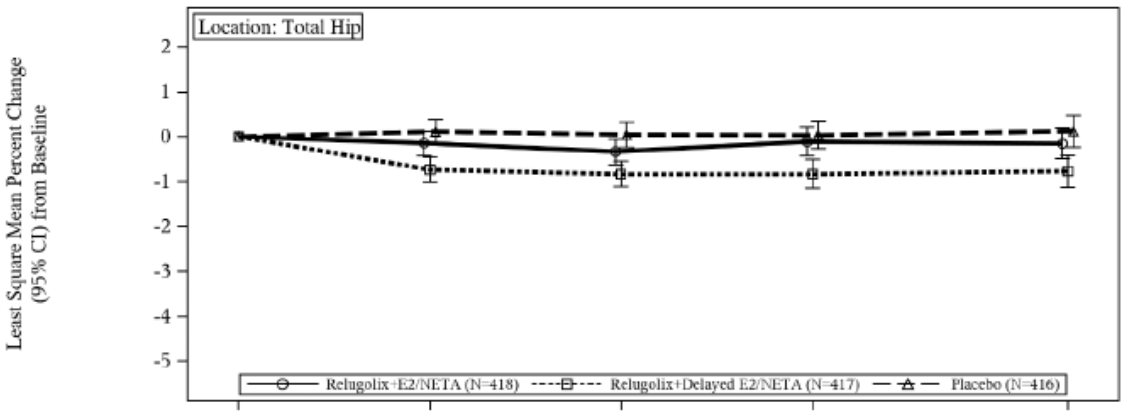
Figure 29. Least Square Mean Percent Change from Baseline in Bone Mineral Density by Location and Visit: Endometriosis Long-Term Combination Therapy Safety Population through Week 52 (MVT-601-3101, MVT-601-3102, and MVT-601-3103)

Panel A: Lumbar Spine (L1-L4)



No. of Evaluable Patients					
R+E2/NETA	418	349	333	241	228
R+Delayed E2/NETA	417	347	338	223	202
Placebo	415	338	319	242	229

Panel B: Total Hip



No. of Evaluable Patients					
R+E2/NETA	418	344	334	240	228
R+Delayed E2/NETA	417	343	336	224	203
Placebo	415	338	320	242	228

Abbreviations: CI = confidence interval; E2 = estradiol; N = number of patients in the treatment group; NETA = norethisterone acetate.
Least square means and corresponding 95% CIs are based on a mixed-effect model with repeated measures. The model has treatment group, age at baseline, visit, baseline bone mineral density value, stratification factors (geographic region and time since initial endometriosis diagnosis), race group, body mass index at baseline and treatment-by-visit interaction as fixed effects using unstructured variance-covariance matrix. Baseline values used are from the pivotal studies, MVT-601-3101 or MVT-601-3102.

At the lumbar spine in the relugolix + E2/NETA group, LS mean percent changes from baseline to Week 36 and Week 52 in BMD were -0.58% (95% CI: -0.94%, -0.21%) and -0.67% (95% CI: -1.09%, -0.25%), respectively. After a small reduction in BMD observed at Weeks 12 [-0.48% (95% CI: -0.80, -0.17%)] and Week 24 [-0.73% (95% CI: -1.06, -0.39%)] in the lumbar spine as shown in

Figure (Panel A), there was evidence of stabilization at Weeks 36 and 52. Of note, for women with either endometriosis or uterine fibroids who completed the pivotal phase 3 studies and enrolled in the respective long-term extension studies, treatment with relugolix + E2/NETA for up to 52 weeks was associated with declines in lumbar spine BMD of -0.81% and - 0.80%, respectively. These data demonstrate the consistency of effect on BMD in premenopausal women with endometriosis or uterine fibroids.

In patients from the placebo group who transitioned to relugolix + E2/NETA, the LS mean percent change was minimal from baseline to Week 12 [0.09% (95%CI: -0.23, 0.40%)] and Week 24 [0.14% (95% CI: -0.19, 0.48%)], and continued to be relatively stable at Week 36 and Week 52 with changes of 0.11% (95% CI: -0.25%, 0.48%) and -0.14% (95% CI: -0.57%, 0.28%), respectively. In the relugolix + delayed E2/NETA group, a plateau in BMD started after Week 12 (when E2 and NETA were added to the ongoing treatment with relugolix) through Week 24, -1.77% (95% CI: -2.09, -1.44%) and -1.94% (95% CI: -2.29, -1.60%), respectively. There was evidence of an upward drift at Week 36 and Week 52, likely reflecting ongoing administration of exogenous E2 in the context of GnRH receptor antagonism with LS mean percent change from baseline to Week 36 and Week 52 of -1.72% (95% CI: -2.10%, -1.34%) and -1.30% (95% CI: -1.74%, -0.86%) respectively.

In the relugolix + E2/NETA group, BMD at the total hip remained relatively unchanged from baseline.

Extension Safety Population through Week 104 (Population 3)

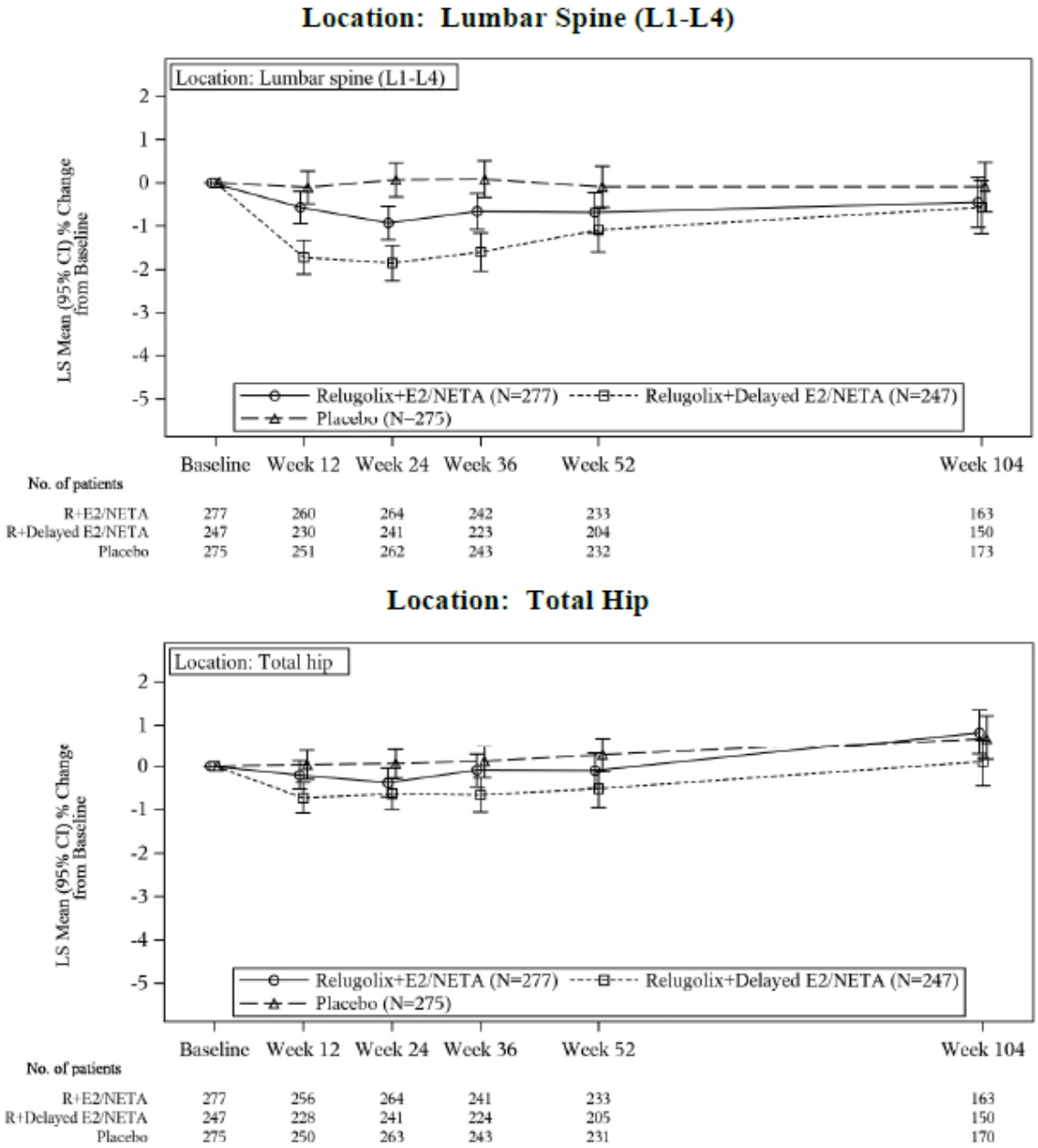
Lumbar spine

- In the relugolix + E2/NETA group, at Weeks 36, 52, and 104, there was stabilization in BMD with a LS mean percent change from baseline of -0.66% (95% CI: -1.08, -0.24), -0.69% (95% CI: -1.16, -0.21), and -0.45% (95% CI: -1.03, 0.13), respectively.
- For patients treated with placebo, with transition to relugolix + E2/NETA at Week 24, the changes remained relatively stable: 0.09% (95% CI: -0.33, 0.51) at Week 36, -0.09% (95% CI: -0.57, 0.39) at Week 52, and -0.09% (95% CI: -0.67, 0.48) at Week 104.
- In the relugolix + delayed E2/NETA group, there was evidence of an upward drift at Weeks 36, 52, and 104 with percent change from baseline of -1.60% (95% CI: -2.04, -1.16) at Week 36, -1.09% (95% CI: -1.59, -0.59) at Week 52, and -0.56% (95% CI: -1.17, 0.05) at Week 104 likely reflecting the effect of the addition of E2/NETA to relugolix at Week 12.

Total hip

- In the relugolix + E2/NETA group, at Weeks 36 and 52, there was stabilization in BMD with percent change from baseline of -0.10% (95% CI: -0.47, 0.28) and -0.10% (95% CI: -0.50, 0.31), respectively with trend towards gain in BMD at Week 104 with percent change from baseline of 0.82% (95% CI: 0.30, 1.35).
- For patients treated with placebo, BMD showed a trend towards gain with a change of 0.12% (95% CI: -0.26, 0.50) at Week 36, 0.27% (95% CI: -0.14, 0.68) at Week 52, and 0.69% (95% CI: 0.17, 1.22) at Week 104.
- In the relugolix + delayed E2/NETA group, BMD showed a trend towards gain at Week 36, Week 52, and Week 104 with percent change from baseline of -0.65% (95% CI: -1.05%, -0.26%), -0.52% (95% CI: -0.95, -0.09), and 0.10% (95% CI: -0.45, 0.65), respectively.

Figure 30. MVT-601-3103: Summary of Percent Change from Baseline in Bone Mineral Density at the Lumbar Spine (L1 – L4) (Upper) and Total Hip (Lower) through Week 104 (Extension Safety Population)



Date of database lock was 23 Feb 2022.
Abbreviations: CI = confidence interval; E2 = estradiol; LS= least squares; N = number of patients (MVT-601-3103) in the pivotal study (MVT-601-3101, MVT-601-3102) treatment group; NETA = norethisterone acetate; R = relugolix.
LS means and 95% CI are generated based on mixed-effects model with BMD at baseline, age at baseline, geographic region (North American vs Rest of World), time since initial surgical diagnosis (<5 years vs >=5 years), body mass index at baseline, race (African American vs Other), visit, pivotal study (MVT-601-3101, MVT-601-3102) treatment group, and treatment-by-visit interaction as fixed effects using an unstructured variance-covariance matrix. The multiple visits for each patient are considered as random effect within each patient.
Error bars represent 95% CI.

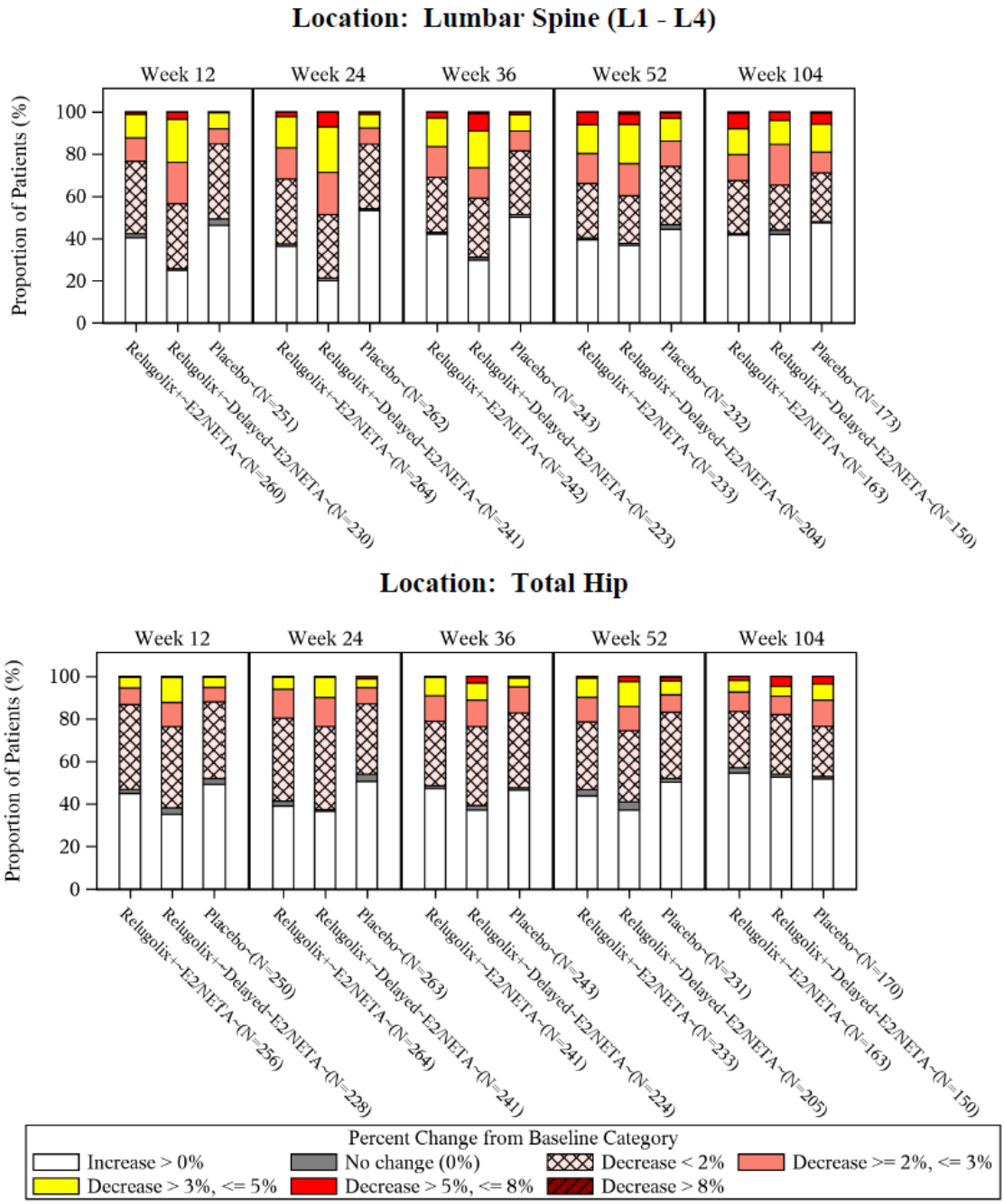
Categorical Analyses of Bone Mineral Density

To understand categorical changes in BMD, including patients who had clinically meaningful changes (ie, > 3% loss in BMD) (Lewiecki 2010) and those with larger losses, so-called outliers, changes from baseline to Week 12, Week 24, Week 36, Week 52, and Week 104 are presented by the number and proportion of patients who had BMD increases of > 0%, no changes, declines of < 2%, 2% to 3%, > 3% to 5%, > 5% to 8%, and > 8% by treatment group and anatomical location. Categorical changes in BMD at the lumbar spine (L1–L4) and total hip are presented in Figure 31.

Lumbar spine
Evaluation of categorical changes in the relugolix + E2/NETA group through 104 weeks showed that the majority of women had gains or clinically insignificant declines in BMD at Week 104 at the lumbar spine, defined as an increase > 0% (41.7% [68 patients]); no change (0.6% [1 patient]); or clinically insignificant BMD loss, defined as decrease ⩽ 3% (37.5% [61 patients]). Smaller percentages of women had losses of > 3% to ⩽ 5% and > 5% to ⩽ 8% (12.3% [20 patients] and 7.4% [12 patients]), respectively. One patient (0.6%) had loss in BMD > 8% through Week 104.

Total Hip
Evaluation of categorical changes in the relugolix + E2/NETA group through 104 weeks showed that the majority of women had gains or clinically insignificant declines in BMD at Week 104 at the total hip, defined as an increase > 0% (54.6% [89 patients]); no change (2.5% [4 patients]); or clinically insignificant BMD loss, defined as decrease ⩽ 3% (35.6% [58 patients]) (Figure 11 and Table 8.4.5.3, MVT-601-3103 104-week CSR). Smaller percentages of women had losses of > 3% to ⩽ 5% and > 5% to ⩽ 8% (5.5% [9 patients] and 1.8% [3 patients]), respectively. No patients had a BMD loss > 8% through Week 104.

Figure 31. Categorical Summary of Percent Change from Baseline in Bone Mineral Density at Week 12 Week 24, Week 36, Week 52, and Week 104 (Extension Safety Population)



Date of database lock was 23 Feb 2022.
Abbreviations: E2 = estradiol; NETA = norethisterone acetate; n = number of patients included in summary statistics.

Change in BMD by age grouping

Since bone mass accrual at the lumbar spine in women may occur up to age 30 with subsequent decline in fifth decades of life prior to menopause, change in BMD was assessed by age grouping (18 to < 35, 35 to < 40, 40 to < 45, and 45 to < 52) in each of the studies. The largest cohort was also found to be the youngest age cohort, 18 to < 35 years which allowed a valid assessment of the potential drug affect in this group. Mean percent change in BMD by age group was found to be

consistent between the relugolix combination therapy group and untreated endometriosis cohort from study MVT-601-034, when assessed at the lumbar spine, total hip and femoral neck

To further investigate the BMD in these younger patients, progression of the BMD in the patients aged 18-24 across 104 weeks of treatment for those patients who continued into study MVT-601-3103 was analysed. It was seen that in the patients aged 18-24 with regards to the percent change in the lumbar spine from baseline to week 24 was -0.74% (95%CI: -1.45%, -0.03), 0.55% (95%CI: -1.58%, 2.69) at week 52 and 3.33% (95%CI: 0.19%, 6.46) at week 104. A similar pattern was seen for the change in BMD of the total hip with a change of 1.86% (95%CI: -1.74%, 5.47) at week 104.

These data demonstrate that combination therapy is associated with a small initial decrease in BMD (<1%) at the most estrogen-sensitive anatomic location – the lumbar spine. The initial decline likely reflects adaptation to the new steady state of E2 concentrations that are consistent with concentrations observed during the early follicular phase (Cramer et al. 2002; Stricker et al. 2006). However, it can be seen that thereafter, BMD remained stable and in fact in these younger patients appears to increase over a total of 104 weeks of therapy.

Post-treatment follow-up

One of the safety endpoints was a 6-months and 12-months post-treatment DXA to assess the percent change from the pivotal phase 3 study Baseline in BMD at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA.

Of the 799 patients who entered the long-term extension study, 501 patients completed Week 104, and 298 (37.3%) patients in the Extension Safety Population terminated early (ie, prior to Week 104). Three hundred twenty-four (40.6%) patients were eligible for post treatment follow-up (PTFU). The evolution of thresholds for BMD loss during (PTFU) in the original protocol and subsequent three amendments (1.0, 2.0, and 3.1) were implemented to protect patient safety. The sponsor amended the protocol (Amendment 4) to obtain PTFU in all patients, regardless of whether or not they met prespecified bone loss criteria as outlined in the previous version of the protocol, Amendment 3.1, of whom 171 (21.4%) patients met protocol-specific BMD loss criteria or had BMD loss > 3% at the lumbar spine or total hip as compared to pivotal-study baseline. This is consistent with PTFU DXA testing in the uterine fibroids population. The findings with relugolix + E2/NETA in the endometriosis population are described as follows:

- There were 56 of 277 (20.2%) patients who met protocol-specific BMD loss criteria and entered the 6-month PTFU period.

- Of these 56 patients, 25 (45%) completed 6-month PTFU, of whom 4 had met the recovery threshold and subsequently required no further follow-up. The remaining 21 patients had not met the recovery threshold at this timepoint and were requested to carry on to the 12-month PTFU. Of those patients who did not undertake a 6-month PTFU, the majority were due to patient lack of agreement to participate.

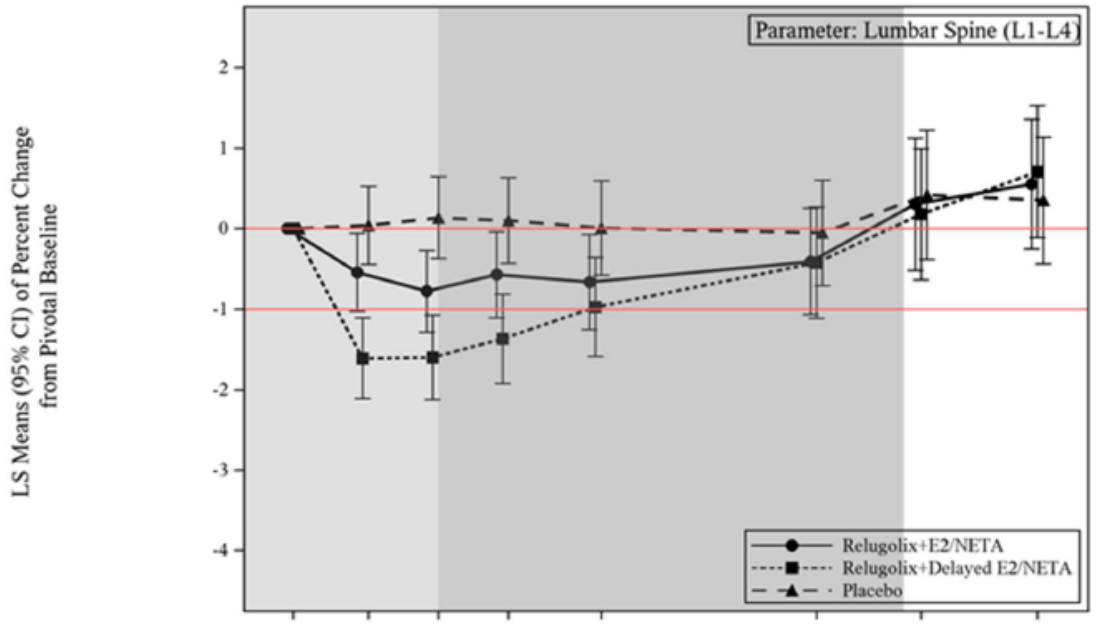
- There were 31 (11.2%) patients who were eligible for the 12-month PTFU assessment and from whom 24 completed this assessment. There were 17 (70.8%) patients who met the recovery threshold (BMD loss $\leqslant$ 1.5% at the lumbar spine and $\leqslant$ 2.5% at the total hip compared with pivotal study baseline) and did not require further follow-up. Seven patients did not meet the recovery threshold and were subsequently referred for a bone specialist consultation. Among these

7 patients, 3 patients declined the referral, and the remaining 4 patients completed the visit, all of whom were determined to have had appropriate lumbar spine and total hip BMD by the consultants and were recommended to begin exercise and supplementation with calcium and vitamin D (MVT-601-3103 104-Week CSR Addendum).

Among those who had PTFU DXA scans performed, recovery (defined as > 0% change from last on-treatment DXA in percent change from pivotal baseline) was observed in all patients treated with relugolix + E2/NETA (27 [100%]), and in most patients treated with placebo (21 [75%]) or relugolix + delayed E2/NETA (27 [84%]). When the degree of recovery is evaluated, defined as recovery of > 50%, most patients show recovery or trend towards recovery. In those patients who did not show recovery, reflecting no change during the PTFU period, no patients who initiated relugolix + E2/NETA at pivotal study baseline had evidence of non-recovery at the lumbar spine, the most-estrogen sensitive anatomical site, and the one patient who showed evidence of non-recovery at the total hip was taking dienogest.

To further characterize BMD after 104 weeks of treatment during PTFU, a mixed-effects model with repeated measures was developed that incorporated all patients who completed 104 weeks of treatment ("completers") and who participated in the PTFU period. Least squares mean percent changes at the lumbar spine from pivotal study baseline through 12-month PTFU are presented in Figure 32.

Figure 9 MVT-601-3103: By-Visit Least Squares Mean Percent Change from Pivotal Baseline in Bone Mineral Density at the Lumbar Spine During 2-Year Treatment and 1-Year PTFU (Week 104 Completers)



No. of Evaluable patients								
Relugolix+E2/NETA	172	164	164	165	168	161	43	55
Relugolix+Delayed E2/NETA	155	145	149	148	149	147	50	53
Placebo	174	157	164	166	168	165	47	58

Date of analysis data cut was 17 Feb 2023.
Abbreviations: CI = confidence interval; E2 = estradiol; LS = least square; NETA = norethindrone acetate; PTFU = post-treatment follow-up.
Includes all patients in MVT-601-3103 who completed 104 weeks of study treatment.
LS means and 95% CIs for percent change from baseline are based on a mixed-effects model with treatment group, age at baseline, BMD value at baseline, visit, stratification factors (geographic region and time since initial endometriosis diagnosis), race group, body mass index at baseline and treatment-by-visit interaction as fixed effects using unstructured variance-covariance matrix. The multiple visits for each patient were the repeated measures as random effect. The reference lines indicate no change at 0, and insignificant change at -1% from baseline.

Hepatic Transaminase Elevation

In the relugolix clinical development program, any increase in ALT and/or AST $\geq 3 \times$ ULN was considered as an adverse event of clinical interest.

The potential for hepatic transaminase elevations associated with relugolix is based on nonclinical observations, clinical study 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 pivotal studies in women with uterine fibroids, asymptomatic transient elevations of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at least 3 times the upper limit of the reference range occurred in < 1% of patients treated with relugolix + E2/NETA.

Hepatic transaminase elevations were monitored closely in accordance with US Food and Drug Administration (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.

Endometriosis 24-Week Combination Therapy (population 1)

In the pooled Endometriosis 24-Week Combination Therapy Safety Population, adverse events in the Drug related hepatic disorders comprehensive SMQ (narrow) were reported with similar frequency in both treatment groups: 1.9% (8 patients) in the relugolix + E2/NETA and 1.7% (7 patients) in the placebo groups. A subset of these events was considered adverse events of clinical interest and are summarized in Table 59 for the Endometriosis 24-Week Combination Therapy Safety Population.

Table 59. Adverse Events of Clinical Interest by Preferred Term: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Patients with ≥ 1 adverse event of clinical interest n (%)	5 (1.2%)	2 (0.5%)	4 (1.0%)
Alanine aminotransferase increased	4 (1.0%)	2 (0.5%)	2 (0.5%)
Aspartate aminotransferase increased	1 (0.2%)	1 (0.2%)	2 (0.5%)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate; ULN = upper limit of normal.
Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Patients with multiple events for a given preferred term or system organ class are counted only once at the worst severity at each level of summarization.
Events are sorted by decreasing frequency of categories in the relugolix + E2/NETA group, followed by the relugolix + delayed E2/NETA group, followed by the placebo group. Adverse events of clinical interest as defined in the protocol (any increase in ALT or AST ≥ 3 × ULN) are taken from the adverse event CRF.
MedDRA version 22.0.

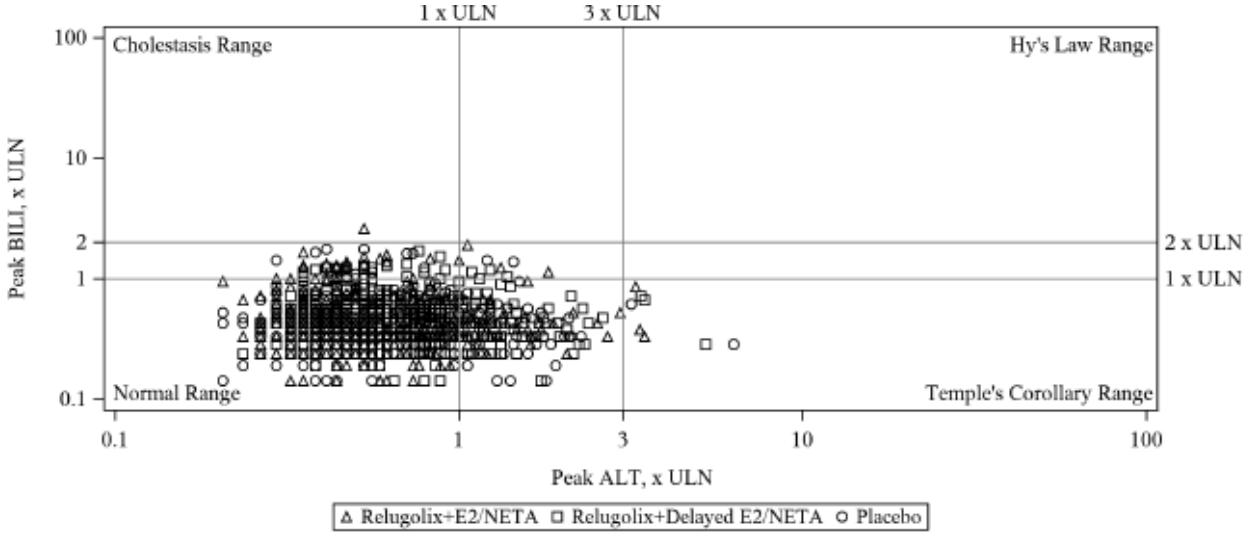
The proportion of patients with liver test values meeting pre-defined limits of change in the Endometriosis 24-week Combination Therapy Safety Population are presented in Table 60. In this table, a given patient may be included in more than one category.

Table 60. Summary of Liver Test Abnormalities: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Postbaseline elevations[a]			
ALT or AST > ULN and < 3X ULN	46 (11.0%)	63 (15.1%)	57 (13.7%)
ALT or AST ≥ 3X ULN and < 5X ULN	4 (1.0%)	2 (0.5%)	2 (0.5%)
ALT or AST ≥ 5X ULN and < 10X ULN	0	1 (0.2%)	2 (0.5%)
ALT or AST ≥ 3X ULN and Total BILI > 2X ULN[b]	0	0	0
Total BILI >2X ULN	1 (0.2%)	0	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; E2 = estradiol; N = number of patients in the treatment group; NETA = norethisterone acetate; ULN = upper limit of normal.
a Most extreme postbaseline results are summarized. Patients can be summarized in more than one row.
b Elevation of AST or ALT and total bilirubin within the same day.

Figure 33. Worst Alanine Aminotransferase and Total Bilirubin in eDISH Concept: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)



Abbreviations: ALT = alanine aminotransferase; BILI = bilirubin; E2 = estradiol; eDISH = evaluation of drug-induced serious hepatotoxicity; NETA = norethisterone acetate; ULN = upper limit of normal.

Figure 33is an evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot of the worst ALT and total bilirubin in individual patients.

No patients had an ALT or AST > 3 × ULN and a total bilirubin > 2 × ULN. The incidence of ALT or AST > 3 × ULN was low and similar in both treatment groups (1.0% and 1.0% of patients, respectively, in the relugolix + E2/NETA and placebo groups).

Endometriosis Long-Term Combination Therapy (population 2)

A summary of all adverse events of clinical interest reported in the Endometriosis Long-Term Combination Therapy Safety Population (studies MVT-601-3101, MVT-601-3102, and MVT-601-3103) is presented in the Table below.

Table 61. Adverse Events of Clinical Interest by Preferred Term: Endometriosis Long-Term Combination Therapy Safety Population through Week 52 (MVT-601-3101, MVT-601-3102, and MVT-601-3103)

Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)	Any Relugolix +E2/NETA (N = 1066)
Patients with at least one adverse event of clinical interest n (%)	6 (1.4%)	3 (0.7%)	5 (1.2%)	9 (0.8%)
Alanine aminotransferase increased	4 (1.0%)	2 (0.5%)	2 (0.5%)	5 (0.5%)
Aspartate aminotransferase increased	2 (0.5%)	2 (0.5%)	3 (0.7%)	5 (0.5%)

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 = norethisterone acetate; ULN = upper limit of normal. Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. 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 or system organ class are counted only once at the worst severity at each level of summarization.
Events are sorted by decreasing frequency of preferred term in the any relugolix + E2/NETA group, followed by relugolix + E2/NETA group, followed by the relugolix + delayed E2/NETA group, followed by the placebo group.
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.

No patients had an ALT or AST > 3 × ULN and a total bilirubin > 2 × ULN. The incidence of ALT or AST > 3 × ULN was low and similar in all treatment groups, increasing by 1 patient in each group compared with the pivotal studies. Lesser elevations of transaminases (ALT or AST > ULN and < 3 × ULN) cumulatively were not much higher (change of ~ +1% in each group) compared with what was observed in the pivotal studies. These findings indicate a lack of cumulative risk of transaminase elevation with long-term treatment with relugolix + E2/NETA. Four patients had a total bilirubin >2 × ULN. In all cases, there was no concurrent increase in transaminases or alkaline phosphatase. The pattern of elevation was consistent with Gilbert's syndrome in all these patients and 2 patients had a known history of Gilbert's syndrome.

Extension Safety Population through Week 104 (Population 3)

A summary of all adverse events of clinical interest reported in the Extension Safety Population is presented in Table .

Table 62. Protocol-Specified Adverse Events of Clinical Interest by Decreasing Frequency of Preferred Term through Week 104 (Extension Safety Population)

Preferred Term	Relugolix + E2/NETA (N = 277)	Relugolix + Delayed E2/NETA (N = 247)	Placebo (N = 275)	Any Relugolix +E2/NETA (N = 799)
No. of patients with at least one AE of clinical interest n (%)	2 (0.7%)	1 (0.4%)	8 (2.9%)	11 (1.4%)
Alanine aminotransferase increased	1 (0.4%)	0	4 (1.5%)	5 (0.6%)
Aspartate aminotransferase increased	1 (0.4%)	1 (0.4%)	4 (1.5%)	6 (0.8%)

Date of database lock was 23 Feb 2022.
Abbreviations: AE = adverse event; E2 = estradiol; N = number of patients (MVT-601-3103) in the pivotal study (MVT-601-3101, MVT-601-3102) treatment group; n = number of patients with AE of interest; NETA = norethisterone acetate.
Percentages are based on the total number of patients in each pivotal study (MVT-601-3101, MVT-601-3102) treatment group or total. Events are sorted by decreasing frequency of preferred term in the relugolix+E2/NETA treatment in the pivotal study (MVT-601-3101, MVT-601-3102).
Patients with multiple events for a given preferred term are counted only once for each preferred term. MedDRA (version 22.0).

Across all treatment groups, a total of 11 patients (1.4%) were reported to have adverse events of clinical interest in the cumulative experience. In the LTE study, adverse events of clinical interest were reported for a total of 6 patients (0.8%). In the cumulative experience and during the LTE study, the numbers of patients with adverse of clinical interest were 2 (0.7%) and 1 (0.4%), respectively in the relugolix + E2/NETA group; 1 (0.4%) and 1 (0.4%), respectively, in the relugolix + delayed E2/NETA group; and 8 (2.9%) and 4 (1.5%), respectively in the placebo group.

Summary of Hepatic Transaminase Elevations

Drug-related hepatic disorder events were uncommonly reported during long-term treatment with relugolix + E2/NETA. Through Week 52, adverse events of clinical interest, defined as an ALT or AST > 3 × ULN, were reported for 1.4% (6/418) women treated with relugolix + E2/NETA and 1.2% (5/416) women treated with placebo and consistent with the findings in the uterine fibroid population. In the Extension Study population, there were five new adverse events of clinical interest from Week 52 to Week 104. No events meeting Hy's Law criteria were observed.

Embolic and Thrombotic Events

To evaluate the potential risk of embolic or thrombotic events, an assessment of adverse events within the MedDRA Embolic and thrombotic events SMQ (broad) was undertaken for each pooled population.

Given that thrombotic and embolic events in premenopausal women are rare, a limitation of this review is the relatively modest number of women included in the analysis and relatively short duration of treatment (up to 52 weeks) to assess for this particular outcome.

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

One (0.2%) patient (in the placebo group) was reported to have a grade 1 serious adverse event of hemiparesis (verbatim term: muscle weakness of the left side). The underlying cause of the event remained unknown.

Endometriosis Long-Term Combination Therapy (Population 2)

Serious adverse events of deep vein thrombosis and pulmonary embolism were reported for one patient (placebo) in study MVT-601-3103. This was a 36-year-old White female patient with a BMI of 38.7 kg/m2 who fell on Day 197, 7 days after initiating treatment with relugolix + E2/NETA, and sustained a grade 2 nonserious adverse event of right knee sprain that was treated with diclofenac from Day 210 to 229. On Day 227, the patient was reported to have grade 3 serious adverse events of deep vein thrombosis and pulmonary embolism. The study drug was permanently discontinued due to these serious adverse events. The patient was treated with anticoagulants. The events resolved on Day 229. The investigator assessed the adverse events of deep vein thrombosis and pulmonary embolism to be related to the study drug.

Extension Safety Population through Week 104 (Population 3)

No other events were described in MVT-601-3103 through 104 weeks of treatment.

Carbohydrate and Lipid Metabolic Effects

The results suggest that treatment with relugolix combination therapy has minimal impact on carbohydrate and lipid metabolism. The mean change from baseline to Week 24 in HbA1c was the same in the relugolix + E2/NETA and placebo groups (0.06%) in both groups and no patient in the relugolix + E2/NETA group had a HbA1c > 6.5% or hemoglobin A1c increase from baseline of > 1% at the last observation on treatment. After up to 52 weeks of treatment with relugolix + E2/NETA, 2 patients met these pre-defined limits at the last observation on treatment. One had a history of diabetes and one had pre-diabetes.

Mean changes in lipids through Week 104 were small and not clinically significant. In the placebo-controlled pivotal studies, the percentage of patients meeting lipid thresholds of change were small and similar in all three treatment groups.

The data overall, with consideration of the change in laboratories at Week 24, suggest that there is not an increased risk for lipid excursions with increased exposure to relugolix combination therapy through Week 104.

Tumors (Breast, Liver)

Acknowledging the limitation of the brief duration of exposure in the relugolix clinical program relative to the development of neoplasms, an assessment of adverse events within the MedDRA Breast neoplasm, malignant and unspecified SMQ (broad), and Liver neoplasms, benign (incl cysts and

polyps) SMQ (narrow), and Liver neoplasms, malignant and unspecified SMQ (broad) was undertaken for the relugolix combination therapy pooled safety populations.

There were no adverse events related to breast or liver tumors reported in any patients in the relugolix + E2/NETA or placebo group in the Endometriosis 24-Week Combination Therapy Safety Population (pooled MVT-601-3101 and MVT-601-3102). In the Endometriosis Long-Term Combination Therapy Safety Population (pooled MVT-601-3102, MVT-601-3102 and MVT-601-3103), two patients in the relugolix + delayed E2/NETA group were reported to have an adverse event related to breast or liver tumors (breast dysplasia and hepatic adenoma). The event of breast dysplasia (Verbatim Term: benign breast dysplasia) was initially diagnosed based on a physical examination; a subsequent mammogram and breast ultrasound revealed no evidence of malignancy (BIRADS 2). The event of hepatic adenoma was reported in a patient with a more than 19-year history of use of oral hormonal contraceptives.

In the cumulative data through Week 104 in the Extension Safety Population (Population 3), there were two adverse events of breast mass. One was reported in the relugolix + E2/NETA group (Verbatim term: left breast nodule); a screening mammogram was reported as "negative" and the patient was referred for follow-up breast imaging. A separate event was reported in the relugolix + delayed E2/NETA group (Verbatim term: non painful nodule on the left breast [BIRADS 3]). An additional, follow up ultrasound was performed and reported as "cystic images of different sizes. There were no relevant changes with previous examinations. Axillary studies were free of lymphadenopathy."

Hypertension

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

A summary of all hypertension-related adverse events in the Endometriosis 24-Week Combination Therapy Safety Population by PT is presented in the Table below.

Table 63. Adverse Event Category: Hypertension by Decreasing Frequency of Preferred Term: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Patients with ≥ 1 adverse event of hypertension, n (%)	6 (1.4%)	10 (2.4%)	5 (1.2%)
Hypertension	4 (1.0%)	7 (1.7%)	3 (0.7%)
Blood pressure increased	1 (0.2%)	1 (0.2%)	1 (0.2%)
Labile hypertension	1 (0.2%)	0	0
Essential hypertension	0	2 (0.5%)	0
Blood pressure diastolic increased	0	0	1 (0.2%)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate; SMQ = Standardised MedDRA Query.
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.

In the pooled Endometriosis 24-Week Combination Therapy Safety Population, hypertension events were reported with low and similar frequency in the relugolix + E2/NETA and placebo groups (6 of 418

patients and 5 of 416 patients, respectively). All events were nonserious and resulted in treatment discontinuation in one patient.

Endometriosis Long-Term Combination Therapy (Population 2)

In the Endometriosis Long-Term Combination Therapy Safety Population, the proportion of patients reporting hypertension adverse events was 2.6% of patients (11 patients) in the relugolix + E2/NETA group compared with 1.4% of patients (6 patients) during the pivotal studies. Incidence rates comparable with the pivotal studies were reported in the relugolix + delayed E2/NETA group (2.9% and 2.4%, respectively) and in the placebo group (1.7% and 1.2%, respectively). In the long-term extension study, hypertension adverse events were reported for 12 patients (6 in the relugolix + E2/NETA group, 1 in the relugolix + delayed E2/NETA group, and 5 in the placebo group). All were nonserious and none resulted in study drug discontinuation.

Extension Safety Population through Week 104 (Population 3)

In the relugolix + E2/NETA group, hypertension adverse events were reported in 6 patients (2.2%) cumulatively and in 5 patients (1.8%) during the LTE; blood pressure increased adverse events were reported in 2 patients cumulatively (0.7%) and 1 patient (0.4%) during the LTE.

In the relugolix + delayed E2/NETA group, hypertension adverse events were reported in 7 patients (2.8%) cumulatively and in 3 patients (1.2%) during the LTE; blood pressure increased adverse events were reported in 1 patient cumulatively (0.4%) and 0 patients during the LTE.

In the placebo group, hypertension adverse events were reported in 8 patients (2.9%) cumulatively and in 6 patients (2.2%) during the LTE; blood pressure increased adverse events were reported in 5 patients (1.8%) cumulatively and in 4 patients (1.5%) during the LTE.

In the LTE study through 52 weeks, hypertension and blood pressure increased adverse events were reported for 12 patients (5 in the relugolix + E2/NETA group, 2 in the relugolix + delayed E2/NETA group, and 5 in the placebo group). During the second year, presenting Weeks 52 to 104, there were 20 events (5 in the relugolix + E2/NETA group, 5 in the relugolix + delayed E2/NETA group, and 10 in the placebo group).

Summary of Hypertension

The mean blood pressure was stable during long-term treatment with relugolix + E2/NETA through up to 104 weeks. There was no disproportionate increase in the frequency of blood pressure excursions or hypertension adverse events with continued treatment beyond 24 weeks.

Mood disorders

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

Table 16. Adverse Event Category - Mood Disorders by Decreasing Frequency of Preferred Term: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Patients with ≥ 1 adverse event of mood disorder, n (%)	33 (7.9%)	36 (8.6%)	24 (5.8%)
Mood swings	10 (2.4%)	12 (2.9%)	9 (2.2%)

Depression	10 (2.4%)	4 (1.0%)	7 (1.7%)
Affect lability	6 (1.4%)	2 (0.5%)	0
Mood altered	3 (0.7%)	1 (0.2%)	1 (0.2%)
Depressed mood	2 (0.5%)	8 (1.9%)	3 (0.7%)
Suicidal ideation	2 (0.5%)	3 (0.7%)	2 (0.5%)
Disturbance in attention	2 (0.5%)	2 (0.5%)	0
Memory impairment	1 (0.2%)	0	1 (0.2%)
Adjustment disorder with depressed mood	0	1 (0.2%)	0
Apathy	0	1 (0.2%)	0
Depressive symptom	0	1 (0.2%)	0
Initial insomnia	0	1 (0.2%)	0
Psychomotor hyperactivity	0	1 (0.2%)	0
Tearfulness	0	1 (0.2%)	0
Emotional distress	0	0	1 (0.2%)
Mixed anxiety and depressive disorder	0	0	1 (0.2%)

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate; SMQ = Standardised MedDRA Query.
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 in the relugolix + E2/NETA group, followed by the relugolix + delayed E2/NETA group, followed by the placebo group.
Mood disorders includes depression and suicide/self-injury SMQ (broad). MedDRA version 22.0.

In the pooled Endometriosis 24-Week Combination Therapy Safety Population, mood disorder events were reported in 7.9% of patients in the relugolix + E2/NETA group and 5.8% of patients in the placebo group. The most common event in both groups was mood swings. The subset of mood-related adverse events of mood swings, depression, and depressed mood were reported with similar frequency in both treatment groups: 5.3% and 4.3% in the relugolix + E2/NETA group and placebo groups, respectively.

The incidence of suicidal ideation was the same in the relugolix + E2/NETA group and placebo group (0.5%, 2 patients each). Additionally, 2 patients reported suicidal ideation during the placebo Run-in period for which placebo treatment was withdrawn. One patient had a psychiatric history and prior history of suicide attempt while other patient did not have a reported history of a psychiatric disorder but had been treated with duloxetine in the past.

Endometriosis Long-Term Combination Therapy (Population 2)

In the Endometriosis Long-Term Combination Therapy Safety Population, the proportion of patients reporting mood disorders adverse events was 10.8% of patients (45 patients) in the relugolix + E2/NETA group compared with 7.9% of patients (33 patients) during the pivotal studies. Incidence of mood disorder adverse events compared with the pivotal studies in the relugolix + delayed E2/NETA group were 11.0% and 8.6%, respectively, and in the placebo group 10.8% and 5.8%, respectively. Events related to suicidal ideation were reported for 3 additional patients during the long-term extension study, all with a prior psychiatric history.

Extension Safety Population through Week 104 (Population 3)

Within the overall study population, 132 patients (16.5%) patients reported a history of a psychiatric disorder, with 64 patients (8.0%) patients reporting anxiety and 61 patients (7.6%) patients reporting depression.

In conclusion, adverse events related to mood were not reported with increasing frequency (ie, higher rate) during long-term treatment with relugolix + E2/NETA or following the transition from placebo to relugolix + E2/NETA

Gallbladder Disease

The relugolix combination therapy core safety information includes a warning and precaution for gallbladder disease, noting that conditions such as cholelithiasis and cholecystitis have been reported to occur or worsen with estrogen and progestogen use.

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

In the pooled Endometriosis 24-Week Combination Therapy Safety Population, gallbladder disease-related events were reported with low frequency in the 2 treatment groups: relugolix + E2/NETA (0.5%, 2 patients) and placebo (0.2%, 1 patient).

Endometriosis Long-Term Combination Therapy (Population 2)

In the pooled Endometriosis Long-Term Combination Therapy Safety Population, gallbladder disease-related events were reported with low frequency in the 3 treatment groups: relugolix + E2/NETA (0.5%, 2 patients), relugolix + delayed E2/NETA (1.2%, 5 patients), and placebo (0.2%, 1 patient) (ISS Table 4.26.2.8 and ISS Table 4.26.6.14, Module 5.3.5.3). In the long-term extension study, 2 new gallbladder events were reported (both in the relugolix + delayed E2/NETA group). Both were serious and neither resulted in withdrawal from treatment.

Extension Safety Population through Week 104 (Population 3)

Serious adverse events of cholelithiasis were reported in 3 patients (0.4%), only one of these events was new since the Week 52 analysis.

Hypersensitivity

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

In the pooled Endometriosis 24-Week Combination Therapy Safety Population, hypersensitivity events were reported in 1.7% (7 patients) in the relugolix + E2/NETA group and in 1.2% (5 patients) in the placebo group. There were no reports of anaphylaxis or anaphylactoid reactions. None of these events was serious and all were grade 1 or 2 in severity.

Urticaria was reported for 1 patient in the relugolix + E2/NETA group with onset on Day 82 of 2-day duration; no action was taken with study drug.

Endometriosis Long-Term Combination Therapy (Population 2)

In the pooled Endometriosis Long-Term Combination Therapy Safety Population, hypersensitivity events in the relugolix + E2/NETA were reported in 2.9% (12 patients) compared with 1.7% (7 patients) in the pivotal studies. The comparable percentages in the relugolix + delayed E2/NETA group were 2.9% and 2.4% of patients, respectively, and were 3.6% and 1.2% in the placebo group.

Most events were reported for 1 patient within a treatment group. Events reported for more than 2 patients in any treatment group were dermatitis allergic, reported for 6 patients (4 [1.0%] in the relugolix + E2/NETA group and 2 [0.5%] in the placebo group) and rhinitis allergic, reported for 6 patients (3 [0.7%] in relugolix + delayed E2/NETA group and 3 [0.7%] in the placebo group).

There was a disproportionate increase in the overall number of events in this SMQ from the pivotal studies to the long-term extension study in the placebo group; however, there was no pattern to these 18 events (reported for 17 patients) as they were disparate in pathogenesis and anatomic location (eg, seasonal allergy, dermatitis allergic, conjunctivitis, etc.) and most were reported in 1 patient each in the long-term extension study. The most common event was rash or rash maculopapular.

Extension Safety Population through Week 104 (Population 3)

There were no reports of hypersensitivity in the Extension Safety Population through Week 104.

Summary of Hypersensitivity

There was no anaphylaxis or anaphylactoid adverse events reported, other than one associated with a bee sting. The incidence of Hypersensitivity SMQ events during long-term treatment with relugolix + E2/NETA up to 52 weeks was low (2.9%), and without evidence of an association with relugolix + E2/NETA and did not increase through 104 weeks of treatment.

Alopecia

Alopecia was classified as an adverse drug reaction in the relugolix combination therapy core safety information as it was observed in the phase 3 placebo-controlled clinical trials in women with heavy menstrual bleeding associated with uterine fibroids As described in the original MAA, more women experienced alopecia, hair loss, or hair thinning (3.5%) with relugolix combination therapy, compared to placebo (0.8%).

Alopecia is not considered an adverse drug reaction for this endometriosis population. In the pivotal studies, the frequency of these events was numerically lower in the relugolix + E2/NETA group [9 (2.2%) patients) relative to the placebo group [15 (3.6%) patients]. There was no disproportionate increase in alopecia during long-term treatment through 52 weeks with relugolix + E2/NETA. The incidence of alopecia did not increase with long-term treatment with relugolix + E2/NETA.

Serious adverse event/deaths/other significant events

No deaths were reported during the conduct of the phase 3 studies supporting women's health indications (patients with uterine fibroids or endometriosis) or phase 1 studies in healthy patients or patients with hepatic or renal impairment.

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

A summary of all serious adverse events by SOC and PT for the Endometriosis 24-Week Combination Therapy Safety Population is presented in Table 65.

Table 65. Serious Adverse Events by System Organ Class and Preferred Term: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102)

System Organ Class Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
No. of patients with ≥ 1 serious adverse event, n (%)	12 (2.9%)	9 (2.2%)	9 (2.2%)
Blood and lymphatic system disorders	1 (0.2%)	0	0
Anaemia	1 (0.2%)	0	0

Cardiac disorders	0	1 (0.2%)	0
Palpitations	0	1 (0.2%)	0
Endocrine disorders	1 (0.2%)	0	0
Goitre	1 (0.2%)	0	0
Gastrointestinal disorders	3 (0.7%)	0	2 (0.5%)
Abdominal pain	2 (0.5%)	0	0
Abdominal pain lower	1 (0.2%)	0	0
Intestinal obstruction	1 (0.2%)	0	0
Abdominal adhesions	0	0	1 (0.2%)
Peptic ulcer	0	0	1 (0.2%)
Hepatobiliary disorders	2 (0.5%)	1 (0.2%)	0
Cholecystitis	1 (0.2%)	1 (0.2%)	0
Cholelithiasis	1 (0.2%)	0	0
Infections and infestations	1 (0.2%)	0	0
Pneumonia	1 (0.2%)	0	0
Injury, poisoning and procedural complications	1 (0.2%)	2 (0.5%)	2 (0.5%)
Ligament rupture	1 (0.2%)	0	0
Clavicle fracture	0	1 (0.2%)	0
Ulnar nerve injury	0	1 (0.2%)	0
Cartilage injury	0	0	1 (0.2%)
Hand fracture	0	0	1 (0.2%)
Neck injury	0	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2%)	0	0
Non-small cell lung cancer stage IIIA	1 (0.2%)	0	0
Nervous system disorders	0	1 (0.2%)	1 (0.2%)
Migraine	0	1 (0.2%)	0
Hemiparesis	0	0	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	0	0
Abortion missed	1 (0.2%)	0	0
Psychiatric disorders	2 (0.5%)	3 (0.7%)	4 (1.0%)
Suicidal ideation	2 (0.5%)	3 (0.7%)	2 (0.5%)
Anxiety	0	0	1 (0.2%)
Depression	0	0	1 (0.2%)
Generalised anxiety disorder	0	0	1 (0.2%)

Renal and urinary disorders	1 (0.2%)	0	0
Urinary retention	1 (0.2%)	0	0
Reproductive system and breast disorders	4 (1.0%)	1 (0.2%)	1 (0.2%)
Pelvic pain	2 (0.5%)	0	0
Ovarian cyst	1 (0.2%)	1 (0.2%)	1 (0.2%)
Endometriosis	1 (0.2%)	0	0
Uterine haemorrhage	1 (0.2%)	0	0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate.
Patients with multiple events for a given preferred term or system organ class are counted only once at each level of summarization. Events are sorted by system organ class alphabetically and then by decreasing frequency of preferred term in the relugolix + E2/NETA group, followed by the relugolix + delayed E2/NETA group, followed by the placebo group. MedDRA version 22.0.

The only events reported in more than one patient overall were abdominal pain (including abdominal pain lower) (0.7% [3 patients] in the relugolix + E2/NETA group), pelvic pain (0.5% [2 patients] in relugolix + E2/NETA group); suicidal ideation (0.5% [2 patients] in the relugolix + E2/NETA group and 0.5% [2 patients] in the placebo group), cholecystitis (0.2% [1 patient each] in the relugolix + E2/NETA and relugolix + delayed E2/NETA groups), and ovarian cyst, reported in 0.2% (1 patient) in each group.

Endometriosis Long-Term Combination Therapy (Population 2)

During long-term treatment up to 52 weeks in the relugolix + E2/NETA group, there was no disproportionate increase in the incidence of serious adverse events between the pivotal studies (24 weeks) and subsequent, ongoing treatment through Week 52: 2.9% (12 patients) versus 3.8% (16 patients). There were no new serious adverse events of abdominal pain/lower abdominal pain/pelvic pain during long term treatment relative to what was reported during the pivotal studies.

The only events reported in more than 2 patients across treatment groups cumulatively through Week 52 were pelvic pain (3 patients), ovarian cyst (3 patients), and suicidal ideation, suicidal threat, or suicidal attempt (10 patients [7 in the pivotal studies and 3 in the long-term extension study]). In the placebo-controlled 24-week pivotal studies, ovarian cyst and suicidality adverse events were reported with the same frequency in the relugolix + E2/NETA and placebo groups and there was no increase in frequency of these events with continued treatment through Week 52.

Two patients were reported to have a cancer; these cancers were of different cell types – one was a central nervous system B-cell lymphoma (onset Day 244, in a patient [relugolix + E2/NETA, MVT-601-3103] with potential symptoms of the event, headaches, reported recurrently starting 40 days prior to baseline Day 1) and the other was a non-small cell lung cancer (onset Day 131) in a patient (relugolix + E2/NETA, MVT-601-3102) with a history of second hand smoke exposure and Lynch Syndrome by genetic testing. These events are likely to be sporadic given the relatively short interval of exposure to study drug, lack of plausible biological association, pre-existing risk factors and/or potential symptoms of the event preceding the start of treatment.

Extension Safety Population through Week 104 (Population 3)

In the relugolix + E2/NETA group, relative to the duration of follow-up, the proportion of patients with serious adverse events did not increase disproportionately during continued treatment with relugolix + E2/NETA during MVT-601-3103 relative to the pivotal studies. The cumulative percentage of patients

with serious adverse events in the pivotal studies and MVT-601-3103 (up to 104 weeks of treatment) was 4.0%.

The events reported in more than one patient were as follows: suicidal ideation (4 patients), cholelithiasis (4 patients), cholecystitis (3 patients), coronavirus infection (3 patients), endometriosis (3 patients), pelvic pain (2 patients), uterine leiomyoma (2 patients), goiter (2 patients), and tibia fracture (2 patients).

Serious adverse events with onset during the LTE study were reported at low frequency in all treatment groups (2.5% in the relugolix + E2/NETA group, 7.7% in the relugolix + delayed E2/NETA group, and 6.5% in the placebo group) with no overall pattern as to the types of events reported or disproportionate increase in frequency with long term treatment up to 104 weeks relative to shorter term treatment.

Laboratory findings

Haematology

In the pivotal studies there was no apparent adverse effect of relugolix + E2/NETA on hematologic parameters compared with placebo. There were small increases in mean haemoglobin with relugolix + E2/NETA compared with placebo and more haemoglobin declines by > 1 g/dL in the placebo group, consistent with higher rates of amenorrhea in the active groups. No new clinically significant trends in haematology were observed with long-term treatment with relugolix + E2/NETA.

Liver test abnormalities have been discussed above.

Vital signs

Heart rate, blood pressure, BMI and weight

There was no apparent effect of relugolix + E2/NETA on heart rate, BMI, or weight compared with placebo. In the long-term extension study, no adverse trends were identified for these vital signs.

The effect on blood pressure (hypertension) has been discussed above.

ECG

Standard 12-lead ECGs were performed baseline, Week 12, Week 24, Week 52, Week 104, and at the post-treatment follow-up visit. No clinically significant changes in electrocardiographic parameters, including QT interval corrected using Fridericia's calculation (QTcF), were observed with relugolix combination therapy in women with endometriosis up to 104 weeks of treatment.

These data together show that there was no evidence for an effect of treatment with relugolix + E2/NETA on cardiac repolarization.

Physical Examination – Visual Acuity

Mean visual acuity scores at baseline in the relugolix + E2/NETA group and placebo groups ranged from 100.1 to 100.8. At Week 24, there were no clinically significant mean changes from baseline in visual acuity score (change from baseline was 0.5 and 0.2, in the relugolix + E2/NETA group and placebo groups, respectively). A total of 10 patients (relugolix + E2/NETA: 4 patients, placebo: 6

patients) with a ≥ 10-point decline was referred for ophthalmologic evaluation, which showed normal findings in those who sought further care.

Endometrial safety

Endometrial biopsies were performed in a subset of patients in the relugolix combination therapy program. In MVT-601-3101, paired biopsies at baseline and Week 24 were required for all patients. In MVT-601-3102, biopsies were required at baseline (unless a biopsy result was available from within 6 months prior to screening). After baseline, biopsies could be conducted if clinically indicated. In MVT-601-3103, biopsies were required at Week 52 and Early Termination Visit for all patients and were recommended at Week 104.

Treatment with relugolix + E2/NETA was not associated with endometrial hyperplasia or carcinoma in the pivotal studies or long-term extension study. One patient was subsequently diagnosed with endometrial carcinoma while on study that resolved (was not identified on subsequent hysteroscopic-directed biopsies) without specific treatment while ongoing treatment with relugolix + E2/NETA. Treatment with relugolix + E2/NETA resulted in a shift from proliferative and/or secretory endometrium to an inactive/atrophic endometrium. These findings are the expected manifestation of estrogen suppression and progestin supplementation on the endometrium.

Safety in special populations

Pregnancy

Patients were required to use nonhormonal contraception during the relugolix combination therapy pivotal studies and long-term extension study. Cumulatively, as of 25 November 2022, a total of 35 pregnancies had been reported overall in the full relugolix clinical development program (including both uterine fibroids and endometriosis data).

- 3 pregnancies in the phase 3 uterine fibroids program,
- 1 pregnancy in a phase 2 uterine fibroids dose-finding study,
- 30 pregnancies in the phase 3 endometriosis program, and
- 1 pregnancy in the phase 3 contraception indication study (MVT-601-050)

Of these 35 pregnancies,

- 16 were in women exposed to relugolix (as relugolix monotherapy or relugolix combination therapy) during pregnancy. One of these 16 pregnancies 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. Of these 4 patients who became pregnant after completing treatment, one had an estimated

conception 13 days after the last dose (t1/2 of 61.5 hours, 5 half-lives = 12.8 days) and the other 3 patients had estimated conception > 13 days after the last dose.

- 15 were in women who were in a placebo group (including the single pregnancy reported in phase 3 randomized withdrawal study MVT-601-035).

Of the 16 women exposed to relugolix (as relugolix monotherapy or relugolix combination therapy) during pregnancy, 9 pregnancies resulted in live birth (8 full term, 1 premature), 2 resulted in spontaneous abortion, 1 resulted in a missed abortion, 1 resulted in elective abortion, and 3 are of unknown status/lost to follow-up.

Note: the pregnancy with estimated conception 13 days after the last dose of relugolix combination therapy resulted in a premature (35 4/7 weeks) live birth.

There were no reports of partner pregnancy in study MVT-601-3201.

No new safety concerns have been identified for relugolix combination therapy based on review of cumulative pregnancy data.

Of the 16 women exposed to relugolix during pregnancy, 3 were reported in women assigned to relugolix monotherapy (one on 10 mg relugolix and two on 40 mg relugolix), and 13 in women assigned to relugolix combination therapy:

- Dosing issue:
  - 1 pregnancy was reported in a participant assigned to treatment with relugolix 10 mg monotherapy, a dose that incompletely inhibits ovulation.
- Timing of treatment initiation:
  - 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.
  - 1 participant became pregnant prior to initiation of relugolix combination therapy. The conception was estimated as Day -24. The screening pregnancy test was negative. On Day 29, the participant had positive urine and serum pregnancy tests. Contraceptive method used included condoms.
- Compliance with dosing and/or failure of non-hormonal contraception: 9 participants
- Unknown reason:
  - 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.
  - 1 participant had a positive serum beta-human chorionic gonadotropin (β-hCG) test after 116 days of treatment initiation with open-label relugolix combination therapy. The participant had experienced a 7-day treatment interruption due to COVID-19 approximately 1 month after treatment initiation but reported full compliance from that point.

- Lost to follow up:
  - 2 participants reported that they were pregnant but were never seen at the site for pregnancy testing. Neither participant provided any information on compliance with study drug or contraceptive measures and were lost to follow-up, thus, conclusions are limited.

Discontinuation due to adverse events

Endometriosis 24-Week Combination Therapy Safety Population (Population 1)

A summary of adverse events leading to study treatment discontinuation by SOC and PT for the Endometriosis 24-Week Combination Therapy Safety Population is presented in Table 66.

Table 66. Adverse Events with Action Taken of Study Treatment Discontinuation in by System Organ Class and Preferred Term: Endometriosis 24-Week Combination Therapy Safety Population (MVT-601-3101, MVT-601-3102 Pooled)

System Organ Class Preferred Term	Relugolix + E2/NETA (N = 418)	Relugolix + Delayed E2/NETA (N = 417)	Placebo (N = 416)
Patients with at least one adverse event leading to study treatment discontinuation, n (%)	19 (4.5%)	24 (5.8%)	12 (2.9%)
Blood and lymphatic system disorders	1 (0.2%)	0	0
Anaemia	1 (0.2%)	0	0
Cardiac disorders	0	1 (0.2%)	0
Tachycardia	0	1 (0.2%)	0
Ear and labyrinth disorders	1 (0.2%)	0	0
Vertigo	1 (0.2%)	0	0
Eye disorders	1 (0.2%)	0	0
Vitreous floaters	1 (0.2%)	0	0
Gastrointestinal disorders	5 (1.2%)	1 (0.2%)	0
Abdominal distension	2 (0.5%)	0	0
Diarrhoea	1 (0.2%)	1 (0.2%)	0
Abdominal pain	1 (0.2%)	0	0
Nausea	1 (0.2%)	0	0
Toothache	1 (0.2%)	0	0
Infections and infestations	0	0	1 (0.2%)
Upper respiratory tract infection	0	0	1 (0.2%)
Investigations	1 (0.2%)	3 (0.7%)	1 (0.2%)

Weight increased	1 (0.2%)	0	1 (0.2%)
Alanine aminotransferase increased	0	3 (0.7%)	0
Aspartate aminotransferase increased	0	3 (0.7%)	0
Gamma-glutamyltransferase increased	0	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	1 (0.2%)	3 (0.7%)	1 (0.2%)
Pain in extremity	1 (0.2%)	0	0
Arthralgia	0	2 (0.5%)	1 (0.2%)
Torticollis	0	1 (0.2%)	0
Nervous system disorders	2 (0.5%)	5 (1.2%)	1 (0.2%)
Headache	2 (0.5%)	1 (0.2%)	0
Dizziness	0	1 (0.2%)	0
Migraine	0	1 (0.2%)	0
Migraine with aura	0	1 (0.2%)	0
Paraesthesia	0	1 (0.2%)	0
Hemiparesis	0	0	1 (0.2%)
Psychiatric disorders	7 (1.7%)	7 (1.7%)	5 (1.2%)
Depression	3 (0.7%)	0	1 (0.2%)
Suicidal ideation	2 (0.5%)	3 (0.7%)	2 (0.5%)
Affect lability	1 (0.2%)	1 (0.2%)	0
Libido decreased	1 (0.2%)	1 (0.2%)	0
Mood altered	1 (0.2%)	1 (0.2%)	0
Mood swings	1 (0.2%)	1 (0.2%)	0
Insomnia	0	1 (0.2%)	0
Anxiety	0	0	1 (0.2%)
Generalised anxiety disorder	0	0	1 (0.2%)
Mixed anxiety and depressive disorder	0	0	1 (0.2%)
Reproductive system and breast disorders	7 (1.7%)	2 (0.5%)	2 (0.5%)
Vaginal haemorrhage	2 (0.5%)	0	0
Ovarian cyst	1 (0.2%)	1 (0.2%)	1 (0.2%)
Dyspareunia	1 (0.2%)	0	0
Endometriosis	1 (0.2%)	0	0
Menopausal symptoms	1 (0.2%)	0	0
Menstruation irregular	1 (0.2%)	0	0
Uterine haemorrhage	1 (0.2%)	0	0
Vulvovaginal dryness	0	1 (0.2%)	0
Metrorrhagia	0	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.2%)	1 (0.2%)
Epistaxis	0	1 (0.2%)	0
Dyspnoea	0	0	1 (0.2%)

Skin and subcutaneous tissue disorders	2 (0.5%)	3 (0.7%)	1 (0.2%)
Hyperhidrosis	1 (0.2%)	1 (0.2%)	0
Rash generalised	1 (0.2%)	0	0
Dermatitis atopic	0	1 (0.2%)	0
Urticaria	0	1 (0.2%)	0
Acne	0	0	1 (0.2%)
Alopecia	0	0	1 (0.2%)
Vascular disorders	4 (1.0%)	6 (1.4%)	2 (0.5%)
Hot flush	2 (0.5%)	6 (1.4%)	2 (0.5%)
Haematoma	1 (0.2%)	0	0
Hypertension	1 (0.2%)	0	0

Abbreviations: E2 = estradiol; N = number of patients in the treatment group; n = number of patients with specified adverse event; NETA = norethisterone acetate.
Patients with multiple events for a given preferred term or system organ class are counted only once at each level of summarization. Events are sorted by system organ class alphabetically and then by decreasing frequency of preferred term in the relugolix + E2/NETA group, followed by the relugolix + delayed E2/NETA group, followed by the placebo group. Adverse events with action taken of study treatment discontinuation are taken from the adverse event case report form.
MedDRA version 22.0.

The percentage of patients who discontinued study drug due to an adverse event was low in the relugolix + E2/NETA and placebo groups. In both MVT-601-3101 and MVT-601-3102, most adverse events leading to discontinuation were reported for only 1 patient in a treatment group. In the pooled studies, the only event resulting in study drug discontinuation reported in more than 2 patients in either treatment group was depression. Depression resulted in treatment discontinuation in 0.7% of patients in the relugolix + E2/NETA group and 0.2% of patients in the placebo group. Suicidal ideation was reported with the same frequency in the relugolix + E2/NETA group and placebo group (0.5% in each group). Hot flush resulted in treatment discontinuation with the same frequency in the relugolix + E2/NETA group and placebo group (0.5%), and at a higher frequency in the relugolix + delayed E2/NETA group (1.4%), as would be expected given the initial 12-week treatment with relugolix monotherapy.

Endometriosis Long-Term Combination Therapy (Population 2)

In the Endometriosis Long-Term Combination Therapy Safety Population, the cumulative incidence of adverse events leading to treatment discontinuation through Week 52 was 7.7%, 10.1%, and 6.7% in the relugolix + E2/NETA group, relugolix + delayed E2/NETA group, and placebo group, respectively.

Notably, adverse events associated with low E2 concentrations were rarely treatment-limiting with long-term relugolix + E2/NETA treatment up to 52 weeks (eg, hot flush, 0.5%; hyperhidrosis, 0.2%; menopausal symptoms, 0.2%, libido decreased, 0.2%). Uterine bleeding type events also rarely resulted in treatment discontinuation (eg, menstruation irregular, 0.5%; vaginal haemorrhage, 0.5%; uterine haemorrhage, 0.2%). No patient in the relugolix + E2/NETA group was discontinued due to transaminase elevation.

Long-term treatment with relugolix + E2/NETA up to 52 weeks was associated with a low overall incidence of adverse events leading to study treatment discontinuation. There was no particular pattern to these events and the rates of discontinuation due to adverse events did not increase disproportionally over time (4.5% in the pivotal studies; 7.7% through up to 52 weeks of treatment). Discontinuations due to adverse events associated with low E2 concentrations were rare as were discontinuations due to uterine bleeding-type events. No patient discontinued due to transaminase

elevation. Among patients randomized to relugolix + E2/NETA, the incidence of adverse events resulting in discontinuation was 4.5% during the first 24-weeks of treatment and 7.7% cumulatively with up to 52 weeks of treatment. The most commonly reported adverse events leading to treatment discontinuation in this group through Week 52 were weight increased, reported in 1.2% of patients and depression, reported in 1.0% of patients.

Extension Safety Population through Week 104 (Population 3)

In the Extension Safety Population, adverse events leading to treatment discontinuation cumulatively through Week 104 were 6.9%, 9.3%, and 8.4% in the relugolix + E2/NETA group, relugolix + delayed E2/NETA group, and placebo group, respectively. A total of 54 patients (6.8%) discontinued study drug treatment for an adverse event with first onset during the LTE study. The majority of adverse events resulting in treatment discontinuation were nonserious. The incidence of these did not increase disproportionately with longer term follow-up.

In summary, during the 80-week treatment period of the LTE study, the incidence of adverse events leading to study drug discontinuation was low (6.8% overall), numerically lowest in the relugolix + E2/NETA group (5.4%) and highest in the placebo group (8.0%). There were no predominant events resulting in treatment discontinuation; all events resulting in treatment discontinuation were reported with an overall frequency of ≤ 0.5%.

Post marketing experience

Based on review of cumulative post-marketing data through 25 May 2022 for the three marketed relugolix-containing products, Myfembree/Ryeqo, Relumina and Orgovyx, a possible causal relationship between events of urticaria and angioedema and administration of relugolix-containing products, including relugolix/estradiol/norethisterone acetate (relugolix combination therapy) and relugolix monotherapy was identified. Accordingly, the company core data sheet (CCDS) for relugolix-containing products was updated to include adverse reactions of urticaria and angioedema at not known frequency, based on post-marketing experience (Skin and subcutaneous disorders SOC: angioedema and urticaria – frequency not known).

Relugolix 40 mg monotherapy

Relugolix 40 mg monotherapy is approved in Japan. The first marketing authorization for relugolix was granted to Takeda Pharmaceutical Company Limited in Japan on 08 Jan 2019 under the trade name Relumina as a 40-mg tablet to be taken once daily for "*the improvement of symptoms associated with uterine myoma (hypermenorrhoea, lower abdominal pain, lower back pain, and anaemia)*".

Relumina 40 mg was launched in Japan on 01 Mar 2019. On 24 Dec 2021, Relumina was approved for the additional indication of the improvement of pain associated with endometriosis. Cumulative post-marketing patient exposure for Relumina is 63, 799 patient-years (01 Mar 2019 to 25 May 2022).

Cumulatively to 25 May 2022, 85 serious postmarketing cases with a total of 103 serious adverse events were reported for Relumina.

The most commonly reported serious adverse reactions for Relumina as of 25 May 2022 were events of uterine bleeding (genital haemorrhage, uterine haemorrhage, heavy menstrual bleeding, intermenstrual bleeding, and menstrual disorder) observed in 53 women receiving relugolix 40 mg monotherapy, predominantly for treatment of symptomatic uterine fibroids.

Relugolix combination therapy

The first marketing authorization for relugolix combination therapy was granted to Myovant in the US on 26 May 2021 (the International Birth Date [IBD]) under the tradename Myfembree for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Marketing authorization for relugolix combination therapy was subsequently granted to Gedeon Richter in the European Economic Area (EEA) on 16 Jul 2021 with approvals following in Great Britain on 09 Aug 2021 and Moldova on 27 Dec 2021, under the tradename Ryeqo® for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. One commercial formulation of relugolix combination therapy is available worldwide which is a fixed-dose combination film-coated tablet containing 40 mg relugolix, 1 mg E2 (as hemihydrate), and 0.5 mg NETA. Cumulative post-marketing patient exposure from the IBD to 25 May 2022 is 2,225 patient-years.

Cumulatively, to 25 May 2022, 35 serious post-marketing cases (22 spontaneous, 13 solicited) with a total of 41 serious adverse events were reported with Myfembree/Ryeqo.

These post-marketing cases included both spontaneous and solicited reports, the latter obtained as a function of a patient support program. The majority of these cases contained limited information on the start date of treatment, event latency, prior medical history, and concomitant medications.

The most commonly reported events were events of uterine bleeding (n = 9). These events are expected per the Myfembree/Ryeqo label, including a labelled warning that severe haemorrhage may occur in patients with submucosal uterine fibroids.

Six cases with thrombotic or thromboembolic events have been reported, including two events of pulmonary embolism and five total events of thrombosis.

A solicited case of spontaneous abortion was reported in a 33-year-old female. No information was provided on the event latency, duration of exposure prior to conception, or timing of last menstrual period. The reporter declined to provide further information.

Supportive studies

MVT-601-034 - Observational BMD data through 52 weeks (natural history study)

MVT-601-034 was a prospective observational study to characterize longitudinal BMD of premenopausal women with uterine fibroids or endometriosis over a 52-week observational period. This study was conducted contemporaneously with the relugolix interventional studies for uterine fibroids (MVT-601-3001 and MVT-601-3002) and endometriosis (MVT-601-3101 and MVT-601-3102) in a subset of the same study sites.

The primary objective was 1) to characterize longitudinal bone mineral density (BMD) (lumbar spine [L1 to L4]) of premenopausal women with uterine fibroids or endometriosis and 2) to further characterize longitudinal BMD, including femoral neck and total hip, of premenopausal women with uterine fibroids or endometriosis.

As age is a strong risk factor for BMD change over time, participants in this observational study were matched by age category with participants enrolled in the interventional studies for uterine fibroids and endometriosis.

Important exclusion criteria were:

- baseline BMD z-score < −2.0 at the lumbar spine, total hip, or femoral neck;

- a history of or currently had osteoporosis or other metabolic bone disease
- history of use of gonadotropin-releasing hormone (GnRH) receptor antagonist or GnRH receptor agonist within six months prior to screening
- Had been a participant in an investigational drug or device study within the one month prior to the screening 1 visit
- currently pregnant or lactating, or intended to become pregnant during the study period

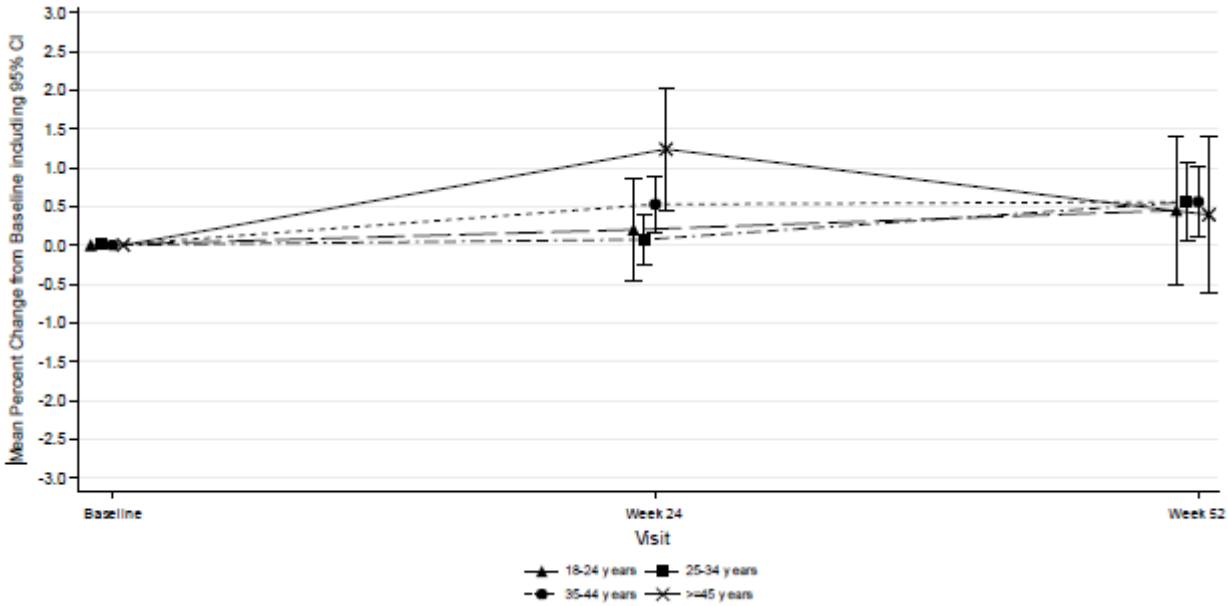
A total of 714 participants (452 with endometriosis and 252 with uterine fibroids) were enrolled. The mean (SD) age for all participants with endometriosis was 33.9 years (7.18), and the two predominant racial representations were White (91.4%) and Black or African American (6.0%).

At baseline, the mean (SD) BMD at the lumbar spine was 1.1564 g/cm2 (0.14568). At Weeks 24 and 52, the mean percent changes (95% CI) from baseline in BMD at the lumbar spine were 0.35% (0.13%, 0.57%) and 0.53% (0.24%, 0.83%), respectively.

At Week 52, the mean (SD) absolute change from baseline was 0.0057 g/cm^2 (0.03049).

A summary of percent change from baseline to Week 52 in BMD at the lumbar spine for the endometriosis cohort by 5-year age band is presented in Figure 34. For the youngest age ranges, mean percent changes from baseline in BMD at the lumbar spine were small and largely within the 95% CIs of each other at Weeks 24 and 52. The $\geq$ 45 year age group, the group with the fewest participants, showed a mean percent increase in BMD at Week 24, although at Week 52 the mean percent change from baseline was similar to the other age groups and likely reflects regression to the mean (Cummings et al. 2000). BMD at the lumbar spine appeared to be stable across all age groups in the endometriosis cohort over 52 weeks.

Figure 34. Mean Percent Change from Baseline in BMD Value at the Lumbar Spine Over Time by Age Group (BMD Analysis Population for Participants with Endometriosis)



At Weeks 24 and 52, the majority of participants had an increase or a non-clinically significant decrease in BMD, defined as a ⩽ 3% decline. There were 22 (4.9%) participants with BMD losses > 3% at Week 24, and 29 (6.4%) participants with BMD losses > 3% at Week 52. There was one participant with a loss > 8% at Week 24, but no loss at Week 52. Categorical changes in the overall cohort were generally similar to that of the endometriosis cohort.

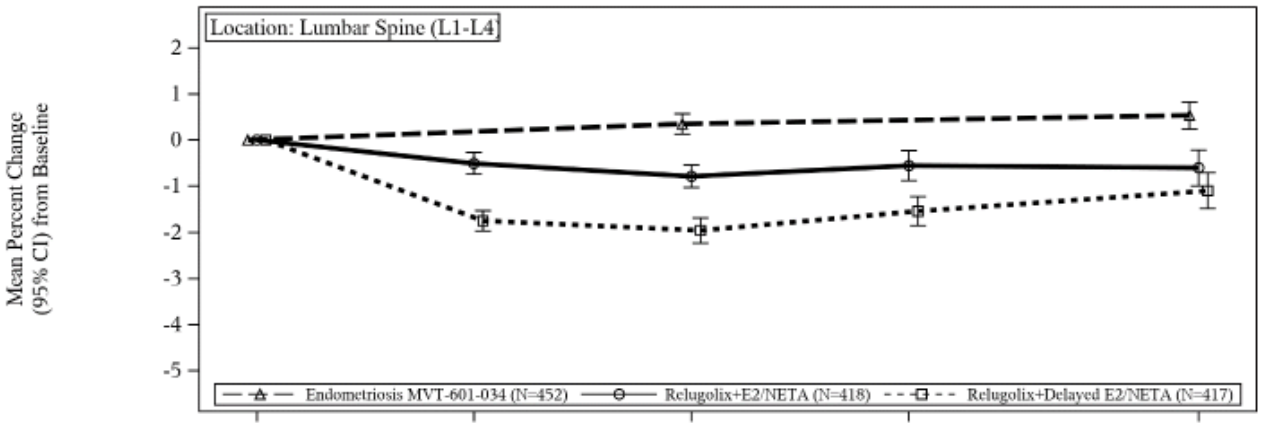
Integrated BMD Analysis of Long-Term Combination Therapy Cohort with Observational Endometriosis Cohort through Week 52

To contextualize BMD outcomes from the pivotal and long-term extension relugolix combination studies, the following section integrates data across studies to inform BMD changes observed in studies MVT-601-3101, MVT-601-3102, and MVT-601-3103 as compared with MVT-601-034.

Assessment of demographics and baseline characteristics in the endometriosis cohort and that of the population in the relugolix combination studies shows that the studies were generally well-matched by number of subjects included in the assessment, age, BMI, race, and ethnicity except for numerical difference in distribution of patients from North America. More study participants were from North America in the endometriosis cohort (169 [37.4%] patients) compared with the relugolix + E2/NETA group (90 [21.5%] patients) and relugolix + delayed E2/NETA (91 [21.8%] patients).

In the endometriosis cohort (MVT-601-034), simple mean percent changes from baseline in BMD at the lumbar spine (0.35%; 95% CI [0.13, 0.57]) at Week 24 were generally comparable to those observed in the pooled (MVT-601-3101 and MVT-601-3102) placebo groups (0.11%; 95%CI [-0.14, 0.36]), respectively, further supporting the validity of this group as a benchmark to the 52-week data from the relugolix + E2/NETA group.

Figure 35. Percent Change from Baseline in Bone Mineral Density Over Time by Location: Long-Term Endometriosis BMD Safety Population through Week 52 (MVT-601-3101, MVT-601-3102, MVT-601-3103, and MVT-601-034) – Lumbar spine



	No. of Evaluable Patients				
EM MVT-601-034	451	0	382	0	320
R+E2/NETA	418	349	333	241	228
R+Delayed E2/NETA	417	347	338	223	202

Abbreviations: CI = confidence interval; E2 = estradiol; EM = endometriosis; N = number of patients in the treatment group; NETA = norethisterone acetate; R = relugolix.
Source: ISS Figure 8.1.2.2, Module 5.3.5.3.

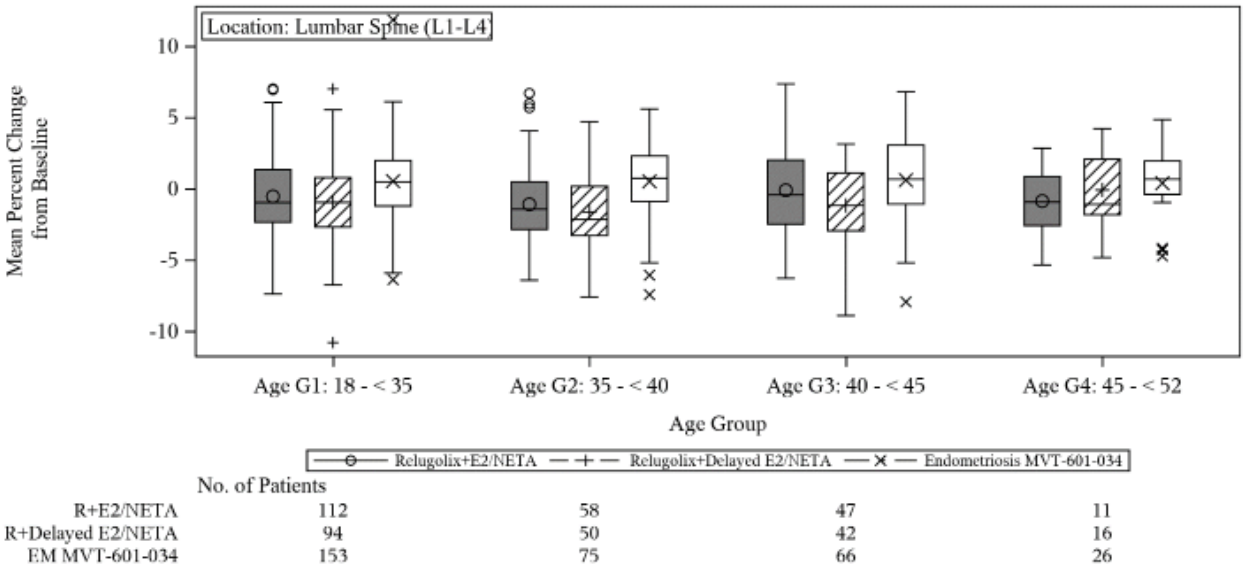
Through 52 weeks of observation, there were small differences in mean percent change in BMD from baseline between the relugolix + E2/NETA group and the endometriosis cohort (Figure). At the lumbar spine, the endometriosis cohort showed a change of 0.53% (95%CI: 0.24, 0.83%) after a year of observation compared with -0.60% (95%CI: -0.99%, -0.22%) in the relugolix + E2/NETA group and -1.09% (95% CI: -1.48, -0.71%) in the relugolix + delayed E2/NETA group. As expected, the small decline in the relugolix + delayed E2/NETA group reflects the initial 12 weeks of relugolix monotherapy, which contrasts with the higher mean percent changes seen with the relugolix + E2/NETA and placebo groups. However, with transition to relugolix + E2/NETA after Week 12, no further bone loss was observed and after Week 24 a trend towards recovery.

Since categorical changes were evaluated in MVT-601-3101, MVT-601-3102, and MVT-601-3103 (see Categorical Analyses of Bone Mineral Density of the Safety section), similar assessments were conducted in MVT-601-034. At Weeks 24 and 52, the majority of women had an increase in lumbar spine BMD (222 [58.1%] patients at Week 24 and 184 [57.5%] patients at Week 52) or a non-clinically significant decline defined as ≤ 3% (135 [35.3%] patients at Week 24 and 102 [31.9%] patients at Week 52). Smaller percentages of women had losses of > 3% to ≤ 5% and > 5% to ≤ 8% (22 [5.8%] patients at Week 24 and 29 [9.1%] patients at Week 52). One patient had losses > 8% at Week 24 and none at Week 52.

Since bone mass accrual at the lumbar spine in women may occur up to age 30 with subsequent decline in fifth decades of life prior to menopause, change in BMD was assessed by age grouping (18 to < 35, 35 to < 40, 40 to < 45, and 45 to < 52). Mean percent change in BMD by age group was consistent between the relugolix + E2/NETA group and endometriosis cohort when assessed at the lumbar spine and total hip (Figure Figure). In each group, the mean percent change from baseline in

the endometriosis cohort shows evidence of increase in BMD while the relugolix + E2/NETA group remains relatively stable.

Figure 36. Box Plot of Percent Change from Baseline to Week 52 in Bone Mineral Density by Location and Age Group: Long-Term Endometriosis BMD Safety Population through Week 52 (MVT-601-3101, MVT-601-3102, MVT-601-3103, and MVT-601-034) – lumbar spine



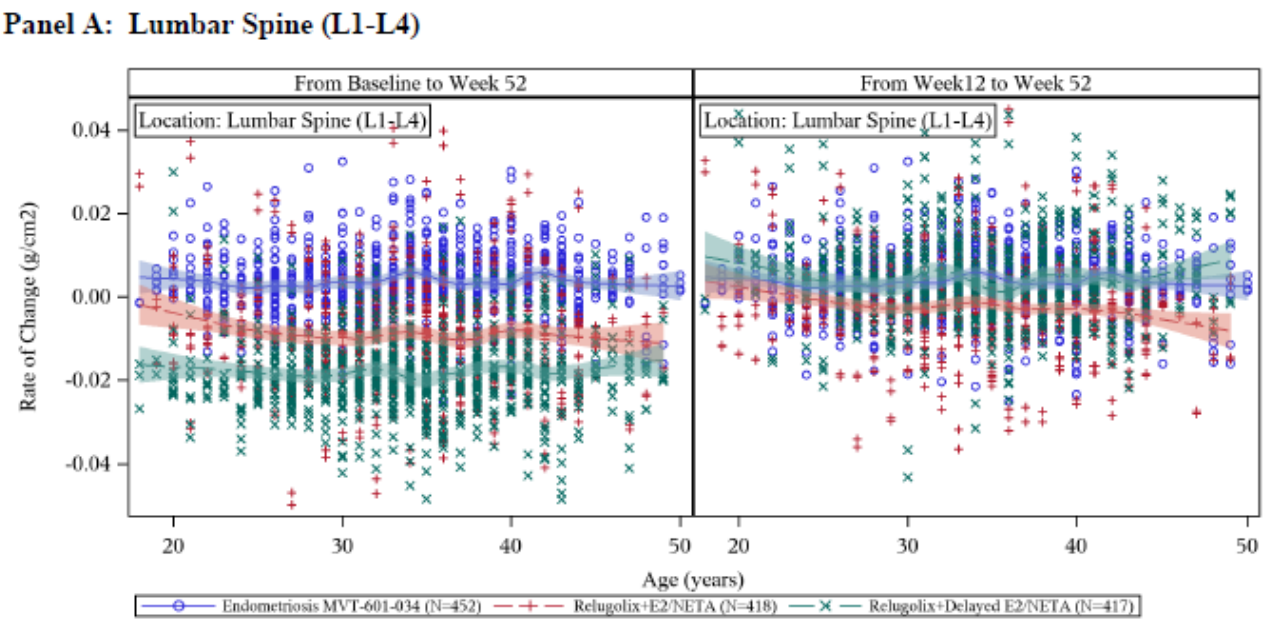
No. of Patients				
R+E2/NETA	112	58	47	11
R+Delayed E2/NETA	94	50	42	16
EM MVT-601-034	153	75	66	26

Abbreviations: E2 = estradiol; EM = Endometriosis; G = group; NETA = norethisterone acetate; R = relugolix.
The top and bottom of the box are 75th and 25th percentiles with median as the band inside the box; bands outside the box are the minimum and maximum within 1.5 - fold interquartile range of the 25th and 75th percentiles.
Source: ISS Figure 8.1.6.4, Module 5.3.5.3.

To further assess the potential long-term effect of relugolix combination therapy on BMD, 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 pattern across cohorts and age groups (Figure Figure). The random-coefficients model is a mixed-effects model with repeated measures of BMD which 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 endometriosis 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 at Week 12 since the small changes observed at Week 12 (considered to be associated with adjustment to the new hormonal steady state) are not considered to be clinically meaningful and the rate of change from that point is likely to be the determinant of long-term effect 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 done in two ways: starting at baseline and started at Week 12, when patients transitioned to relugolix + E2/NETA, where onset of a plateau in BMD change was observed that continued through Week 52.

The BMD rate of change from baseline to Week 52 and from Week 12 to Week 52 is presented in Figure (left and right panel, respectively) for the relugolix + E2/NETA and the relugolix + delayed E2/NETA groups. The rate of change for the endometriosis cohort (MVT-601-034) was assessed from baseline to Week 52 and is presented in both panels alongside with that of the relugolix groups.

Figure 37. Bone Mineral Density Rate of Change by Age: Long-Term Endometriosis BMD Safety Population through Week 52 (MVT-601-3101, MVT-601-3102, MVT-601-3103, and MVT-601-034)



Abbreviations: E2 = estradiol; N = number of patients in the treatment group; NETA = norethisterone 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.
Source: I SS Figure 8.1.6.2, Module 5.3.5.3.

As shown in Figure for lumbar spine, the rate of change from baseline versus patient age in the relugolix + E2/NETA group shows a minimal decrease while the relugolix + delayed E2/NETA group a greater decrease compared with the endometriosis cohort through 52 weeks of treatment. When this time interval is truncated at Week 12, the rate of change in the relugolix + E2/NETA group approximates that of the age-matched cohort at the lumbar spine and is nearly superimposable at the total hip and femoral neck. Small changes in BMD at Week 12 likely reflect adaptation to the new steady state of E2 concentrations associated with relugolix combination therapy, which are lower than the average concentrations observed over the course of a natural menstrual cycle (Stricker et al. 2006) and are consistent with concentrations observed during the early follicular phase (Cramer et al. 2002; Stricker et al. 2006).

These data demonstrate that relugolix + E2/NETA is associated with a small decrease in BMD during the first 12-24 weeks of therapy, as expected because of lower exposure to estrogen associated with beginning relugolix combination therapy. Thereafter, BMD remained stable over a total of 52 weeks of therapy. In the relugolix + delayed E2/NETA group, bone loss was noted, which was independent of age, while patients received relugolix monotherapy, though bone density stabilized when patients began relugolix combination therapy. These data further support that initiation of E2/NETA minimizes progressive BMD loss associated with estrogen suppression and trend towards recovery.

2.5.2. Discussion on clinical safety

2.5.2.1. Safety profile

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 with longer duration of use. Addition of E2/NETA is meant to mitigate the BMD loss and to decrease postmenopausal symptoms, without relevant loss of efficacy in reducing pain associated with endometriosis (i.e. without negating the effect of relugolix).

Since 2021, relugolix is registered in the EU for the *"treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age"*. As such, in view of the mechanism of action and considering that treatment is based on reduction of circulating estradiol, its safety profile in this population can be predictable to a large extent.

Safety data sets endometriosis population

The endometriosis safety database is based on 3 populations: the 2 phase 3 placebo-controlled pivotal studies of 24 weeks, its long-term extension study:

1) The main safety data set is the pooled data of the two randomized, double-blind, placebo-controlled phase 3 pivotal studies (MVT-601-3101 and MVT-601-3102) for 24 weeks.
2) The open label extension study MVT-601-3103 of the two pivotal phase 3 studies MVT-601-3101 and MVT-601-3102 with data up to Week 52
3) A data set with completers of the pivotal phase 3 studies who participated in the open-label extension study, who used relugolix combination therapy for in total up to 104 weeks

Further, 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 or endometriosis. These women were enrolled concurrently with the clinical studies at a subset of the participating study sites.

This long-term safety data package is comparable to that submitted for the initial indication of myoma. The extended long-term safety data were primarily requested to support that bone mineral density (BMD) loss remains within acceptable limits, about 1% from baseline.

Patient exposure

In the clinical programme, a total of 1381 patients received at least one dose of relugolix combination therapy. In the studies for uterine fibroids and endometriosis together, 912 participants were exposed for at least 6 months, 627 participants for at least one year, 440 participants for at least 18 months, and 212 participants were exposed for at least 24 months. Of these, 139 patients used the combination therapy for at least 104 weeks (50.2%).

In the two pivotal placebo-controlled studies (MVT-601-3101 and MVT-601-3102) together, a total of 1251 patients were enrolled, for 24 weeks. In the long-term open label extension study (MVT-601-3103), a total of 799 received relugolix combination therapy for 80 weeks (in total up to 104 weeks). The median duration of treatment was 104.1 weeks for the relugolix+E2/NETA group, 92.1weeks for the relugolix+delayed E2/NETA group and 79.6 for the placebo group.

2.5.2.2. Adverse events

Adverse events will mainly be discussed by using the pooled data from the two pivotal phase 3 studies. The safety endpoint of special interest, bone mineral density, will also be discussed with data from the long-term extension study.

Short term safety over 24 weeks in placebo-controlled setting

The **overall incidence of AEs** over the treatment period of 24 weeks was slightly higher in the relugolix +E2/NETA group (75.8%) compared to the placebo group (70.4%),and was highest in the relugolix+ delayed E2/NETA (79.4%). 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.

The **most common adverse events** (relugolix+E2/NETA vs. placebo, respectively) were Headache (33.0% vs 26.4%), Hot flush (12.0% vs 6.7%), Nasopharyngitis (10.0 vs 7.0%), Nausea (6.0% vs 4.1%), Toothache 5.5% vs 2.4%), Back pain (4.8% vs 2.9%), Bone density decreased (3.8% vs 2.2%), Libido decreased (3.8% vs 1.2%), Urinary tract infection (3.6% vs 2.6%), Arthralgia (3.6% vs 2.2%), Influenza (3.3% vs 2.4%), Fatigue (3.1% vs 2.4%), Dizziness (3.1% vs 1.2%), Metrorrhagia (3.1% vs 1.4%), Vulvovaginal dryness (2.2% vs 0.5%), Insomnia (1.9% vs 2.2%), Migraine (1.9%vs 1.4%). Percentages in the relugolix+ delayed E2/NETA were higher than observed in the relugolix +E2/NETA group.

The **most common drug-related adverse events** (reported in at least 1% of patients in any treatment group) were headache (17% in the relugolix+E2/NETA group and 13.5% in the placebo group) and hot flush (11.7% in the relugolix+E2/NETA group, 33.6% in the relugolix+ delayed E2/NETA group and 6.5% in the placebo group. The difference between the combination treatment and the delayed group in number of hot flush events indicates that the addition of E2/NETA considerably reduces the frequency of postmenopausal symptoms.

Other drug-related adverse events, i.e. which are considered reported more frequently in the relugolix + E2/NETA group than the placebo group (at 24 Weeks) included headache (17% vs 13.5%), libido decreased (3.8% vs. 1.2%), nausea (3.6% vs. 2.2%), metrorrhagia (2.6% vs 1.4%), vulvovaginal dryness (2.2% vs 0.5%), arthralgia (2.2% vs. 1.0%) and dizziness (2.2% vs. 1.0%).

Adverse drug reactions associated with relugolix combination therapy were assessed by review of adverse events observed at a frequency of ≥2% for relugolix combination therapy and at greater frequency than placebo (based on the observed frequencies of adverse events at higher incidence than placebo in the context of sample size), with consideration of other supporting data inclusive of medical judgment. ADRs included headache (33.0%), hot flush, hyperhidrosis, or night sweats (12.9%), abnormal uterine bleeding (6.7%), back pain (4.8%), libido decreased (4.1%), and arthralgia (3.6%)

Serious adverse events were reported in 12 (2.9%) of the relugolix/E2/NETA patients and 9 (2.2%) patients in both the placebo and relugolix+delayed E2/NETA groups. The incidence of serious adverse events is considered low.

Safety over 52 weeks of treatment

The **common adverse events** at 52 weeks were comparable to those reported during the first 24 weeks.

Most commonly reported drug-related adverse events in patients treated with relugolix + E2/NETA for up to 52 weeks were, headache (20.1%), hot flush (13.4%), and bone density decreased (5.7%). The frequency of these events did not disproportionally increase with long term treatment compared with the first 24 weeks of treatment in the pivotal studies, in which these incidences were 17.0% (headache), 11.7% (hot flush), and 3.8% (bone density decreased).

Regarding **serious adverse events**, there was no disproportionate increase in the incidence compared to the pivotal studies. At week 52, the incidence was 3.8%.

Safety over 104 weeks of treatment (patients who completed 104 weeks of relugolix + E2/NETA)

The most frequently reported drug-related adverse events included headache (71 patients [25.6%]), hot flush (38 patients [13.7%]) and bone density decrease (25 patients [9.0%]).

The onset of **serious adverse events during the LTE study** was low in all treatment groups 2.5% in the relugolix + E2/NETA group, 7.7% in the relugolix + delayed E2/NETA group, and 6.5% in the placebo group) with no overall pattern as to the types of events reported or disproportionate increase in frequency with long term treatment up to 104 weeks relative to shorter term treatment.

Of note, bone mineral density-related adverse events were reported predominantly by a single site, contrary to adverse event reporting guidelines and, thus, reporting was not systematic. As such, the frequency of these adverse events is not interpretable. Bone density was formally evaluated with DXA scanning in all patients at protocol-specified time points, bone mineral density-related AE were an option to report, fractures were obligatory to report.

Adverse events of interest

BMD loss (leading to osteoporosis and fractures) is an important risk of the postmenopausal state that is induced by relugolix monotherapy. Addition of E2/NETA to relugolix is added to mitigate this risk.

Adverse events related to lone of bone mineral density (BMD)

Adverse events of BMD in the 24 weeks studies was reported in 5.8% of the relugolix+ delayed E2/NETA group (patients receiving 12 weeks of relugolix monotherapy), 4.3% in the relugolix+E2/NETA group and 3.1% in the placebo group. The slightly higher percentage of adverse events in the delayed E2/NETA group in comparison to the relugolix+E2/NETA group supports the protective effect on BMD of E2/NETA.

Percent change from baseline in BMD

- Percent change in BMD between baseline and 12 weeks

At 12 weeks, the percent change from baseline in BMD at lumbar spine in the relugolix + delayed E2/NETA group (12 weeks monotherapy followed by 12 weeks combination therapy) was -1.76%. The change in the relugolix + E2/NETA group was -0.49% and in the placebo group this was 0.09%. The difference between relugolix + E2/NETA and relugolix + delayed E2/NETA was 1.28, which was significant, suggesting the protective effect of E2/NETA.

- Percent change in BMD between baseline and 24 weeks

After 24 weeks, the percent change from baseline in BMD at lumbar spine in the relugolix + delayed

E2/NETA group was 1.94%, meaning that there was only a small decrease compared to the first 12 weeks when relugolix monotherapy was used. The percent change in the relugolix + E2/NETA group was -0.72% and in the placebo group this was 0.12%. This small difference supports the protective effect of E2/NETA. A similar pattern was seen at total hip, however the percentages decrease were in general lower.

- Long term up to 52 weeks

After 52 Weeks of treatment in the relugolix +E2/NETA group, the LS mean percent change at lumbar spine from baseline was -0.67% (95% CI: -1.09%, -0.25%). After the small reduction in BMD observed at Weeks 12 and Week 24 in the lumbar spine, there was evidence of stabilization at Weeks 36 and 52. In the relugolix + E2/NETA group, BMD at the total hip remained relatively unchanged from baseline.

- Natural history data vs. long term safety data up to 52 weeks in the endometriosis safety set

A 1-year prospective, observational study was undertaken to characterize longitudinal BMD in a cohort of premenopausal women with endometriosis (natural history study). 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. Weeks 24 and 52, the mean percent changes from baseline in BMD was 0.35% and 0.53%, respectively. At 52 weeks, the majority of the patients had no BMD decrease or a decrease <= 3%, which was defined as non-clinically significant.

The integrated analysis of the pivotal studies and natural history data support the safety analysis of relugolix combination therapy. As also noted in the initial MAA, there is a small decrease in BMD during the first 12-24 weeks of relugolix combination treatment, suggesting adaptation to a new steady state of E2. Truncating the analysis at 12 Weeks, the rate of change in the active treatment groups is comparable to the age-matched natural control group.

- Long term treatment of relugolix combination therapy up to 104 weeks

In the relugolix + E2/NETA group after 104 weeks of treatment, there was stabilization in BMD with a LS mean percent change from baseline of -0.45% (95% CI: -1.03, 0.13), n= 163 patients. This means that during the 2 years of treatment with relugolix + E2/NETA the percent change from baseline remains below 1%.

In conclusion, the data from the BMD measurements in patients suffering from moderate to severe pain associated with endometriosis are comparable with results on BMD change noted in the initial MAA in patients with uterine myoma. Also in this population, the summary data on BMD effects of relugolix + E2/NETA over a treatment period of 104 weeks, 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. Analysis of progression in BMD over time in patients aged 18-24 indicated an increase in BMD in lumbar spine and total hip over time, supporting that Ryeqo does not seem to have an effect on the ability to create new bone mass.

Meaningful reduction in BMD (>3%) up to 104 weeks

The majority of the women had no significant decline in BMD. A total of 20 (12.3%) and 12 patients (7.4%) had a losses of > 3% to ⩽ 5% and > 5% to ⩽ 8% during 104 weeks of therapy. One patient

(0.6%) had loss in BMD > 8% through Week 104. At total hip, these numbers were lower, 9 (5.5%) and 3 (1.8%) patients had losses of > 3% to ⩽ 5% and > 5% to ⩽ 8% and no patient had a loss of >8%.

The noted percentage of patients with a meaningful reduction in BMD (>3%) up to 104 weeks is comparable with the percentage noted in the initial MAA. As discussed in the initial MAA, to address the concerns that women experiencing the BMD loss of (> 3%) could not be identified a priori, the SmPC includes several risk minimization measures to address this safety issue.

BMD data collected at the 6- and 12-month post-treatment evaluations (PTFU) of patients who participated in the long-term extension study for the endometriosis population showed that for the proportion of patients in whom bone loss > 3 % is observed during treatment with relugolix + E2/NETA and for whom PTFU DXAs are available, recovery or trend toward recovery is observed in all patients at the lumbar spine and in 89% of patients at the total hip.

Hepatic Transaminase Elevations

In the relugolix clinical development program, any increase in ALT and/or AST ≥ 3 × ULN was considered as an adverse event of clinical interest. The potential for hepatic transaminase elevations associated with relugolix is based on nonclinical observations, clinical study data, and data reported for drugs that work on the hypothalamic-pituitary-gonadal axis GnRH receptor agonists and the GnRH receptor antagonists.

In the phase 3 placebo-controlled studies (24 weeks), no patients had an ALT or AST > 3 × ULN and a total bilirubin > 2 × ULN. The incidence of ALT or AST > 3 × ULN was low and similar in both treatment groups (1.0% in both the relugolix + E2/NETA and placebo groups).

During the 104 weeks of treatment, for any relugolix +E2/NETA duration, 11 cases (out of 799, 1.4%) of ALT or AST > 3 × ULN) were reported. There are no signals of cumulative risk during prolonged treatment. There were no events meeting Hy's law criteria (i.e. ALT >3 x ULN and bilirubin >2 x ULN.

Embolic and Thrombotic Events

One patient with history of obesity (BMI 38.7 kg/m2) was reported to have a deep vein thrombosis and pulmonary embolism following a knee injury during the long-term extension study. This SAE was considered to be related to the study drug. The risk of VTE, associated with the E2 component, and is extensively reflected in the SmPC.

Gallbladder disease

There was a low incidence of gallbladder disease related events in relation with the relugolix combination treatment, comparable with that reported in the initial MAA.

Hypertension

Frequency of hypertension was comparable across treatment groups during the pivotal studies for endometriosis (ranging from 0.7% in the placebo group to 1.7% in the delayed treatment group). During the long-term study, there was no disproportional increase in the frequency of hypertension. Nevertheless, based on the assessment of uterine fibroids, hypertension is already included in the SmPC, section 4.4.

Mood disorders

The frequency of reporting mood disorders as well as suicidal ideation similar in the relugolix+E2/NETA group and placebo during the pivotal studies. There was no increase in these adverse events during the long-term study. Based on the assessment of uterine fibroids, depression is already included in the SmPC, section 4.4.

Alopecia

Alopecia was not observed as adverse drug reaction in endometriosis patients but was in observed in the initial MAA for uterine myoma. Alopecia could be drug-related due to the hormonal background. Therefore, alopecia is already included in section 4.8.

Tumours (breast, liver)

There were no adverse events related to malignant breast or liver tumours reported in any patients in the relugolix + E2/NETA groups. One event of benign breast dysplasia and one event of breast cysts were reported and one event of hepatic adenoma. As concluded in the initial MAA, no evidence of a pattern of tumour development was identified in the relugolix combination clinical program.

Endometrial safety

In study MVT-601-3101, paired biopsies at baseline and Week 24 were required for all patients. In MVT-601-3102, biopsies were required at baseline (unless a biopsy result was available from within 6 months prior to screening). After baseline, biopsies could be conducted if clinically indicated. In MVT-601-3103, biopsies were required at Week 52 and Early Termination Visit for all patients and were recommended at Week 104.

No events of endometrial hyperplasia or carcinoma in the pivotal studies or long-term extension study. Biopsies taken indicated that treatment with relugolix + E2/NETA resulted in a shift from proliferative and/or secretory endometrium to an inactive/atrophic endometrium. These findings are the expected manifestation of estrogen suppression and progestin supplementation on the endometrium.

Pregnancy

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 nonhormonal contraception throughout the clinical studies, including through 30 days following the last dose of study drug.

Cumulatively, as of 25 November 2022, a total of 16 pregnancies were reported in women who became pregnant during treatment with relugolix (as relugolix monotherapy or relugolix combination therapy).

- Dosing issue: 1 pregnancy was reported in a participant assigned to treatment with relugolix 10 mg monotherapy, a dose that incompletely inhibits ovulation.
- Timing of treatment initiation:
  - 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.
  - 1 participant became pregnant prior to initiation of relugolix combination therapy. The conception was estimated as Day -24. The screening pregnancy test was negative. On Day

29, the participant had positive urine and serum pregnancy tests. Contraceptive method used included condoms.

- Compliance with dosing and/or failure of non-hormonal contraception: 9 participants
- Unknown reason:
  - 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.
  - 1 participant had a positive serum beta-human chorionic gonadotropin (β-hCG) test after 116 days of treatment initiation with open-label relugolix combination therapy. The participant had experienced a 7-day treatment interruption due to COVID-19 approximately 1 month after treatment initiation but reported full compliance from that point.
- Lost to follow up: 2 participants 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.

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 SmPC.

Amenorrhea

Amenorrhea (based on 56 days interval) at week 24 was achieved in 65.2% of the combination treatment patients and in 1.4% of the placebo group. The percentage of amenorrheic women at the 104 Week of combined treatment (82.3%) and are described in the SmPC.

Discontinuations due to AEs

The rates of discontinuation due to AEs did not increase disproportionally over time (4.5% in the pivotal studies; 7.7% through up to 52 weeks of treatment). Over time, the incidence remained low, with in the group with a total exposure up to 104 weeks (relugolix +E2/NETA), the cumulatively incidence was 6.9%. The incidence in the (former) relugolix + delayed E2/NETA group was slightly higher (9.3%) but can still considered to be low.

There was no clear pattern in adverse events leading to discontinuation. Events associated with low estrogen levels, as well as due to bleeding related adverse events were rare. Discontinuation due to hot flush was highest in the relugolix + delayed E2/NETA group during the first 24 Weeks (6 patients, 1.4%) compared to 2 (0.5%) in the combination treatment group.

2.5.3. Conclusions on clinical safety

Relugolix + E2/NETA indicated for symptomatic treatment of endometriosis appeared to be generally well tolerated with only 4.5% of patients discontinued due to an adverse event over the treatment period of 24 weeks, and 7.7% through up to 52 weeks of treatment. The rate was 6.9% in the patient group who was treated with the combination treatment for up to 104 weeks.

The safety profile, based on the adverse events pattern, was consistent with the adverse event pattern that is expected for a GnRH-antagonist, and comparable with the safety pattern noted in the initial MAA for the treatment of symptoms associated with uterine fibroids.

2.5.4. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

No changes to the summary of safety concerns are proposed by the applicant. The summary of safety concerns remains unchanged as follows:

Summary of safety concerns	
Important identified risks	None
Important potential risks	Loss of bone mineral density Embryo-foetal toxicity
Missing information	Long-term use beyond 24 months

This is acceptable, as the safety profile of relugolix combination therapy in the endometriosis indication was assessed to be comparable with the safety profile in the initial uterine fibroids indication.

Pharmacovigilance plan

No changes are proposed to the pharmacovigilance plan. Routine pharmacovigilance is considered sufficient to further characterise the risks and missing information associated with the product.

The pharmacovigilance plan includes specific adverse reaction follow-up forms for exposure during pregnancy and suspected ADRs related to BMD loss as a tool of routine pharmacovigilance. The follow-up form for BMD loss was updated with the endometriosis indication, which is endorsed.

Risk minimisation measures

No changes are proposed to the RMP part concerning risk minimisation measures. Routine risk minimisation is considered sufficient to mitigate the risk associated with this product.

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
Long-term use beyond 24 months	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ryeqo. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The intended extension of the indication is:

"*Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (see Section 5.1).*". As with the initial indication, the posology is 1 tablet daily taken orally.

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 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 resulting low systemic concentration of estradiol minimizes the hormone-related proliferative effects on endometriosis foci and will stabilize the endometrium. The suppression of proliferation is expected to reduce symptoms of pain associated with endometriosis.

The estradiol/progesterone (1mg E2 / 0.5mg NETA) component, EU registered hormone replacement therapy (Activelle) 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.

3.1.1. Disease or condition

Endometriosis is an inflammatory disease characterised by extra-uterine endometriosis implants outside of the uterine endometrium and myometrium associated with pelvic pain and infertility, affecting 10% of women in their reproductive years. The most frequent location is the pelvis, although also extra-pelvic locations are reported. Most commonly, the endometriosis-associated pain may occur with menses (dysmenorrhea), between menses (non-menstrual pelvic pain [NMPP]), and/or with sexual intercourse (dyspareunia). Some women also experience painful urination (dysuria) or painful bowel movements (dyschezia).

A definitive diagnosis requires laparoscopy (keyhole surgery) with direct visualization and/or biopsy with histologic confirmation. Ultrasound and MRI may contribute in visualization of the locations and size of the endometriotic lesions. However, women may see multiple healthcare providers over several years before endometriosis is diagnosed.

3.1.2. Available therapies and unmet medical need

Based on the European Society of Human Reproduction and Embryology (ESHRE) endometriosis guideline and other EU guidelines, the following existing therapies for endometriosis within the EU.

Combined hormonal contraceptives (CHCs), are the first-line treatment, but are not approved for treatment of endometriosis. Nevertheless, recent reviews showed important reductions in endometriosis-related pain. Additionally, progestogens are used, of which norethisterone, medroxyprogesterone, dydrogesterone and lynestrenol are approved for treatment of endometriosis since a very long time, while dienogest is more recently (2009) registered specifically based on the efficacy in reduction of endometriosis related pain. Additionally, progestogen-containing intra-uterine devices (IUD) are recommended (off-label, ESHRE).

Both CHCs and progestins suppress ovarian function, and with continuous use, the mechanism is decidualization and subsequent atrophy of endometrial tissue, which is assumed to reduce endometriosis disease activity and subsequent pain (UptoDate 2022).

If hormonal contraceptives or progestogens have been suboptimal in managing symptoms, GnRH receptor agonists (leuprolide acetate, nafarelin acetate, and goserelin acetate) are used as second-line therapy as suppression of estradiol production is much stronger. The subsequent hypoestrogenic state causes the side effect of decrease in bone mineral density (BMD) which limits duration of use to 6 months. Concomitant use with low doses of estrogen and a progestin may prevent the hypoestrogenic state associated decrease in BMD (estrogen/progestin add-back therapy). At start of the GnRH agonist, an initial hormonal and clinical flare is observed over several weeks, before clinical benefit can be observed.

GnRH antagonists are included in the guidelines, but none are approved for treatment of endometriosis in the EU, but like GnRH-agonists they are also considered second line treatments due to the hypoestrogenic side effects (decrease in BMD) which limit duration of use (without add-back) (ESHRE 2022).

Summarized, all medicinal products directly or indirectly suppress endogenous sex hormone production with the goal to inhibit endometrial tissue growth by causing initial decidualization and then atrophy of the endometrial tissue. However, both GnRH-agonists and GnRH-antagonists have much stronger suppression of endogenous estradiol production leading to levels that are observed in postmenopausal women. Subsequently, they are restricted in use due to the clinically relevant decrease in BMD already after 6 months treatment in the range of 5%. Off-label add-back therapy is concomitantly given to counteract these adverse effects.

Surgery

Surgical treatment could be considered as one of the options to reduce endometriosis associated pain. Surgical treatment of endometriosis focuses on the elimination of peritoneal endometriosis/ endometrioma/deep endometriosis and division of adhesions. In the past, open surgery (laparotomy) was used routinely. Nowadays, keyhole surgery (laparoscopy) is used and preferred since it usually results in less pain, shorter hospital stay, quicker recovery and a smaller scar. Clinicians should consider surgical treatment (elimination of endometriotic lesions) when they see endometriotic lesions during laparoscopy for diagnosis.

3.1.3. Main clinical studies

Main placebo-controlled studies with duration of 24 weeks

Two large replicate double-blind, placebo-controlled phase 3 trials with a duration of 24 weeks have been performed in the US and Canada and Rest of World (Argentina, Belgium, Bulgaria, Czech Republic, Finland, Hungary, Poland, Portugal, South Africa, Spain, and Ukraine) (study MVT-601-3101 and MVT-601-3102). The studies compared relugolix-E2/NETA with placebo in premenopausal women 18 to 50 years of age with a confirmed diagnosis of women with moderate-to-severe pain associated with endometriosis. The co-primary endpoints of dysmenorrhea and non-menstrual pelvic pain (corrected for rescue medication) and several key secondary endpoints focus on a reduction in pain, the most common symptom of endometriosis. Additional key secondary endpoints included improvement in function as measured by the EHP-30, and reduction of the need for analgesics, including opioid, use.

As present in the initial MAA on uterine fibroids, 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. The type I error protection did not include these safety endpoints.

The design is in accordance with legal requirements, available guidelines, and the several national scientific advice 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 80 weeks

Subjects who completed their participation in one of the 24-week phase 3 studies could enrol in an uncontrolled, long-term efficacy and safety extension study (MVT-601-3003) of 80 weeks.

Supportive studies

Supportive studies included a 12 week dose response study TAK-385/CCT-101 and its 12 week extension study TAK-385/OCT-101, an exit interview substudy (MVT 601 038), providing the patient's perspective, an instrumental development study (MVT-601-3104) and a prospective observational (natural history) study (MVT-601-034) on BMD in women aged 18-50 years with uterine fibroids or endometriosis, already submitted during the initial MAA.

3.2. Favourable effects

Selection of 40 mg dose

Efficacy of relugolix 40 mg monotherapy on moderate to severe endometriosis-associated pain observed at a 40-mg dose were shown to be similar to the active comparator leuprorelin (GnRH-antagonist) and significantly more improved than observed with placebo.

Co-primary endpoints. In both studies MVT-601-3101 and MVT-601-3102 the proportion of women in the relugolix + E2/NETA met both co-primary efficacy endpoints, in being statistically significantly and clinically relevant superior compared with placebo. The results were consistent between the studies. For dysmenorrhea, the proportion of responders in the relugolix combination group was 74.5% and 75.1%, respectively, compared to 26.9% and 30.5% in the placebo group, respectively. The observed between group differences were 47.6% and 44.9%. For NMPP, the proportion of responders was 58.5% and 65.9%, respectively, which met the responders criteria in the relugolix combinations treatment group compared to 39.6% and 42.5% in the placebo group, respectively. The observed between group differences were 18.9% and 23.4%. The outcomes are corrected for intake of rescue medication.

Key secondary endpoints. The results were supportive of the primary endpoint findings, in particular the change in EHP-30 pain domain (quality of life) in both studies was statistically significant greater in the relugolix + E2/NETA groups versus placebo (-33.8 and -32.2 vs -18.7 and -19.9). Additionally, the changes in dysmenorrhea, NMPP, pelvic pain and dyspareunia were a reduction of -5.1, -2.8, -3, -2.4 (mean of the two study point estimates), respectively in the relugolix + E2/NETA groups compared to -1.9, -2, -1.95 and -1.8 for placebo. The differences were all statistically significant. Regarding the proportion of patients not using opioids, a statistically significant greater proportion of patients in the relugolix combination group did no longer use opioids versus placebo in both studies (85.8% in the relugolix combination treatment vs 66.2% in the placebo group in MVT-601-3101, and 82% vs. 66.2% in MVT-601-3102 study, respectively). A similar pattern was observed with regard to the proportion of patients not using analgesics in MVT-

601-3101, (56.1% in the relugolix+E2/NETA group compared to 30.7% in the placebo group (p<0.0001)). In MVT-601-3102, this 7th secondary endpoint was the change in mean analgesic pill count, of which the mean change in the relugolix +E2/NETA was -0.5 compared to -0.4 in the placebo group was not statistically significant (p=0.1141).

Other secondary endpoints. A large set of other secondary endpoints has been evaluated which results suggested trends in favour of the combination therapy. In addition, information on Onset of effect indicated that in the relugolix+E2/NETA treatment groups, 16-19% met the responder criteria for dysmenorrhea after 4 weeks of treatment and > 50% after 8 weeks, while for NMPP, these percentages were 14-22% at 4 weeks and ≥50% after 12-16 weeks. For both endpoints, a proportion >50% was never reached in the placebo group.

As to Changes in protocol-specified rescue analgesic medications - tier 1 (ibuprofen) and tier 2 use (opioids) in the relugolix combination treatment, average daily pill count of ibuprofen by 65% and 53.6% in MVT-601-3101 and MVT-601-3102, respectively. For the placebo group this decrease was 51.4% and 29.9% in MVT-601-3101 and MVT-601-3102, respectively. As to opioid use, in the relugolix combination treatment, considerably greater decreases were noted by 41% and 75.7% in MVT-601-3101 and MVT-601-3102, respectively, versus the placebo groups in which this decrease was 5.1% and 42.2%, respectively.

Subgroups. Across all subgroups, e.g. geographic region, time since surgical diagnosis of endometriosis (the two stratification factors at randomization), AFS endometriosis stage, age, race, ethnicity, BMI, dysmenorrhea NRS score at baseline, NMPP NRS score at baseline, and renal function, 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.

Efficacy during open-label long term use up to 104 weeks. Maintenance of effect in dysmenorrhoea and NMPP up to at least 104 weeks has been shown by the results of the open label long-term extension study. At the end of the open label long-term extension study (Week 104), 235 of 277 patients (84.8%) in the (former) relugolix + E2/NETA group met the co-primary endpoint for dysmenorrhea; for co-primary endpoint of NMPP, the proportion responders at 104 weeks was 210 out of 277 patients (75.8%) in the (former) relugolix + E2/NETA group, which outcome supports maintenance of efficacy.

3.3. Uncertainties and limitations about favourable effects

Not applicable.

3.4. Unfavourable effects

The endometriosis safety database is based on 3 populations: the 2 phase 3 placebo-controlled pivotal studies of 24 weeks, its long-term extension study up to 52 weeks, and a third population, based on completers of the pivotal phase 3 studies who participated in an open-label extension study, who used relugolix combination therapy for in total 104 weeks.

Adverse events

Short term safety over 24 weeks in placebo-controlled setting

The **overall incidence of AEs** over the placebo-controlled treatment period of 24 weeks was slightly higher in the relugolix +E2/NETA group (75.8%) compared to the placebo group (70.4%) and was highest in the relugolix+ delayed E2/NETA (79.4%). 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.

The **most common adverse events** were Headache (33.0% vs 26.4%), Hot flush (12.0% vs 6.7%), Nasopharyngitis (10.0 vs 7.0%), Nausea (6.0% vs 4.1%), Toothache 5.5% vs 2.4%), Back pain (4.8% vs 2.9%), Bone density decreased (3.8% vs 2.2%), Libido decreased (3.8% vs 1.2%), Urinary tract infection (3.6% vs 2.6%), Arthralgia (3.6% vs 2.2%), Influenza (3.3% vs 2.4%), Fatigue (3.1% vs 2.4%), Dizziness (3.1% vs 1.2%), Metrorrhagia (3.1% vs 1.4%), Vulvovaginal dryness (2.2% vs 0.5%), Insomnia (1.9% vs 2.2%), Migraine (1.9%vs 1.4%). Percentages in the relugolix+ delayed E2/NETA were higher than observed in the relugolix +E2/NETA group.

Adverse drug reactions associated with relugolix combination therapy were assessed by review of adverse events observed at a frequency of ≥3% for relugolix combination therapy and at greater frequency than placebo (based on the observed frequencies of adverse events at higher incidence than placebo in the context of sample size), with consideration of other supporting data inclusive of medical judgment. ADRs included headache (33.0%), hot flush, hyperhidrosis, or night sweats (12.9%), abnormal uterine bleeding (6.7%), back pain (4.8%), libido decreased (4.1%), and arthralgia (3.6%). A difference was noted in the most common drug-related adverse events between the combination treatment and the delayed group in number of hot flush events, supporting that the addition of E2/NETA considerably reduces the frequency of postmenopausal symptoms.

Serious adverse events were reported in 12 (2.9%) of the relugolix/E2/NETA patients and 9 (2.2%) patients in both the placebo and relugolix+delayed E2/NETA groups. The incidence of serious adverse events is considered low, and most were reported in one patient each. Serious adverse events of abdominal pain (including abdominal pain, lower), pelvic pain, suicidal ideation, and ovarian cyst were reported for more than one patient taking relugolix combination therapy. No **deaths** were reported.

Long term safety up to 104 weeks of relugolix + E2/NETA
Safety over 52 weeks of treatment (placebo-controlled 24 weeks + 28 weeks open-label period) was consistent with that reported during the first placebo-controlled 24 weeks and did not disproportionally increase with further long term treatment up to 104 weeks compared with the first 24 weeks of treatment in the pivotal studies.

Adverse events of interest:

Bone safety In the 24 weeks placebo-controlled studies adverse events of BMD (fractures, BMD loss). were reported in 5.8% of the relugolix+ delayed E2/NETA group (patients receiving 12 weeks of relugolix monotherapy), 4.3% in the relugolix+E2/NETA group and 3.1% in the placebo group.
The change in BMD lumbar spine was slightly higher in the relugolix + E2/NETA group compared to placebo (12 week - 0.49% vs 0.09%, 24 week -0.72% vs 0.12%, 52 Weeks -0.67% (95% CI: -1.09%, -0.25%, 104 weeks -0.45% (95% CI: -1.03, 0.13)). These results indicate that after the small reduction in BMD observed at Week 12 and Week 24, there was evidence of stabilization at Weeks 36, 52, and 104 weeks in the relugolix + E2/NETA group. The observed decrease fell within the range of BMD loss observed in the 52 weeks BMD data of Natural history study vs. 52 weeks BMD data in endometriosis safety set in which study, the majority of the patients had no BMD decrease or a decrease <= 3%, which was defined as non-clinically significant. At the total hip, the percentages decrease in BMD were in general lower and remained relatively unchanged from baseline. In the

relugolix + delayed E2/NETA group (12 weeks monotherapy followed by 12 weeks combination therapy) the percent change from baseline in BMD at lumbar spine was -1.76 at 12 weeks, and -1.94% at 24 weeks. The difference between relugolix + E2/NETA and relugolix + delayed E2/NETA at 12 weeks was 1.28, which was significant, suggesting the protective effect of E2/NETA.
A total of 20 (12.3%) and 12 patients (7.4%) had meaningful reduction in BMD bone loss of > 3% to ⩽ 5% and > 5% to ⩽ 8%. One patient (0.6%) had loss in BMD > 8% through Week 104. At total hip, these numbers were lower. This noted percentage of patients with a meaningful reduction in BMD (>3%) up to 104 weeks is comparable with the percentage noted in the initial MAA. These data support that during the 2 years of treatment with relugolix + E2/NETA the percent change from baseline remains stable below 1%.
An analysis of progression of BMD over time in lumbar spine and total hip in the youngest group of women (18-24 years) in the population investigated indicated an increase in BMD in lumbar spine and total hip, supporting that Ryeqo does not seem to have an effect on the ability to create new bone mass.
The SmPC includes already several risk minimization measures to address this safety issue. Additional analyses for the age group 18-<35, 35-<40, 40-<45 and 45-<52 years lumbar indicated that for the first three age groups it appears that after 24 weeks of combined treatment, BMD stabilizes or slightly improves at 52 and 104-weeks treatment. For the age group 45-<52 years, the BMD slightly decreases from -0.48 to -0.86 and -1.64% at 24, 52 and 104 weeks, respectively.
The post treatment follow-up study, 6 and 12 months after stopping of treatment showed that for the proportion of patients in whom bone loss > 3 % is observed during treatment with relugolix + E2/NETA and for whom PTFU DXAs are available, recovery or trend toward recovery is observed in all patients at the lumbar spine and in 89% of patients at the total hip.

Hepatic Transaminase Elevations In the phase 3 placebo-controlled studies (24 weeks), no patients had an ALT or AST > 3 × ULN and a total bilirubin > 2 × ULN. The incidence of ALT or AST > 3 × ULN was low and similar in both treatment groups (1.0% in both the relugolix + E2/NETA and placebo groups. During the 104 weeks of treatment, for any relugolix +E2/NETA duration, 11 cases (out of 799, 1.4%) of ALT or AST > 3 × ULN) were reported. There were no signals of cumulative risk during prolonged treatment or events meeting Hy's law criteria.

Embolic and Thrombotic Events One deep vein thrombosis with pulmonary embolism was reported in a patient with obesity (BMI 38.7 kg/m2) following a knee injury. Although high BMI and trauma are considered additional risk factors, the MAH considered this SAE drug-related. Risk of VTE, associated with the E2 component, is reflected in the SmPC.

The incidence of **gallbladder disease** related events, **mood disorder** and **hypertension** was low and comparable with that reported in the initial MAA. No cases of **alopecia, malignant breast** or **liver tumours** were reported in any patients in the relugolix + E2/NETA groups.

Endometrial safety No events of endometrial hyperplasia or carcinoma in the pivotal studies or long-term extension study. Endometrial biopsies taken indicated that treatment with relugolix + E2/NETA resulted in a shift from proliferative and/or secretory endometrium to an inactive/atrophic endometrium. These findings are the expected manifestation of estrogen suppression and progestin supplementation on the endometrium.

No **deaths** were reported in the two pivotal phase 3 studies. Over time the rates of **discontinuation due to AEs** remained low and AEs did not increase disproportionally over time (4.5% in the pivotal studies; 7.7% through up to 52 weeks of treatment). There was no clear pattern in adverse events leading to discontinuation. Discontinuation due to hot flush was highest in the relugolix + delayed

E2/NETA group during the first 24 Weeks (6 patients, 1.4%) compared to 2 (0.5%) in the combination treatment group.

Pregnancy 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 nonhormonal contraception throughout the clinical studies, including through 30 days following the last dose of study drug. Cumulatively, as of 25 November 2022, 16 pregnancies were in women who became pregnant during treatment with relugolix (as relugolix monotherapy or relugolix combination therapy). In the initial MAA, background information indicated that compliance problems with contraceptive measures were the major cause for pregnancy occurrence. Further, 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 SmPC.

Amenorrhea Amenorrhea (based on 56 days interval) at week 24 was achieved in 65.2% of the combination treatment patients and in 1.4% of the placebo group. Changes in bleeding pattern, including amenorrhoea were already covered in section 4.4 of the SmPC. The percentage women having amenorrhea in the endometriosis population is added to this paragraph.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable

3.6. Effects Table

Table 67 Effects Table for relugolix+E2/NETA for treatment of moderate to severe pain associated with endometriosis 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 endometriosis treatment <(data cut-off: 17-06-2020 (MVT-601-3101) and 15-04-2022 MVT-601-3102))>

Effect	Short Description	Relugolix +E2/NETA	Relugolix +delayed E2/NETA	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Efficacy population	MVT-601-3101 MVT-601-3102	N=212 N=208	N=213 N=207	N=213 N=208		MVT-601-3101 MVT-601-3102
Co-Primary endpoint Week 24	Dysmenorrhea responder rate, without increased analgesics use	74.5% 75.1%	71.6% 72.8%	26.9% 30.5%	p<0.0001 for relugolix+E2/NETA vs placebo (primary endpoint) and for relugolix +delayed E2/NETA	MVT-601-3101 MVT-601-3102
Co-Primary endpoint Week 24	NMPP responder rate, without increased analgesics use	58.5% 65.9%	57.8% 52.9%	39.6% 42.5%	p<0.0001 for relugolix+E2/NETA vs placebo (primary endpoint), p=0.0001 for relugolix+delayed E2/NETA in MVT601-3101 and p=0.0285 in MVT-601-3102	MVT-601-3101 MVT-601-3102
Key secondary endpoint*	Change from baseline to Week 24 in the EHP-30 Pain Domain score – LS mean	-33.8 -32.2	-32.1 -30.8	-18.7 -19.9	For both studies , p<0.0001 for relugolix+E2/NETA vs placebo and for relugolix +delayed E2/NETA	MVT-601-3101 MVT-601-3102

Effect	Short Description	Relugolix +E2/NETA	Relugolix +delayed E2/NETA	Placebo	Uncertainties/ Strength of evidence	References
Key secondary endpoint*	Change from baseline to Week 24/EOT in the mean dysmenorrhea NRS score – LS mean	-5.1 -5.1		-1.8 -2.0	For both studies, p<0.0001 for relugolix+E2/NETA vs placebo	MVT-601-3101 MVT-601-3102
Key secondary endpoint*	Change from baseline to Week 24/EOT in the mean NMPP NRS score – LS mean	-2.9 -2.7		-2.0 -2.0	p=0.0002 p=0.0012	MVT-601-3101 MVT-601-3102
Key secondary endpoint*	Change from baseline to Week 24/EOT in the mean overall pelvic pain NRS score – LS mean	-3.1 -2.9		-1.9 -2.0	For both studies , p<0.0001 for relugolix+E2/NETA vs placebo	MVT-601-3101 MVT-601-3102
Key secondary endpoint*	3101: Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain at Week 24/EOT, n (%) 3102: Change from baseline to Week 24/EOT in the mean dyspareunia NRS score – LS mean	85.8% -2.4		76.4% -1.9	p=0.0005 p=0.0037	MVT-601-3101 MVT-601-3102
Key secondary endpoint*	3101: Change from baseline to Week 24/EOT in the mean dyspareunia NRS score – LS mean 3102: Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain at Week 24/EOT, n (%)	-2.4 82%		-1.7 66.2%	p=0.00149 p<0.0001	MVT-601-3101 MVT-601-3102
Key secondary endpoint*	3101: Proportion of patients who are not using analgesics for endometriosis-associated pain at Week 24/EOT, n (%) 3102: Change from baseline to Week 24/EOT in protocol-specified analgesic use for endometriosis-associated pain based on mean pill count – LS mean	56.1% -0.5		30.7% -0.4	p<0.0001 p=0.1141	MVT-601-3101 MVT-601-3102
*hierarchical hypothesis testing						

Unfavourable Effects (24 weeks, placebo-controlled)

Safety population (population 1)	MVT-601-3001 + MVT-601-3002	N=418	N=417	N=416		MVT-601-3101/ MVT-601-3102 pooled

Effect	Short Description	Relugolix +E2/NETA	Relugolix +delayed E2/NETA	Placebo	Uncertainties/ Strength of evidence	References
Patients with ≥ 1 adverse event, Week 24	Any / serious / treatment-related, n (%)	317 (75.8%) 12 (2.9%) 198 (47.4%)	331 (79.4%) 9 (2.2%) 242 (58%)	293 (70.4%) 9 (2.2%) 156 (37.5%)		MVT-601-3101/ MVT-601-3102 pooled
AEs related to loss of BMD, Week 24	Including ankle fracture, avulsion fracture, wrist fracture, BMD decreased, bone loss, facial bones fracture, osteopenia, radius fracture	18 (4.3%)	24 (5.8%)	13 (3.1%)		MVT-601-3101/ MVT-601-3102 pooled
% change from baseline in BMD, Week 24	Lumbar spine LS Mean Percent Change (SE)	-0.72%	-1.94%	0.12%		MVT-601-3101/ MVT-601-3102 pooled
% of patients with clinically meaningful bone loss at lumbar spine at Week 24	Decrease >3%,≤5% >5%, ≤8% >8%	48 (14.4%) 8 (2.4%) 1 (0.3%)	74 (21.9%) 26 (7.7%) 6 (1.8%)	25 (7.8%) 3 (0.9%) 0		MVT-601-3101/ MVT-601-3102/ MVT-601-3103 pooled
;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	7	17	2		MVT-601-3001-/3002 pooled
Vasomotor symptoms, Week 24	Including hot flush, hyperhidrosis, night sweats, flushing	55 (13.2%)	145 (34.8%)	30 (7.2%)	Effect was maintained after all 3 groups received relugolix +E2/NETA for 80 weeks until week 104 (MVT-601-3103): 46 (16.6%), 107 (43.3%), 43 (15.6%), resp.	MVT-601-3001-/3002 pooled
Hepatic transaminase elevations Week 24	Any increase in ALT or AST ≥ 3 × ULN and <5 x ULN	4 (1.0%)	2 (0.5%)	2 (0.5%)	No bilirubin elevation was observed.	MVT-601-3001-/3002 pooled
Unfavourable Effects (104 weeks, all 3 groups received relugolix +E2/NETA for 80 weeks (MVT-601-3103):						
Safety population	Patients enrolled in open-label extension study	N=277	N=247	N=275	relugolix+E2/ NETA in all 3 arms	(MVT-601-3103)
% change from baseline in BMD, Week 52	Lumbar spine LS Mean % Change Week 52	-0.69%	-1.09%	-0.09%	After 52, 40, and 28 weeks relugolix+E2/ NETA, respectively	(MVT-601-3103)

Effect	Short Description	Relugolix +E2/NETA	Relugolix +delayed E2/NETA	Placebo	Uncertainties/ Strength of evidence	References
% change from baseline in BMD, Week 104	Lumbar spine LS Mean % Change Week 104	-0.45%	-0.56%	-0.09%	After 104, 92, and 80 weeks relugolix+E2/ NETA, respectively	(MVT-601-3103)
Proportion of patients with clinically meaningful bone loss at lumbar spine at Week 104	Decrease >3%,≤5% >5%, ≤8% >8%	 20 (12.3%) 12 (7.4%) 1 (0.6%)	 17 (11.3 %) 6 (4%) 0	 23 (13.3%) 9 (5.2%) 1 (0.6%)	After 104, 92, and 80 weeks relugolix+E2/ NETA, respectively	(MVT-601-3103)

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-601-3101 and MVT-601-3102:

- 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-601-3103: one-arm 80-week extension study where ALL subjects who wished to enrol from studies MVT-601-3101 and MVT-601-3102 received relugolix+E2/NETA.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the initial MAA, relugolix + E2/NETA combination was approved for the *treatment of moderate-to-severe symptoms of uterine fibroids in adult women of reproductive age*", with no restriction in duration of use and no restriction regarding previous treatments. In the current type II variation, an extension of the indication is requested for "*Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (see Section 5.1)*"

The main symptom of endometriosis is pain, which fluctuates with the stages of the menstrual cycle. In those patients in which the pain is of moderate or severe intensity, QoL is significantly affected and will interfere with work, daily activities and intimacy. First line therapies, e.g. combined hormonal contraceptives and progestogens may not be sufficiently effective and although surgery could be effective, the implants may return and there are risks of complications due to adhesions. Therefore, these patients are candidates for treatments that have stronger effects on estradiol production, i.e. GnRH agonists (and GnRH-antagonists off-label). These suppress estradiol production to postmenopausal values and are therefore more effective. However, as this effect is accompanied with significant bone loss, treatment is restricted to 6 months. Off-label add-back therapy is given (estradiol + progestogen) to counteract these effects.

Data from 2 robustly designed, randomised placebo-controlled phase 3 studies of 24-week duration showed that relugolix + E2/NETA substantially, significantly and reproducibly improves the symptoms of disease in this study population with endometriosis. The treatment effects were shown to be maintained at least up to 104 weeks of treatment in a longer-term extension study. Moreover, support was provided by alpha controlled secondary endpoints and the results from the dose-finding studies performed with the monotherapy.

The results are considered clinically relevant and overall, the benefit of treatment has been robustly

demonstrated.

As to the indication requested, the population enrolled in the pivotal phase 3 endometriosis studies is consistent with the standard of care for endometriosis in treatment guidelines. Nearly all patients included in the phase 3 trials had antecedent surgical procedures and/or prior medical management for their endometriosis. Administration of relugolix + E2/NETA as part of clinical trial participation represented de facto second-line treatment in the management of their disease. It is therefore acceptable to include in the indication that Ryeqo is indicated for patients who have had prior management for endometriosis, which is consistent with treatment guidelines and the relugolix combination therapy clinical development program. To further specify previous medical or surgical interventions in the SmPC, a reference is made to section 5.1 for the description of the study population.

Regarding safety, the observed adverse event pattern is in line with previous experience with relugolix + E2/NETA in the MAA presented for the indication of uterine fibroids, as most frequently observed AEs were related to low estrogen levels, a comparable low level of severe AEs (3%) and low percentage of discontinuations (4.5%). As to prevention of BMD loss, a similar pattern as observed in the initial MAA in the population of women with uterine fibroids is observed i.e. after an initial slight decrease, the degree of BMD loss stabilizes at a level of around 1% over a period of 104 weeks treatment. The vast majority of subjects had no BMD decrease or a decrease <= 3%, which was defined as non-clinically significant. This together indicates that the risk of BMD is adequately managed by the addition of E2/NETA. Importantly, recommendations are in place in the SmPC to ensure that no patient will have an unwanted degree of BMD loss.

It is noted that the product also has adequate contraceptive effects, after intake of at least 1 month.

3.7.2. Balance of benefits and risks

The B/R balance for the studied population is considered positive.

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 review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation,

concerning the following changes:

Variations accepted		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include symptomatic treatment of endometriosis for RYEQO in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis, based on final results from studies MVT-601-3101 and MVT-601-3102 and final results up to 104 weeks from study MVT-601-3103. Studies 3101 and 3102 are pivotal, phase III, randomised, double-blind, placebo-controlled, safety and efficacy studies to evaluate relugolix with E2 and NETA as a combination therapy for pain associated with endometriosis. Study 3103 is an open-label extension study including patients who completed one of the two pivotal studies and met the eligibility criteria, regardless of their treatment assignment in the pivotal studies. In the extension part all patients received relugolix combination therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC were updated. The Package Leaflet is updated in accordance.
Update of section 4.5 of the SmPC to update information regarding Drug-Drug Interaction based on final results of DDI studies MVT-601-54, MVT-601-55 and MVT-601-57. Study MVT-601-54 is a 2-part interventional open-label study to assess the potential effects of erythromycin on the PK of the 3 components of Ryeqo. Study MVT-601-55 is an interventional open label fixed single sequence cross-over study to assess whether a 6-hour dose separation is sufficient to mitigate absorption mediated increased exposure to relugolix and study MVT-601-057 is a 2-part study to assess the potential effect of relugolix on the PK of total dabigatran.
The updated RMP version (2.1) has also been submitted. As part of the application, the MAH also requests an extension of the market protection by one additional year.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).