Clinical trial results:
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

Summary

EudraCT number	2017-004066-10
Trial protocol	GB ES HU BE FI SE PL CZ BG PT IT RO
Global end of trial date	23 January 2023

Results information

Result version number	v1 (current)
This version publication date	20 August 2023
First version publication date	20 August 2023

Trial information

Trial identification

Sponsor protocol code	MVT-601-3103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03654274
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 076642

Notes:

Sponsors

Sponsor organisation name	Myovant Sciences GmbH
Sponsor organisation address	Viaduktstrasse 8, Basel, Switzerland, 4051
Public contact	VP of Clinical Operations, Myovant Sciences GmbH, +1 (650)238 0250, SPIRIT@myovant.com
Scientific contact	VP of Clinical Operations, Myovant Sciences GmbH, +1 (650)238 0250, SPIRIT@myovant.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2021
Global end of trial reached?	Yes
Global end of trial date	23 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate long-term efficacy of relugolix 40 mg once daily co administered with low-dose estradiol and norethindrone acetate for up to 52 and 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT 601-3102), on endometriosis-associated pain.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) E6 (R2) (Guideline for Good Clinical Practice [GCP]), applicable patient privacy requirements, and the ethical principles outlined in the Declaration of Helsinki 2013. Additionally, the study was conducted in accordance with the United States (US) Code of Federal Regulations, the European Union Clinical Trials Directive, and applicable local/regional regulations and guidelines regarding the conduct of clinical studies.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 297
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Romania: 31
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Bulgaria: 29
Country: Number of subjects enrolled	Czechia: 28
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	United States: 147
Country: Number of subjects enrolled	Argentina: 34
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Brazil: 41
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Georgia: 7

Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	South Africa: 32
Country: Number of subjects enrolled	Ukraine: 63
Worldwide total number of subjects	802
EEA total number of subjects	448

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	802
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All participants who completed their participation in one of the pivotal studies (MVT-601-3101 or MVT-601-3102) were eligible to enroll in this study. Due to data integrity concerns at 1 US site, 3 patients (1 relugolix + E2/NETA; 2 Placebo) were excluded from efficacy and safety analyses, but included in demographic and disposition tables.

Pre-assignment

Screening details:

The study results were presented by pivotal study treatment but all the participants only received relugolix plus Estradiol (E2)/Norethindrone Acetate (NETA). Three participants (1 in the relugolix plus E2/NETA group; 2 in the placebo group) were excluded due to GCP noncompliance and no data is reported for these participants.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Relugolix Plus E2/NETA (Group A)

Arm description:

Relugolix 40 mg once daily co-administered with E2 (1 mg) and NETA (0.5 mg) for 24 weeks in the pivotal
study followed by Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension
study.

Arm type	Experimental
Investigational medicinal product name	Relugolix
Investigational medicinal product code	
Other name	TAK-385, MVT-601
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Relugolix 40-mg tablet administered orally once daily.

Investigational medicinal product name	Estradiol/Norethindrone acetate
Investigational medicinal product code	
Other name	E2/NETA, low-dose hormonal add-back
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsule containing co-formulated tablet of E2 (1 mg)/NETA (0.5 mg) administered orally once daily.

Arm title	Relugolix Plus Delayed E2/NETA (Group B)

Arm description:

Relugolix 40 mg monotherapy (once daily) for 12 weeks, followed by oral relugolix 40 mg once daily coadministered with E2 (1mg) and NETA (0.5 mg) for 12 weeks in the pivotal study and Relugolix 40 mg once
daily co-administered with E2/NETA for 80 weeks in this extension study.

Arm type	Experimental

Investigational medicinal product name	Relugolix
Investigational medicinal product code	
Other name	TAK-385, MVT-601
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Relugolix 40-mg tablet administered orally once daily.

Investigational medicinal product name	Estradiol/Norethindrone acetate
Investigational medicinal product code	
Other name	E2/NETA, low-dose hormonal add-back
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsule containing co-formulated tablet of E2 (1 mg)/NETA (0.5 mg) administered orally once daily.

Arm title	Placebo (Group C)

Arm description:

Relugolix placebo co-administered with E2/NETA placebo for up to 24 weeks in the pivotal study followed by
Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension study.

Arm type	Experimental
Investigational medicinal product name	Relugolix
Investigational medicinal product code	
Other name	TAK-385, MVT-601
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Relugolix 40-mg tablet administered orally once daily.

Investigational medicinal product name	Estradiol/Norethindrone acetate
Investigational medicinal product code	
Other name	E2/NETA, low-dose hormonal add-back
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsule containing co-formulated tablet of E2 (1 mg)/NETA (0.5 mg) administered orally once daily.

Number of subjects in period 1	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)
Started	278	247	277
Completed	172	155	175
Not completed	106	92	102
Consent withdrawn by subject	46	25	33
Adverse event, non-fatal	19	23	24
Other	27	-	32
Pregnancy	2	2	1
Unspecified	-	29	-
Lost to follow-up	8	6	5

Lack of efficacy	4	5	7
Protocol deviation	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Relugolix Plus E2/NETA (Group A)
Reporting group description:	
Relugolix 40 mg once daily co-administered with E2 (1 mg) and NETA (0.5 mg) for 24 weeks in the pivotal study followed by Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension study.	
Reporting group title	Relugolix Plus Delayed E2/NETA (Group B)
Reporting group description:	
Relugolix 40 mg monotherapy (once daily) for 12 weeks, followed by oral relugolix 40 mg once daily coadministered with E2 (1mg) and NETA (0.5 mg) for 12 weeks in the pivotal study and Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension study.	
Reporting group title	Placebo (Group C)
Reporting group description:	
Relugolix placebo co-administered with E2/NETA placebo for up to 24 weeks in the pivotal study followed by Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension study.	

Reporting group values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)
Number of subjects	278	247	277
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	278	247	277
From 65-84 years	0	0	0
85 years and over	0	0	0
Between 18 and 65 years	0	0	0
Gender categorical			
Units: Subjects			
Female	278	247	277
Male	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	27	31	42
Not Hispanic or Latino	249	215	233
Unknown or Not reported	2	1	2
Race/Ethnicity, Customized			
Number of participants based on their race.			
Units: Subjects			
American Indian or Alaska Native	1	1	0

Asian	0	1	0
Black or African American	17	7	13
Native Hawaiian or Other Pacific Islander	0	0	1
White	254	236	248
Other	1	0	8
Multiple	4	2	5
Not reported	1	0	2
Time Since Surgical Diagnosis of Endometriosis			
Units: Years			
arithmetic mean	4.0	4.7	3.9
standard deviation	± 3.52	± 4.00	± 3.24
Dysmenorrhea Numerical Rating Scale Score at Baseline			
Assessed using an numerical rating scale (NRS) score (11-point scale) for pain recorded daily in an electronic diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine).			
Units: score on a scale			
arithmetic mean	7.1	7.0	7.2
standard deviation	± 1.66	± 1.65	± 1.63
Nonmenstrual Pelvic Pain Numerical Rating Scale Score at Baseline			
Assessed using an numerical rating scale (NRS) score (11-point scale) for pain recorded daily in an electronic diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine).			
Units: score on a scale			
arithmetic mean	5.7	5.5	5.7
standard deviation	± 1.93	± 1.98	± 1.91
Bone Mineral Density Lumbar Spine L1-L4			
Units: g/cm^2			
arithmetic mean	1.14	1.14	1.14
standard deviation	± 0.163	± 0.144	± 0.149
Bone Mineral Density Total Hip			
Units: g/cm^2			
arithmetic mean	0.98	0.97	0.98
standard deviation	± 0.133	± 0.120	± 0.123
Bone Mineral Density Femoral Neck			
Units: g/cm^2			
arithmetic mean	0.93	0.92	0.93
standard deviation	± 0.157	± 0.136	± 0.151

Reporting group values	Total		
Number of subjects	802		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	802		
From 65-84 years	0		
85 years and over	0		
Between 18 and 65 years	0		
Gender categorical Units: Subjects			
Female	802		
Male	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	100		
Not Hispanic or Latino	697		
Unknown or Not reported	5		
Race/Ethnicity, Customized			
Number of participants based on their race.			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	1		
Black or African American	37		
Native Hawaiian or Other Pacific Islander	1		
White	738		
Other	9		
Multiple	11		
Not reported	3		
Time Since Surgical Diagnosis of Endometriosis Units: Years			
arithmetic mean			
standard deviation	-		
Dysmenorrhea Numerical Rating Scale Score at Baseline			
Assessed using an numerical rating scale (NRS) score (11-point scale) for pain recorded daily in an electronic diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine).			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Nonmenstrual Pelvic Pain Numerical Rating Scale Score at Baseline			
Assessed using an numerical rating scale (NRS) score (11-point scale) for pain recorded daily in an electronic diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine).			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Bone Mineral Density Lumbar Spine L1-L4 Units: g/cm^2			
arithmetic mean			
standard deviation	-		
Bone Mineral Density Total Hip Units: g/cm^2			
arithmetic mean			

standard deviation	-		
Bone Mineral Density Femoral Neck Units: g/cm^2 arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Relugolix Plus E2/NETA (Group A)
Reporting group description:	
Relugolix 40 mg once daily co-administered with E2 (1 mg) and NETA (0.5 mg) for 24 weeks in the pivotal study followed by Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension study.	
Reporting group title	Relugolix Plus Delayed E2/NETA (Group B)
Reporting group description:	
Relugolix 40 mg monotherapy (once daily) for 12 weeks, followed by oral relugolix 40 mg once daily coadministered with E2 (1mg) and NETA (0.5 mg) for 12 weeks in the pivotal study and Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension study.	
Reporting group title	Placebo (Group C)
Reporting group description:	
Relugolix placebo co-administered with E2/NETA placebo for up to 24 weeks in the pivotal study followed by Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension study.	

Primary: Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 52

End point title	Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 52[1]
End point description:	
Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. A participant was defined as a responder if the NRS score for dysmenorrhea declined from baseline to Week 52 by at least 2.8 points without increased use of protocol-specified analgesics for pelvic pain at Week 52 relative to baseline. Participants rated their pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine.	
End point type	Primary
End point timeframe:	
Week 52	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The responder rate and two-sided 95% CI will be presented by the pivotal phase 3 study treatment group. No treatment comparisons will be performed for this extension study.

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	277	247	275	
Units: percentage of participants				
number (confidence interval 95%)	84.8 (80.06 to 88.85)	82.2 (76.83 to 86.75)	75.6 (70.12 to 80.59)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage Of Participants Who Meet The Nonmenstrual Pelvic Pain Responder Criteria At Week 52

End point title	Percentage Of Participants Who Meet The Nonmenstrual Pelvic Pain Responder Criteria At Week 52[2]

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. A participant was defined as a responder if the NRS score for NMPP declined from baseline to Week 52 by at least 2.1 points without increased use of protocol-specified analgesics for pelvic pain at Week 52 relative to baseline. Participants rated their pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine.

End point type	Primary

End point timeframe:

Week 52

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The responder rate and two-sided 95% CI will be presented by the pivotal phase 3 study treatment group. No treatment comparisons will be performed for this extension study.

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	277	247	275	
Units: percentage of participants				
number (confidence interval 95%)	73.6 (68.04 to 78.74)	70.4 (64.33 to 76.06)	68.0 (62.13 to 73.47)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 104

End point title	Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 104[3]

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. A participant was defined as a responder if the NRS score for dysmenorrhea declined from baseline to Week 104 by at least 2.8 points without increased use of protocol-specified analgesics for pelvic pain at Week 104 relative to baseline. Participants rated their pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine.

End point type	Primary

End point timeframe:

Week 104

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: .

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	277	247	275	
Units: Percentage of participants				
number (confidence interval 95%)	84.8 (80.06 to 88.85)	83.0 (77.72 to 87.46)	80.4 (75.17 to 84.89)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage Of Participants Who Meet The Nonmenstrual Pelvic Pain Responder Criteria At Week 104

End point title	Percentage Of Participants Who Meet The Nonmenstrual Pelvic Pain Responder Criteria At Week 104[4]

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. A participant was defined as a responder if the NRS score for NMPP declined from baseline to Week 104 by at least 2.1 points without increased use of protocol-specified analgesics for pelvic pain at Week 104 relative to baseline. Participants rated their pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine.

End point type	Primary

End point timeframe:

Week 104

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The responder rate and two-sided 95% CI will be presented by the pivotal phase 3 study treatment group. No treatment comparisons will be performed for this extension study.

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	277	247	275	
Units: Percentage of participants				
number (confidence interval 95%)	75.8 (70.33 to 80.74)	71.7 (65.60 to 77.19)	73.1 (67.44 to 78.24)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Endometriosis Health Profile (EHP)-30 Pain Domain Scores At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In The Endometriosis Health Profile (EHP)-30 Pain Domain Scores At Week 52

End point description:

Assessed using the pain domain of the EHP-30 questionnaire. The EHP-30 questionnaire was completed on an
electronic tablet (eTablet) device. Participants reported the frequency (never, rarely, sometimes, often, and always) with which they had difficulty with activities such as standing, sitting, walking, sleeping, and performing jobs around the house because of pain. The Pain Domain normalized scores ranged from 0 to 100, with higher scores denoting greater functional impact of pain. The least squares (LS) mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	207	229	
Units: score on a scale				
least squares mean (standard error)	-37.7 (± 1.34)	-36.1 (± 1.37)	-35.1 (± 1.32)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Endometriosis Health Profile (EHP)-30 Pain Domain Scores At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In The Endometriosis Health Profile (EHP)-30 Pain Domain Scores At Week 104

End point description:

Assessed using the pain domain of the EHP-30 questionnaire. The EHP-30 questionnaire was completed on an
electronic tablet (eTablet) device. Participants reported the frequency (never, rarely, sometimes, often, and always) with which they had difficulty with activities such as standing, sitting, walking, sleeping, and performing jobs around the house because of pain. The Pain Domain normalized scores ranged from 0 to 100, with higher scores denoting greater functional impact of pain. The least squares (LS) mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	151	173	
Units: Score on a scale				

least squares mean (standard error)	-41.3 (± 1.33)	-38.9 (± 1.36)	-37.7 (± 1.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Have A Reduction Of At Least 20 Points In The EHP-30 Pain Domain Scores From The Pivotal Phase 3 Study Baseline At Week 52

End point title	Percentage Of Participants Who Have A Reduction Of At Least 20 Points In The EHP-30 Pain Domain Scores From The Pivotal Phase 3 Study Baseline At Week 52

End point description:

Assessed using the Pain Domain of the EHP-30 questionnaire. The EHP-30 questionnaire was completed on an
electronic tablet (eTablet) device. Participants reported the frequency (never, rarely, sometimes, often, and always) with which they had difficulty with activities such as standing, sitting, walking, sleeping, and performing jobs around the house because of pain. The Pain Domain normalized scores ranged from 0 to 100, with higher scores denoting greater functional impact of pain.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	207	229	
Units: Percentage of participants				
number (confidence interval 95%)	83.6 (78.22 to 88.14)	81.2 (75.16 to 86.25)	79.5 (73.66 to 84.51)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Have A Reduction Of At Least 20 Points In The EHP-30 Pain Domain Scores From The Pivotal Phase 3 Study Baseline At Week 104

End point title	Percentage Of Participants Who Have A Reduction Of At Least 20 Points In The EHP-30 Pain Domain Scores From The Pivotal Phase 3 Study Baseline At Week 104

End point description:

Assessed using the Pain Domain of the EHP-30 questionnaire. The EHP-30 questionnaire was completed on an
electronic tablet (eTablet) device. Participants reported the frequency (never, rarely, sometimes, often,

and always)
with which they had difficulty with activities such as standing, sitting, walking, sleeping, and performing jobs around the house because of pain. The Pain Domain normalized scores ranged from 0 to 100, with higher scores denoting greater functional impact of pain.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	151	173	
Units: Percentage of participants				
number (confidence interval 95%)	88.6 (82.80 to 93.01)	85.4 (78.78 to 90.64)	86.1 (80.06 to 90.90)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean Dysmenorrhea NRS Score At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean Dysmenorrhea NRS Score At Week 52

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. Participants rated their
pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	235	204	233	
Units: Score on a scale				
least squares mean (standard error)	-5.9 (± 0.15)	-5.7 (± 0.16)	-5.3 (± 0.15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean Dysmenorrhea NRS Score At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean Dysmenorrhea NRS Score At Week 104

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. Participants rated their
pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	112	124	
Units: Score on a scale				
least squares mean (standard error)	-5.9 (± 0.17)	-5.7 (± 0.18)	-5.6 (± 0.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Are "Better" Or "Much Better" On The Patient Global Impression Of Change (PGIC) For Dysmenorrhea At Week 52

End point title	Percentage Of Participants Who Are "Better" Or "Much Better" On The Patient Global Impression Of Change (PGIC) For Dysmenorrhea At Week 52

End point description:

The PGIC for dysmenorrhea is a 1-item questionnaire designed to assess participant’s impression of change in the
severity of pain during their menstrual cycle. The questionnaire used a 7-point response scale: much better, better, a little better, the same, a little worse, worse, or much worse.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	221	202	230	
Units: Percentage of participants				
number (confidence interval 95%)	89.1 (84.27 to 92.92)	87.1 (81.71 to 91.42)	83.0 (77.56 to 87.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean NMPP NRS Score At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean NMPP NRS Score At Week 52

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. Participants rated their
pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	235	204	233	
Units: Score on a scale				
least squares mean (standard error)	-3.6 (± 0.15)	-3.4 (± 0.16)	-3.4 (± 0.15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean NMPP NRS Score At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean NMPP NRS Score At Week 104

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. Participants rated their
pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	112	124	
Units: Score on a scale				
least squares mean (standard error)	-4.0 (± 0.16)	-3.5 (± 0.17)	-3.8 (± 0.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean Overall Pelvic Pain NRS Score At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean Overall Pelvic Pain NRS Score At Week 52

End point description:

Assessed using an NRS score (11-point scale) for overall pain recorded daily in an electronic diary. Participants rated their overall pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	235	204	233	
Units: Score on a scale				
least squares mean (standard error)	-3.9 (± 0.15)	-3.6 (± 0.16)	-3.6 (± 0.15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean Overall

Pelvic Pain NRS Score At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean Overall Pelvic Pain NRS Score At Week 104

End point description:

Assessed using an NRS score (11-point scale) for overall pain recorded daily in an electronic diary. Participants rated their overall pelvic pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	112	124	
Units: Score on a scale				
least squares mean (standard error)	-4.2 (± 0.16)	-3.9 (± 0.17)	-4.0 (± 0.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Not Using Opioids For Endometriosis-associated Pain At Week 104

End point title	Percentage Of Participants Not Using Opioids For Endometriosis-associated Pain At Week 104

End point description:

Assessed based on usage of study-specified opioids for endometriosis-associated pain recorded daily in an electronic diary. Participants received protocol-specified opioids for treatment of endometriosis-associated pain as needed for pain but not prophylactically.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	277	247	275	
Units: Percentage of participants				
number (confidence interval 95%)	91.0 (87.0 to 94.1)	88.3 (83.6 to 92.0)	90.5 (86.5 to 93.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Not Using Analgesics For Endometriosis-associated Pain At Week 104

End point title	Percentage Of Participants Not Using Analgesics For Endometriosis-associated Pain At Week 104

End point description:

Assessed based on usage of study-specified analgesics for endometriosis-associated pain recorded daily in an
electronic diary. Participants received protocol-specified analgesics for treatment of endometriosis-associated pain as needed for pain but not prophylactically.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	277	247	275	
Units: Percentage of Participants				
number (confidence interval 95%)	75.1 (69.6 to 80.1)	76.5 (70.7 to 81.7)	76.0 (70.5 to 80.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Are "Better" Or "Much Better" On The PGIC For NMPP At Week 52

End point title	Percentage Of Participants Who Are "Better" Or "Much Better" On The PGIC For NMPP At Week 52

End point description:

The PGIC for NMPP is a 1-item questionnaire designed to assess participant’s impression of change in the severity
of pain when they are not menstruating. The questionnaire used a 7-point response scale: much better, better, a little better, the same, a little worse, worse, or much worse.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	221	202	230	
Units: Percentage of participants				
number (confidence interval 95%)	85.5 (80.18 to 89.88)	86.1 (80.59 to 90.59)	79.1 (73.30 to 84.19)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean Dyspareunia NRS Scores At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean Dyspareunia NRS Scores At Week 52

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. Participants were to report whether they had vaginal sexual intercourse and rated their level of pelvic pain during intercourse on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	151	126	140	
Units: Score on a scale				
least squares mean (standard error)	-3.3 (± 0.18)	-3.0 (± 0.19)	-3.0 (± 0.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean Dyspareunia NRS Scores At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean Dyspareunia NRS Scores At Week 104

End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary. Participants were to report whether they had vaginal sexual intercourse and rated their level of pelvic pain during intercourse on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	61	69	
Units: Score on a scale				
least squares mean (standard error)	-3.5 (± 0.21)	-2.9 (± 0.22)	-3.4 (± 0.21)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Are "Better" Or "Much Better" On The PGIC For Dyspareunia At Week 52

End point title	Percentage Of Participants Who Are "Better" Or "Much Better" On The PGIC For Dyspareunia At Week 52

End point description:

The PGIC for dyspareunia is a 1-item questionnaire designed to assess participant’s impression of change in the
severity of their pain during sexual intercourse. The questionnaire used a 7-point response scale: much better, better, a little better, the same, a little worse, worse, or much worse.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	210	194	210	
Units: Percentage of participants				
number (confidence interval 95%)	61.0 (54.00 to 67.59)	61.9 (54.62 to 68.72)	60.0 (53.03 to 66.68)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean Dyspareunia Functional Impairment At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean Dyspareunia Functional Impairment At Week 52

End point description:

Assessed using the participant-modified Biberoglu and Behrman 5-point scale for dyspareunia recorded daily in an electronic diary. Participants were to report their pain during intercourse daily using the following response options: Severe (avoids intercourse because of pain), Moderate (intercourse painful to the point of causing interruption), Mild (tolerated pain), No pain (no pain during intercourse), or No intercourse (no intercourse for other reasons). Participants gave a possible score of 0 (no pain) to 3 (severe). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	143	160	
Units: Score on a scale				
least squares mean (standard error)	-0.9 (± 0.06)	-0.9 (± 0.06)	-0.8 (± 0.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In The Mean Dyspareunia Functional Impairment At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In The Mean Dyspareunia Functional Impairment At Week 104

End point description:

Assessed using the participant-modified Biberoglu and Behrman 5-point scale for dyspareunia recorded daily in an electronic diary. Participants were to report their pain during intercourse daily using the following response options: Severe (avoids intercourse because of pain), Moderate (intercourse painful to the point of causing interruption), Mild (tolerated pain), No pain (no pain during intercourse), or No intercourse (no intercourse for other reasons). Participants gave a possible score of 0 (no pain) to 3 (severe). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	68	73	
Units: Score on a scale				
least squares mean (standard error)	-1.0 (± 0.06)	-0.9 (± 0.07)	-1.0 (± 0.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In Severity Scores On The Patient Global Assessment (PGA) For Overall Pelvic Pain At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In Severity Scores On The Patient Global Assessment (PGA) For Overall Pelvic Pain At Week 52

End point description:

The PGA for pelvic pain severity is a 1-item questionnaire designed to assess participant's impression of the severity of their pain. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), or very severe (4). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	206	226	
Units: Score on a scale				
least squares mean (standard error)	-1.3 (± 0.06)	-1.2 (± 0.06)	-1.2 (± 0.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In Severity Scores On The Patient Global Assessment (PGA) For Overall Pelvic Pain At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In Severity Scores On The Patient Global Assessment (PGA) For Overall Pelvic Pain At Week 104

End point description:

The PGA for pelvic pain severity is a 1-item questionnaire designed to assess participant's impression of the severity of their pain. The questionnaire used a 5-point response scale; each response was given a

numerical score: absent (0), mild (1), moderate (2), severe (3), or very severe (4). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	146	168	
Units: Score on a scale				
least squares mean (standard error)	-1.4 (± 0.07)	-1.4 (± 0.07)	-1.3 (± 0.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Overall Pelvic Pain At Week 52

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Overall Pelvic Pain At Week 52

End point description:

The PGA for pelvic pain severity is a 1-item questionnaire designed to assess participant's impression of the severity of their pain. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), or very severe (4).

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	206	226	
Units: Percentage of Participants				
number (not applicable)				
Improvement (-1 to -4)	81.5	69.9	72.6	
No Change (0)	14.7	26.2	23.0	
Deterioration (+1 to +4)	3.9	3.9	4.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Overall Pelvic Pain At Week 104

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Overall Pelvic Pain At Week 104

End point description:

The PGA for pelvic pain severity is a 1-item questionnaire designed to assess participant's impression of the severity of their pain. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), or very severe (4).

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	146	168	
Units: Percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	85.5	82.2	80.4	
No Change (0)	13.8	15.8	16.7	
Deterioration (+1 to +4)	0.6	2.1	3.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In Function Impairment On The PGA For Function At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In Function Impairment On The PGA For Function At Week 52

End point description:

The PGA for functional impairment is a 1-item questionnaire designed to assess participant’s impression of how their pain affected their usual activities. The participants responded to the question: “How much were your daily activities limited by endometriosis over the last 4 weeks?” using a 5-point response scale; each response was given a numerical score: not at all (0), minimally (1), moderately (2), significantly (3), or very significantly (4). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	235	206	230	
Units: Score on a scale				
least squares mean (standard error)	-1.6 (± 0.06)	-1.6 (± 0.06)	-1.6 (± 0.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In Function Impairment On The PGA For Function At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In Function Impairment On The PGA For Function At Week 104

End point description:

The PGA for functional impairment is a 1-item questionnaire designed to assess participant’s impression of how their pain affected their usual activities. The participants responded to the question: “How much were your daily activities limited by endometriosis over the last 4 weeks?” using a 5-point response scale; each response was given a numerical score: not at all (0), minimally (1), moderately (2), significantly (3), or very significantly (4). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	150	170	
Units: Score on a scale				
least squares mean (standard error)	-1.9 (± 0.07)	-1.9 (± 0.07)	-1.8 (± 0.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Function At Week 52

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Function At Week 52

End point description:

The PGA for functional impairment is a 1-item questionnaire designed to assess participant's impression

of how their pain affected their usual activities. The participants responded to the question: "How much were your daily activities limited by endometriosis over the last 4 weeks?" using a 5-point response scale; each response was given a numerical score: not at all (0), minimally (1), moderately (2), significantly (3), or very significantly (4).

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	235	206	230	
Units: Percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	88.9	86.9	86.1	
No Change (0)	8.1	12.6	10.0	
Deterioration (+1 to +4)	3.0	0.5	3.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Function At Week 104

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Function At Week 104

End point description:

The PGA for functional impairment is a 1-item questionnaire designed to assess participant's impression of how their pain affected their usual activities. The participants responded to the question: "How much were your daily activities limited by endometriosis over the last 4 weeks?" using a 5-point response scale; each response was given a numerical score: not at all (0), minimally (1), moderately (2), significantly (3), or very significantly (4).

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	150	170	
Units: Percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	92.7	92.0	91.2	

No Change (0)	6.7	7.3	8.8	
Deterioration (+1 to +4)	0.6	0.7	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In Each Of The Non-Pain EHP-30 Domains At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In Each Of The Non-Pain EHP-30 Domains At Week 52

End point description:

Assessed using the following non-pain domains of the EHP-30 questionnaire: Control and Powerlessness (questions 12 through 17), Emotional Well-Being (questions 18 through 23), Social Support (questions 24 through 27), and Self-Image (questions 28 through 30). The score for each domain ranged from 0 to 100. Higher scores represent a greater impact of endometriosis. The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	207	229	
Units: Score on a Scale				
least squares mean (standard error)				
Control and Powerlessness	-43.7 (± 1.61)	-40.1 (± 1.66)	-39.5 (± 1.59)	
Emotional Well-being	-26.7 (± 1.51)	-24.4 (± 1.56)	-23.7 (± 7.49)	
Social Support	-28.8 (± 1.69)	-28.9 (± 1.74)	-28.7 (± 1.67)	
Self Image	-26.4 (± 1.70)	-23.1 (± 1.75)	-22.8 (± 1.68)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In Each Of The Non-Pain EHP-30 Domains At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In Each Of The Non-Pain EHP-30 Domains At Week 104

End point description:

Assessed using the following non-pain domains of the EHP-30 questionnaire: Control and Powerlessness (questions 12 through 17), Emotional Well-Being (questions 18 through 23), Social Support (questions 24 through 27), and Self-Image (questions 28 through 30). The score for each domain ranged from 0 to 100. Higher scores represent a greater impact of endometriosis. The LS mean was presented by pivotal

study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	151	173	
Units: Score on a scale				
least squares mean (standard error)				
Control and Powerlessness	-47.5 (± 1.59)	-43.7 (± 1.63)	-41.9 (± 1.54)	
Emotional Well-being	-30.7 (± 1.60)	-26.5 (± 1.65)	-25.6 (± 1.56)	
Social Support	-33.2 (± 1.85)	-24.9 (± 1.90)	-29.7 (± 1.80)	
Self Image	-29.5 (± 1.88)	-25.8 (± 1.94)	-25.2 (± 1.83)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In Dysmenorrhea Functional Impairment Score At Week 52

End point title	Change From The Pivotal Phase 3 Study Baseline In Dysmenorrhea Functional Impairment Score At Week 52

End point description:

Assessed using the participant-modified Biberoglu and Behrman 5-point scale for dysmenorrhea recorded daily in an electronic diary. Participants were to report their pain as related to functional impairment daily in an electronic diary using the following response options: Severe (in bed all day, incapacitation), Moderate (in bed part of the day, some loss of work efficiency), Mild (some loss of work efficiency), No pain (no pain associated with menstruation during past 24 hours), or did not menstruate during the past 24 hours. Participants gave a possible score of 0 (no pain) to 4 (did not menstruate). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	235	204	233	
Units: Score on a Scale				
least squares mean (standard error)	-1.3 (± 0.04)	-1.3 (± 0.04)	-1.2 (± 0.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From The Pivotal Phase 3 Study Baseline In Dysmenorrhea Functional Impairment Score At Week 104

End point title	Change From The Pivotal Phase 3 Study Baseline In Dysmenorrhea Functional Impairment Score At Week 104

End point description:

Assessed using the participant-modified Biberoglu and Behrman 5-point scale for dysmenorrhea recorded daily in an electronic diary. Participants were to report their pain as related to functional impairment daily in an electronic diary using the following response options: Severe (in bed all day, incapacitation), Moderate (in bed part of the day, some loss of work efficiency), Mild (some loss of work efficiency), No pain (no pain associated with menstruation during past 24 hours), or did not menstruate during the past 24 hours. Participants gave a possible score of 0 (no pain) to 4 (did not menstruate). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	112	124	
Units: Score on a scale				
least squares mean (standard error)	-1.3 (± 0.04)	-1.3 (± 0.05)	-1.2 (± 0.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pivotal Phase 3 Study Baseline In NMPP Functional Impairment Score At Week 52

End point title	Change From Pivotal Phase 3 Study Baseline In NMPP Functional Impairment Score At Week 52

End point description:

Assessed using the participant-modified Biberoglu and Behrman 4-point scale for pelvic pain recorded daily in an electronic diary. Participants reported their pain daily in an electronic diary using the following response options: Severe (requires strong analgesics), Moderate (noticeable pelvic pain), Mild (occasional pelvic pain), or No pain (no pain during past 24 hours). Participants gave a possible score of 0 (no pain) to 3 (severe). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	235	204	233	
Units: Score on a scale				
least squares mean (standard error)	-1.0 (± 0.04)	-1.0 (± 0.05)	-1.0 (± 0.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pivotal Phase 3 Study Baseline In NMPP Functional Impairment Score At Week 104

End point title	Change From Pivotal Phase 3 Study Baseline In NMPP Functional Impairment Score At Week 104

End point description:

Assessed using the participant-modified Biberoglu and Behrman 4-point scale for pelvic pain recorded daily in an electronic diary. Participants reported their pain daily in an electronic diary using the following response options: Severe (requires strong analgesics), Moderate (noticeable pelvic pain), Mild (occasional pelvic pain), or No pain (no pain during past 24 hours). Participants gave a possible score of 0 (no pain) to 3 (severe). The LS mean was presented by pivotal study treatment group and by visit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	112	124	
Units: Score on a scale				
least squares mean (standard error)	-1.2 (± 0.05)	-1.1 (± 0.05)	-1.1 (± 0.05)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From The Pivotal Phase 3 Study Baseline In BMD At

Lumbar Spine (L1-L4), Femoral Neck, And Total Hip At Week 52

End point title	Percent Change From The Pivotal Phase 3 Study Baseline In BMD At Lumbar Spine (L1-L4), Femoral Neck, And Total Hip At Week 52

End point description:

Assessed by dual-energy X-ray absorptiometry (DXA) scan at lumbar spine, total hip, and femoral neck (same leg for each participant) at each designated time point. All participants who completed treatment or terminated from the study early were required to return for a 6-month post-treatment follow-up (PTFU) and a 12-month PTFU DXA scan (except if participant was beyond 14 months from last day on treatment). Participants were also to have clinical laboratory evaluations (vitamin D, thyroid stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous) at the 6-month and 12-month PTFU only if the PTFU DXA scans showed a bone loss of ≥3% at the lumbar spine and/or total hip compared with the parent study baseline.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	205[5]	232[6]	
Units: Percent change measure				
least squares mean (standard error)				
Lumbar Spine (L1-L4)	-0.69 (± 0.241)	-1.09 (± 0.256)	-0.09 (± 0.244)	
Femoral Neck	-0.21 (± 0.277)	-0.084 (± 0.294)	0.06 (± 0.280)	
Total Hip	-0.10 (± 0.207)	-0.52 (± 0.219)	0.27 (± 0.210)	

Notes:

[5] - Note that the number of participants analyzed for Lumbar Spine was n=204.

[6] - Note that the number of participants analyzed for Femoral Neck was n=231 and for Total hip was n=231

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From The Pivotal Phase 3 Study Baseline In BMD At Lumbar Spine (L1-L4), Femoral Neck, And Total Hip At Week 104

End point title	Percent Change From The Pivotal Phase 3 Study Baseline In BMD At Lumbar Spine (L1-L4), Femoral Neck, And Total Hip At Week 104

End point description:

Assessed by dual-energy X-ray absorptiometry (DXA) scan at lumbar spine, total hip, and femoral neck (same leg for each participant) at each designated time point. All participants who completed treatment or terminated from the study early were required to return for a 6-month post-treatment follow-up (PTFU) and a 12-month PTFU DXA scan (except if participant was beyond 14 months from last day on treatment). Participants were also to have clinical laboratory evaluations (vitamin D, thyroid stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous) at the 6-month and 12-month PTFU only if the PTFU DXA scans showed a bone loss of ≥3% at the lumbar spine and/or total hip compared with the parent study baseline.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	150	173[7]	
Units: Percent change measure				
least squares mean (standard error)				
Lumbar Spine (L1-L4)	-0.45 (± 0.295)	-0.56 (± 0.310)	-0.09 (± 0.292)	
Femoral Neck	0.24 (± 0.325)	-0.44 (± 0.341)	-0.05 (± 0.324)	
Total Hip	0.82 (± 0.268)	0.10 (± 0.281)	0.69 (± 0.267)	

Notes:

[7] - Note that the number of participants analyzed for Femoral Neck was and for Total hip was n=170

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pivotal Phase 3 Study Baseline In Predose Serum Concentrations Of Estradiol At Week 52

End point title	Change From Pivotal Phase 3 Study Baseline In Predose Serum Concentrations Of Estradiol At Week 52

End point description:

Blood samples were collected from participants for estradiol measurements at each specified timepoints. Estradiol concentrations were measured using an immuno-enzymatic assay based on a commercially available kit.

End point type	Secondary

End point timeframe:

Week 52

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	210	185	201	
Units: pg/mL				
arithmetic mean (standard deviation)	-55.22 (± 99.636)	-77.76 (± 125.791)	-62.07 (± 90.031)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pivotal Phase 3 Study Baseline In Predose Serum Concentrations Of Estradiol At Week 104

End point title	Change From Pivotal Phase 3 Study Baseline In Predose Serum Concentrations Of Estradiol At Week 104

End point description:

Blood samples were collected from participants for estradiol measurements at each specified timepoints. Estradiol concentrations were measured using an immuno-enzymatic assay based on a commercially available kit.

End point type	Secondary

End point timeframe:

Week 104

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	133	157	
Units: pg/mL				
arithmetic mean (standard deviation)	-51.72 (± 106.801)	-74.68 (± 138.840)	-64.39 (± 104.463)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 24/Baseline up to Week 104

Adverse event reporting additional description:

Extension Safety Population: all enrolled participants who received any amount of open-label study drug in MVT-601-3103. Study results are reported by pivotal study treatment, but all participants only received relugolix Plus E2/NETA.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Relugolix Plus E2/NETA (Group A)

Reporting group description:

Relugolix 40 mg once daily co-administered with E2 (1 mg) and NETA (0.5 mg) for 24 weeks in the pivotal
study followed by Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension
study.

Reporting group title	Relugolix Plus Delayed E2/NETA (Group B)

Reporting group description:

Relugolix 40 mg monotherapy (once daily) for 12 weeks, followed by oral relugolix 40 mg once daily coadministered with E2 (1mg) and NETA (0.5 mg) for 12 weeks in the pivotal study and Relugolix 40 mg once
daily co-administered with E2/NETA for 80 weeks in this extension study.

Reporting group title	Placebo (Group C)

Reporting group description:

Relugolix placebo co-administered with E2/NETA placebo for up to 24 weeks in the pivotal study followed by
Relugolix 40 mg once daily co-administered with E2/NETA for 80 weeks in this extension study.

Serious adverse events	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 277 (2.53%)	19 / 247 (7.69%)	18 / 275 (6.55%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic adenoma			

subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian adenoma			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid adenoma			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Broad ligament tear			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	2 / 275 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			

subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Borderline personality disorder			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug dependence			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic disorder			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Persistent depressive disorder			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Personality disorder			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 277 (0.00%)	3 / 247 (1.21%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide threat			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 277 (0.00%)	2 / 247 (0.81%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Eye pain			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 247 (0.40%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 277 (0.00%)	2 / 247 (0.81%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	2 / 275 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	0 / 277 (0.00%)	2 / 247 (0.81%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 247 (0.00%)	0 / 275 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			

subjects affected / exposed	0 / 277 (0.00%)	0 / 247 (0.00%)	1 / 275 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	173 / 277 (62.45%)	106 / 247 (42.91%)	151 / 275 (54.91%)
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 277 (13.72%)	18 / 247 (7.29%)	38 / 275 (13.82%)
occurrences (all)	38	18	38
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	15 / 277 (5.42%)	7 / 247 (2.83%)	9 / 275 (3.27%)
occurrences (all)	15	7	9
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	15 / 277 (5.42%)	7 / 247 (2.83%)	15 / 275 (5.45%)
occurrences (all)	15	7	15
Infections and infestations			
Corona virus infection			
subjects affected / exposed	13 / 277 (4.69%)	18 / 247 (7.29%)	21 / 275 (7.64%)
occurrences (all)	13	18	21
Nasopharyngitis			
subjects affected / exposed	24 / 277 (8.66%)	14 / 247 (5.67%)	22 / 275 (8.00%)
occurrences (all)	24	14	22
Urinary tract infection			
subjects affected / exposed	18 / 277 (6.50%)	12 / 247 (4.86%)	14 / 275 (5.09%)
occurrences (all)	18	12	14
Vaginal infection			
subjects affected / exposed	22 / 277 (7.94%)	18 / 247 (7.29%)	17 / 275 (6.18%)
occurrences (all)	22	18	17
Vulvovaginal mycotic infection			

subjects affected / exposed occurrences (all)	28 / 277 (10.11%) 28	12 / 247 (4.86%) 12	15 / 275 (5.45%) 15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2018	Amendment 1: to align the protocol with changes made to the parent protocols MVT-601-3101/3102. - Secondary endpoint responder analyses for EHP-30 pain domain added at Week 52. - For endpoint of proportion of responders at Week 52/EOT based on EHP-30 Pain Domain scores, a responder is defined using the same within-patient score change threshold determined from the parent studies. - Updated exclusion criteria 1 to simplify wording to improve clarity. - Clarified that "throughout the study" also included the 30 days following the last dose of study drug. - Clarified that early termination visit DXA is not required if the early termination visit occurred prior to the Week 32 visit or within 4 weeks after completion of the Week 36 DXA. - Procedural details for IVRS/IWRS and e-Diary deactivation added. - Referred reader to study drug labeling for details of study drug storage to ensure most current storage information is used. - New section ("Rescue Analgesic Medications") added to provide further procedural information and to allow short-term non-study specified analgesics for intercurrent events, if needed. - Clarified the visits at which unused drug kits should be returned to sites. - Clarified procedure to be followed for patients who terminated early but did not undergo an ET visit. - Changed safety vendor. - "ITT" was updated to "modified ITT" to better reflect that planned analysis. - Lot numbers to be maintained during drug accountability to reflect the fact that study drug kits contain lot numbers. - Clarified that safety reporting and protocol modifications will be in accordance with US and non-US health authority requirements. - Updated to specify Tier 1 and Tier 2 study-specified analgesic examples and prescribing procedures.

11 December 2018	Amendment 2: Extended study to 104 weeks of treatment, inclusive of the 24 weeks in parent study. - Updated primary and secondary objectives to reflect study extension and plan to conduct analyses on data through Week 52 and 104, resulting in a CSR for each analysis. - Included endometrial biopsy at Week 52 and optional endometrial biopsy at Week 104. - Clarified open-label nature of study. - Updated timing elements to reflect extension to 104 total weeks of treatment. - Clarified that first dose of study drug could be initiated up to 10 days after completion of parent study. - Clarified when DXA scans would be conducted and follow-up rules for DXA results. - Clarified visual acuity criteria. - Updated Statistical Methods to reflect extension of treatment and provide a description of analyses to be conducted on Week 104 data. - Updated Schedule of Activities to reflect extension of treatment. - Add telephone contact at Weeks 57, 71, 85,and 98. - Clarified what would be reviewed during telephone contact. - Clarified which physical examinations would include a breast examination. - Clarified timing of eDiary entries. - Reference documents (Lab and Study Reference Manuals) updated to Investigator Site File. - Clarified pregnancy test procedures for patients whose parent study Week 24 visit was different than baseline visit for this study. - Updated pregnancy testing language so that testing would coincide with patient visits from Week 52 to Week 104. - Clarified cannabinoids are prohibited during study. - Clarified where concomitant medications should be recorded. - Indicated that last scheduled ECG is planned for Week 52 visit. - Added language regarding assessment of bone densitometry and follow-up procedures. - Clarified safety assessments that could be performed at unscheduled visits. - Removed PK plasma samples included in error. - Clarified timepoints to be used in efficacy analyses. - Clarified which baseline visit is referenced in text.
01 July 2020	Amendment 3: included a mammogram at Week 52 or Week 104/Early Termination for women ≥ 40 years old. - Included additional objectives and endpoints to evaluate pelvic pain and analgesic use. - Added mammogram for patients over 40 years age. - Clarified timing of mammograms. - Added details to correspond with the addition of mammograms. - Clarified follow-up procedures for bone mineral density loss. - Clarified procedures for when a patient is lost to follow-up. - Added ECG at Week 104/Early Termination visit. - Added bone densitometry follow-up. - Added clinical laboratory tests during follow-up period since they may be included as part of bone densitometry follow-up. - Added endometrial biopsy follow up. - Added clarifying footnote to Schedule of Activities for status of menstruation recovery during safety follow-up. - Clarified endometrial biopsy procedures and timing. - Included removal criteria for findings resulting from mammogram. - Added language for increased counselling on contraception. - Included COVID-19 guidance. - Removed copper from IUD description to reduce confusion with inclusion criterion 6c. - Clarified investigator role in communicating to sponsor when a patient refuses the endometrial biopsy. - Clarified reporting instructions for adverse events. - Clarified timing of overdose reporting requirements. - Added clarification about the documentation of pregnancy. - Included added assessments of mammograms for patients over 40 and endometrial biopsy to list of safety assessments.

25 August 2020	Amendment 3.1: included a mammogram at Week 52 or Week 104/Early Termination (ET) for women ≥ 40 years old and revised threshold for post-treatment follow-up. - Included additional objectives and endpoints to evaluate pelvic pain and analgesic use. - Added mammogram for patients ≥ 40 years age details to correspond with this addition. - Clarified timing of mammograms. - Clarified follow-up procedures for bone mineral density (BMD) loss. Lowered threshold for post-treatment follow-up. Specified follow up procedure for BMD loss at Week 104 visit. - Clarified procedures for when a patient is lost to follow-up. - Corrected "modified ITT" population to "Extension Study" population. - Added ECG at Week 104/ET visit. - Added bone densitometry follow-up. - Added clinical laboratory tests during follow-up period since they may be included as part of bone densitometry follow-up. - Added endometrial biopsy follow up. - Added clarifying footnote to Schedule of Activities for status of menstruation recovery during safety follow-up. - Clarified endometrial biopsy procedures and timing. Added an endometrial biopsy at ET visit. - Included removal criteria for findings resulting from mammogram. - Added language for increased counselling on contraception. - Included COVID-19 guidance. - Removed copper from IUD description to reduce confusion with inclusion criterion 6c. - Clarified procedure for laboratory assessment during study and post database lock. - Clarified investigator role in communicating to sponsor when a patient refuses the endometrial biopsy. - Clarified reporting instructions for adverse events. - Clarified timing of overdose reporting requirements. - Added clarification about the documentation of pregnancy. - Included added assessments of mammograms for patients ≥ 40 and endometrial biopsy to list of safety assessments. - Added guidance on site closure and pending follow up procedures - Clarified analysis populations for efficacy/safety data.
01 July 2021	Amendment 4: added 6-month and 12-month post-treatment follow-up dual-energy x-ray absorptiometry (DXA) scans for all patients. - added 6-month and 12-month post-treatment follow-up DXA scans - Added 6-month and 12-month post-treatment follow-up assessments and labs. - Extended eDiary entry collection to 30-day follow-up visit. - Added new safety objective. - Added new section for collection of fracture events based on recent FDA recommendations. - Clarified patients should only take study-specified analgesics approved in their country. - Defined fragility fracture and request for them to be reported in the posttreatment period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported