



Clinical trial results:

A Phase 2b Study to Evaluate the Safety and Efficacy of Elagolix in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Summary

EudraCT number	2013-000082-37
Trial protocol	GB
Global end of trial date	08 December 2015

Results information

Result version number	v1 (current)
This version publication date	24 December 2016
First version publication date	24 December 2016

Trial information

Trial identification

Sponsor protocol code	M12-813
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01817530
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbvie Deutschland GmbH & Co.KG
Sponsor organisation address	Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4XE
Public contact	Charlotte Owens, Abbvie Deutschland GmbH & Co.KG, charlotte.owens@Abbvie.com
Scientific contact	Charlotte Owens, Abbvie Deutschland GmbH & Co.KG, charlotte.owens@Abbvie.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	08 December 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy of elagolix (ABT-620) alone and in combination with two different strengths of add-back therapy (estradiol/norethindrone acetate tablets [E2/NETA]), versus placebo to reduce heavy menstrual bleeding (HMB) (which is defined as greater than 80 mL blood loss per menstrual cycle) associated with uterine fibroids, and to reduce fibroid volume and uterine volume in premenopausal women 18 to 51 years of age.

Protection of trial subjects:

Participant and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Chile: 23
Country: Number of subjects enrolled	Puerto Rico: 12
Country: Number of subjects enrolled	United States: 524
Worldwide total number of subjects	567
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	567
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 567 female subjects were enrolled into the study across 86 sites (5 sites in the UK, 4 in Chile, 2 in Canada, 4 in Puerto Rico, and 71 in the US). (Four subjects were randomized in error; they were not dosed and were excluded from all analyses including demographic summaries).

Pre-assignment

Screening details:

The study included a Screening Period of approximately 2.5 to 3.5 months prior to first dose. A Washout Period of up to 6 months prior to screening, if applicable, may have also been required.

Period 1

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

Blinding implementation details:

Each active elagolix dose was identical in appearance to its matched placebo; each active E2/NETA dose was identical in appearance to its matched placebo. The study site personnel and subject remained blinded to each subject's treatment throughout the course of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Placebo

Arm description:

Placebo for elagolix and placebo for E2/NETA twice daily (BID)

Arm type	Placebo
Investigational medicinal product name	Elagolix placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: A morning dose of 2 tablets and an evening dose of 2 tablets were taken each day approximately 12 hours apart.

Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: A morning dose of 1 capsule was taken each day.

Arm title	Cohort 1: Elagolix 300 mg BID
Arm description:	
Elagolix 300 mg BID alone	
Arm type	Experimental

Investigational medicinal product name	Elagolix
Investigational medicinal product code	ABT-620
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: A morning dose of 2 tablets and an evening dose of 2 tablets were taken each day approximately 12 hours apart.

Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: A morning dose of 1 capsule was taken each day.

Arm title	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD
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Arm description:

Elagolix 300 mg BID plus low-dose (LD) E2/NETA once daily (QD)

Arm type	Experimental
Investigational medicinal product name	Elagolix
Investigational medicinal product code	ABT-620
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: A morning dose of 2 tablets and an evening dose of 2 tablets were taken each day approximately 12 hours apart.

Investigational medicinal product name	0.5 mg estradiol / 0.1 mg norethindrone acetate
Investigational medicinal product code	
Other name	Activelle, Activella, LD E2/NETA
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: 1 capsule was taken each day.

Arm title	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD
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Arm description:

Elagolix 300 mg BID plus standard-dose (SD) E2/NETA QD

Arm type	Experimental
Investigational medicinal product name	Elagolix
Investigational medicinal product code	ABT-620
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: A morning dose of 2 tablets and an evening dose of 2 tablets were taken each day approximately 12 hours apart.

Investigational medicinal product name	1 mg estradiol / 0.5 mg norethindrone acetate
Investigational medicinal product code	
Other name	Activelle, Activella, SD E2/NETA

Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: A morning dose of 1 capsule was taken each day approximately 12 hours apart.

Arm title	Cohort 2: Placebo
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Arm description:

Placebo for elagolix and E2/NETA QD

Arm type	Placebo
Investigational medicinal product name	Elagolix placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: A morning dose of 4 tablets was taken each day.

Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: A morning dose of 1 capsule was taken each day.

Arm title	Cohort 2: Elagolix 600 mg QD
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Arm description:

Elagolix 600 mg QD alone

Arm type	Experimental
Investigational medicinal product name	Elagolix
Investigational medicinal product code	ABT-620
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: A morning dose of 4 tablets was taken each day.

Investigational medicinal product name	E2/NETA placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: A morning dose of 1 capsule was taken each day.

Arm title	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD
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Arm description:

Elagolix 600 mg QD plus LD E2/NETA QD

Arm type	Experimental
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Investigational medicinal product name	Elagolix
Investigational medicinal product code	ABT-620
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: A morning dose of 4 tablets was taken each day.

Investigational medicinal product name	0.5 mg estradiol / 0.1 mg norethindrone acetate
Investigational medicinal product code	
Other name	Activelle, Activella, LD E2/NETA
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: A morning dose of 1 capsule was taken each day.

Arm title	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD
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Arm description:

Elagolix 600 mg QD plus SD E2/NETA QD

Arm type	Experimental
Investigational medicinal product name	Elagolix
Investigational medicinal product code	ABT-620
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: A morning dose of 4 tablets was taken each day.

Investigational medicinal product name	1 mg estradiol / 0.5 mg norethindrone acetate
Investigational medicinal product code	
Other name	Activelle, Activella, SD E2/NETA
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: A morning dose of 1 capsule was taken each day.

Number of subjects in period 1	Cohort 1: Placebo	Cohort 1: Elagolix 300 mg BID	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD
Started	65	65	64
Completed	50	52	53
Not completed	15	13	11
Consent withdrawn by subject	3	4	7
Surgery or invasive intervention	1	-	-
Not specified	-	1	-
Pregnancy	-	-	-
Adverse event	6	3	2

Lost to follow-up	1	4	2
Subject noncompliant	3	1	-
Exclusionary medication received	-	-	-
Lack of efficacy	1	-	-

Number of subjects in period 1	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD	Cohort 2: Placebo	Cohort 2: Elagolix 600 mg QD
Started	65	78	77
Completed	52	67	58
Not completed	13	11	19
Consent withdrawn by subject	3	5	3
Surgery or invasive intervention	-	1	1
Not specified	-	1	-
Pregnancy	-	-	1
Adverse event	5	-	10
Lost to follow-up	1	3	2
Subject noncompliant	4	-	1
Exclusionary medication received	-	1	-
Lack of efficacy	-	-	1

Number of subjects in period 1	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD
Started	76	77
Completed	53	53
Not completed	23	24
Consent withdrawn by subject	3	10
Surgery or invasive intervention	1	-
Not specified	5	-
Pregnancy	-	-
Adverse event	5	8
Lost to follow-up	8	4
Subject noncompliant	1	1
Exclusionary medication received	-	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: Placebo
Reporting group description:	
Placebo for elagolix and placebo for E2/NETA twice daily (BID)	
Reporting group title	Cohort 1: Elagolix 300 mg BID
Reporting group description:	
Elagolix 300 mg BID alone	
Reporting group title	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD
Reporting group description:	
Elagolix 300 mg BID plus low-dose (LD) E2/NETA once daily (QD)	
Reporting group title	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD
Reporting group description:	
Elagolix 300 mg BID plus standard-dose (SD) E2/NETA QD	
Reporting group title	Cohort 2: Placebo
Reporting group description:	
Placebo for elagolix and E2/NETA QD	
Reporting group title	Cohort 2: Elagolix 600 mg QD
Reporting group description:	
Elagolix 600 mg QD alone	
Reporting group title	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD
Reporting group description:	
Elagolix 600 mg QD plus LD E2/NETA QD	
Reporting group title	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD
Reporting group description:	
Elagolix 600 mg QD plus SD E2/NETA QD	

Reporting group values	Cohort 1: Placebo	Cohort 1: Elagolix 300 mg BID	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD
Number of subjects	65	65	64
Age categorical			
Units: Subjects			
Adults (18-64 years)	65	65	64
Age continuous			
Units: years			
arithmetic mean	42.5	42	43
standard deviation	± 6.14	± 4.76	± 5.02
Gender categorical			
Units: Subjects			
Female	65	65	64
Male	0	0	0

Reporting group values	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD	Cohort 2: Placebo	Cohort 2: Elagolix 600 mg QD
Number of subjects	65	78	77

Age categorical			
Units: Subjects			
Adults (18-64 years)	65	78	77
Age continuous			
Units: years			
arithmetic mean	43.8	42.3	42.1
standard deviation	± 4.66	± 4.78	± 4.93
Gender categorical			
Units: Subjects			
Female	65	78	77
Male	0	0	0

Reporting group values	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD	Total
Number of subjects	76	77	567
Age categorical			
Units: Subjects			
Adults (18-64 years)	76	77	567
Age continuous			
Units: years			
arithmetic mean	41.1	42.2	-
standard deviation	± 5.74	± 5.4	
Gender categorical			
Units: Subjects			
Female	76	77	567
Male	0	0	0

End points

End points reporting groups

Reporting group title	Cohort 1: Placebo
Reporting group description: Placebo for elagolix and placebo for E2/NETA twice daily (BID)	
Reporting group title	Cohort 1: Elagolix 300 mg BID
Reporting group description: Elagolix 300 mg BID alone	
Reporting group title	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD
Reporting group description: Elagolix 300 mg BID plus low-dose (LD) E2/NETA once daily (QD)	
Reporting group title	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD
Reporting group description: Elagolix 300 mg BID plus standard-dose (SD) E2/NETA QD	
Reporting group title	Cohort 2: Placebo
Reporting group description: Placebo for elagolix and E2/NETA QD	
Reporting group title	Cohort 2: Elagolix 600 mg QD
Reporting group description: Elagolix 600 mg QD alone	
Reporting group title	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD
Reporting group description: Elagolix 600 mg QD plus LD E2/NETA QD	
Reporting group title	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD
Reporting group description: Elagolix 600 mg QD plus SD E2/NETA QD	
Subject analysis set title	Cohort 1: Placebo, mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomized subjects who received at least 1 dose of randomized, double-blind study drug (placebo) in this study.	
Subject analysis set title	Cohort 1: Elagolix 300 mg BID, mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomized subjects who received at least 1 dose of randomized, double-blind study drug (elagolix 300 mg BID) in this study.	
Subject analysis set title	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomized subjects who received at least 1 dose of randomized, double-blind study drug (elagolix 300 mg BID plus LD E2/NETA QD) in this study.	
Subject analysis set title	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomized subjects who received at least 1 dose of randomized, double-blind study drug (elagolix 300 mg BID plus SD E2/NETA QD) in this study.	
Subject analysis set title	Cohort 2: Placebo, mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomized subjects who received at least 1 dose of randomized, double-blind study drug (placebo) in this study.	

Subject analysis set title	Cohort 2: Elagolix 600 mg QD, mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomized subjects who received at least 1 dose of randomized, double-blind study drug (elagolix 600 mg QD) in this study.	
Subject analysis set title	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomized subjects who received at least 1 dose of randomized, double-blind study drug (elagolix 600 mg QD plus LD E2/NETA QD) in this study.	
Subject analysis set title	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomized subjects who received at least 1 dose of randomized, double-blind study drug (elagolix 600 mg QD plus SD E2/NETA QD) in this study.	

Primary: Percentage of Participants With a MBL Volume of < 80 mL at the Final Month and a ≥ 50% Reduction in MBL Volume from Baseline to the Final Month

End point title	Percentage of Participants With a MBL Volume of < 80 mL at the Final Month and a ≥ 50% Reduction in MBL Volume from Baseline to the Final Month
End point description: The percentage of subjects meeting a composite endpoint consisting of these 2 bleeding assessments: a MBL Volume of < 80 mL at the Final Month and a ≥50% Reduction in MBL Volume from Baseline to the Final Month (last 28 days of treatment). Baseline is defined as the last qualified menstrual cycle during the screening period.	
End point type	Primary
End point timeframe: Baseline, Final Month (last 28 days of treatment)	

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64 ^[1]	62 ^[2]	61 ^[3]	62 ^[4]
Units: percentage of subjects				
number (not applicable)	26.56	91.94	85.25	79.03

Notes:

- [1] - excludes subjects with < 28 days of treatment
- [2] - excludes subjects with < 28 days of treatment
- [3] - excludes subjects with < 28 days of treatment
- [4] - excludes subjects with < 28 days of treatment

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76 ^[5]	71 ^[6]	73 ^[7]	76 ^[8]
Units: percentage of subjects				
number (not applicable)	31.58	90.14	72.6	81.58

Notes:

[5] - excludes subjects with < 28 days of treatment

[6] - excludes subjects with < 28 days of treatment

[7] - excludes subjects with < 28 days of treatment

[8] - excludes subjects with < 28 days of treatment

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	32.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.12
upper limit	95.05

Notes:

[9] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[10]
Method	Chi-squared

Notes:

[10] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[11]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.72
upper limit	41.3

Notes:

[11] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[12]
Method	Chi-squared

Notes:

[12] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.79
upper limit	25.84

Notes:

[13] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[14]
Method	Chi-squared

Notes:

[14] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 7
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	19.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.81
upper limit	49.27

Notes:

[15] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 8
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[16]
Method	Chi-squared

Notes:

[16] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 9
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.95
upper limit	12.3

Notes:

[17] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 10
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[18]
Method	Chi-squared

Notes:

[18] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 11
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.79
upper limit	22.34

Notes:

[19] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 12
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[20]
Method	Chi-squared

Notes:

[20] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Secondary: Percentage of Subjects With a MBL volume < 80 mL and a ≥ 50% Reduction in MBL Volume From Baseline During the Last 56 to 29 days of Treatment

End point title	Percentage of Subjects With a MBL volume < 80 mL and a ≥ 50% Reduction in MBL Volume From Baseline During the Last 56 to 29 days of Treatment
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End point description:

The percentage of subjects meeting a composite endpoint consisting of these 2 bleeding assessments: a MBL volume < 80 mL and a ≥ 50% reduction in MBL volume from baseline during the last 56 to 29 days of last treatment. Baseline is defined as the last qualified menstrual cycle during the screening period.

End point type	Secondary
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End point timeframe:

Baseline, second last 28 days of treatment (last 56 to 29 days of treatment)

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62 ^[21]	58 ^[22]	59 ^[23]	60 ^[24]
Units: percentage of subjects				
number (not applicable)	11.29	94.83	88.14	85

Notes:

[21] - excludes subjects with < 56 days of treatment

[22] - excludes subjects with < 56 days of treatment

[23] - excludes subjects with < 56 days of treatment

[24] - excludes subjects with < 56 days of treatment

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76 ^[25]	68 ^[26]	64 ^[27]	70 ^[28]
Units: percentage of subjects				
number (not applicable)	18.42	85.29	67.19	77.14

Notes:

[25] - excludes subjects with < 56 days of treatment

[26] - excludes subjects with < 56 days of treatment

[27] - excludes subjects with < 56 days of treatment

[28] - excludes subjects with < 56 days of treatment

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[29]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	156.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	38.04
upper limit	641.22

Notes:

[29] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[30]
Method	Chi-squared

Notes:

[30] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[31]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	66.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.1
upper limit	206.88

Notes:

[31] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[32]
Method	Chi-squared

Notes:

[32] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[33]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	52.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	17.42
upper limit	156.09

Notes:

[33] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[34]
Method	Chi-squared

Notes:

[34] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 7
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[35]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	25.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.45
upper limit	61.96

Notes:

[35] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 8
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[36]
Method	Chi-squared

Notes:

[36] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 9
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[37]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.38
upper limit	21.25

Notes:

[37] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 10
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[38]
Method	Chi-squared

Notes:

[38] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 11
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[39]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.13
upper limit	36.67

Notes:

[39] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 12
Comparison groups	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT v Cohort 2: Placebo, mITT

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[40]
Method	Chi-squared

Notes:

[40] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Secondary: Percentage of Subjects With a MBL volume < 80 mL and a \geq 50% Reduction in MBL Volume From Baseline During the Last 84 to 57 days of Treatment

End point title	Percentage of Subjects With a MBL volume < 80 mL and a \geq 50% Reduction in MBL Volume From Baseline During the Last 84 to 57 days of Treatment
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End point description:

The percentage of subjects meeting a composite endpoint consisting of these 2 bleeding assessments: a MBL volume < 80 mL and a \geq 50% reduction in MBL volume from baseline during the last 84 to 57 days of last treatment. Baseline is defined as the last qualified menstrual cycle during the screening period.

End point type	Secondary
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End point timeframe:

Baseline, third last 28 days of treatment (last 84 to 57 days of treatment)

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61 ^[41]	56 ^[42]	57 ^[43]	58 ^[44]
Units: percentage of subjects				
number (not applicable)	19.67	96.43	89.47	79.31

Notes:

[41] - excludes subjects with < 84 days of treatment

[42] - excludes subjects with < 84 days of treatment

[43] - excludes subjects with < 84 days of treatment

[44] - excludes subjects with < 84 days of treatment

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	74 ^[45]	66 ^[46]	62 ^[47]	65 ^[48]
Units: percentage of subjects				
number (not applicable)	21.62	86.36	74.19	72.31

Notes:

[45] - excludes subjects with < 84 days of treatment

[46] - excludes subjects with < 84 days of treatment

[47] - excludes subjects with < 84 days of treatment

[48] - excludes subjects with < 84 days of treatment

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[49]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	123.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.93
upper limit	584.85

Notes:

[49] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[50]
Method	Chi-squared

Notes:

[50] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[51]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	40.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.59
upper limit	121.03

Notes:

[51] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[52]
Method	Chi-squared

Notes:

[52] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[53]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	19.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.44
upper limit	48.58

Notes:

[53] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[54]
Method	Chi-squared

Notes:

[54] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 7
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[55]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	22.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	9.29
upper limit	55.77

Notes:

[55] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 8
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[56]
Method	Chi-squared

Notes:

[56] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 9
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[57]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.88
upper limit	24.27

Notes:

[57] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 10
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[58]
Method	Chi-squared

Notes:

[58] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 11
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[59]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.46
upper limit	21.22

Notes:

[59] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 12
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[60]
Method	Chi-squared

Notes:

[60] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Secondary: Percentage of Subjects Who Achieved an MBL Volume of < 80 mL at the Final Month

End point title	Percentage of Subjects Who Achieved an MBL Volume of < 80 mL at the Final Month
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End point description:

Percentage of participants who achieved an MBL volume of < 80 mL at the Final Month (last 28 days of treatment). Baseline is defined as the last qualified menstrual cycle during the screening period.

End point type	Secondary
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End point timeframe:

Final Month (last 28 days of treatment)

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64 ^[61]	62 ^[62]	61 ^[63]	62 ^[64]
Units: percentage of subjects				
number (not applicable)	32.81	91.94	88.52	79.03

Notes:

[61] - excludes subjects with < 28 days of treatment

[62] - excludes subjects with < 28 days of treatment

[63] - excludes subjects with < 28 days of treatment

[64] - excludes subjects with < 28 days of treatment

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76 ^[65]	71 ^[66]	73 ^[67]	76 ^[68]
Units: percentage of subjects				
number (not applicable)	36.84	91.55	72.6	85.53

Notes:

[65] - excludes subjects with < 28 days of treatment

[66] - excludes subjects with < 28 days of treatment

[67] - excludes subjects with < 28 days of treatment

[68] - excludes subjects with < 28 days of treatment

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[69]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	24.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.57
upper limit	71.32

Notes:

[69] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[70]
Method	Chi-squared

Notes:

[70] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[71]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	17.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.57
upper limit	45.05

Notes:

[71] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[72]
Method	Chi-squared

Notes:

[72] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[73]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.79
upper limit	19.92

Notes:

[73] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[74]
Method	Chi-squared

Notes:

[74] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 7
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[75]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	18.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.11
upper limit	49.02

Notes:

[75] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 8
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[76]
Method	Chi-squared

Notes:

[76] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 9
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[77]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.43
upper limit	10.04

Notes:

[77] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 10
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[78]
Method	Chi-squared

Notes:

[78] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 11
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[79]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.17
upper limit	26.79

Notes:

[79] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 12
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[80]
Method	Chi-squared

Notes:

[80] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Secondary: Percentage of Subjects With a \geq 50% Reduction in MBL Volume from Baseline to the Final Month

End point title	Percentage of Subjects With a \geq 50% Reduction in MBL Volume from Baseline to the Final Month
End point description:	
Percentage of participants with a \geq 50% reduction from baseline in MBL to the Final Month (last 28 days of treatment). Baseline is defined as the last qualified menstrual cycle during the screening period.	
End point type	Secondary

End point timeframe:

Baseline, Final Month (last 28 days of treatment)

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64 ^[81]	62 ^[82]	61 ^[83]	62 ^[84]
Units: percentage of subjects				
number (not applicable)	31.25	93.55	86.89	82.26

Notes:

[81] - excludes subjects with < 28 days of treatment

[82] - excludes subjects with < 28 days of treatment

[83] - excludes subjects with < 28 days of treatment

[84] - excludes subjects with < 28 days of treatment

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76 ^[85]	71 ^[86]	73 ^[87]	76 ^[88]
Units: percentage of subjects				
number (not applicable)	35.53	90.14	79.45	85.53

Notes:

[85] - excludes subjects with < 28 days of treatment

[86] - excludes subjects with < 28 days of treatment

[87] - excludes subjects with < 28 days of treatment

[88] - excludes subjects with < 28 days of treatment

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[89]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	31.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.02
upper limit	98.83

Notes:

[89] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[90]
Method	Chi-squared

Notes:

[90] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[91]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	14.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.77
upper limit	35.91

Notes:

[91] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[92]
Method	Chi-squared

Notes:

[92] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[93]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.23
upper limit	22.8

Notes:

[93] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[94]
Method	Chi-squared

Notes:

[94] - b. P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 7
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[95]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.66
upper limit	41.26

Notes:

[95] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 8
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[96]
Method	Chi-squared

Notes:

[96] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 9
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[97]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.36
upper limit	14.68

Notes:

[97] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 10
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[98]
Method	Chi-squared

Notes:

[98] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Statistical analysis title	Statistical Analysis 11
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[99]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.85
upper limit	23.76

Notes:

[99] - P value for test of difference between each elagolix dose group and placebo is from a logistic regression model including treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 12
Comparison groups	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT v Cohort 2: Placebo, mITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[100]
Method	Chi-squared

Notes:

[100] - P value for test of difference between each elagolix dose group and placebo is from a chi-square test.

Secondary: Percentage of Subjects Who Achieved Amenorrhea During the Last 56 Days of Treatment

End point title	Percentage of Subjects Who Achieved Amenorrhea During the Last 56 Days of Treatment
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End point description:

Amenorrhea is defined as having 0 days of bleeding or spotting based on observed validated and non-validated alkaline hematin data and having 0 days of bleeding or spotting, based on imputed electronic diary data during the last 56 days of treatment. Participants needed to have at least 66 days on treatment.

End point type	Secondary
End point timeframe:	
Last 56 days of treatment (after 10 days from first dose date)	

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61 ^[101]	57 ^[102]	57 ^[103]	60 ^[104]
Units: percentage of participants				
number (not applicable)	1.6	56.1	33.3	28.3

Notes:

[101] - excludes subjects with less than 66 days of treatment

[102] - excludes subjects with less than 66 days of treatment

[103] - excludes subjects with less than 66 days of treatment

[104] - excludes subjects with less than 66 days of treatment

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD,	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD,
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			mITT	mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	75 ^[105]	67 ^[106]	63 ^[107]	66 ^[108]
Units: percentage of participants				
number (not applicable)	1.3	50.7	17.5	22.7

Notes:

[105] - excludes subjects with less than 66 days of treatment

[106] - excludes subjects with less than 66 days of treatment

[107] - excludes subjects with less than 66 days of treatment

[108] - excludes subjects with less than 66 days of treatment

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Secondary: Percentage of Subjects Who Achieved Suppression of Bleeding During the Last 56 Days of Treatment

End point title	Percentage of Subjects Who Achieved Suppression of Bleeding During the Last 56 Days of Treatment
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End point description:

Suppression of bleeding is defined as having 0 days of bleeding based on observed validated and non-validated alkaline hematin data and having 0 days of bleeding (spotting is allowed) based on imputed electronic diary data during the last 56 days of treatment.

End point type	Secondary
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End point timeframe:

Last 56 days of treatment (after 10 days from first dose date)

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61 ^[109]	57 ^[110]	57 ^[111]	60 ^[112]
Units: percentage of subjects				
number (not applicable)	1.6	75.4	52.6	43.3

Notes:

[109] - excludes subjects with < 66 days of treatment

[110] - excludes subjects with < 66 days of treatment

[111] - excludes subjects with < 66 days of treatment

[112] - excludes subjects with < 66 days of treatment

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	75 ^[113]	67 ^[114]	63 ^[115]	66 ^[116]
Units: percentage of subjects				
number (not applicable)	2.7	67.2	31.7	34.8

Notes:

[113] - excludes subjects with < 66 days of treatment

[114] - excludes subjects with < 66 days of treatment

[115] - excludes subjects with < 66 days of treatment

[116] - excludes subjects with < 66 days of treatment

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Secondary: Mean Change in the Number of Bleeding Days from Baseline to Month 6

End point title	Mean Change in the Number of Bleeding Days from Baseline to Month 6
End point description: The number of days with any bleeding including spotting was calculated using data collected on daily bleeding diary. Baseline is defined as the last 28 days prior to the first dose day of study drug.	
End point type	Secondary

End point timeframe:

Baseline, Month 6

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37 ^[117]	11 ^[118]	26 ^[119]	30 ^[120]
Units: percentage of subjects				
least squares mean (standard error)	-1.2 (± 0.63)	-4.9 (± 1.15)	-2.7 (± 0.75)	-1.1 (± 0.69)

Notes:

[117] - subjects with an assessment at baseline and Month 6

[118] - subjects with an assessment at baseline and Month 6

[119] - subjects with an assessment at baseline and Month 6

[120] - subjects with an assessment at baseline and Month 6

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47 ^[121]	15 ^[122]	26 ^[123]	28 ^[124]
Units: percentage of subjects				
least squares mean (standard error)	-1.4 (± 0.49)	-3.3 (± 0.87)	-1.3 (± 0.66)	-1.8 (± 0.64)

Notes:

[121] - subjects with an assessment at baseline and Month 6

[122] - subjects with an assessment at baseline and Month 6

[123] - subjects with an assessment at baseline and Month 6

[124] - subjects with an assessment at baseline and Month 6

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 ^[125]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.28
upper limit	-1.03
Variability estimate	Standard error of the mean
Dispersion value	1.32

Notes:

[125] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132 ^[126]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.44
upper limit	0.46
Variability estimate	Standard error of the mean
Dispersion value	0.98

Notes:

[126] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.876 ^[127]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.94

Notes:

[127] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055 ^[128]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.92
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[128] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.898 ^[129]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.52
upper limit	1.74
Variability estimate	Standard error of the mean
Dispersion value	0.82

Notes:

[129] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59 ^[130]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.05
upper limit	1.17
Variability estimate	Standard error of the mean
Dispersion value	0.81

Notes:

[130] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Secondary: Mean Change in the Number of Heavy Bleeding Days from Baseline to Month 6

End point title	Mean Change in the Number of Heavy Bleeding Days from Baseline to Month 6
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End point description:

The number of days with heavy bleeding (either heavy or very heavy/gushing bleeding) was calculated using data collected on daily bleeding diary. Baseline is defined as the last 28 days prior to the first dose day of study drug.

End point type	Secondary
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End point timeframe:

Baseline, Month 6

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37 ^[131]	11 ^[132]	26 ^[133]	30 ^[134]
Units: percentage of subjects				
least squares mean (standard error)	-1 (± 0.15)	-2 (± 0.27)	-1.9 (± 0.18)	-1.7 (± 0.16)

Notes:

[131] - subjects with an assessment at baseline and Month 6

[132] - subjects with an assessment at baseline and Month 6

[133] - subjects with an assessment at baseline and Month 6

[134] - subjects with an assessment at baseline and Month 6

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47 ^[135]	15 ^[136]	26 ^[137]	28 ^[138]
Units: percentage of subjects				
least squares mean (standard error)	-0.7 (± 0.14)	-1.2 (± 0.25)	-1.4 (± 0.19)	-1.8 (± 0.18)

Notes:

[135] - subjects with an assessment at baseline and Month 6

[136] - subjects with an assessment at baseline and Month 6

[137] - subjects with an assessment at baseline and Month 6

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 ^[139]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.64
upper limit	-0.42
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[139] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[140]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	-0.48
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[140] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus

	SD E2/NETA QD, mITT
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[141]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[141] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.118 ^[142]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[142] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[143]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[143] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[144]
Method	ANCOVA
Parameter estimate	difference in LS mean change
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	-0.59
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[144] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Secondary: Change in Bleeding Severity Scores From Baseline at the Final Month

End point title	Change in Bleeding Severity Scores From Baseline at the Final Month
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End point description:

The average bleeding score was calculated for each 28-day interval starting on Day 29 using data collected on daily bleeding diary using the Mansfield-Voda-Jorgenson (MVJ) Menstrual Bleeding Scale (1=spotting, 2 = very light bleeding, 3 = light bleeding, 4 = moderate bleeding, 5 = heavy bleeding, 6 = very heavy/gushing bleeding). Baseline is defined as the last 28 days prior to the first day of study drug.

End point type	Secondary
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End point timeframe:

Baseline, Final Month (last 28 days of treatment)

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	51 ^[145]	19 ^[146]	33 ^[147]	37 ^[148]
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.08)	-0.7 (± 0.14)	-0.4 (± 0.1)	-0.1 (± 0.1)

Notes:

[145] - subjects with an assessment at baseline and final month

[146] - subjects with an assessment at baseline and final month

[147] - subjects with an assessment at baseline and final month

[148] - subjects with an assessment at baseline and final month

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61 ^[149]	24 ^[150]	48 ^[151]	42 ^[152]
Units: units on a scale				
least squares mean (standard error)	-0.2 (± 0.08)	-0.4 (± 0.14)	-0.3 (± 0.1)	-0.1 (± 0.1)

Notes:

[149] - subjects with an assessment at baseline and final month

[150] - subjects with an assessment at baseline and final month

[151] - subjects with an assessment at baseline and final month

[152] - subjects with an assessment at baseline and final month

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[153]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[153] - P-value for test of difference between each elagolix dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus

	LD E2/NETA QD, mITT
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.314 ^[154]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[154] - P-value for test of difference between each elagolix dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307 ^[155]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[155] - P-value for test of difference between each elagolix dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106 ^[156]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[156] - P-value for test of difference between each elagolix dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.424 ^[157]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[157] - P-value for test of difference between each elagolix dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment as the main effect and baseline as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.528 ^[158]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.35
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[158] - P-value for test of difference between each elagolix dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment as the main effect and baseline as a covariate.

Secondary: Change from Baseline to Each Month in Non-Bleeding Uterine Fibroids Symptom (NBUFSQ) Questionnaire

End point title	Change from Baseline to Each Month in Non-Bleeding Uterine Fibroids Symptom (NBUFSQ) Questionnaire
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End point description:

The NBUFSQ (8 items) is a brief patient-reported daily diary that assesses non-bleeding symptoms experienced by women with uterine fibroids. It includes 6 items, asking women to rate their symptoms (abdominal/pelvic pain, pressure, and cramping, back pain, bloating, and urinary problems) in the past 24 hours using an 11-point numeric response scale that ranges from 0 (i.e., no symptom) to 10 (i.e., worst possible symptom) and 2 items to address urinary frequency during the daytime and at night. Data presented in the sum of scores to the 6 symptom questions, ranging from 0 (no symptoms) to 60 (worst possible symptoms). Baseline is defined as the last 28 days prior to the first day of study drug.

End point type	Secondary
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End point timeframe:

Baseline, Days 1-28, Days 29-58, Days 57-84, Days 85-112, Days 113-140, Days 141-168, Final Month of treatment, Post-treatment (PT) Days 1-28, PT Days 29-56, PT Days 57-84, PT Days 85-112, PT Days 113-140, PT Days 141-168

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65 ^[159]	65 ^[160]	64 ^[161]	65 ^[162]
Units: units on a scale				
arithmetic mean (standard deviation)				
Days 1-28; n=37, 36, 36, 34, 71, 74, 71, 67	-3.3 (± 10.11)	-3.4 (± 8.21)	-3.1 (± 7.88)	-1.4 (± 6.42)
Days 29-56; n=35, 34, 34, 28, 68, 65, 63, 63	-4.5 (± 13.12)	-5.8 (± 8.78)	-4.4 (± 6.59)	-2.9 (± 9.44)
Days 57-84; n=34, 31, 34, 28, 61, 63, 56, 54	-5.6 (± 10.94)	-7.2 (± 11.04)	-4.1 (± 8.4)	-3.2 (± 11.26)
Days 85-112; n=31, 31, 31, 28, 55, 62, 55, 53	-7 (± 10.74)	-7.8 (± 11.75)	-5.2 (± 9.05)	-3.7 (± 10.76)
Days 113-140; n=28, 29, 32, 28, 56, 57, 48, 47	-4.1 (± 13.16)	-7.6 (± 12.03)	-5.3 (± 9.43)	-3.4 (± 12.1)
Days 141-168; n=26, 29, 30, 27, 53, 51, 47, 45	-6.8 (± 14.28)	-8 (± 12.65)	-5.1 (± 9.94)	-3.3 (± 13.01)
Final Month; n=37, 34, 33, 31, 66, 70, 65, 61	-5.3 (± 13.19)	-6.7 (± 11.94)	-4.1 (± 10.15)	-3.5 (± 12.59)
PT Days 1-28; n=29, 30, 28, 27, 61, 63, 59, 57	-5.6 (± 13.39)	-5.2 (± 12.13)	-3.8 (± 10.37)	-3 (± 10.69)
PT Days 29-56; n=28, 29, 30, 26, 59, 58, 53, 53	-5.7 (± 15.83)	-4.1 (± 13.1)	-1 (± 11.57)	0 (± 9.89)
PT Days 57-84; n=26, 27, 27, 24, 58, 55, 49, 47	-5.4 (± 17.08)	-4 (± 14.11)	-2.1 (± 10.91)	-1.1 (± 10.5)
PT Days 85-112; n=12, 10, 10, 11, 23, 26, 23, 19	-4.4 (± 17.82)	-6.4 (± 12.99)	-4.8 (± 10.33)	0.7 (± 6.59)
PT Days 113-140; n=4, 2, 1, 3, 4, 4, 4, 3	3.4 (± 27.8)	-3.1 (± 2.15)	1.3 (± 99999)	1.4 (± 1.75)
PT Days 141-168; n=3, 2, 1, 1, 1, 1, 4, 3	7.5 (± 27.75)	-8 (± 1.42)	4.1 (± 99999)	-3.3 (± 99999)

Notes:

[159] - n = subjects with an assessment at baseline and given time point

[160] - n = subjects with an assessment at baseline and given time point

[161] - n = subjects with an assessment at baseline and given time point; 99999 = not applicable (n=1)

[162] - n = subjects with an assessment at baseline and given time point; 99999 = not applicable (n=1)

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78 ^[163]	77 ^[164]	76 ^[165]	77 ^[166]
Units: units on a scale				
arithmetic mean (standard deviation)				
Days 1-28; n=37, 36, 36, 34, 71, 74, 71, 67	0.4 (± 4.71)	-2.7 (± 7.27)	-2.1 (± 4.44)	0 (± 6.26)
Days 29-56; n=35, 34, 34, 28, 68, 65, 63, 63	-0.3 (± 7.13)	-4.2 (± 7.72)	-2.2 (± 5.54)	-2.3 (± 9.31)
Days 57-84; n=34, 31, 34, 28, 61, 63, 56, 54	0.1 (± 7.34)	-4.5 (± 8.55)	-2.2 (± 6.22)	-3.8 (± 8.92)
Days 85-112; n=31, 31, 31, 28, 55, 62, 55, 53	-0.2 (± 7.47)	-5.1 (± 9.4)	-3.6 (± 7.35)	-4.1 (± 8.96)
Days 113-140; n=28, 29, 32, 28, 56, 57, 48, 47	0.1 (± 11.92)	-5.5 (± 8.44)	-4 (± 8.13)	-5.3 (± 8.99)
Days 141-168; n=26, 29, 30, 27, 53, 51, 47, 45	-0.4 (± 10.46)	-5.9 (± 9.45)	-4.4 (± 8.21)	-4.8 (± 9.3)
Final Month; n=37, 34, 33, 31, 66, 70, 65, 61	-0.8 (± 11.34)	-4 (± 9.4)	-3.3 (± 8.09)	-2.3 (± 10.56)
PT Days 1-28; n=29, 30, 28, 27, 61, 63, 59, 57	-0.8 (± 12.46)	-3.8 (± 10.53)	-2 (± 8.23)	-2.3 (± 7.82)
PT Days 29-56; n=28, 29, 30, 26, 59, 58, 53, 53	-0.2 (± 12.49)	-2.8 (± 11.85)	-2.7 (± 7.58)	-2.5 (± 8.54)
PT Days 57-84; n=26, 27, 27, 24, 58, 55, 49, 47	-0.5 (± 13.08)	-2 (± 9.79)	-1.6 (± 8.35)	-3.9 (± 6.87)
PT Days 85-112; n=12, 10, 10, 11, 23, 26, 23, 19	-2.7 (± 7.15)	-2.4 (± 14.37)	-3 (± 7.48)	-5 (± 5.12)
PT Days 113-140; n=4, 2, 1, 3, 4, 4, 4, 3	-6.2 (± 1.51)	-17.3 (± 26.2)	-5.6 (± 6.45)	-7 (± 7.12)
PT Days 141-168; n=3, 2, 1, 1, 1, 1, 4, 3	-10.5 (± 99999)	-3.1 (± 99999)	-3.3 (± 6.42)	-6.4 (± 5.94)

Notes:

[163] - n = subjects with an assessment at baseline and given time point; 99999 = not applicable (n=1)

[164] - n = subjects with an assessment at baseline and given time point; 99999 = not applicable (n=1)

[165] - n = subjects with an assessment at baseline and given time point

[166] - n = subjects with an assessment at baseline and given time point

Attachments (see zip file)	Table 14.2_12.2.1 stat analysis Cohort 1.pdf Table 14.2_12.2.1 stat analysis Cohort 2.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percentage Change from Baseline in Primary Fibroid Volume at Month 3, Month 6, and Final Visit

End point title	Mean Percentage Change from Baseline in Primary Fibroid
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End point description:

Volume of the largest fibroid (primary fibroid), as measured by transvaginal ultrasound, or transabdominal ultrasound.

End point type Secondary

End point timeframe:

Baseline, Month 3, Month 6, and Final Visit

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65 ^[167]	65 ^[168]	64 ^[169]	65 ^[170]
Units: percentage change				
arithmetic mean (standard deviation)				
Month 3; n=53, 49, 52, 47, 64, 57, 53, 58	6.9 (± 35.31)	-35.5 (± 26.32)	-20.3 (± 33.54)	-3.7 (± 39.13)
Month 6; n=45, 44, 48, 42, 55, 50, 44, 46	13.2 (± 48.65)	-36.1 (± 30.59)	-19.6 (± 32.1)	0 (± 47.07)
Final Visit; n=53, 53, 54, 51, 66, 59, 55, 60	9 (± 46.63)	-35.6 (± 30.81)	-20 (± 31.73)	-2.7 (± 46.63)

Notes:

[167] - n=subjects with an assessment at baseline and given time point

[168] - n=subjects with an assessment at baseline and given time point

[169] - n=subjects with an assessment at baseline and given time point

[170] - n=subjects with an assessment at baseline and given time point

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78 ^[171]	77 ^[172]	76 ^[173]	77 ^[174]
Units: percentage change				
arithmetic mean (standard deviation)				
Month 3; n=53, 49, 52, 47, 64, 57, 53, 58	6.7 (± 27.66)	-33.6 (± 23.74)	-17.2 (± 27.39)	-1.9 (± 39.22)
Month 6; n=45, 44, 48, 42, 55, 50, 44, 46	1.4 (± 30.03)	-33.5 (± 31.89)	-12.2 (± 40.59)	-0.7 (± 42.98)
Final Visit; n=53, 53, 54, 51, 66, 59, 55, 60	3 (± 28.7)	-34.8 (± 30.36)	-12.8 (± 39.65)	0 (± 40.17)

Notes:

[171] - n=subjects with an assessment at baseline and given time point

[172] - n=subjects with an assessment at baseline and given time point

[173] - n=subjects with an assessment at baseline and given time point

[174] - n=subjects with an assessment at baseline and given time point

Attachments (see zip file) Table 30_statistical analyses.docx

Statistical analyses

Secondary: Mean Percentage Change from Baseline in Total Fibroid Volume at Month 3, Month 6, and Final Visit

End point title	Mean Percentage Change from Baseline in Total Fibroid Volume at Month 3, Month 6, and Final Visit
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End point description:

Volume of the total fibroid volume (3 largest fibroids), as measured by transvaginal ultrasound, or transabdominal ultrasound.

End point type	Secondary
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End point timeframe:

Baseline, Month 3, Month 6, and Final Visit

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65 ^[175]	65 ^[176]	64 ^[177]	65 ^[178]
Units: percentage change				
arithmetic mean (standard deviation)				
Month 3; n=53, 49, 52, 47, 64, 57, 53, 58	1.7 (± 33.61)	-41.9 (± 24.87)	-24.6 (± 27.58)	-9.8 (± 40.31)
Month 6; n=45, 44, 48, 42, 55, 50, 44, 46	8.3 (± 50.97)	-40.2 (± 27.6)	-23.3 (± 30.34)	-8.8 (± 47.81)
Final Visit; n=53, 53, 54, 51, 66, 59, 55, 60	4.6 (± 48.59)	-39.6 (± 28.66)	-24 (± 29.93)	-12.9 (± 46.2)

Notes:

[175] - n=subjects with an assessment at baseline and given time point

[176] - n=subjects with an assessment at baseline and given time point

[177] - n=subjects with an assessment at baseline and given time point

[178] - n=subjects with an assessment at baseline and given time point

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78 ^[179]	77 ^[180]	76 ^[181]	77 ^[182]
Units: percentage change				
arithmetic mean (standard deviation)				
Month 3; n=53, 49, 52, 47, 64, 57, 53, 58	5.4 (± 27.18)	-34.4 (± 25.56)	-17.5 (± 27.76)	-4.6 (± 39.97)
Month 6; n=45, 44, 48, 42, 55, 50, 44, 46	-1.8 (± 30.1)	-34.2 (± 31.14)	-17.8 (± 30.49)	-1.1 (± 46.66)
Final Visit; n=53, 53, 54, 51, 66, 59, 55, 60	0.1 (± 28.82)	-36.4 (± 30.07)	-16.6 (± 32.65)	-1.6 (± 42.75)

Notes:

[179] - n=subjects with an assessment at baseline and given time point

[180] - n=subjects with an assessment at baseline and given time point

[181] - n=subjects with an assessment at baseline and given time point

Attachments (see zip file)	Table 31_statistical analyses.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percentage Change from Baseline in Uterine Volume at Month 3, Month 6, and Final Visit

End point title	Mean Percentage Change from Baseline in Uterine Volume at Month 3, Month 6, and Final Visit
End point description:	Uterine volume, as measured by transvaginal ultrasound or transabdominal ultrasound.
End point type	Secondary
End point timeframe:	Baseline, Month 3, Month 6, and Final Visit

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65 ^[183]	65 ^[184]	64 ^[185]	65 ^[186]
Units: percentage change				
arithmetic mean (standard deviation)				
Month 3; n=58, 52, 56, 54, 72, 63, 57, 63	7.3 (± 25.12)	-30.9 (± 28.87)	-19.4 (± 22.48)	-7.3 (± 20.7)
Month 6; n=51, 47, 50, 47, 61, 56, 49, 50	17.5 (± 40.25)	-35.6 (± 25.74)	-21.9 (± 27.64)	-13.2 (± 23.86)
Final Visit; n=58, 56, 56, 56, 72, 65, 58, 64	15.9 (± 38.06)	-31.5 (± 31.44)	-22 (± 28.52)	-11.8 (± 22.56)

Notes:

[183] - n=subjects who had an assessment at baseline and given time point

[184] - n=subjects who had an assessment at baseline and given time point

[185] - n=subjects who had an assessment at baseline and given time point

[186] - n=subjects who had an assessment at baseline and given time point

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78 ^[187]	77 ^[188]	76 ^[189]	77 ^[190]
Units: percentage change				
arithmetic mean (standard deviation)				

Month 3; n=58, 52, 56, 54, 72, 63, 57, 63	8.4 (± 24.26)	-24.7 (± 21.98)	-15.7 (± 21.84)	-6.1 (± 18.81)
Month 6; n=51, 47, 50, 47, 61, 56, 49, 50	10.7 (± 20.73)	-26 (± 29.51)	-13.5 (± 25.09)	-9 (± 22.12)
Final Visit; n=58, 56, 56, 56, 72, 65, 58, 64	11.6 (± 25.38)	-26.6 (± 28.26)	-11.5 (± 25.33)	-6.7 (± 21.8)

Notes:

[187] - n=subjects who had an assessment at baseline and given time point

[188] - n=subjects who had an assessment at baseline and given time point

[189] - n=subjects who had an assessment at baseline and given time point

[190] - n=subjects who had an assessment at baseline and given time point

Attachments (see zip file)	Table 34_statistical analyses.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With ≥ 25% Reduction From Baseline in Primary Fibroid Volume at Month 3, Month 6, and Final Visit

End point title	Percentage of Subjects With ≥ 25% Reduction From Baseline in Primary Fibroid Volume at Month 3, Month 6, and Final Visit
End point description: Volume of the largest fibroid (primary fibroid) was measured by transvaginal ultrasound or transabdominal ultrasound.	
End point type	Secondary
End point timeframe: Baseline, Month 3, Month 6, and Final Visit	

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65 ^[191]	65 ^[192]	64 ^[193]	65 ^[194]
Units: percentage of subjects				
number (not applicable)				
Month 3; n=53, 49, 52, 47, 64, 57, 53, 58	13.2	67.3	46.2	23.4
Month 6; n=45, 44, 48, 42, 55, 50, 44, 46	24.4	70.5	47.9	26.2
Final Visit; n=53, 53, 54, 51, 66, 59, 55, 60	24.5	69.8	50	27.5

Notes:

[191] - n=subjects with an assessment at baseline and given time point

[192] - n=subjects with an assessment at baseline and given time point

[193] - n=subjects with an assessment at baseline and given time point

[194] - n=subjects with an assessment at baseline and given time point

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD,	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD,
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			mITT	mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78 ^[195]	77 ^[196]	76 ^[197]	77 ^[198]
Units: percentage of subjects				
number (not applicable)				
Month 3; n=53, 49, 52, 47, 64, 57, 53, 58	10.9	63.2	37.7	22.4
Month 6; n=45, 44, 48, 42, 55, 50, 44, 46	14.5	64	38.6	34.8
Final Visit; n=53, 53, 54, 51, 66, 59, 55, 60	13.6	66.1	40	30

Notes:

[195] - n=subjects with an assessment at baseline and given time point

[196] - n=subjects with an assessment at baseline and given time point

[197] - n=subjects with an assessment at baseline and given time point

[198] - n=subjects with an assessment at baseline and given time point

Attachments (see zip file)	Table 32_statistical analyses.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with $\geq 25\%$ Reduction From Baseline in Total Fibroid Volume at Month 3, Month 6, and Final Visit

End point title	Percentage of Subjects with $\geq 25\%$ Reduction From Baseline in Total Fibroid Volume at Month 3, Month 6, and Final Visit
End point description: Total fibroid volume (3 largest fibroids) was measured by transvaginal ultrasound, or transabdominal ultrasound.	
End point type	Secondary
End point timeframe: Baseline, Month 3, Month 6, and Final Visit	

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65 ^[199]	65 ^[200]	64 ^[201]	65 ^[202]
Units: percentage of subjects				
number (not applicable)				
Month 3; n=53, 49, 52, 47, 64, 57, 53, 58	13.2	79.6	50	31.9
Month 6; n=45, 44, 48, 42, 55, 50, 44, 46	24.4	75	54.2	40.5
Final Visit; n=53, 53, 54, 51, 66, 59, 55, 60	24.5	73.6	57.4	41.2

Notes:

[199] - n=subjects with an assessment at baseline and given time point

[200] - n=subjects with an assessment at baseline and given time point

[201] - n=subjects with an assessment at baseline and given time point

[202] - n=subjects with an assessment at baseline and given time point

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78 ^[203]	77 ^[204]	76 ^[205]	77 ^[206]
Units: percentage of subjects				
number (not applicable)				
Month 3; n=53, 49, 52, 47, 64, 57, 53, 58	9.4	66.7	34	22.4
Month 6; n=45, 44, 48, 42, 55, 50, 44, 46	18.2	62	40.9	34.8
Final Visit; n=53, 53, 54, 51, 66, 59, 55, 60	16.7	64.4	40	30

Notes:

[203] - n=subjects with an assessment at baseline and given time point

[204] - n=subjects with an assessment at baseline and given time point

[205] - n=subjects with an assessment at baseline and given time point

[206] - n=subjects with an assessment at baseline and given time point

Attachments (see zip file)	Table 33_statistical analyses.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with $\geq 25\%$ Reduction From Baseline in Uterine Volume at Month 3, Month 6, and Final Visit

End point title	Percentage of Subjects with $\geq 25\%$ Reduction From Baseline in Uterine Volume at Month 3, Month 6, and Final Visit
End point description:	Uterine volume was measured by transvaginal ultrasound or transabdominal ultrasound.
End point type	Secondary
End point timeframe:	Baseline, Month 3, Month 6, and Final Visit

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65 ^[207]	65 ^[208]	64 ^[209]	65 ^[210]
Units: percentage of subjects				
number (not applicable)				
Month 3; n=58, 52, 56, 54, 72, 63, 57, 63	5.2	73.1	42.9	18.5

Month 6; n=51, 47, 50, 47, 61, 56, 49, 50	2	78.7	58	31.9
Final Visit; n=58, 56, 56, 56, 72, 65, 58, 64	3.4	73.2	58.9	26.8

Notes:

[207] - n=subjects with an assessment at baseline and given time point

[208] - n=subjects with an assessment at baseline and given time point

[209] - n=subjects with an assessment at baseline and given time point

[210] - n=subjects with an assessment at baseline and given time point

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78 ^[211]	77 ^[212]	76 ^[213]	77 ^[214]
Units: percentage of subjects				
number (not applicable)				
Month 3; n=58, 52, 56, 54, 72, 63, 57, 63	1.4	57.1	36.8	17.5
Month 6; n=51, 47, 50, 47, 61, 56, 49, 50	1.6	62.5	32.7	26
Final Visit; n=58, 56, 56, 56, 72, 65, 58, 64	1.4	63.1	29.3	23.4

Notes:

[211] - n=subjects with an assessment at baseline and given time point

[212] - n=subjects with an assessment at baseline and given time point

[213] - n=subjects with an assessment at baseline and given time point

[214] - n=subjects with an assessment at baseline and given time point

Attachments (see zip file)	Table 35_statistical analyses.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Successfully Avoided Surgical or Invasive Procedures for Uterine Fibroids

End point title	Percentage of Subjects Who Successfully Avoided Surgical or Invasive Procedures for Uterine Fibroids
End point description:	
End point type	Secondary
End point timeframe:	
Month 6	

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[215]	0 ^[216]	0 ^[217]	0 ^[218]
Units: percentage of subjects				
number (not applicable)				

Notes:

[215] - This was not completed due to lack of data collection.

[216] - This was not completed due to lack of data collection.

[217] - This was not completed due to lack of data collection.

[218] - This was not completed due to lack of data collection.

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[219]	0 ^[220]	0 ^[221]	0 ^[222]
Units: percentage of subjects				
number (not applicable)				

Notes:

[219] - This was not completed due to lack of data collection.

[220] - This was not completed due to lack of data collection.

[221] - This was not completed due to lack of data collection.

[222] - This was not completed due to lack of data collection.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Hemoglobin Concentration from Baseline to Final Visit

End point title	Mean Change in Hemoglobin Concentration from Baseline to Final Visit
End point description: Baseline is defined as the last measurement prior to the first dose of study drug.	
End point type	Secondary
End point timeframe: Baseline, Final Visit during treatment period (Month 6 or early termination)	

End point values	Cohort 1: Placebo, mITT	Cohort 1: Elagolix 300 mg BID, mITT	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64 ^[223]	61 ^[224]	59 ^[225]	61 ^[226]
Units: g/dL				
least squares mean (standard error)	0.6 (± 0.17)	1.9 (± 0.17)	1.9 (± 0.17)	1.4 (± 0.17)

Notes:

- [223] - subjects with an assessment at baseline and final visit
- [224] - subjects with an assessment at baseline and final visit
- [225] - subjects with an assessment at baseline and final visit
- [226] - subjects with an assessment at baseline and final visit

End point values	Cohort 2: Placebo, mITT	Cohort 2: Elagolix 600 mg QD, mITT	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76 ^[227]	71 ^[228]	72 ^[229]	74 ^[230]
Units: g/dL				
least squares mean (standard error)	0.3 (± 0.15)	1.4 (± 0.16)	1.1 (± 0.16)	1.2 (± 0.16)

Notes:

- [227] - subjects with an assessment at baseline and final visit
- [228] - subjects with an assessment at baseline and final visit
- [229] - subjects with an assessment at baseline and final visit
- [230] - subjects with an assessment at baseline and final visit

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID, mITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[231]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.74
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[231] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD, mITT
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[232]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	1.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.72
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[232] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1: Placebo, mITT v Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD, mITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[233]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.27
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[233] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD, mITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[234]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.52
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[234] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 2: Placebo, mITT v Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD, mITT
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[235]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.16
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[235] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD, mITT v Cohort 2: Placebo, mITT
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[236]
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.26
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[236] - P value for test of difference between each elagolix dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment as the main effect and baseline value as a covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of study drug administration through Final Visit (Month 6 or early termination) plus 30 days

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Cohort 1: Placebo
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Reporting group description:

Placebo for elagolix and placebo for estradiol/norethindrone acetate (E2/NETA) twice daily (BID)

Reporting group title	Cohort 1: Elagolix 300 mg BID
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Reporting group description:

Elagolix 300 mg BID alone

Reporting group title	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD
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Reporting group description:

Elagolix 300 mg BID plus low-dose (LD) E2/NETA QD once daily (QD)

Reporting group title	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD
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Reporting group description:

Elagolix 300 mg BID plus standard-dose (SD) E2/NETA QD

Reporting group title	Cohort 2: Placebo
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Reporting group description:

Placebo for elagolix and E2/NETA QD

Reporting group title	Cohort 2: Elagolix 600 mg QD
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Reporting group description:

Elagolix 600 mg QD alone

Reporting group title	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD
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Reporting group description:

Elagolix 600 mg QD plus LD E2/NETA QD

Reporting group title	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD
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Reporting group description:

Elagolix 600 mg QD plus SD E2/NETA QD

Serious adverse events	Cohort 1: Placebo	Cohort 1: Elagolix 300 mg BID	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 65 (9.23%)	3 / 65 (4.62%)	3 / 64 (4.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (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
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (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
Gastrinoma malignant			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (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
Road traffic accident			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (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
Haematoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (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			
Diverticular perforation			

subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysmenorrhoea			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (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

Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (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
Varicella			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD	Cohort 2: Placebo	Cohort 2: Elagolix 600 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 65 (1.54%)	1 / 78 (1.28%)	5 / 77 (6.49%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrinoma malignant			

subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysmenorrhoea			

subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 76 (3.95%)	4 / 77 (5.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrinoma malignant			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysmenorrhoea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			

subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1: Placebo	Cohort 1: Elagolix 300 mg BID	Cohort 1: Elagolix 300 mg BID plus LD E2/NETA QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 65 (50.77%)	45 / 65 (69.23%)	37 / 64 (57.81%)
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Bone density decreased			
subjects affected / exposed	1 / 65 (1.54%)	5 / 65 (7.69%)	2 / 64 (3.13%)
occurrences (all)	1	5	2
Lipids increased			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	0	1	1
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 65 (3.08%)	29 / 65 (44.62%)	16 / 64 (25.00%)
occurrences (all)	2	32	16
Hypertension			
subjects affected / exposed	3 / 65 (4.62%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	3	1	1
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	3 / 65 (4.62%) 3	1 / 64 (1.56%) 1
Headache subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 7	8 / 65 (12.31%) 8	9 / 64 (14.06%) 9
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 6	1 / 65 (1.54%) 1	2 / 64 (3.13%) 2
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	3 / 65 (4.62%) 3	4 / 64 (6.25%) 4
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 65 (1.54%) 1	0 / 64 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	1 / 65 (1.54%) 1	2 / 64 (3.13%) 2
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	4 / 65 (6.15%) 4	0 / 64 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 65 (0.00%) 0	1 / 64 (1.56%) 4
Diarrhoea subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	1 / 65 (1.54%) 1	2 / 64 (3.13%) 2
Nausea subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 6	4 / 65 (6.15%) 4	4 / 64 (6.25%) 4
Vomiting subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 2	1 / 65 (1.54%) 1	0 / 64 (0.00%) 0

Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 65 (3.08%)	2 / 65 (3.08%)	1 / 64 (1.56%)
occurrences (all)	2	2	1
Menorrhagia			
subjects affected / exposed	1 / 65 (1.54%)	2 / 65 (3.08%)	3 / 64 (4.69%)
occurrences (all)	1	2	3
Pelvic pain			
subjects affected / exposed	0 / 65 (0.00%)	2 / 65 (3.08%)	1 / 64 (1.56%)
occurrences (all)	0	2	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 65 (1.54%)	7 / 65 (10.77%)	5 / 64 (7.81%)
occurrences (all)	1	7	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 65 (4.62%)	3 / 65 (4.62%)	3 / 64 (4.69%)
occurrences (all)	3	6	3
Back pain			
subjects affected / exposed	6 / 65 (9.23%)	5 / 65 (7.69%)	2 / 64 (3.13%)
occurrences (all)	6	5	2
Muscle spasms			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	2	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 65 (1.54%)	4 / 65 (6.15%)	1 / 64 (1.56%)
occurrences (all)	1	4	1
Pain in extremity			
subjects affected / exposed	2 / 65 (3.08%)	4 / 65 (6.15%)	2 / 64 (3.13%)
occurrences (all)	2	4	2
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	4 / 65 (6.15%)	4 / 65 (6.15%)	4 / 64 (6.25%)
occurrences (all)	4	6	5
Nasopharyngitis			

subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4	3 / 65 (4.62%) 3	4 / 64 (6.25%) 4
Sinusitis subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	2 / 65 (3.08%) 2	2 / 64 (3.13%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 2	3 / 65 (4.62%) 3	1 / 64 (1.56%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	2 / 65 (3.08%) 3	5 / 64 (7.81%) 7
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	0 / 65 (0.00%) 0	2 / 64 (3.13%) 3

Non-serious adverse events	Cohort 1: Elagolix 300 mg BID plus SD E2/NETA QD	Cohort 2: Placebo	Cohort 2: Elagolix 600 mg QD
Total subjects affected by non-serious adverse events subjects affected / exposed	44 / 65 (67.69%)	42 / 78 (53.85%)	59 / 77 (76.62%)
Investigations			
Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 78 (0.00%) 0	4 / 77 (5.19%) 4
Bone density decreased subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	2 / 78 (2.56%) 2	1 / 77 (1.30%) 1
Lipids increased subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 78 (0.00%) 0	4 / 77 (5.19%) 4
Weight increased subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 78 (0.00%) 0	6 / 77 (7.79%) 6
Vascular disorders			
Hot flush subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 7	4 / 78 (5.13%) 4	38 / 77 (49.35%) 39
Hypertension			

subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5	0 / 78 (0.00%) 0	5 / 77 (6.49%) 6
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 65 (4.62%)	3 / 78 (3.85%)	3 / 77 (3.90%)
occurrences (all)	3	4	3
Headache			
subjects affected / exposed	13 / 65 (20.00%)	8 / 78 (10.26%)	13 / 77 (16.88%)
occurrences (all)	14	9	15
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 65 (3.08%)	6 / 78 (7.69%)	3 / 77 (3.90%)
occurrences (all)	2	6	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 65 (4.62%)	3 / 78 (3.85%)	0 / 77 (0.00%)
occurrences (all)	3	3	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 65 (1.54%)	3 / 78 (3.85%)	6 / 77 (7.79%)
occurrences (all)	1	3	6
Abdominal pain			
subjects affected / exposed	2 / 65 (3.08%)	2 / 78 (2.56%)	3 / 77 (3.90%)
occurrences (all)	2	3	3
Abdominal pain lower			
subjects affected / exposed	0 / 65 (0.00%)	2 / 78 (2.56%)	1 / 77 (1.30%)
occurrences (all)	0	2	1
Abdominal pain upper			
subjects affected / exposed	0 / 65 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	5 / 65 (7.69%)	4 / 78 (5.13%)	5 / 77 (6.49%)
occurrences (all)	6	4	5
Nausea			
subjects affected / exposed	12 / 65 (18.46%)	3 / 78 (3.85%)	10 / 77 (12.99%)
occurrences (all)	13	4	11

Vomiting subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	4 / 78 (5.13%) 5	4 / 77 (5.19%) 6
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	2 / 78 (2.56%) 2	2 / 77 (2.60%) 2
Menorrhagia subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 6	2 / 78 (2.56%) 2	1 / 77 (1.30%) 1
Pelvic pain subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	1 / 78 (1.28%) 1	0 / 77 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	2 / 78 (2.56%) 2	4 / 77 (5.19%) 4
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	3 / 78 (3.85%) 3	5 / 77 (6.49%) 5
Back pain subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	2 / 78 (2.56%) 2	6 / 77 (7.79%) 7
Muscle spasms subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	2 / 78 (2.56%) 4	5 / 77 (6.49%) 5
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	0 / 78 (0.00%) 0	3 / 77 (3.90%) 3
Pain in extremity subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4	0 / 78 (0.00%) 0	2 / 77 (2.60%) 2
Infections and infestations Bacterial vaginosis			

subjects affected / exposed	1 / 65 (1.54%)	2 / 78 (2.56%)	2 / 77 (2.60%)
occurrences (all)	1	2	2
Nasopharyngitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 78 (1.28%)	2 / 77 (2.60%)
occurrences (all)	0	1	2
Sinusitis			
subjects affected / exposed	2 / 65 (3.08%)	5 / 78 (6.41%)	2 / 77 (2.60%)
occurrences (all)	2	5	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 78 (0.00%)	4 / 77 (5.19%)
occurrences (all)	2	0	6
Urinary tract infection			
subjects affected / exposed	4 / 65 (6.15%)	5 / 78 (6.41%)	1 / 77 (1.30%)
occurrences (all)	4	5	1
Vulvovaginal mycotic infection			
subjects affected / exposed	4 / 65 (6.15%)	2 / 78 (2.56%)	1 / 77 (1.30%)
occurrences (all)	4	2	1

Non-serious adverse events	Cohort 2: Elagolix 600 mg QD plus LD E2/NETA QD	Cohort 2: Elagolix 600 mg QD plus SD E2/NETA QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 76 (56.58%)	51 / 77 (66.23%)	
Investigations			
Blood cholesterol increased			
subjects affected / exposed	4 / 76 (5.26%)	2 / 77 (2.60%)	
occurrences (all)	5	2	
Bone density decreased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Lipids increased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 77 (0.00%)	
occurrences (all)	0	0	
Weight increased			
subjects affected / exposed	1 / 76 (1.32%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Vascular disorders			

Hot flush subjects affected / exposed occurrences (all)	14 / 76 (18.42%) 14	11 / 77 (14.29%) 11	
Hypertension subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	1 / 77 (1.30%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 5	5 / 77 (6.49%) 5	
Headache subjects affected / exposed occurrences (all)	11 / 76 (14.47%) 11	14 / 77 (18.18%) 14	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 6	4 / 77 (5.19%) 4	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	5 / 77 (6.49%) 5	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	3 / 77 (3.90%) 3	
Abdominal pain subjects affected / exposed occurrences (all)	3 / 76 (3.95%) 3	4 / 77 (5.19%) 4	
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	4 / 77 (5.19%) 5	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	4 / 77 (5.19%) 5	
Diarrhoea			

subjects affected / exposed occurrences (all)	3 / 76 (3.95%) 3	4 / 77 (5.19%) 5	
Nausea subjects affected / exposed occurrences (all)	12 / 76 (15.79%) 12	20 / 77 (25.97%) 23	
Vomiting subjects affected / exposed occurrences (all)	3 / 76 (3.95%) 3	5 / 77 (6.49%) 7	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 6	3 / 77 (3.90%) 4	
Menorrhagia subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	7 / 77 (9.09%) 8	
Pelvic pain subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	5 / 77 (6.49%) 5	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	5 / 77 (6.49%) 5	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 4	1 / 77 (1.30%) 1	
Back pain subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 7	7 / 77 (9.09%) 7	
Muscle spasms subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	3 / 77 (3.90%) 3	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	0 / 77 (0.00%) 0	
Pain in extremity			

subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	2 / 77 (2.60%) 2	
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	3 / 76 (3.95%)	4 / 77 (5.19%)	
occurrences (all)	3	5	
Sinusitis			
subjects affected / exposed	2 / 76 (2.63%)	1 / 77 (1.30%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 76 (2.63%)	2 / 77 (2.60%)	
occurrences (all)	2	2	
Urinary tract infection			
subjects affected / exposed	2 / 76 (2.63%)	2 / 77 (2.60%)	
occurrences (all)	2	2	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2013	<ul style="list-style-type: none">• Removed baseline observation carried forward method (BOCF) from the repeat primary analysis when imputing subjects who prematurely discontinued prior to Month 6.• Defined treatment-emergent AEs and updated per treatment group the events that were calculated.• Changed sample size from 70 subjects per treatment group to 65 and added 260 subjects for Cohort 2, increasing the total number of subjects to 520.
15 August 2014	<ul style="list-style-type: none">• Clarified statistical analysis of primary and secondary efficacy endpoints
20 April 2015	<ul style="list-style-type: none">• Clarified when the end-of-treatment-period analyses was conducted, added an interim analysis of Cohort 2 for internal planning purposes, and clarified the statistical analysis of primary and secondary efficacy endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported