



Clinical trial results:

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

Summary

EudraCT number	2017-001632-19
Trial protocol	SE CZ PL GB IT RO
Global end of trial date	31 May 2021

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-601-3102
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03204331
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	01 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2020
Global end of trial reached?	Yes
Global end of trial date	31 May 2021
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 (E2) and norethindrone acetate (NETA) compared with placebo on dysmenorrhea;
- 2.To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose E2 and NETA compared with placebo on non-menstrual pelvic pain (NMPP).

Protection of trial subjects:

This study was conducted in accordance with International Council for 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	21 September 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: 206
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Brazil: 55
Country: Number of subjects enrolled	Chile: 9
Country: Number of subjects enrolled	Georgia: 12
Country: Number of subjects enrolled	New Zealand: 17
Country: Number of subjects enrolled	Romania: 113
Country: Number of subjects enrolled	United States: 155
Worldwide total number of subjects	623
EEA total number of subjects	357

Notes:

Subjects enrolled per age group

In utero	0
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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)	623
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Only the participants 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 questions were enrolled into the run-in period.

Pre-assignment

Screening details:

One participant in the placebo group was randomized in error and did not receive study drug.

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

Relugolix 40-mg tablet administered orally once daily.

Investigational medicinal product name	Estradiol/Norethindrone acetate
Investigational medicinal product code	
Other name	E2/NETA
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

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

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

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

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

Dosage and administration details:

Relugolix 40-mg tablet administered orally once daily.

Investigational medicinal product name	Estradiol/Norethindrone acetate
Investigational medicinal product code	
Other name	E2/NETA
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

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

Arm title	Placebo (Group C)
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Arm description:

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

Arm type	Placebo
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, and color.

Investigational medicinal product name	Estradiol/Norethindrone acetate 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, and color.

Number of subjects in period 1	Relugolix Plus E2/NETA (Group A)	Relugolix Plus Delayed E2/NETA (Group B)	Placebo (Group C)
Started	208	207	208
Received At Least 1 Dose of Study Drug	208	207	207
Completed	174	165	168
Not completed	34	42	40
Participants who did not receive any study drug	-	-	1
Adverse Event	11	15	8
Pregnancy	3	-	5
Withdrawal by Subject	12	16	13
Unspecified	1	5	1
Lost to follow-up	2	3	3
Lack of efficacy	4	3	9
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Relugolix Plus E2/NETA (Group A)
Reporting group description: Relugolix 40 mg co-administered with E2 (1 mg) and NETA (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 co-administered with E2 (1 mg) and NETA (0.5 mg) for 12 weeks.	
Reporting group title	Placebo (Group C)
Reporting group description: Relugolix placebo co-administered with E2 and 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	208	207	208
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)	208	207	208
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	208	207	208
Male	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	0	0	0
Other	0	0	0
Multiple	0	0	0
Not Reported	208	207	208
Ethnicity Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Not Reported	208	207	208

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 - Lumbar L1-L4 Units: g/cm ² arithmetic mean standard deviation	±	±	±
Bone Mineral Density - Total Hip Units: g/cm ² arithmetic mean standard deviation	±	±	±
Bone Mineral Density - Femoral Neck Units: g/cm ² arithmetic mean standard deviation	±	±	±

Reporting group values	Total		
Number of subjects	623		
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)	623		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	623		
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	623		
Ethnicity			
Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	0		
Not Reported	623		
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 - Lumbar L1-L4			
Units: g/cm ²			
arithmetic mean			
standard deviation	-		
Bone Mineral Density - Total Hip			
Units: g/cm ²			
arithmetic mean			
standard deviation	-		
Bone Mineral Density - Femoral Neck			
Units: g/cm ²			
arithmetic mean			
standard deviation	-		

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:	
All randomized participants who received relugolix 40 mg co-administered with estradiol (E2, 1 mg) and norethindrone acetate (NETA, 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:	
All randomized participants who received relugolix monotherapy 40 mg for 12 weeks, followed by relugolix co-administered with E2 (1 mg) and NETA (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	206	206	204
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	206	206	204
Race Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Other Multiple Not Reported	1 0 14 0 186 3 2 0	0 0 10 2 188 2 4 0	1 0 12 1 183 5 2 0
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not Reported	30 175 1	36 170 0	36 167 1
Time Since Surgical Diagnosis Of Endometriosis Units: years			
arithmetic mean standard deviation	4.1 ± 3.46	4.2 ± 3.52	3.8 ± 3.02
Dysmenorrhea Numerical Rating Score (NRS) Score at Baseline Units: score on a scale			
arithmetic mean standard deviation	7.1 ± 1.57	6.9 ± 1.51	7.0 ± 1.57
Nonmenstrual Pelvic Pain (NMPP) NRS score at Baseline Units: score on a scale			
arithmetic mean	5.8	5.5	5.5

standard deviation	± 1.94	± 1.93	± 1.94
Bone Mineral Density - Lumbar L1-L4 Units: g/cm ² arithmetic mean standard deviation	1.158 ± 0.1584	1.154 ± 0.1554	1.167 ± 0.1508
Bone Mineral Density - Total Hip Units: g/cm ² arithmetic mean standard deviation	0.989 ± 0.1401	0.980 ± 0.1315	0.988 ± 0.1285
Bone Mineral Density - Femoral Neck Units: g/cm ² arithmetic mean standard deviation	0.944 ± 0.1572	0.936 ± 0.1566	0.951 ± 0.1612

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 (1 mg) and NETA (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 co-administered with E2 (1 mg) and NETA (0.5 mg) for 12 weeks.	
Reporting group title	Placebo (Group C)
Reporting group description: Relugolix placebo co-administered with E2 and 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: All randomized participants who received relugolix 40 mg co-administered with estradiol (E2, 1 mg) and norethindrone acetate (NETA, 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: All randomized participants who received relugolix monotherapy 40 mg for 12 weeks, followed by relugolix co-administered with E2 (1 mg) and NETA (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: All participants who received relugolix placebo co-administered with E2 and 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 a Numerical Rating Scale (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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating 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: 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 were 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	206	204		
Units: percentage of participants				
number (confidence interval 95%)	75.2 (68.77 to 80.98)	30.4 (24.16 to 37.20)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	44.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.21
upper limit	53.49

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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating 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:	
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 were 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	206	204		
Units: percentage of participants				
number (confidence interval 95%)	66.0 (59.11 to 72.46)	42.6 (35.77 to 49.74)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[4]
Method	Regression, Logistic
Parameter estimate	Treatment difference
Point estimate	23.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	14
upper limit	32.75

Notes:

[4] - P-value 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).

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. The EHP-30 questionnaire was completed on an electronic tablet (eTablet) device. Participants 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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-32.2 (± 1.68)	-19.9 (± 1.69)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.7
upper limit	-7.9
Variability estimate	Standard error of the mean
Dispersion value	2.25

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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS 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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-5.1 (\pm 0.19)	-2.0 (\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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[8]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-2.7
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]
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End point description:

Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-2.7 (\pm 0.17)	-2.0 (\pm 0.17)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 ^[10]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[10] - 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 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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS 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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-2.9 (± 0.16)	-2.0 (± 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[12]
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	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.22

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: Change From Baseline In Dyspareunia NRS Score At Week 24

End point title	Change From Baseline In Dyspareunia NRS Score 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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-2.4 (± 0.19)	-1.9 (± 0.19)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0371 ^[14]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[14] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 ^[15]
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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:

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 were 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	206	204		
Units: percentage of participants				
number (confidence interval 95%)	82.0 (76.1 to 87.0)	66.2 (59.2 to 72.6)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	15.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.5
upper limit	24.2

Notes:

[16] - 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 Analgesic Use For Endometriosis-Associated Pain Based On Mean Pill Count At Week 24

End point title	Change From Baseline In Analgesic Use For Endometriosis-Associated Pain Based On Mean Pill Count At Week 24 ^[17]
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End point description:

Assessed based on usage of protocol-specified analgesic for endometriosis-associated pain recorded daily in an e-Diary. 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:

[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 were 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	206	204		
Units: pill count				
least squares mean (standard error)	-0.5 (± 0.06)	-0.4 (± 0.06)		

Statistical analyses

Statistical analysis title	Treatment difference in Analgesic Use
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1141 ^[18]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[18] - Nominal p-value. Treatment, baseline value, visit, geographic 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 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. The EHP-30 questionnaire was completed on an eTablet device. Participants 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:

Baseline Day 1 up to 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 were 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	206 ^[20]	204 ^[21]		
Units: percentage of participants				
number (confidence interval 95%)				
Week 12	63.8 (56.41 to 70.71)	37.4 (30.48 to 44.79)		
Week 24	72.9 (65.61 to 79.46)	52.5 (44.49 to 60.36)		

Notes:

[20] - Wk 12: n=185

Wk 24: n=170

[21] - Wk 12: n=187

Wk 24: n=162

Statistical analyses

Statistical analysis title	Treatment difference in EHP-30 Pain Domain (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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	26.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.55
upper limit	36.15

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)
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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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 ^[23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	20.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	10.29
upper limit	30.66

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 By Month

End point title	Percentage Of Participants Classified As Dysmenorrhea Responder 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 were 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	206	204		
Units: percentage of participants				
number (confidence interval 95%)				
Week 4	19.4 (14.25 to 25.49)	13.2 (8.91 to 18.6)		
Week 8	57.8 (50.71 to 64.60)	22.1 (16.57 to 28.38)		
Week 12	64.6 (57.62 to 71.08)	24.5 (18.77 to 31.00)		
Week 16	72.3 (65.69 to 78.32)	28.9 (22.80 to 35.66)		
Week 20	68.0 (61.12 to 74.28)	30.9 (24.62 to 37.71)		
Week 24	75.2 (68.77 to 80.98)	30.4 (24.16 to 37.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Classified As NMPP Responder By Month

End point title	Percentage Of Participants Classified As NMPP Responder 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 were 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	206	204		
Units: percentage of participants				
number (confidence interval 95%)				
Week 4	22.3 (16.84 to 28.64)	16.2 (11.40 to 21.96)		
Week 8	35.0 (28.46 to 41.89)	28.9 (22.80 to 35.66)		
Week 12	52.4 (45.37 to 59.41)	32.8 (26.45 to 39.75)		
Week 16	55.8 (48.76 to 62.72)	40.7 (33.88 to 47.77)		
Week 20	58.7 (51.69 to 65.53)	38.2 (31.54 to 45.28)		
Week 24	66.0 (59.11 to 72.46)	42.6 (35.77 to 49.74)		

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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS 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 were 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	206 ^[27]	204 ^[28]		
Units: score on a scale				
least squares mean (standard error)				
Baseline	7.2 (± 0.11)	7.2 (± 0.12)		
Week 4	-1.2 (± 0.17)	-0.8 (± 0.17)		
Week 8	-4.1 (± 0.20)	-1.3 (± 0.20)		
Week 12	-4.6 (± 0.19)	-1.6 (± 0.19)		
Week 16	-4.9 (± 0.19)	-1.9 (± 0.19)		
Week 20	-4.9 (± 0.19)	-2.0 (± 0.19)		
Week 24	-5.1 (± 0.19)	-2.0 (± 0.19)		

Notes:

[27] - Wk 4: n=200

Wk 8: n=190

Wk 12: n=186

Wk 16: n=182

Wk 20: n=178

Wk 24: n=205

[28] - Wk 4: n=200

Wk 8: n=192

Wk 12: n=188

Wk 16: n=178

Wk 20: n=176

Wk 24: n=203

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[29]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-2.5
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[29] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<5 years versus ≥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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[30]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-2.7
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 initial surgical diagnosis of endometriosis (<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]
End point description: Assessed using an NRS score (11-point scale) for pain recorded daily in an e-Diary. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS 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:

[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 were 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	206 ^[32]	204 ^[33]		
Units: score on a scale				
least squares mean (standard error)				
Baseline	5.9 (± 0.14)	5.7 (± 0.15)		
Week 4	-1.1 (± 0.13)	-0.8 (± 0.14)		

Week 8	-1.5 (\pm 0.15)	-1.3 (\pm 0.15)		
Week 12	-2.1 (\pm 0.16)	-1.6 (\pm 0.16)		
Week 16	-2.5 (\pm 0.16)	-1.9 (\pm 0.16)		
Week 20	-2.6 (\pm 0.17)	-1.9 (\pm 0.17)		
Week 24	-2.7 (\pm 0.17)	-2.0 (\pm 0.17)		

Notes:

[32] - Wk 4: n=200

Wk 8: n=190

Wk 12: n=186

Wk 16: n=182

Wk 20: n=178

Wk 24: n=205

[33] - Wk 4: n=200

Wk 8: n=192

Wk 12: n=188

Wk 16: n=178

Wk 20: n=176

Wk 24: n=203

Statistical analyses

Statistical analysis title	Treatment difference in NMPP 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0226 ^[34]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

[34] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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)
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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 ^[35]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[35] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS 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 were 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	206 ^[37]	204 ^[38]		
Units: score on a scale				
least squares mean (standard error)				
Baseline	6.2 (± 0.13)	6.0 (± 0.13)		
Week 4	-1.0 (± 0.13)	-0.8 (± 0.13)		
Week 8	-1.7 (± 0.15)	-1.3 (± 0.15)		
Week 12	-2.2 (± 0.15)	-1.6 (± 0.16)		
Week 16	-2.6 (± 0.16)	-1.8 (± 0.16)		
Week 20	-2.7 (± 0.16)	-1.9 (± 0.16)		
Week 24	-2.9 (± 0.16)	-2.0 (± 0.17)		

Notes:

[37] - Wk 4: n=200

Wk 8: n=190

Wk 12: n=186

Wk 16: n=182

Wk 20: n=178

Wk 24: n=205

[38] - Wk 4: n=200

Wk 8: n=192

Wk 12: n=188

Wk 16: n=178

Wk 20: n=176

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033 ^[39]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

[39] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[40]
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	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[40] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The LS 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:

[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 were 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	206 ^[42]	204 ^[43]		
Units: score on a scale				
least squares mean (standard error)				
Baseline	5.7 (± 0.18)	5.5 (± 0.19)		
Week 4	-0.8 (± 0.17)	-0.9 (± 0.18)		
Week 8	-1.2 (± 0.17)	-1.2 (± 0.18)		
Week 12	-1.8 (± 0.18)	-1.5 (± 0.19)		
Week 16	-2.2 (± 0.18)	-1.8 (± 0.19)		
Week 20	-2.3 (± 0.18)	-1.7 (± 0.19)		
Week 24	-2.4 (± 0.19)	-1.9 (± 0.19)		

Notes:

[42] - Baseline: n=173

Wk 4: n=147

Wk 8: n=143

Wk 12: n=143

Wk 16: n=140

Wk 20: n=135

Wk 24: n=149

[43] - Baseline: n=162

Wk 4: n=139

Wk 8: n=139

Wk 12: n=134

Wk 16: n=122

Wk 20: n=125

Wk 24: n=130

Statistical analyses

Statistical analysis title	Difference in Dyspareunia 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2036 ^[44]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[44] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0371 ^[45]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[45] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 were 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	206	204		
Units: pill count				
arithmetic mean (standard deviation)	-14.7 (± 30.31)	-13.4 (± 31.75)		

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 Day 1 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 were 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	206	204		
Units: pill count				
arithmetic mean (standard deviation)	-4.0 (± 11.05)	-2.4 (± 9.42)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline In Dysmenorrhea Functional Impairment
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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 as related to functional impairment daily in an e-Diary using the following response options: Severe (in bed all day, incapacitation), Moderate (in bed part of the day, some loss of work efficiency), Mild (some loss of work efficiency), No pain (no pain associated with menstruation during past 24 hours), or did not menstruate during the past 24 hours. Participants gave a possible score of 0 (no pain) to 4 (severe). 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-1.2 (± 0.05)	-0.3 (± 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[49]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.7
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 initial surgical diagnosis of endometriosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

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

End point title	Change From Baseline In NMPP Functional Impairment Score 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). 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-0.7 (± 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0111 ^[51]
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	0.07

Notes:

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

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

End point title	Change From Baseline In Dyspareunia Functional Impairment
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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 daily using the following response options: Severe (avoids intercourse because of pain), Moderate (intercourse painful to the point of causing interruption), Mild (tolerated pain), No pain (no pain during intercourse), or No intercourse (no intercourse for other reasons). Participants gave a possible score of 0 (no pain) to 3 (severe). The LS 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-0.6 (± 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2026 ^[53]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1
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 initial surgical diagnosis of endometriosis (<5 years versus ≥5 years), and treatment-by-visit interaction included as fixed effects.

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

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

The PGA score 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), or 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-2.4 (± 0.09)	-0.8 (± 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[55]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-1.3
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 initial surgical diagnosis of endometriosis (<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 Score For Dysmenorrhea At Week 24

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Dysmenorrhea At
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End point description:

The PGA score 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), or 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 were 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	206 ^[57]	204 ^[58]		
Units: percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	92.4	64.9		
No Change (0)	6.3	24.6		
Deterioration (+1 to +4)	1.4	10.4		

Notes:

[57] - All categories: n=144

[58] - All categories: n=134

Statistical analyses

No statistical analyses for this end point

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

End point title

Change From Baseline In PGA Score For NMPP Symptom Severity At Week 24^[59]

End point description:

The PGA score 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), or 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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-1.4 (\pm 0.07)	1.0 (\pm 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 ^[60]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.2
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 initial surgical diagnosis of endometriosis (<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 Score For NMPP At Week 24

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For NMPP At Week 24 ^[61]
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End point description:

The PGA score 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), or 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:

[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 were 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	206 ^[62]	204 ^[63]		
Units: percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	86.2	72.4		
No Change (0)	11.7	23.1		
Deterioration (+1 to +4)	2.1	4.5		

Notes:

[62] - All categories: n=145

[63] - All categories: n=134

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline In PGA Score For Pain Severity At Week 24 ^[64]
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End point description:

The PGA score 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), or 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-1.1 (± 0.07)	-0.8 (± 0.07)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 ^[65]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[65] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 Score For Pain Severity At Week 24

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Pain Severity At Week 24 ^[66]
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End point description:

The PGA score 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), or 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:

[66] - 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 were 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	206 ^[67]	204 ^[68]		
Units: percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	77.4	60.1		
No Change (0)	17.3	32.3		
Deterioration (+1 to +4)	5.4	7.6		

Notes:

[67] - All categories: n=168

[68] - All categories: n=158

Statistical analyses

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

End point title	Change From Baseline In PGA Score For Function At Week
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End point description:

The PGA score 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), or 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
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End point timeframe:

Baseline Day 1 up to Week 24

Notes:

[69] - 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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-1.5 (\pm 0.07)	-0.8 (\pm 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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[70]
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	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[70] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 Score For Function At Week 24

End point title	Percentage Of Participants With Improvement, No Change, Or Worsening From Baseline In PGA Score For Function At Week 24 ^[71]
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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), or 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:

[71] - 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 were 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	206 ^[72]	204 ^[73]		
Units: percentage of participants				
number (not applicable)				
Improvement (-1 to -4)	86.5	65.2		
No Change (0)	12.4	26.6		
Deterioration (+1 to +4)	1.2	8.2		

Notes:

[72] - All categories: n=170

[73] - All categories: n=158

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 ^[74]
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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:

[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 were 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	206	204		
Units: percentage of participants				
number (confidence interval 95%)	78.5 (71.59 to 84.38)	42.6 (34.87 to 50.59)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [75]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	35.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.11
upper limit	45.68

Notes:

[75] - 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 ^[76]
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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:

[76] - 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 were 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	206	204		
Units: percentage of participants				
number (confidence interval 95%)	76.2 (69.08 to 82.32)	54.3 (46.32 to 62.16)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[77]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	21.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.87
upper limit	31.81

Notes:

[77] - 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 ^[78]
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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
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End point timeframe:

Week 12 and Week 24

Notes:

[78] - 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 were 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	206	204		
Units: percentage of participants				
number (confidence interval 95%)	58.3 (50.31 to 65.94)	33.8 (26.29 to 41.91)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[79]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.82
upper limit	35.19

Notes:

[79] - 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 Score At Week 24

End point title	Change From Baseline In The Non-Pain Of The EHP-30 Domains Score At Week 24 ^[80]
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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
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End point timeframe:

Baseline Day 1, Week 12, and Week 24

Notes:

[80] - 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 were 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	206 ^[81]	204 ^[82]		
Units: score on a scale				
least squares mean (standard error)				
Control and Powerlessness	-34.5 (± 1.93)	-21.8 (± 1.94)		
Emotional Well-Being	-21.9 (± 1.76)	-13.2 (± 1.77)		
Social Support	-21.8 (± 1.95)	-13.6 (± 1.96)		
Self-Image	-24.0 (± 2.01)	-13.2 (± 2.02)		

Notes:

[81] - All categories: n=170

[82] - All categories: n=162

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[83]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-12.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.7
upper limit	-7.6
Variability estimate	Standard error of the mean
Dispersion value	2.59

Notes:

[83] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 the Emotional Well-Being domain.	
Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 ^[84]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-8.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	-4
Variability estimate	Standard error of the mean
Dispersion value	2.37

Notes:

[84] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 the Social Support domain.

Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [85]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-8.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	-3.1
Variability estimate	Standard error of the mean
Dispersion value	2.61

Notes:

[85] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 the Self-Image domain.

Comparison groups	Relugolix Plus E2/NETA (Group A) v Placebo (Group C)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [86]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-10.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.1
upper limit	-5.6

Variability estimate	Standard error of the mean
Dispersion value	2.69

Notes:

[86] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 ^[87]
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End point description:

Assessed using the total score (all 5 domains [Pain, Control and Powerlessness, Emotional Well-Being, Social Support, and Self-Image] were included) of the EHP-30 questionnaire. The total 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-28.5 (± 1.62)	-17.5 (± 1.63)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[88]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	-6.8
Variability estimate	Standard error of the mean
Dispersion value	2.18

Notes:

[88] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 ^[89]
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End point description:

The EHP Work domain is a 5-item questionnaire that assessed the impact of pain on ability to 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:

[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 were 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	206	204		
Units: score on a scale				
least squares mean (standard error)	-32.7 (± 1.84)	-18.2 (± 1.85)		

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	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[90]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-14.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.3
upper limit	-9.8
Variability estimate	Standard error of the mean
Dispersion value	2.42

Notes:

[90] - Nominal p-value. Treatment, baseline value, visit, region (North America versus Rest of World), time since initial surgical diagnosis of endometriosis (<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 ^[91]
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End point description:

The EQ-5D-5L is a 5-item questionnaire designed to assess quality of life. The 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 were each assessed on a 5-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:

[91] - 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 were 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	206 ^[92]	204 ^[93]		
Units: participants				
Mobility - 4 Category deterioration	0	0		
Mobility - 3 Category deterioration	0	0		
Mobility - 2 Category deterioration	1	3		
Mobility - 1 Category deterioration	5	11		
Mobility - No Change	86	88		
Mobility - 1 Category improvement	47	36		
Mobility - 2 Category improvement	31	22		
Mobility - 3 Category improvement	3	2		
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	2		
Self-care - 1 Category deterioration	3	2		
Self-care - No change	122	125		
Self-care - 1 Category improvement	32	24		
Self-care - 2 Category improvement	15	7		
Self-care - 3 Category improvement	1	2		
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	2	2		
Usual activities - 1 Category deterioration	11	15		
Usual activities - No Change	58	66		
Usual activities - 1 Category improvement	56	52		
Usual activities - 2 Category improvement	35	22		
Usual activities - 3 Category improvement	10	4		
Usual activities - 4 Category improvement	1	1		
Pain/discomfort - 4 Category deterioration	0	0		
Pain/discomfort - 3 Category deterioration	1	0		
Pain/discomfort - 2 Category deterioration	2	4		
Pain/discomfort - 1 Category deterioration	9	17		
Pain/discomfort - No change	27	50		
Pain/discomfort - 1 Category improvement	66	48		
Pain/discomfort - 2 Category improvement	55	39		
Pain/discomfort - 3 Category improvement	12	4		
Pain/discomfort - 4 Category improvement	1	0		
Anxiety/depression - 4 Category deterioration	0	0		
Anxiety/depression - 3 Category deterioration	1	1		
Anxiety/depression - 2 Category deterioration	5	6		
Anxiety/depression - 1 Category deterioration	17	20		
Anxiety/depression - No Change	64	66		
Anxiety/depression - 1 Category improvement	41	37		
Anxiety/depression - 2 Category improvement	39	29		
Anxiety/depression - 3 Category improvement	4	3		
Anxiety/depression - 4 Category improvement	2	0		

Notes:

[92] - All categories: n=173

[93] - All categories: n=162

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 ^[94]
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End point description:

The EQ-5D-5L is a 5-item questionnaire designed to assess quality of life. The 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 up to Week 24

Notes:

[94] - 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 were 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	206	204		
Units: score on a scale				
arithmetic mean (standard deviation)	20.2 (± 23.68)	12.7 (± 24.75)		

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 ^[95]
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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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating 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:

Week 24

Notes:

[95] - 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 were 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	206			
Units: percentage of participants				
number (confidence interval 95%)	72.8 (66.20 to 78.77)			

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 ^[96]
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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. Participants rated their pain on a scale from 0 to 10, with 0 indicating no pain and 10 indicating 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:

Week 24

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 were 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	206			
Units: percentage of participants				
number (confidence interval 95%)	52.9 (45.85 to 59.89)			

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 ^[97]
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End point description:

Assessed using the pain domain of the EHP-30 questionnaire. The EHP-30 questionnaire was completed on an eTablet device. Participants answered the questions using the following options: never, rarely, sometimes, often, or always. The LS means at Week 24 was compared with other treatment 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:

[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 were 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	206			
Units: score on a scale				
least squares mean (standard error)	-30.8 (± 1.70)			

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 ^[98]
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End point description:

Assessed using the pain domain of the EHP-30 questionnaire. The EHP-30 questionnaire was completed on an eTablet device. Participants 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 up to Week 24

Notes:

[98] - 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 were 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	206 ^[99]			
Units: percentage of participants				
number (confidence interval 95%)				
Week 12	64.7 (57.30 to 71.56)			
Week 24	73.3 (65.90 to 79.91)			

Notes:

[99] - Wk 12: n=184

Wk 24: n=165

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage Change From Baseline In Bone Mineral Density At The Lumbar Spine (L1-L4) At Week 12 ^[100]
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End point description:

Assessed by dual-energy X-ray absorptiometry (DXA) scan at each designated time points. If participants experienced bone mineral density 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 the 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 and are presented in this outcome measure.

End point type	Secondary
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End point timeframe:

Baseline Day 1 and Week 12

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 were 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	206	206		
Units: g/cm ²				
least squares mean (standard error)	-0.47 (± 0.217)	-1.87 (± 0.224)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage Change From Baseline In Bone Mineral Density At Lumbar Spine (L1-L4), Femoral Neck, And Total Hip At Week 24 ^[101]
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End point description:

Bone mineral density was assessed by DXA scan at the lumbar spine, total hip, and femoral neck (same leg for each participant) at each designated time point. The LS means at Week 24 were compared between the 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 and are presented in this outcome measure.

End point type	Secondary
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End point timeframe:

Baseline Day 1, Week 12, 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 were 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	206 ^[102]	206 ^[103]		
Units: g/cm ²				
least squares mean (standard error)				
Lumbar Spine (L1-L4)	-0.78 (± 0.233)	-1.92 (± 0.239)		
Total Hip	-0.56 (± 0.196)	-0.89 (± 0.202)		
Femoral Neck	-0.92 (± 0.304)	-1.18 (± 0.314)		

Notes:

[102] - Lumbar Spine: n=168

Total Hip and Femoral Neck: n=169

[103] - All categories: n=163

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 ^[104]
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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 and are presented in this outcome measure.

End point type	Secondary
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End point timeframe:

Week 12

Notes:

[104] - 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 were 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	206	206		
Units: percentage of participants				
number (confidence interval 95%)	11.17 (7.21 to 16.28)	32.04 (25.72 to 38.88)		

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	412
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.54

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 ^[105]
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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:

[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 were 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	206 ^[106]	204 ^[107]		
Units: IU/L				
arithmetic mean (standard deviation)				
Luteinizing Hormone - Baseline	11.03 (± 14.096)	9.57 (± 13.349)		
Luteinizing Hormone - Week 12	-8.24 (± 13.795)	1.06 (± 19.654)		
Luteinizing Hormone - Week 24	-7.63 (± 13.484)	-0.92 (± 16.769)		
Follicle Stimulating Hormone - Baseline	11.73 (± 17.744)	9.16 (± 12.449)		
Follicle Stimulating Hormone - Week 12	-6.27 (± 16.573)	1.37 (± 14.163)		
Follicle Stimulating Hormone - Week 24	-7.06 (± 16.762)	-0.11 (± 11.421)		

Notes:

[106] - LH and FSH Baseline: n=199

LH and FSH Wk 12: n=175

LH and FSH Wk 24: n=161

[107] - LH and FSH Baseline: n=201

LH and FSH Wk 12: n=180

LH and FSH Wk 24: n=152

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:

[108] - 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 were 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	206	204		
Units: pg/mL				
arithmetic mean (standard deviation)				
Estradiol - Baseline	115.52 (± 74.839)	117.02 (± 80.321)		
Estradiol - Week 12	-64.98 (± 100.905)	1.19 (± 121.432)		
Estradiol - Week 24	-64.18 (± 95.626)	-1.77 (± 101.259)		

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 ^[109]
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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:

[109] - 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 were 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	206	204		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	3.81 (± 5.306)	3.90 (± 5.441)		
Week 12	-3.05 (± 5.860)	-0.56 (± 6.209)		
Week 24	-3.23 (± 5.064)	0.46 (± 6.831)		

Statistical analyses

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 (1 mg) and NETA (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 co-administered with E2 (1 mg) and NETA (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 and 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	9 / 206 (4.37%)	6 / 206 (2.91%)	4 / 204 (1.96%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer stage IIIA			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 204 (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
Ulnar nerve injury			

subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 204 (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
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 204 (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
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 206 (0.97%)	0 / 206 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 204 (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
Pelvic pain			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (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
Cholelithiasis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	2 / 206 (0.97%)	2 / 206 (0.97%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Depression			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalized anxiety disorder			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 204 (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	166 / 206 (80.58%)	168 / 206 (81.55%)	140 / 204 (68.63%)
Investigations			
Bone density decreased			
subjects affected / exposed	11 / 206 (5.34%)	13 / 206 (6.31%)	5 / 204 (2.45%)
occurrences (all)	11	13	5
Vascular disorders			
Hot flush			
subjects affected / exposed	28 / 206 (13.59%)	72 / 206 (34.95%)	7 / 204 (3.43%)
occurrences (all)	28	72	7
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	81 / 206 (39.32%) 81	79 / 206 (38.35%) 79	64 / 204 (31.37%) 64
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	18 / 206 (8.74%)	7 / 206 (3.40%)	7 / 204 (3.43%)
occurrences (all)	18	7	7
Nausea			
subjects affected / exposed	12 / 206 (5.83%)	9 / 206 (4.37%)	6 / 204 (2.94%)
occurrences (all)	12	9	6
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	7 / 206 (3.40%)	7 / 206 (3.40%)	11 / 204 (5.39%)
occurrences (all)	7	7	11
Psychiatric disorders			
Libido decreased			
subjects affected / exposed	11 / 206 (5.34%)	8 / 206 (3.88%)	4 / 204 (1.96%)
occurrences (all)	11	8	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 206 (5.83%)	12 / 206 (5.83%)	7 / 204 (3.43%)
occurrences (all)	12	12	7
Arthralgia			
subjects affected / exposed	11 / 206 (5.34%)	10 / 206 (4.85%)	7 / 204 (3.43%)
occurrences (all)	11	10	7
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	29 / 206 (14.08%)	14 / 206 (6.80%)	17 / 204 (8.33%)
occurrences (all)	29	14	17
Urinary tract infection			
subjects affected / exposed	11 / 206 (5.34%)	10 / 206 (4.85%)	5 / 204 (2.45%)
occurrences (all)	11	10	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2018	<p>Amendment 1</p> <ul style="list-style-type: none">- Included additional anchors for the co-primary end points.- Added end points corresponding to the additional anchors for the co-primary end points.- Supported the key secondary objective related to function.- Allowed more time for Screening procedures to accommodate participant scheduling needs.- Allowed for logistics related to Run-In procedures and to allow additional time, if needed, for requisite number of dysmenorrhea scores during Run-In.- Allowed regular cycles to be demonstrated 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.- Made the duration of required contraception to be 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 the wording of Exclusion Criterion #6 to improve clarity.- Extended screening window for more testing to be done earlier.- Allowed participants with recent biopsies to avoid another procedure.- Removed the need to perform a repeat DXA when one was recently performed.- Clarified the tests to be obtained for pharmacodynamics blood drawing.- Removed parathyroid hormone testing since participants with abnormal calcium and phosphorus were excluded.- Facilitated compliance with procedures previously described in other documents only.- Added a discontinuation criterion to align with other sections of the protocol.- Ensured that 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	<p>Amendment 1</p> <ul style="list-style-type: none"> - Provided guidance for situations where P-glycoprotein inducers or inhibitors are needed while the participant is being treated with study drug. - Better accommodation of drugs requiring a 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 to 14 of menstrual cycle. - Standardized Run-In Day 1 duration as Screening Period duration was more variable with the permitted longer window. - Added consistency in which paper and eTablet questionnaires should be completed during each visit. - Aligned with the intent of testing participants with low visual acuity scores (<90) at baseline. - 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 early termination visit. - Simplified criteria for determining when follow-up visual acuity testing is required. - Clarified requirements for endometrial biopsies. - Clarified requirements for electrocardiogram (ECG) procedure given that central ECG reading is not available on the same day. - Reflected a change in the safety vendor. - Clarified scores collected through the first dose of randomized study drug to be used for the baseline period. - The term "ITT" was updated to "modified ITT" to better reflect that planned analysis was not changed. - Clarified that safety reporting will be in accordance with United States (US) and non-US health authority requirements. - Clarified that protocol modifications will be in accordance with US and non-US health authority requirements. - Provided greater specificity and to further detail prescribing procedures.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported