



Clinical trial results:

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

Summary

EudraCT number	2017-001588-19
Trial protocol	CZ ES HU BE PL BG PT FI
Global end of trial date	09 June 2020

Results information

Result version number	v1 (current)
This version publication date	18 September 2022
First version publication date	18 September 2022

Trial information

Trial identification

Sponsor protocol code	MVT-601-3101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03204318
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Myovant Sciences GmbH
Sponsor organisation address	Viaduktstrasse 8, Basel, Switzerland, 4051
Public contact	Clinical Trials at Myovant, Myovant Sciences GmbH, +1 (650) 238 0250, clinicaltrials@myovant.com
Scientific contact	Clinical Trials at Myovant, Myovant Sciences GmbH, +1 (650) 238 0250, clinicaltrials@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	09 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2020
Global end of trial reached?	Yes
Global end of trial date	09 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- 1.To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on dysmenorrhea;
- 2.To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on non-menstrual pelvic pain (NMPP).

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 165
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Bulgaria: 50
Country: Number of subjects enrolled	Czechia: 36
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	Hungary: 41
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United States: 110
Country: Number of subjects enrolled	Argentina: 38
Country: Number of subjects enrolled	South Africa: 45
Country: Number of subjects enrolled	Ukraine: 112
Worldwide total number of subjects	638
EEA total number of subjects	322

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)	638
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with endometriosis-associated pain 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 Endometriosis-Associated Pain Severity (EAPS) questionnaire.

Pre-assignment

Screening details:

Three participants, 2 participants in the relugolix + delayed estradiol (E2)/norethindrone acetate (NETA) group and 1 participant in the placebo group were randomized but did not receive study drug since they were randomized in error as they had not met all eligibility requirements.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

All participants, investigators, and sponsor staff or representatives involved in the conduct of the study were blinded to treatment assignment.

Arms

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

Arm description:

Relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 24 weeks.

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	E2/NETA
Investigational medicinal product code	
Other name	E2/NETA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capsule containing co-formulated tablet of E2 (1.0 mg)/NETA (0.5 mg) administered orally once daily.

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

Relugolix monotherapy 40 mg for 12 weeks, followed by relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 12 weeks.

Arm type	Experimental
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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	E2/NETA
Investigational medicinal product code	
Other name	E2/NETA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Capsule containing co-formulated tablet of E2 (1.0 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 24 weeks.	
Arm type	Experimental
Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
E2 (0 mg)/NETA (0 mg) placebo capsule administered orally once daily and designed to match the E2/NETA capsule in size, shape, color, and odor.	
Investigational medicinal product name	Relugolix placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Relugolix (0 mg) placebo tablet administered orally once daily and manufactured to match the relugolix tablet in size, shape, color, and odor.	

Number of subjects in period 1	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)
Started	212	213	213
Received at Least 1 Dose of Study Drug	212	211	212
Completed	181	182	174
Not completed	31	31	39
Participants who did not receive any study drug	-	2	1
Adverse Event	7	9	4
Not specified	2	-	3
Pregnancy	1	2	3
Withdrawal by Subject	12	12	15

Lost to follow-up	5	2	3
Lack of efficacy	4	3	8
Protocol deviation	-	1	2

Baseline characteristics

Reporting groups

Reporting group title	Relugolix Plus E2/NETA (Group A)
Reporting group description: Relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 24 weeks.	
Reporting group title	Relugolix Plus Delayed E2/NETA (Group B)
Reporting group description: Relugolix monotherapy 40 mg for 12 weeks, followed by relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 12 weeks.	
Reporting group title	Placebo (Group C)
Reporting group description: Relugolix placebo co-administered with E2/NETA placebo for 24 weeks.	

Reporting group values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)
Number of subjects	212	213	213
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)	212	213	213
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	212	213	213
Male	0	0	0
Race Units: Subjects			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			
White			
Other			
Multiple			
Not Reported	212	213	213
Ethnicity Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Not Reported	212	213	213

Time Since Surgical Diagnosis of Endometriosis Units: years arithmetic mean standard deviation	±	±	±
Dysmenorrhea Numerical Rating Score (NRS) Score at Baseline Units: score on a scale arithmetic mean standard deviation	±	±	±
Nonmenstrual Pelvic Pain (NMPP) NRS score at Baseline Units: score on a scale arithmetic mean standard deviation	±	±	±
Bone Mineral Density (BMD) Lumbar L1-L4 Units: g/cm ² arithmetic mean standard deviation	±	±	±
BMD Total Hip Units: g/cm ² arithmetic mean standard deviation	±	±	±
BMD Femoral Neck Units: g/cm ² arithmetic mean standard deviation	±	±	±

Reporting group values	Total		
Number of subjects	638		
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)	638		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	638		
Male	0		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Black or African American	0		

Native Hawaiian or Other Pacific Islander	0		
White	0		
Other	0		
Multiple	0		
Not Reported	638		
Ethnicity			
Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	0		
Not Reported	638		
Time Since Surgical Diagnosis of Endometriosis			
Units: years			
arithmetic mean			
standard deviation	-		
Dysmenorrhea Numerical Rating Score (NRS) Score at Baseline			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Nonmenstrual Pelvic Pain (NMPP) NRS score at Baseline			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Bone Mineral Density (BMD) Lumbar L1-L4			
Units: g/cm ²			
arithmetic mean			
standard deviation	-		
BMD Total Hip			
Units: g/cm ²			
arithmetic mean			
standard deviation	-		
BMD Femoral Neck			
Units: g/cm ²			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Relugolix Plus E2/NETA (Group A)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 24 weeks.	
Subject analysis set title	Relugolix Plus Delayed E2/NETA (Group B)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Relugolix monotherapy 40 mg for 12 weeks, followed by relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 12 weeks.	
Subject analysis set title	Placebo (Group C)
Subject analysis set type	Modified intention-to-treat

Reporting group values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)
Number of subjects	212	211	212
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female Male			
Race Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Other Multiple Not Reported	0 0 13 0 194 1 4 0	1 2 10 0 194 4 0 0	0 0 12 0 193 4 3 0
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not Reported	13 198 1	17 192 2	17 195 0
Time Since Surgical Diagnosis of Endometriosis Units: years			
arithmetic mean standard deviation	3.8 ± 3.20	4.4 ± 4.08	3.8 ± 3.27
Dysmenorrhea Numerical Rating Score (NRS) Score at Baseline Units: score on a scale			
arithmetic mean standard deviation	7.2 ± 1.70	7.0 ± 1.78	7.1 ± 1.66
Nonmenstrual Pelvic Pain (NMPP) NRS score at Baseline Units: score on a scale			
arithmetic mean	5.9	5.6	5.8

standard deviation	± 1.96	± 2.03	± 1.81
Bone Mineral Density (BMD) Lumbar L1-L4			
Units: g/cm ²			
arithmetic mean	1.143	1.138	1.129
standard deviation	± 0.1512	± 0.1550	± 0.1462
BMD Total Hip			
Units: g/cm ²			
arithmetic mean	0.971	0.971	0.971
standard deviation	± 0.1227	± 0.1263	± 0.1183
BMD Femoral Neck			
Units: g/cm ²			
arithmetic mean	0.925	0.931	0.922
standard deviation	± 0.1431	± 0.1466	± 0.1450

End points

End points reporting groups

Reporting group title	Relugolix Plus E2/NETA (Group A)
Reporting group description: Relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 24 weeks.	
Reporting group title	Relugolix Plus Delayed E2/NETA (Group B)
Reporting group description: Relugolix monotherapy 40 mg for 12 weeks, followed by relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 12 weeks.	
Reporting group title	Placebo (Group C)
Reporting group description: Relugolix placebo co-administered with E2/NETA placebo for 24 weeks.	
Subject analysis set title	Relugolix Plus E2/NETA (Group A)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 24 weeks.	
Subject analysis set title	Relugolix Plus Delayed E2/NETA (Group B)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Relugolix monotherapy 40 mg for 12 weeks, followed by relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 12 weeks.	
Subject analysis set title	Placebo (Group C)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Relugolix placebo co-administered with E2/NETA placebo for 24 weeks.	

Primary: Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 24

End point title	Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 24 ^[1]
End point description: Assessed using an NRS score (11-point scale) for pain recorded daily in an electronic diary (e-Diary). The criteria for a responder was based on a threshold of greater than or equal to 2.8 points and no increase in analgesic use. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). As per the objective of the study, the pre-specified primary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.	
End point type	Primary
End point timeframe: Baseline Day 1 up to Week 24	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (confidence interval 95%)	74.5 (68.11 to 80.25)	26.9 (21.04 to 33.39)		

Statistical analyses

Statistical analysis title	Treatment difference in Dysmenorrhea Responder
Statistical analysis description: The primary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	47.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.27
upper limit	56.01

Notes:

[2] - P-value was stratified by treatment, baseline average pain score, time since initial surgical diagnosis of endometriosis (<5 years versus ≥5 years), and geographical region (North America versus Rest of World).

Primary: Percentage Of Participants Who Meet The NMPP Responder Criteria At Week 24

End point title	Percentage Of Participants Who Meet The NMPP Responder Criteria At Week 24 ^[3]
End point description: Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. The criteria for a responder was based on a threshold of greater than or equal to 2.1 points and no increase in analgesic use. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). As per the objective of the study, the pre-specified primary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.	
End point type	Primary

End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (confidence interval 95%)	58.5 (51.54 to 65.20)	39.6 (32.99 to 46.55)		

Statistical analyses

Statistical analysis title	Treatment difference in NMPP Responder
Statistical analysis description:	
The primary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[4]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	18.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.52
upper limit	28.21

Notes:

[4] - P-value stratified by treatment, baseline average pain score, time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and geographical region (North America versus Rest of World).

Secondary: Change From Baseline In The Endometriosis Health Profile (EHP)-30 Pain Score At Week 24

End point title	Change From Baseline In The Endometriosis Health Profile (EHP)-30 Pain Score At Week 24 ^[5]
End point description:	
Assessed using the Pain Domain of the EHP-30 questionnaire. Participants completed the EHP-30 questionnaire on an eTablet device and answered the questions using the following options: never, rarely, sometimes, often, or always. The least squares (LS) means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.	
End point type	Secondary

End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-33.8 (± 1.83)	-18.7 (± 1.83)		

Statistical analyses

Statistical analysis title	Treatment difference in EHP-30 Pain Score
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-15.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7
upper limit	-10.5
Variability estimate	Standard error of the mean
Dispersion value	2.33

Notes:

[6] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In Dysmenorrhea NRS Score At Week 24

End point title	Change From Baseline In Dysmenorrhea NRS Score At Week
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-5.1 ($\pm$ 0.19)	-1.8 ($\pm$ 0.19)		

Statistical analyses

Statistical analysis title	Treatment difference in Dysmenorrhea NRS Score
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[8]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	-2.8
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[8] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus $\geq$ 5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In NMPP NRS Score At Week 24

End point title	Change From Baseline In NMPP NRS Score At Week 24 ^[9]
End point description:	Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.
End point type	Secondary
End point timeframe:	
Baseline Day 1 up to Week 24	

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-2.9 (± 0.18)	-2.0 (± 0.18)		

Statistical analyses

Statistical analysis title	Treatment difference in NMPP NRS Score
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 ^[10]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[10] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In Overall Pelvic Pain NRS Score At Week 24

End point title	Change From Baseline In Overall Pelvic Pain NRS Score At Week 24 ^[11]
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-3.1 (± 0.17)	-1.9 (± 0.17)		

Statistical analyses

Statistical analysis title	Difference in Overall Pelvic Pain NRS Score
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[12]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.7
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[12] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Percentage Of Participants Who Are Not Using Opioids For Endometriosis-associated Pain At Week 24

End point title	Percentage Of Participants Who Are Not Using Opioids For Endometriosis-associated Pain At Week 24 ^[13]
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End point description:

Assessed based on usage of protocol-specified opioids for endometriosis-associated pain recorded daily in an e-Diary. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (confidence interval 95%)	85.8 (80.4 to 90.2)	76.4 (70.1 to 82.0)		

Statistical analyses

Statistical analysis title	Treatment difference in Opioid-free Participants
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 ^[14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	16.8

Notes:

[14] - Nominal p-value. P-value was stratified by baseline opioid use, time since initial surgical diagnosis of endometriosis (<5 years versus ≥5 years), and geographic region (North America versus Rest of World).

Secondary: Change From Baseline In Dyspareunia NRS Scores At Week 24

End point title	Change From Baseline In Dyspareunia NRS Scores At Week
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End point description:

Assessed using an NRS score (11-point scale) for dyspareunia recorded daily in an e-Diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: dyspareunia NRS score				
least squares mean (standard error)	-2.4 (± 0.21)	-1.7 (± 0.22)		

Statistical analyses

Statistical analysis title	Treatment difference in Dyspareunia NRS Scores
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0149 ^[16]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[16] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Percentage of Participants Who Are Not Using Analgesics For Endometriosis-associated Pain At Week 24

End point title	Percentage of Participants Who Are Not Using Analgesics For Endometriosis-associated Pain At Week 24 ^[17]
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End point description:

Assessed based on usage of protocol-specified analgesic use for endometriosis-associated pain recorded daily in an e-Diary. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (confidence interval 95%)	56.1 (49.2 to 62.9)	30.7 (24.5 to 37.3)		

Statistical analyses

Statistical analysis title	Difference in Analgesic-free Participants
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	25.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.4
upper limit	34.6

Notes:

[18] - Nominal p-value. P-value was stratified by baseline analgesic use, time since initial surgical diagnosis of endometriosis (<5 years versus ≥5 years), and geographic region (North America versus Rest of World).

Secondary: Percentage Of Participants Who Have A Reduction Of At Least 20 Points In The EHP-30 Pain Domain From Baseline To Week 24

End point title	Percentage Of Participants Who Have A Reduction Of At Least 20 Points In The EHP-30 Pain Domain From Baseline To Week 24 ^[19]
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End point description:

Assessed using the pain domain of the EHP-30 questionnaire. Participants completed the EHP-30 questionnaire on an eTablet device and answered the questions using the following options: never, rarely, sometimes, often, or always. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Week 12 and Week 24

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[20]	212 ^[21]		
Units: percentage of participants				
number (confidence interval 95%)				
Week 12	67.4 (60.16 to 74.04)	39.8 (32.70 to 47.20)		
Week 24	76.3 (69.25 to 82.42)	48.5 (40.64 to 56.38)		

Notes:

[20] - Week 12: n=187

Week 24: n=173

[21] - Week 12: n=186

Week 24: n=165

Statistical analyses

Statistical analysis title	Treatment difference in EHP-30 Pain Domain (Wk 12)
Statistical analysis description:	
The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 12.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	27.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.87
upper limit	37.32

Notes:

[22] - Nominal p-value. P-value was stratified by time since initial surgical diagnosis of endometriosis (<5 years versus ≥5 years) and geographic region (North America versus Rest of World).

Statistical analysis title	Treatment difference in EHP-30 Pain Domain (Wk 24)
Statistical analysis description:	
The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 24.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	27.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	17.9
upper limit	37.73

Notes:

[23] - Nominal p-value. P-value was stratified by time since initial surgical diagnosis of endometriosis (<5 years versus ≥5 years) and geographic region (North America versus Rest of World).

Secondary: Percentage of Participants Classified As Dysmenorrhea Responder Rate By Month

End point title	Percentage of Participants Classified As Dysmenorrhea Responder Rate By Month ^[24]
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End point description:

The criteria for a responder was based on a pre-defined threshold of greater than or equal to 2.8 points and no increase in analgesic use. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Week 4 up to Week 24

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (confidence interval 95%)				
Week 4	16.0 (11.37 to 21.68)	7.5 (4.38 to 11.97)		
Week 8	59.0 (52.02 to 65.65)	17.5 (12.60 to 23.24)		
Week 12	65.1 (58.27 to 71.49)	20.3 (15.09 to 26.33)		
Week 16	69.3 (62.66 to 75.47)	24.5 (18.89 to 30.89)		
Week 20	70.3 (63.64 to 76.35)	30.2 (24.09 to 36.85)		
Week 24	74.5 (68.11 to 80.25)	26.9 (21.04 to 33.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Classified As NMPP Responder Rate By Month

End point title	Percentage of Participants Classified As NMPP Responder Rate By Month ^[25]
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End point description:

The criteria for a responder was based on a pre-defined threshold of greater than or equal to 2.1 points and no increase in analgesic use. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Week 4 up to Week 24

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (confidence interval 95%)				
Week 4	14.2 (9.76 to 19.58)	9.4 (5.86 to 14.19)		
Week 8	32.5 (26.29 to 39.30)	22.6 (17.19 to 28.87)		
Week 12	41.0 (34.35 to 47.98)	28.3 (22.34 to 34.88)		
Week 16	50.0 (43.08 to 56.92)	31.6 (25.41 to 38.32)		
Week 20	52.8 (45.88 to 59.70)	37.3 (30.74 to 44.15)		
Week 24	58.5 (51.54 to 65.20)	39.6 (32.99 to 46.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Dysmenorrhea NRS Score By Month

End point title	Change From Baseline In Dysmenorrhea NRS Score By
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group

A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[27]	212 ^[28]		
Units: score on a scale				
least squares mean (standard error)				
Baseline	7.3 ($\pm$ 0.13)	7.2 ($\pm$ 0.13)		
Week 4	-1.2 ($\pm$ 0.18)	-0.7 ($\pm$ 0.18)		
Week 8	-4.2 ($\pm$ 0.20)	-1.2 ($\pm$ 0.20)		
Week 12	-4.7 ($\pm$ 0.20)	-1.4 ($\pm$ 0.20)		
Week 16	-5.0 ($\pm$ 0.20)	-1.6 ($\pm$ 0.20)		
Week 20	-5.2 ($\pm$ 0.20)	-1.9 ($\pm$ 0.20)		
Week 24	-5.1 ($\pm$ 0.19)	-1.8 ($\pm$ 0.19)		

Notes:

[27] - Wk 4: n=202

Wk 8: n=196

Wk 12: n=193

Wk 16: n=187

Wk 20: n=184

Wk 24: n=211

[28] - Wk 4: n=205

Wk 8: n=198

Wk 12: n=189

Wk 16: n=180

Wk 20: n=178

Statistical analyses

Statistical analysis title	Difference in Dysmenorrhea NRS Score (Wk 12)
Statistical analysis description:	
The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 12.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[29]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	-2.7
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[29] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus $\geq$ 5 years), and treatment-by-visit interaction included as fixed effects.

Statistical analysis title	Difference in Dysmenorrhea NRS Score (Wk 24)
Statistical analysis description:	
The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 24.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[30]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	-2.8
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[30] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In NMPP NRS Score By Month

End point title	Change From Baseline In NMPP NRS Score By Month ^[31]
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[32]	212 ^[33]		
Units: score on a scale				
least squares mean (standard error)				
Baseline	5.8 (± 0.15)	5.8 (± 0.15)		
Week 4	-0.8 (± 0.10)	-0.6 (± 0.10)		
Week 8	-1.5 (± 0.14)	1.2 (± 0.14)		
Week 12	-2.2 (± 0.16)	-1.5 (± 0.16)		
Week 16	-2.5 (± 0.17)	-1.8 (± 0.17)		
Week 20	-2.6 (± 0.17)	-2.0 (± 0.17)		

Week 24	-2.9 ($\pm$ 0.18)	-2.0 ($\pm$ 0.18)		
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Notes:

[32] - Wk 4: n=202

Wk 8: n=196

Wk 12: n=193

Wk 16: n=187

Wk 20: n=184

Wk 24: n=211

[33] - Wk 4: n=205

Wk 8: n=198

Wk 12: n=189

Wk 16: n=180

Wk 20: n=178

Statistical analyses

Statistical analysis title	Treatment difference in NMPP NRS Score (Wk 12)
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Statistical analysis description:

The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 12.

Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0041 ^[34]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[34] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus $\geq$ 5 years), and treatment-by-visit interaction included as fixed effects.

Statistical analysis title	Treatment difference in NMPP NRS Score (Wk 24)
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Statistical analysis description:

The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 24.

Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 ^[35]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[35] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In Overall Pelvic Pain NRS Score By Month

End point title	Change From Baseline In Overall Pelvic Pain NRS Score By Month ^[36]
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[37]	212 ^[38]		
Units: score on a scale				
least squares mean (standard error)				
Baseline	6.2 (± 0.14)	6.0 (± 0.14)		
Week 4	-0.7 (± 0.10)	-0.6 (± 0.10)		
Week 8	-1.6 (± 0.14)	-1.2 (± 0.14)		
Week 12	-2.3 (± 0.16)	-1.4 (± 0.16)		
Week 16	-2.6 (± 0.17)	-1.7 (± 0.17)		
Week 20	-2.8 (± 0.17)	-1.9 (± 0.17)		
Week 24	-3.1 (± 0.17)	-1.9 (± 0.17)		

Notes:

[37] - Wk 4: n=202

Wk 8: n=196

Wk 12: n=193

Wk 16: n=187

Wk 20: n=184

Wk 24: n=211

[38] - Wk 4: n=205

Wk 8: n=198

Wk 12: n=189

Wk 16: n=180

Wk 20: n=178

Statistical analyses

Statistical analysis title	Difference in Overall Pelvic Pain Score (Wk 12)
Statistical analysis description: The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 12.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 ^[39]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[39] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Statistical analysis title	Difference in Overall Pelvic Pain Score (Wk 24)
Statistical analysis description: The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 24.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[40]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.7
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[40] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In Dyspareunia NRS Score By Month

End point title	Change From Baseline In Dyspareunia NRS Score By Month ^[41]
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). The LS means at Week

24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
End point timeframe:	
Baseline Day 1 up to Week 24	

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[42]	212 ^[43]		
Units: score on a scale				
least squares mean (standard error)				
Baseline	5.8 (± 0.20)	5.8 (± 0.20)		
Week 4	-0.5 (± 0.15)	-0.5 (± 0.15)		
Week 8	-1.1 (± 0.18)	-1.0 (± 0.19)		
Week 12	-1.7 (± 0.20)	-1.5 (± 0.21)		
Week 16	-2.1 (± 0.21)	-1.5 (± 0.22)		
Week 20	-2.2 (± 0.21)	-1.7 (± 0.22)		
Week 24	-2.4 (± 0.21)	-1.7 (± 0.22)		

Notes:

[42] - Baseline: n=174

Wk 4: n=149

Wk 8: n=142

Wk 12: n=136

Wk 16: n=137

Wk 20: n=136

Wk 24: n=148

[43] - Baseline: n=165

Wk 4: n=140

Wk 8: n=140

Wk 12: n=126

Wk 16: n=120

Wk 20: n=123

Wk 24: n=138

Statistical analyses

Statistical analysis title	Difference in Dyspareunia NRS Score (Wk 12)
Statistical analysis description:	
The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 12.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4374 ^[44]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[44] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Statistical analysis title	Difference in Dyspareunia NRS Score (Wk 24)
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Statistical analysis description:

The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate at Week 24.

Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0149 ^[45]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[45] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In Ibuprofen Use At Week 24

End point title	Change From Baseline In Ibuprofen Use At Week 24 ^[46]
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End point description:

Assessed using ibuprofen pill counts for endometriosis-associated pain recorded daily in an e-Diary. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: pill count				
arithmetic mean (standard deviation)	-19.2 (± 42.69)	-17.3 (± 34.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Opioid Use At Week 24

End point title	Change From Baseline In Opioid Use At Week 24 ^[47]
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End point description:

Assessed using opioid pill counts for endometriosis-associated pain recorded daily in an e-Diary. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline up to Week 24

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: pill count				
arithmetic mean (standard deviation)	-1.4 (± 9.05)	-0.2 (± 17.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In The Mean Dysmenorrhea Functional Impairment At Week 24

End point title	Change From Baseline In The Mean Dysmenorrhea Functional Impairment At Week 24 ^[48]
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End point description:

Assessed using the participant modified Biberoglu and Behrman 5-point scale for dysmenorrhea recorded daily in an e-Diary. Participants were to report their pain using the following response options: Severe (in bed all day, incapacitation), Moderate (in bed part of 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 (severe) for this scale. The LS means at Week 24 were compared between the relugolix plus E2/NETA

and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
End point timeframe:	
Baseline Day 1 up to Week 24	

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-1.0 ($\pm$ 0.05)	-0.3 ($\pm$ 0.05)		

Statistical analyses

Statistical analysis title	Difference in Dysmenorrhea Functional Impairment
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[49]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[49] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus $\geq$ 5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In The Mean NMPP Functional Impairment At Week 24

End point title	Change From Baseline In The Mean NMPP Functional Impairment At Week 24 ^[50]
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End point description:

Assessed using the participant modified Biberoglu and Behrman 4-point scale for pelvic pain recorded daily in an e-Diary. Participants reported their pain 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) for this scale. The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo

groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
End point timeframe:	
Baseline Day 1 up to Week 24	

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-0.8 (± 0.05)	-0.6 (± 0.05)		

Statistical analyses

Statistical analysis title	Difference in NMPP Functional Impairment
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 ^[51]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[51] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In The Mean Dyspareunia Functional Impairment At Week 24

End point title	Change From Baseline In The Mean Dyspareunia Functional Impairment At Week 24 ^[52]
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End point description:

Assessed using the participant modified Biberoglu and Behrman 5-point scale for dyspareunia recorded daily in an e-Diary. Participants were to report their pain during intercourse 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) for this

scale. The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
End point timeframe:	
Baseline Day 1 up to Week 24	

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-0.7 (± 0.06)	-0.5 (± 0.06)		

Statistical analyses

Statistical analysis title	Difference in Dyspareunia Functional Impairment
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0352 [53]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

[53] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In Patient Global Assessment (PGA) For Dysmenorrhea Symptom Severity At Week 24

End point title	Change From Baseline In Patient Global Assessment (PGA) For Dysmenorrhea Symptom Severity At Week 24 ^[54]
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End point description:

The PGA for dysmenorrhea is a 1-item questionnaire designed to assess participants' impression of the severity of pain during their menstrual cycle. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), and very severe (4). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups.

As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
End point timeframe:	
Baseline Day 1 up to Week 24	

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-2.6 ($\pm$ 0.09)	-0.7 ($\pm$ 0.09)		

Statistical analyses

Statistical analysis title	Treatment difference in PGA For Dysmenorrhea
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[55]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[55] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus $\geq$ 5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA For Dysmenorrhea At Week 24

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA For Dysmenorrhea At Week 24 ^[56]
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End point description:

The PGA for dysmenorrhea is a 1-item questionnaire designed to assess participants' impression of the severity of pain during their menstrual cycle. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), and very severe (4). As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary			
End point timeframe:				
Baseline Day 1 up to Week 24				
Notes:				
[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.				
Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.				
End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[57]	212 ^[58]		
Units: percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	93.4	58.6		
No Change (0)	5.9	31.7		
Deterioration (+1 to +4)	0.7	9.7		

Notes:

[57] - All categories: n=152

[58] - All categories: n=145

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In PGA For NMPP Symptom Severity At Week 24

End point title	Change From Baseline In PGA For NMPP Symptom Severity At Week 24 ^[59]			
End point description:				
The PGA for NMPP is a 1-item questionnaire designed to assess participants' impression of the severity of pain when they are not menstruating. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), and very severe (4). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.				
End point type	Secondary			
End point timeframe:				
Baseline Day 1 up to Week 24				
Notes:				
[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.				
Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.				
End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-1.4 (± 0.08)	-0.9 (± 0.08)		

Statistical analyses

Statistical analysis title	Treatment difference in PGA For NMPP
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[60]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[60] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA For NMPP At Week 24

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA For NMPP At Week 24 ^[61]
End point description:	
The PGA for NMPP is a 1-item questionnaire designed to assess participants' impression of the severity of pain when they are not menstruating. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), and very severe (4). As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.	
End point type	Secondary

End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	81.6	61.2		
No Change (0)	15.8	32.7		
Deterioration (+1 to +4)	2.6	6.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In PGA For Pain Severity At Week 24

End point title	Change From Baseline In PGA For Pain Severity At Week 24 ^[62]
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End point description:

The PGA for pain severity is a 1-item questionnaire designed to assess participants' impression of how their pain affected their usual activities. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), and very severe (4). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-1.2 (± 0.08)	-0.7 (± 0.08)		

Statistical analyses

Statistical analysis title	Treatment difference in PGA For Pain Severity
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[63]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[63] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA For Pain Severity At Week 24

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA For Pain Severity At Week 24 ^[64]
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End point description:

The PGA for pain severity is a 1-item questionnaire designed to assess participants' impression of how their pain affected their usual activities. The questionnaire used a 5-point response scale; each response was given a numerical score: absent (0), mild (1), moderate (2), severe (3), and very severe (4). As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	75.9	57.0		
No Change (0)	18.2	26.7		
Deterioration (+1 to +4)	5.9	16.4		

Statistical analyses

Secondary: Change From Baseline In PGA For Function At Week 24

End point title	Change From Baseline In PGA For Function At Week 24 ^[65]
End point description:	
The PGA for function is a 1-item questionnaire designed to assess participants' impression of how their pain affected their usual activities. The questionnaire used a 5-point response scale; each response was given a numerical score: not at all (0), minimally (1), moderately (2), significantly (3), and very significantly (4). The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.	
End point type	Secondary
End point timeframe:	
Baseline Day 1 up to Week 24	

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-1.5 (± 0.07)	-0.9 (± 0.07)		

Statistical analyses

Statistical analysis title	Treatment difference in PGA for Function
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[66]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[66] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA For Function At Week 24

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA For Function At Week 24 ^[67]
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End point description:

The PGA for function is a 1-item questionnaire designed to assess participants' impression of how their pain affected their usual activities. The questionnaire used a 5-point response scale; each response was given a numerical score: not at all (0), minimally (1), moderately (2), significantly (3), and very significantly (4). As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	86.5	64.9		
No Change (0)	10.5	29.8		
Deterioration (+1 to +4)	2.9	5.4		

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 24

End point title	Percentage Of Participants Who Are "Better" Or "Much Better" On The Patient Global Impression Of Change (PGIC) For Dysmenorrhea At Week 24 ^[68]
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End point description:

The PGIC for dysmenorrhea is a 1-item questionnaire designed to assess participants' 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. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Week 12 and Week 24

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group

A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (not applicable)	76.8	41.1		

Statistical analyses

Statistical analysis title	Treatment difference in PGIC for Dysmenorrhea
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[69]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	35.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.07
upper limit	45.46

Notes:

[69] - Nominal p-value. P-value was stratified by time since initial surgical diagnosis of endometriosis (<5 years versus ≥5 years) and geographic region (North America versus Rest of World).

Secondary: Percentage Of Participants Who Are "Better" Or "Much Better" On The PGIC For NMPP At Week 24

End point title	Percentage Of Participants Who Are "Better" Or "Much Better" On The PGIC For NMPP At Week 24 ^[70]
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End point description:

The PGIC for NMPP is a 1-item questionnaire designed to assess participants' 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. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Week 12 and Week 24

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (not applicable)	75.1	47.0		

Statistical analyses

Statistical analysis title	Treatment difference in PGIC For NMPP
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[71]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	28.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.24
upper limit	37.99

Notes:

[71] - Nominal p-value. P-value was stratified by time since initial surgical diagnosis of endometriosis (<5 years versus ≥5 years) and geographic region (North America versus Rest of World).

Secondary: Percentage Of Participants Who Are "Better" Or "Much Better" On The PGIC For Dyspareunia At Week 24

End point title	Percentage Of Participants Who Are "Better" Or "Much Better" On The PGIC For Dyspareunia At Week 24 ^[72]
End point description:	The PGIC for dyspareunia is a 1-item questionnaire designed to assess participants' impression of change in the severity of 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. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.
End point type	Secondary
End point timeframe:	
Week 12 and Week 24	

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: percentage of participants				
number (not applicable)	56.2	32.7		

Statistical analyses

Statistical analysis title	Treatment difference in PGIC For Dyspareunia
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[73]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	23.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.99
upper limit	34.08

Notes:

[73] - Nominal p-value. P-value was stratified by time since initial surgical diagnosis of endometriosis (<5 years versus ≥5 years) and geographic region (North America versus Rest of World).

Secondary: Change From Baseline In The Non-Pain Of The EHP-30 Domains At Week 24

End point title	Change From Baseline In The Non-Pain Of The EHP-30 Domains At Week 24 ^[74]
End point description:	Assessed using the non-pain domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image) of the EHP-30 questionnaire. The score for each domain ranged from 0 to 100. Higher scores represent a greater (that is, more negative) impact of endometriosis. The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.
End point type	Secondary
End point timeframe:	
Baseline Day 1, Week 12, and Week 24	

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[75]	212 ^[76]		
Units: score on a scale				
least squares mean (standard error)				
Control and Powerlessness	-40.7 (± 2.12)	23.7 (± 2.13)		
Emotional Well-being	-25.1 (± 1.91)	-16.3 (± 1.93)		
Social Support	-28.0 (± 2.12)	-17.5 (± 2.14)		
Self Image	-22.5 (± 2.18)	-11.3 (± 2.20)		

Notes:

[75] - All categories: n=173

[76] - All categories: n=165

Statistical analyses

Statistical analysis title	Non-Pain EHP-30 Domain (Control and Powerlessness)
Statistical analysis description:	
The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate for Control and Powerlessness domain.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[77]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.3
upper limit	-11.7
Variability estimate	Standard error of the mean
Dispersion value	2.7

Notes:

[77] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Statistical analysis title	Non-Pain EHP-30 Domain (Emotional Well-being)
Statistical analysis description:	
The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate for Emotional Well-being domain.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 ^[78]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-8.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.6
upper limit	-3.9
Variability estimate	Standard error of the mean
Dispersion value	2.45

Notes:

[78] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Statistical analysis title	Non-Pain EHP-30 Domain (Social Support)
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Statistical analysis description:

The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate for Social Support domain.

Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [79]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-10.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.8
upper limit	-5.2
Variability estimate	Standard error of the mean
Dispersion value	2.71

Notes:

[79] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Statistical analysis title	Non-Pain EHP-30 Domain (Self-image)
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Statistical analysis description:

The secondary efficacy analysis was the comparison of the relugolix plus E2/NETA group with the placebo group with respect to responder rate for Self-image domain.

Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [80]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-11.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.7
upper limit	-5.7

Variability estimate	Standard error of the mean
Dispersion value	2.81

Notes:

[80] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In The EHP-30 Scale Total Score At Week 24

End point title	Change From Baseline In The EHP-30 Scale Total Score At Week 24 ^[81]
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End point description:

Assessed using the total score of the EHP-30 questionnaire. The score ranged from 0 to 100. Higher scores represent a greater (that is, more negative) impact of endometriosis. The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[81] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-31.5 (± 1.77)	-18.3 (± 1.78)		

Statistical analyses

Statistical analysis title	Treatment difference in EHP-30 Scale Total Score
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[82]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.7
upper limit	-8.8
Variability estimate	Standard error of the mean
Dispersion value	2.26

Notes:

[82] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Change From Baseline In The EHP Work Domain Score At Week 24

End point title	Change From Baseline In The EHP Work Domain Score At Week 24 ^[83]
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End point description:

The EHP Work domain is a 5-item questionnaire that assesses impact of pain on ability to work. The questionnaire assessed the effects of endometriosis on work (for example, frequency of needing to take time off from work due to pain, inability to carry out work duties due to pain). The EHP Work Domain score ranged from 0 to 100. Higher scores represent a greater (that is, more negative) impact of endometriosis on work-related activities. The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 and Week 24

Notes:

[83] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
least squares mean (standard error)	-31.9 (± 1.98)	-18.3 (± 2.05)		

Statistical analyses

Statistical analysis title	Treatment difference in EHP Work Domain Score
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[84]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-13.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	-8.8
Variability estimate	Standard error of the mean
Dispersion value	2.44

Notes:

[84] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since surgical endometriosis diagnosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

Secondary: Categorical Change From Baseline In Quality Of Life Assessed By European Quality Of Life Five Dimension Five Level (EQ-5D-5L) Questionnaire At Week 24

End point title	Categorical Change From Baseline In Quality Of Life Assessed By European Quality Of Life Five Dimension Five Level (EQ-5D-5L) Questionnaire At Week 24 ^[85]
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End point description:

The EQ-5D-5L is a 5-item questionnaire designed to assess quality of life. EQ-5D-5L asks about limitations and problems at an instantaneous point in time ("today"). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on a five-level categorical scale ranging from "no problem" to "severe problem." As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 and Week 24

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: participants				
Mobility - 4 Category deterioration	0	0		
Mobility - 3 Category deterioration	0	0		
Mobility - 2 Category deterioration	0	2		
Mobility - 1 Category deterioration	12	4		
Mobility - No change	58	85		
Mobility - 1 Category improvement	56	46		
Mobility - 2 Category improvement	41	25		
Mobility - 3 Category improvement	6	3		
Mobility - 4 Category improvement	0	0		
Self-care - 4 Category deterioration	0	0		
Self-care - 3 Category deterioration	0	0		
Self-care - 2 Category deterioration	0	4		
Self-care - 1 Category deterioration	3	4		
Self-care - No change	106	120		
Self-care - 1 Category improvement	45	24		
Self-care - 2 Category improvement	18	13		
Self-care - 3 Category improvement	1	0		
Self-care - 4 Category improvement	0	0		
Usual activities - 4 Category deterioration	0	0		
Usual activities - 3 Category deterioration	0	0		

Usual activities - 2 Category deterioration	0	1		
Usual activities - 1 Category deterioration	6	15		
Usual activities - No change	53	54		
Usual activities - 1 Category improvement	62	53		
Usual activities - 2 Category improvement	42	37		
Usual activities - 3 Category improvement	10	4		
Usual activities - 4 Category improvement	0	1		
Pain/discomfort - 4 Category deterioration	0	0		
Pain/discomfort - 3 Category deterioration	0	0		
Pain/discomfort - 2 Category deterioration	0	4		
Pain/discomfort - 1 Category deterioration	7	20		
Pain/discomfort - No change	33	45		
Pain/discomfort - 1 Category improvement	64	60		
Pain/discomfort - 2 Category improvement	53	27		
Pain/discomfort - 3 Category improvement	15	9		
Pain/discomfort - 4 Category improvement	1	0		
Anxiety/depression - 4 Category deterioration	0	1		
Anxiety/depression - 3 Category deterioration	0	0		
Anxiety/depression - 2 Category deterioration	2	8		
Anxiety/depression - 1 Category deterioration	15	27		
Anxiety/depression - No change	63	64		
Anxiety/depression - 1 Category improvement	53	38		
Anxiety/depression - 2 Category improvement	32	21		
Anxiety/depression - 3 Category improvement	8	6		
Anxiety/depression - 4 Category improvement	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 24 In EQ-5D-5L Visual Analogue Scale Score At Week 24

End point title	Change From Baseline To Week 24 In EQ-5D-5L Visual Analogue Scale Score At Week 24 ^[86]
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End point description:

The EQ-5D-5L is a 5-item questionnaire designed to assess quality of life. EQ-5D-5L asks about limitations and problems at an instantaneous point in time ("today"). It also includes an assessment of overall health status that the participant rates on a 100-point visual analogue scale where 0 was "the worst health you could imagine" and 100 was "the best health you could imagine." As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 and Week 24

Notes:

[86] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	212		
Units: score on a scale				
arithmetic mean (standard deviation)	22.8 (± 21.31)	14.0 (± 23.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 24 For Relugolix Plus Delayed E2/NETA

End point title	Percentage Of Participants Who Meet The Dysmenorrhea Responder Criteria At Week 24 For Relugolix Plus Delayed E2/NETA ^[87]
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. The criteria for a responder was based on a threshold of greater than or equal to 2.8 points and no increase in analgesic use. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). As per the objective of the study, only relugolix plus delayed E2/NETA arm is presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[87] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus Delayed E2/NETA (Group B)			
Subject group type	Reporting group			
Number of subjects analysed	211			
Units: percentage of participants				
number (confidence interval 95%)	71.6 (64.97 to 77.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Meet The NMPP Responder Criteria At Week 24 For Relugolix Plus Delayed E2/NETA

End point title	Percentage Of Participants Who Meet The NMPP Responder Criteria At Week 24 For Relugolix Plus Delayed E2/NETA ^[88]
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. The criteria for a responder was based on a threshold of greater than or equal to 2.1 points and no increase in analgesic use. Higher NRS score means worse condition (0 = no pain to 10 = pain as bad as you can imagine). As per the objective of the study, only relugolix plus delayed E2/NETA arm is presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[88] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus Delayed E2/NETA (Group B)			
Subject group type	Reporting group			
Number of subjects analysed	211			
Units: percentage of participants				
number (confidence interval 95%)	57.8 (50.85 to 64.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In The EHP-30 Pain Score At Week 24 For Relugolix Plus Delayed E2/NETA

End point title	Change From Baseline In The EHP-30 Pain Score At Week 24 For Relugolix Plus Delayed E2/NETA ^[89]
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End point description:

Assessed using the Pain Domain of the EHP-30 questionnaire. Participants completed the EHP-30 questionnaire on an eTablet device and answered the questions using the following options: never, rarely, sometimes, often, or always. The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, only relugolix plus delayed E2/NETA arm is presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[89] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus Delayed E2/NETA (Group B)			
Subject group type	Reporting group			
Number of subjects analysed	211			
Units: score on a scale				
least squares mean (standard error)	-32.1 (± 1.76)			

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 From Baseline To Week 24 For Relugolix Plus Delayed E2/NETA

End point title	Percentage Of Participants Who Have A Reduction Of At Least 20 Points In The EHP-30 Pain Domain From Baseline To Week 24 For Relugolix Plus Delayed E2/NETA ^[90]
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End point description:

Assessed using the pain domain of the EHP-30 questionnaire. Participants completed the EHP-30 questionnaire on an eTablet device and answered the questions using the following options: never, rarely, sometimes, often, or always. As per the objective of the study, only relugolix plus delayed E2/NETA arm is presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[90] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus Delayed E2/NETA (Group B)			
Subject group type	Reporting group			
Number of subjects analysed	211 ^[91]			
Units: percentage of participants				
number (confidence interval 95%)				
Week 12	62.1 (54.80 to 69.03)			
Week 24	71.3 (64.11 to 77.86)			

Notes:

[91] - Week 12: n=190

Week 24: n=178

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline In BMD At The Lumbar Spine (L1-L4) At Week 12

End point title	Percentage Change From Baseline In BMD At The Lumbar Spine (L1-L4) At Week 12 ^[92]
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End point description:

Assessed by dual-energy X-ray absorptiometry (DXA) scan at each designated time points. If participants experienced BMD loss of >2% from baseline, they were to undergo another bone densitometry 6 months after discontinuation of study drug. The LS means at Week 24 were compared between relugolix plus E2/NETA and relugolix plus delayed E2/NETA groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with relugolix plus delayed E2/NETA. Therefore, only relugolix plus E2/NETA and relugolix plus delayed E2/NETA are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[92] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	211		
Units: g/cm ²				
least squares mean (standard error)	-0.52 (± 0.239)	-1.69 (± 0.243)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline In BMD At Lumbar Spine (L1-L4), Femoral Neck, And Total Hip At Week 24

End point title	Percentage Change From Baseline In BMD At Lumbar Spine (L1-L4), Femoral Neck, And Total Hip At Week 24 ^[93]
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End point description:

BMD was assessed by DXA scan at the lumbar spine, total hip, and femoral neck (same leg for each participant) at each designated time points. The LS means at Week 24 were compared between the relugolix plus E2/NETA and placebo groups. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with relugolix plus delayed E2/NETA. Therefore, only relugolix plus E2/NETA and relugolix plus delayed E2/NETA are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1, week 12, and Week 24

Notes:

[93] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[94]	211 ^[95]		
Units: g/cm ²				
least squares mean (standard error)				
Lumbar spine (L1-L4)	-0.70 (± 0.255)	-1.99 (± 0.256)		
Total hip	-0.11 (± 0.216)	-0.74 (± 0.217)		
Femoral neck	-0.39 (± 0.295)	-1.19 (± 0.297)		

Notes:

[94] - All categories: n=164

[95] - All categories: n=161

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Experiencing Vasomotor Symptoms At Week 12 Between Relugolix Plus E2/NETA and Relugolix Plus Delayed E2/NETA

End point title	Percentage Of Participants Experiencing Vasomotor Symptoms At Week 12 Between Relugolix Plus E2/NETA and Relugolix Plus Delayed E2/NETA ^[96]
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End point description:

Vasomotor symptoms include preferred terms of hyperhidrosis, feeling hot, hot flush, night sweats and flushing. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with relugolix plus delayed E2/NETA. Therefore, only relugolix plus E2/NETA and relugolix plus delayed E2/NETA are presented.

End point type	Secondary
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End point timeframe:

Week 12

Notes:

[96] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	211		
Units: percentage of participants				
number (confidence interval 95%)	8.02 (4.74 to 12.53)	32.70 (26.42 to 39.48)		

Statistical analyses

Statistical analysis title	Treatment difference in Vasomotor Symptoms
Comparison groups	Relugolix Plus E2/NETA (Group A) v Relugolix Plus Delayed E2/NETA (Group B)
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.4

Secondary: Change From Baseline In Serum Concentrations Of Luteinizing Hormone and Follicle Stimulating Hormone

End point title	Change From Baseline In Serum Concentrations Of Luteinizing Hormone and Follicle Stimulating Hormone ^[97]
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End point description:

Blood samples were collected from participants to determine serum concentrations of luteinizing hormone and follicle stimulating hormone using a validated method based on immuno-enzymatic assay. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[97] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[98]	212 ^[99]		
Units: IU/L				
arithmetic mean (standard deviation)				
Luteinizing Hormone - Baseline	9.27 (± 11.513)	9.21 (± 13.753)		
Luteinizing Hormone - Week 12	-6.78 (± 12.591)	-0.53 (± 16.583)		
Luteinizing Hormone - Week 24	-6.10 (± 13.601)	-0.03 (± 17.316)		
Follicle Stimulating Hormone - Baseline	9.83 (± 13.469)	9.23 (± 11.026)		
Follicle Stimulating Hormone - Week 12	-4.87 (± 14.894)	-0.67 (± 9.380)		
Follicle Stimulating Hormone - Week 24	-4.39 (± 19.943)	-0.32 (± 11.601)		

Notes:

[98] - LH and FSH Baseline: n=209

LH and FSH Wk 12: n=185

LH and FSH Wk 24: n=168

[99] - LH Baseline: n=209

LH Wk 12: n=182

LH and FSH Wk 24: n=165

FSH Baseline: n=207

FSH Wk 12: n=181

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Relugolix Plasma Concentrations At Week 4

End point title	Pre-dose Relugolix Plasma Concentrations At Week 4 ^[100]
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End point description:

Blood samples were collected from participants to determine plasma concentrations of relugolix using a validated bioanalytical methodology based on high performance liquid chromatography coupled to tandem mass spectrometry. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with relugolix plus delayed E2/NETA. Therefore, only relugolix plus E2/NETA and relugolix plus delayed E2/NETA arms are presented.

End point type	Secondary
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End point timeframe:

Week 4

Notes:

[100] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	211		
Units: ng/mL				
arithmetic mean (standard deviation)	2.09 (± 2.494)	2.94 (± 4.679)		

Statistical analyses

No statistical analyses for this end point

Secondary: Endometrial Biopsy At Week 24

End point title	Endometrial Biopsy At Week 24 ^[101]
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End point description:

Primary diagnosis of endometrial biopsy assessment by pathologist. Endometrial biopsy is not required at the early termination visit if the last dose of the study drug taken was during week 6 or earlier. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with relugolix plus delayed E2/NETA. Therefore, only relugolix plus E2/NETA and relugolix plus delayed E2/NETA arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1 and Week 24

Notes:

[101] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Relugolix Plus Delayed E2/NETA (Group B) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	211		
Units: participants				
Normal-proliferative	18	36		
Normal-secretory/Menstrual/Mixed	13	15		
Normal-atrophic or Indeterminate/Inactive	83	76		
Hyperplasia	0	0		
Carcinoma	0	0		
Inadequate	46	39		
Additional diagnosis (other reported findings)	12	15		
Missing	33	33		
Biopsy not required	14	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Serum Concentrations Of Estradiol

End point title	Change From Baseline In Serum Concentrations Of
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End point description:

Blood samples were collected from participants to determine serum concentrations of estradiol using a validated method based on immuno-enzymatic assay. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[102] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[103]	212 ^[104]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline	113.48 (± 83.527)	114.29 (± 85.254)		
Week 12	-58.83 (± 97.954)	2.94 (± 107.122)		
Week 24	-53.29 (± 94.375)	-4.91 (± 103.567)		

Notes:

[103] - Baseline: n=209

Wk 12: n=185

Wk 24: n=168

[104] - Baseline: n=207

Wk 12: n=179

Wk 24: n=164

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Serum Concentrations Of Progesterone

End point title	Change From Baseline In Serum Concentrations Of Progesterone ^[105]
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End point description:

Blood samples were collected from participants to determine serum concentrations of progesterone using a validated method based on immuno-enzymatic assay. As per the objective of the study, the pre-specified secondary efficacy analyses compared relugolix plus E2/NETA with placebo. Therefore, only relugolix plus E2/NETA and placebo arms are presented.

End point type	Secondary
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End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[105] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only reporting groups in which participants randomized to Relugolix Plus E2/NETA (Group A) and Placebo (Group C) were analyzed in this end point.

End point values	Relugolix Plus E2/NETA (Group A)	Placebo (Group C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212 ^[106]	212 ^[107]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	3.81 (± 5.219)	4.20 (± 5.856)		
Week 12	-2.83 (± 5.467)	0.30 (± 7.980)		
Week 24	-2.86 (± 5.576)	0.26 (± 7.842)		

Notes:

[106] - Baseline: n=209

Week 12: n=185

Week 24: n=168

[107] - Baseline: n=209

Week 12: n=182

Week 24: n=165

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline Day 1 up to Week 24

Adverse event reporting additional description:

All randomized participants who received any amount of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

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

Relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 24 weeks.

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

Relugolix monotherapy 40 mg for 12 weeks, followed by relugolix 40 mg co-administered with E2/NETA (1 mg/0.5 mg) for 12 weeks.

Reporting group title	Placebo (Group C)
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Reporting group description:

Relugolix placebo co-administered with E2/NETA placebo for 24 weeks.

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	3 / 212 (1.42%)	3 / 211 (1.42%)	5 / 212 (2.36%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	0 / 212 (0.00%)	0 / 211 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 212 (0.00%)	0 / 211 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			

subjects affected / exposed	1 / 212 (0.47%)	0 / 211 (0.00%)	0 / 212 (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
Neck injury			
subjects affected / exposed	0 / 212 (0.00%)	0 / 211 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 212 (0.00%)	1 / 211 (0.47%)	0 / 212 (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
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 212 (0.00%)	0 / 211 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	0 / 212 (0.00%)	0 / 211 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 211 (0.00%)	0 / 212 (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
Ovarian cyst			
subjects affected / exposed	1 / 212 (0.47%)	0 / 211 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	1 / 212 (0.47%)	0 / 211 (0.00%)	0 / 212 (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

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 212 (0.00%)	1 / 211 (0.47%)	0 / 212 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 212 (0.00%)	1 / 211 (0.47%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 212 (0.47%)	0 / 211 (0.00%)	0 / 212 (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

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	111 / 212 (52.36%)	163 / 211 (77.25%)	118 / 212 (55.66%)
Investigations			
Vitamin D decreased			
subjects affected / exposed	4 / 212 (1.89%)	8 / 211 (3.79%)	15 / 212 (7.08%)
occurrences (all)	4	8	15
Vascular disorders			
Hot flush			
subjects affected / exposed	22 / 212 (10.38%)	71 / 211 (33.65%)	21 / 212 (9.91%)
occurrences (all)	22	71	21
Nervous system disorders			
Headache			
subjects affected / exposed	57 / 212 (26.89%)	67 / 211 (31.75%)	46 / 212 (21.70%)
occurrences (all)	57	67	46
Gastrointestinal disorders			
Nausea			

subjects affected / exposed occurrences (all)	13 / 212 (6.13%) 13	9 / 211 (4.27%) 9	11 / 212 (5.19%) 11
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	2 / 212 (0.94%) 2	1 / 211 (0.47%) 1	13 / 212 (6.13%) 13
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 212 (6.13%) 13	10 / 211 (4.74%) 10	12 / 212 (5.66%) 12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2018	- Corrected list of locations. - Included additional anchors for the co-primary endpoints. - Added endpoints corresponding to the additional anchors for the co-primary endpoints. - Supported the key secondary objective related to function. - Allowed more time for Screening procedures and accommodated participant scheduling needs. - Allowed for logistics related to Run-In procedures and allowed additional time, if needed, for requisite number of dysmenorrhea scores during Run-In. - Allowed demonstration of regular cycles during Run-In in order to reduce the time to randomized treatment for participants who completed hormonal washout. - Clarified the intent of Inclusion Criterion #5. - Allowed consecutive dysmenorrhea scores from an extended Run-In Period to fulfill the minimum requirements for eligibility determination. - Made duration of required contraception consistent with Section 4.7 of the protocol. - Clarified the intent of Exclusion Criterion #2 to exclude participants with multiple procedures that may cause adhesions. - Simplified wording for Exclusion Criterion #6 to improve clarity. - Allowed longer screening window since it permits more testing to be done earlier. - Removed the need to perform a repeat DXA when one was recently performed. - Clarified tests to obtain for pharmacokinetics vs. pharmacodynamics blood drawing. - Removed parathyroid hormone testing because participants with abnormal calcium and phosphorus were excluded. - Facilitated compliance with procedures previously described in other documents. - Added discontinuation criterion to align with other sections of the protocol. - Ensured most current storage information is used. - Provided further procedural information and allowed short-term non-study specified analgesics for intercurrent events, if needed. - Clarified visits at which unused drug kits should be returned to sites

12 March 2018	- Provided guidance for situations where P-gp inducers or inhibitors are needed while the participant is being treated with study drug. - Accommodated drugs requiring longer washout and ensured that participants' pain was being monitored and managed during washout. - Acknowledged that procedural requirements and other scheduling constraints do not always allow for Baseline Day 1 to occur during Days 1-14 of menstrual cycle. - Standardized duration (10 weeks of Run-In Day 1) as Screening Period duration will now be more variable with the longer window permitted. - Added consistency in which paper and electronic tablet questionnaires should be completed during each visit. - Acknowledged limited value of baseline testing for study objectives. - Updated guidance on ingestion of tea or coffee during fasting. - Clarified procedure to be followed for participants who terminated early but did not undergo an ET visit. - Simplified criteria for determining when follow-up visual acuity testing is required. - Clarified requirements for endometrial biopsies procedure. - Clarified requirements for ECG procedure given that central ECG reading is not available on the same day. - Reflected a change in the safety vendor. - Clarified that scores collected through the first dose of randomized study drug will be used for the baseline period. - The term "ITT" was updated to "modified ITT" to better reflect that the planned analysis was not changed. - Clarified that safety reporting and protocol modifications will be in accordance with US and non-US health authority requirements. - Provided greater specificity and further detail procedures for Tier 1 and Tier 2 study-specific analgesics.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported