Clinical trial results:
Extension Study to Evaluate the Long-Term Safety and Efficacy of Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain

Summary

EudraCT number	2013-001047-31
Trial protocol	CZ GB AT IT ES HU
Global end of trial date	23 May 2017

Results information

Result version number	v1 (current)
This version publication date	06 June 2018
First version publication date	06 June 2018

Trial information

Trial identification

Sponsor protocol code	M12-821

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02143713
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbvie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, Abbvie, 011 800-633-9110,
Scientific contact	Michael Snabes, Abbvie, michael.snabes@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	23 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to evaluate the long-term safety and efficacy of elagolix for the management of moderate to severe endometriosis-associated pain in subjects administered elagolix for up to 12 months (initial 6 months if on active treatment in pivotal Study M12-671 and an additional 6 months in this extension study).

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Brazil: 16
Country: Number of subjects enrolled	Czech Republic: 41
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	New Zealand: 15
Country: Number of subjects enrolled	Poland: 105
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 225
Worldwide total number of subjects	495
EEA total number of subjects	216

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)	495
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who completed the 6-month Treatment Period in the pivotal Study M12-671 (NCT01931670) could enter this extension study.
The study was conducted at 148 sites in North and South America, Europe, Australia/New Zealand, and South Africa.
One patient was enrolled but did not receive study drug and is not included in the results.

Pre-assignment

Screening details:

The study consisted of a 6-month Treatment Period and a Post-treatment Follow-up (PTFU) of up to 12 months. Participants who received elagolix in the pivotal study continued to receive the same dose for a further 6 months; participants on placebo in the pivotal study were randomized 1:1 to either elagolix 150 mg once daily or 200 mg twice daily.

Period 1

Period 1 title	Treatment Period (6 Months) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Elagolix 150 mg QD

Arm description:

Participants who received placebo in pivotal Study M12-671 and were randomized to elagolix 150 mg once daily (QD) for 6 months in this extension Study M12-821.

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

Dosage and administration details:

Elagolix tablets administered orally

Arm title	Placebo/Elagolix 200 mg BID

Arm description:

Participants who received placebo in pivotal Study M12-671 and were randomized to elagolix 200 mg twice a day (BID) for 6 months in this extension Study M12-821.

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

Dosage and administration details:

Elagolix tablets administered orally

Arm title	Elagolix/Elagolix 150 mg QD

Arm description:

Participants were randomized to elagolix 150 mg QD in pivotal Study M12-671 and continued to receive elagolix 150 mg QD for 6 months in this extension Study M12-821.

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

Dosage and administration details:

Elagolix tablets administered orally

Arm title	Elagolix/Elagolix 200 mg BID

Arm description:

Participants were randomized to elagolix 200 mg BID in pivotal Study M12-671 and continued to receive elagolix 200 mg BID for 6 months in this extension Study M12-821.

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

Dosage and administration details:

Elagolix tablets administered orally

Number of subjects in period 1	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD
Started	102	111	142
Completed	82	99	120
Not completed	20	12	22
Exclusionary medication	2	-	-
Consent withdrawn by subject	1	2	5
Surgery or invasive intervention	2	-	-
Other	3	-	3
Pregnancy	-	2	2
Adverse event	7	8	8
Non-compliance	1	-	-
Bone mineral density decrease	-	-	-
Lost to follow-up	3	-	4
Lack of efficacy	1	-	-

Number of subjects in period 1	Elagolix/Elagolix 200 mg BID
Started	140
Completed	112
Not completed	28
Exclusionary medication	-
Consent withdrawn by subject	4
Surgery or invasive intervention	2

Other	2
Pregnancy	-
Adverse event	9
Non-compliance	3
Bone mineral density decrease	4
Lost to follow-up	3
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/Elagolix 150 mg QD
Reporting group description:	
Participants who received placebo in pivotal Study M12-671 and were randomized to elagolix 150 mg once daily (QD) for 6 months in this extension Study M12-821.	
Reporting group title	Placebo/Elagolix 200 mg BID
Reporting group description:	
Participants who received placebo in pivotal Study M12-671 and were randomized to elagolix 200 mg twice a day (BID) for 6 months in this extension Study M12-821.	
Reporting group title	Elagolix/Elagolix 150 mg QD
Reporting group description:	
Participants were randomized to elagolix 150 mg QD in pivotal Study M12-671 and continued to receive elagolix 150 mg QD for 6 months in this extension Study M12-821.	
Reporting group title	Elagolix/Elagolix 200 mg BID
Reporting group description:	
Participants were randomized to elagolix 200 mg BID in pivotal Study M12-671 and continued to receive elagolix 200 mg BID for 6 months in this extension Study M12-821.	

Reporting group values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD
Number of subjects	102	111	142
Age categorical Units: Subjects			
18 - 65 years	102	111	142
Age continuous Units: years			
arithmetic mean	33.5	33.2	33.2
standard deviation	± 7.00	± 6.32	± 7.02
Gender categorical Units: Subjects			
Female	102	111	142
Male	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	14	11	15
Not Hispanic or Latino	88	100	127
Race Units: Subjects			
White	94	100	127
Black or African American	7	9	14
Asian	0	1	1
Multi race	0	1	0
Native Hawaiian or other Pacific Islander	1	0	0

Reporting group values	Elagolix/Elagolix 200 mg BID	Total	
Number of subjects	140	495	

Age categorical Units: Subjects			
18 - 65 years	140	495	
Age continuous Units: years			
arithmetic mean	34.1		
standard deviation	± 6.70	-	
Gender categorical Units: Subjects			
Female	140	495	
Male	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	21	61	
Not Hispanic or Latino	119	434	
Race Units: Subjects			
White	126	447	
Black or African American	12	42	
Asian	1	3	
Multi race	1	2	
Native Hawaiian or other Pacific Islander	0	1	

End points

End points reporting groups

Reporting group title	Placebo/Elagolix 150 mg QD
Reporting group description:	
Participants who received placebo in pivotal Study M12-671 and were randomized to elagolix 150 mg once daily (QD) for 6 months in this extension Study M12-821.	
Reporting group title	Placebo/Elagolix 200 mg BID
Reporting group description:	
Participants who received placebo in pivotal Study M12-671 and were randomized to elagolix 200 mg twice a day (BID) for 6 months in this extension Study M12-821.	
Reporting group title	Elagolix/Elagolix 150 mg QD
Reporting group description:	
Participants were randomized to elagolix 150 mg QD in pivotal Study M12-671 and continued to receive elagolix 150 mg QD for 6 months in this extension Study M12-821.	
Reporting group title	Elagolix/Elagolix 200 mg BID
Reporting group description:	
Participants were randomized to elagolix 200 mg BID in pivotal Study M12-671 and continued to receive elagolix 200 mg BID for 6 months in this extension Study M12-821.	

Primary: Percentage of Participants With a Response for Dysmenorrhea at Month 6 Based on Daily Assessment

End point title	Percentage of Participants With a Response for Dysmenorrhea at Month 6 Based on Daily Assessment[1]
End point description:	
Response was defined as a reduction of -0.85 or more from baseline in dysmenorrhea (pain during menstruation) as well as no increase in rescue analgesic use for endometriosis-associated pain (defined as a < 15% increase in average rescue analgesic pill count and no additional analgesic). The response threshold represents a clinically meaningful response that was determined in pivotal Study M12-671. Participants recorded rescue analgesic use for endometriosis-associated pain daily and dysmenorrhea and its impact on daily activities each day of their period in an electronic diary (e-Diary). Dysmenorrhea was assessed according to the following: • 0: No discomfort • 1: Mild discomfort but I was easily able to do the things I usually do • 2: Moderate discomfort or pain that made it difficult to do some of the things I usually do • 3: Severe pain that made it difficult to do the things I usually do. Analgesic use and pain scores were averaged over the 35 days prior to each visit.	
End point type	Primary
End point timeframe:	
Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and Month 6	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Statistical comparisons between dose groups were not prespecified and not performed since the extension studies were not designed or powered for these analyses.	

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81[2]	98[3]	122[4]	116[5]
Units: percentage of participants				
number (not applicable)	37.0	57.1	50.8	75.9

Notes:

[2] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[3] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[4] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[5] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With a Response for Non-menstrual Pelvic Pain at Month 6 Based on Daily Assessment

End point title	Percentage of Participants With a Response for Non-menstrual Pelvic Pain at Month 6 Based on Daily Assessment[6]

End point description:

Response was defined as a reduction of −0.43 or greater from baseline for non-menstrual pelvic pain as well as no increase in rescue analgesic use for endometriosis-associated pain (defined as a < 15% increase in average pill count of rescue analgesics and no additional analgesics). The response threshold represents a clinically meaningful response that was determined in pivotal Study M12-671.
Participants recorded rescue analgesic medication for endometriosis-associated pain and assessed non-menstrual pelvic pain and its impact on their daily activities each day in an e-Diary according to the following response options:
• 0: No discomfort
• 1: Mild discomfort but I was easily able to do the things I usually do
• 2: Moderate discomfort or pain that made it difficult to do some of the things I usually do
• 3: Severe pain that made it difficult to do the things I usually do.
Pain scores and analgesic use were averaged over the 35 days prior to each visit.

End point type	Primary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and Month 6

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical comparisons between dose groups were not prespecified and not performed since the extension studies were not designed or powered for these analyses.

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81[7]	98[8]	122[9]	116[10]
Units: percentage of participants				
number (not applicable)	27.2	32.7	66.4	67.2

Notes:

[7] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[8] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[9] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[10] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Response for Dysmenorrhea at Each Month Based on Daily Assessment

End point title	Percentage of Participants With a Response for Dysmenorrhea

	at Each Month Based on Daily Assessment

End point description:

Response was defined as a reduction of -0.85 or more from baseline in dysmenorrhea (pain during menstruation) as well as no increase in rescue analgesic use for endometriosis-associated pain (defined as a < 15% increase in average rescue analgesic pill count and no additional analgesic). The response threshold represents a clinically meaningful response that was determined in pivotal Study M12-671. Participants recorded rescue analgesic use for endometriosis-associated pain daily and dysmenorrhea and its impact on daily activities each day of their period in an electronic diary (e-Diary). Dysmenorrhea was assessed according to the following:
• 0: No discomfort
• 1: Mild discomfort but I was easily able to do the things I usually do
• 2: Moderate discomfort or pain that made it difficult to do some of the things I usually do
• 3: Severe pain that made it difficult to do the things I usually do.
Analgesic use and pain scores were averaged over the 35 days prior to each visit.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, and 5

End point values	Placebo/Elagoli x 150 mg QD	Placebo/Elagoli x 200 mg BID	Elagolix/Elagoli x 150 mg QD	Elagolix/Elagoli x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102[11]	111[12]	142[13]	140[14]
Units: percentage of participants				
number (not applicable)				
Month 1 (N = 102, 110, 141, 140)	11.8	24.5	56.7	74.3
Month 2 (N = 96, 106, 136, 134)	36.5	62.3	52.2	79.1
Month 3 (N = 90, 103, 133, 131)	30.0	64.1	48.1	77.1
Month 4 (N = 88, 102, 128, 125)	33.0	64.7	47.7	80.0
Month 5 (N = 81, 100, 126, 117)	30.9	59.0	53.2	82.9

Notes:

[11] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[12] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[13] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[14] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Response for Non-menstrual Pelvic Pain at Each Month Based on Daily Assessment

End point title	Percentage of Participants With a Response for Non-menstrual Pelvic Pain at Each Month Based on Daily Assessment

End point description:

Response was defined as a reduction of −0.43 or greater from baseline for non-menstrual pelvic pain as well as no increase in rescue analgesic use for endometriosis-associated pain (defined as a < 15% increase in average pill count of rescue analgesics and no additional analgesics). The response threshold represents a clinically meaningful response that was determined in pivotal Study M12-671.
Participants recorded rescue analgesic medication for endometriosis-associated pain and assessed non-menstrual pelvic pain and its impact on their daily activities each day in an e-Diary according to the following response options:
• 0: No discomfort
• 1: Mild discomfort but I was easily able to do the things I usually do
• 2: Moderate discomfort or pain that made it difficult to do some of the things I usually do

• 3: Severe pain that made it difficult to do the things I usually do.
Pain scores and analgesic use were averaged over the 35 days prior to each visit.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, and 5

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102[15]	111[16]	142[17]	140[18]
Units: percentage of participants				
number (not applicable)				
Month 1 (N = 102, 110, 141, 140)	12.7	18.2	61.7	62.1
Month 2 (N = 96, 106, 136, 134)	20.8	27.4	61.8	63.4
Month 3 (N = 90, 103, 133, 131)	18.9	29.1	66.2	65.6
Month 4 (N = 88, 102, 128, 125)	27.3	34.3	64.8	66.4
Month 5 (N = 81, 100, 126, 117)	28.4	33.0	67.5	72.6

Notes:

[15] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[16] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[17] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[18] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Response for Dyspareunia at Each Month Based on Daily Assessment

End point title	Percentage of Participants With a Response for Dyspareunia at Each Month Based on Daily Assessment

End point description:

Response was defined as a reduction of −0.29 or more from baseline in dyspareunia (pain during sexual intercourse) as well as no increase in rescue analgesic use for endometriosis-associated pain (defined as a < 15% increase in average rescue analgesic pill count and no additional analgesics).
Participants recorded rescue analgesic medication for endometriosis-associated pain and assessed dyspareunia each day in an e-Diary. Dyspareunia was assessed according to the following:
• 0: None; No discomfort during sexual intercourse
• 1: Mild; Able to tolerate the discomfort during sexual intercourse
• 2: Moderate; Intercourse was interrupted due to pain
• 3: Severe; Avoided intercourse because of pain
• Not applicable; I was not sexually active for reasons other than endometriosis or did not have sexual intercourse.
Pain scores and analgesic use were averaged over the 35 days prior to each visit. Responses of "Not Applicable" were excluded.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102[19]	111[20]	142[21]	140[22]
Units: percentage of participants				
number (not applicable)				
Month 1 (N = 78, 77, 101, 93)	23.1	27.3	50.5	63.4
Month 2 (N = 72, 77, 100, 95)	30.6	35.1	47.0	65.3
Month 3 (N = 67, 72, 97, 85)	37.3	33.3	55.7	61.2
Month 4 (N = 66, 65, 98, 83)	34.8	32.3	54.1	60.2
Month 5 (N = 60, 65, 86, 74)	30.0	40.0	52.3	63.5
Month 6 (N = 59, 67, 85, 74)	28.8	31.3	45.9	58.1

Notes:

[19] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[20] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[21] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[22] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Dyspareunia Based on Daily Assessment

End point title	Percent Change From Baseline in Dyspareunia Based on Daily Assessment

End point description:

Participants assessed dyspareunia each day in an e-Diary according to the following response options:
• 0: None; No discomfort during sexual intercourse
• 1: Mild; Able to tolerate the discomfort during sexual intercourse
• 2: Moderate; Intercourse was interrupted due to pain
• 3: Severe; Avoided intercourse because of pain
• Not applicable; I was not sexually active for reasons other than endometriosis or did not have sexual intercourse.
Pain scores were averaged over the 35 days prior to each visit. Responses of "Not Applicable" were excluded.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83[23]	87[24]	118[25]	108[26]
Units: percent change				
arithmetic mean (standard deviation)				

Month 1 (N = 63, 64, 95, 87)	-10.4 (± 52.31)	-16.9 (± 59.04)	-43.7 (± 64.77)	-48.7 (± 66.94)
Month 2 (N = 60, 64, 93, 89)	-12.0 (± 51.80)	-19.2 (± 65.67)	-38.0 (± 74.89)	-51.1 (± 52.74)
Month 3 (N = 54, 62, 91, 78)	-22.1 (± 46.07)	-26.4 (± 69.18)	-43.4 (± 55.71)	-49.1 (± 46.47)
Month 4 (N = 53, 57, 93, 77)	-22.3 (± 51.64)	-12.6 (± 141.47)	-49.1 (± 48.27)	-48.5 (± 56.42)
Month 5 (N = 48, 55, 80, 68)	-25.7 (± 45.51)	-9.5 (± 191.05)	-57.0 (± 43.57)	-42.7 (± 64.12)
Month 6 (N = 46, 55, 79, 69)	-18.8 (± 54.07)	-28.3 (± 53.62)	-51.3 (± 45.87)	-49.7 (± 54.23)

Notes:

[23] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[24] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[25] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[26] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Dysmenorrhea Based on Daily Assessment

End point title	Percent Change From Baseline in Dysmenorrhea Based on Daily Assessment

End point description:

Participants assessed dysmenorrhea (pain during menstruation) and its impact on their daily activities each day of their period in an e-Diary according to the following response options:
• 0: No discomfort
• 1: Mild discomfort but I was easily able to do the things I usually do
• 2: Moderate discomfort or pain that made it difficult to do some of the things I usually do
• 3: Severe pain that made it difficult to do the things I usually do.
Pain scores were averaged over the 35 days prior to each visit.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagolix x 150 mg QD	Placebo/Elagolix x 200 mg BID	Elagolix/Elagolix x 150 mg QD	Elagolix/Elagolix x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102[27]	111[28]	142[29]	140[30]
Units: percent change				
arithmetic mean (standard deviation)				
Month 1 (N = 98, 108, 141, 140)	-18.4 (± 41.71)	-27.0 (± 55.50)	-54.6 (± 41.79)	-81.3 (± 36.00)
Month 2 (N = 92, 104, 136, 134)	-47.6 (± 50.17)	-70.2 (± 55.81)	-50.7 (± 41.16)	-84.0 (± 33.76)
Month 3 (N = 86, 101, 133, 131)	-40.2 (± 51.63)	-76.7 (± 48.73)	-49.0 (± 41.98)	-84.8 (± 32.01)
Month 4 (N = 84, 100, 128, 125)	-40.3 (± 51.25)	-77.5 (± 41.25)	-50.5 (± 39.97)	-83.0 (± 36.23)
Month 5 (N = 78, 98, 126, 117)	-38.0 (± 50.01)	-75.6 (± 47.88)	-51.8 (± 39.25)	-82.7 (± 33.89)

Month 6 (N = 78, 96, 122, 116)	-44.6 (± 45.08)	-80.7 (± 38.43)	-52.9 (± 39.52)	-81.8 (± 33.57)

Notes:

[27] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[28] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[29] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[30] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Non-menstrual Pelvic Pain Based on Daily Assessment

End point title	Percent Change From Baseline in Non-menstrual Pelvic Pain Based on Daily Assessment

End point description:

Participants assessed non-menstrual pelvic pain and its impact on their daily activities each day in an e-Diary according to the following response options:
• 0: No discomfort
• 1: Mild discomfort but I was easily able to do the things I usually do
• 2: Moderate discomfort or pain that made it difficult to do some of the things I usually do
• 3: Severe pain that made it difficult to do the things I usually do.
Pain scores were averaged over the 35 days prior to each visit.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagoli x 150 mg QD	Placebo/Elagoli x 200 mg BID	Elagolix/Elagoli x 150 mg QD	Elagolix/Elagoli x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102[31]	111[32]	142[33]	140[34]
Units: percent change				
arithmetic mean (standard deviation)				
Month 1 (N = 98, 107, 141, 140)	-7.3 (± 57.59)	-11.3 (± 64.29)	-47.9 (± 39.03)	-54.0 (± 41.77)
Month 2 (N = 92, 103, 136, 134)	-7.8 (± 71.50)	-12.8 (± 143.81)	-48.6 (± 38.70)	-53.1 (± 42.04)
Month 3 (N = 86, 100, 133, 131)	-24.5 (± 53.77)	-17.8 (± 130.92)	-50.7 (± 38.41)	-54.5 (± 41.70)
Month 4 (N = 84, 99, 128, 125)	-25.0 (± 53.14)	-23.1 (± 123.65)	-53.2 (± 37.47)	-54.4 (± 40.89)
Month 5 (N = 77, 97, 126, 117)	-30.4 (± 44.88)	-31.2 (± 113.03)	-54.9 (± 39.53)	-57.4 (± 42.84)
Month 6 (N = 77, 95, 122, 116)	-24.0 (± 62.40)	-27.2 (± 164.50)	-53.6 (± 40.41)	-55.9 (± 41.01)

Notes:

[31] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[32] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[33] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

[34] - Subjects who received at least 1 dose of study drug in Study M12-821 with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Any Rescue Analgesic Use

End point title	Change From Baseline in Any Rescue Analgesic Use

End point description:

Permitted rescue analgesics varied by country and were limited to non-steroidal anti-inflammatory drugs (NSAID) (naproxen 500 mg), or opioid analgesics (hydrocodone 5 mg + acetaminophen 300 mg or 325 mg, or codeine 30 mg + acetaminophen 300 mg, or codeine 30 mg, or tramadol 37.5 mg + acetaminophen 325 mg). Use of rescue analgesic medications taken for endometriosis-associated pain was recorded by the participant daily in the e-Diary as the total number of pills/tablets of each type taken within a 24-hour period. Any rescue analgesic use (NSAID and/or opioid) was calculated as the total number of pills divided by the number of days in the window (i.e. average daily pill count) over the 35-day window prior to and including the reference study day.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	111	142	140
Units: pills/day				
arithmetic mean (standard deviation)				
Month 1 (N = 102, 110, 141, 140)	-0.07 (± 0.320)	-0.16 (± 0.389)	-0.44 (± 0.745)	-0.47 (± 0.711)
Month 2 (N = 96, 106, 136, 134)	-0.16 (± 0.375)	-0.24 (± 0.510)	-0.49 (± 0.829)	-0.52 (± 0.774)
Month 3 (N = 90, 103, 133, 131)	-0.14 (± 0.391)	-0.24 (± 0.524)	-0.46 (± 0.806)	-0.53 (± 0.774)
Month 4 (N = 88, 102, 128, 125)	-0.13 (± 0.460)	-0.28 (± 0.483)	-0.48 (± 0.815)	-0.54 (± 0.811)
Month 5 (N = 81, 100, 126, 117)	-0.16 (± 0.446)	-0.29 (± 0.539)	-0.46 (± 0.817)	-0.57 (± 0.758)
Month 6 (N = 81, 98, 122, 116)	-0.16 (± 0.410)	-0.28 (± 0.513)	-0.45 (± 0.834)	-0.59 (± 0.799)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in NSAID Rescue Analgesic Use

End point title	Change From Baseline in NSAID Rescue Analgesic Use

End point description:

Permitted rescue analgesics varied by country and were limited to non-steroidal anti-inflammatory drugs (NSAID) (naproxen 500 mg), or opioid analgesics (hydrocodone 5 mg + acetaminophen 300 mg or 325 mg, or codeine 30 mg + acetaminophen 300 mg, or codeine 30 mg, or tramadol 37.5 mg + acetaminophen 325 mg). Use of rescue analgesic medications taken for endometriosis-associated pain was recorded by the participant daily in the e-Diary as the total number of pills/tablets of each type taken within a 24-hour period. NSAID rescue analgesic use was calculated as the total number of NSAID

pills divided by the number of days in the window (i.e. average daily pill count) over the 35-day window prior to and including the reference study day.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	111	142	140
Units: pills/day				
arithmetic mean (standard deviation)				
Month 1 (N = 102, 110, 141, 140)	-0.05 (± 0.209)	-0.12 (± 0.263)	-0.25 (± 0.590)	-0.28 (± 0.363)
Month 2 (N = 96, 106, 136, 134)	-0.10 (± 0.271)	-0.18 (± 0.343)	-0.29 (± 0.624)	-0.29 (± 0.389)
Month 3 (N = 90, 103, 133, 131)	-0.11 (± 0.281)	-0.18 (± 0.336)	-0.27 (± 0.550)	-0.30 (± 0.370)
Month 4 (N = 88, 102, 128, 125)	-0.09 (± 0.297)	-0.20 (± 0.334)	-0.28 (± 0.531)	-0.30 (± 0.379)
Month 5 (N = 81, 100, 126, 117)	-0.11 (± 0.316)	-0.21 (± 0.353)	-0.27 (± 0.556)	-0.31 (± 0.376)
Month 6 (N = 81, 98, 122, 116)	-0.10 (± 0.241)	-0.20 (± 0.369)	-0.26 (± 0.569)	-0.32 (± 0.380)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Opioid Rescue Analgesic Use

End point title	Change From Baseline in Opioid Rescue Analgesic Use

End point description:

Permitted rescue analgesics varied by country and were limited to non-steroidal anti-inflammatory drugs (NSAID) (naproxen 500 mg), or opioid analgesics (hydrocodone 5 mg + acetaminophen 300 mg or 325 mg, or codeine 30 mg + acetaminophen 300 mg, or codeine 30 mg, or tramadol 37.5 mg + acetaminophen 325 mg). Use of rescue analgesic medications taken for endometriosis-associated pain was recorded by the participant daily in the e-Diary as the total number of pills/tablets of each type taken within a 24-hour period. Opioid rescue analgesic use was calculated as the total number of opioid pills divided by the number of days in the window (i.e. average daily pill count) over the 35-day window prior to and including the reference study day.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagoli x 150 mg QD	Placebo/Elagoli x 200 mg BID	Elagolix/Elagoli x 150 mg QD	Elagolix/Elagoli x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	111	142	140
Units: pills/day				
arithmetic mean (standard deviation)				
Month 1 (N = 102, 110, 141, 140)	-0.02 (± 0.197)	-0.04 (± 0.243)	-0.19 (± 0.526)	-0.20 (± 0.596)
Month 2 (N = 96, 106, 136, 134)	-0.06 (± 0.214)	-0.06 (± 0.270)	-0.19 (± 0.573)	-0.23 (± 0.655)
Month 3 (N = 90, 103, 133, 131)	-0.04 (± 0.217)	-0.06 (± 0.309)	-0.19 (± 0.613)	-0.23 (± 0.662)
Month 4 (N = 88, 102, 128, 125)	-0.05 (± 0.262)	-0.08 (± 0.231)	-0.20 (± 0.620)	-0.24 (± 0.693)
Month 5 (N = 81, 100, 126, 117)	-0.05 (± 0.227)	-0.08 (± 0.273)	-0.19 (± 0.613)	-0.26 (± 0.643)
Month 6 (N = 81, 98, 122, 116)	-0.06 (± 0.237)	-0.07 (± 0.271)	-0.20 (± 0.623)	-0.27 (± 0.680)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Endometriosis-Associated Pain Score Assessed With Numeric Rating Scale (NRS)

End point title	Percent Change From Baseline in Endometriosis-Associated Pain Score Assessed With Numeric Rating Scale (NRS)

End point description:

The NRS measured endometriosis-associated pain with and without menstruation on an 11-point scale from 0 = no pain to 10 = worst pain ever. Participants were asked to assess their endometriosis pain over the past 24 hours at it's worst at approximately the same time every day in the e-Diary. Pain scores were averaged over the 35 days prior to each visit.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagoli x 150 mg QD	Placebo/Elagoli x 200 mg BID	Elagolix/Elagoli x 150 mg QD	Elagolix/Elagoli x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	111	142	140
Units: percent change				
arithmetic mean (standard deviation)				
Month 1 (N = 102, 110, 141, 140)	-12.0 (± 44.71)	-18.2 (± 51.75)	-50.8 (± 36.58)	-58.7 (± 37.07)
Month 2 (N = 96, 106, 136, 134)	-20.7 (± 40.87)	-25.8 (± 87.35)	-50.7 (± 36.08)	-58.7 (± 36.31)
Month 3 (N = 90, 103, 133, 131)	-27.7 (± 39.61)	-35.0 (± 65.06)	-52.7 (± 36.40)	-59.5 (± 35.99)
Month 4 (N = 88, 102, 128, 125)	-31.2 (± 43.28)	-38.8 (± 58.04)	-54.7 (± 33.26)	-60.4 (± 34.77)

Month 5 (N = 81, 100, 126, 117)	-29.2 (± 52.99)	-45.6 (± 60.86)	-56.1 (± 35.81)	-62.3 (± 34.99)
Month 6 (N = 81, 98, 122, 116)	-30.7 (± 42.08)	-41.7 (± 83.80)	-53.9 (± 35.06)	-61.1 (± 33.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a PGIC Response of Much Improved or Very Much Improved

End point title	Percentage of Participants With a PGIC Response of Much Improved or Very Much Improved

End point description:

The Patient Global Impression of Change (PGIC) is a questionnaire-based assessment of the change in endometriosis pain since the initiation of study drug. The participant was asked to select from one of seven response categories:
1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. Not Changed
5. Minimally Worse
6. Much Worse
7. Very Much Worse

End point type	Secondary

End point timeframe:

Months 1, 2, 3, 4, 5, and 6

End point values	Placebo/Elagoli x 150 mg QD	Placebo/Elagoli x 200 mg BID	Elagolix/Elagoli x 150 mg QD	Elagolix/Elagoli x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	111	142	140
Units: percentage of participants				
number (not applicable)				
Month 1 (N = 98, 111, 137, 138)	50.0	56.8	65.7	78.3
Month 2 (N = 92, 106, 136, 133)	58.7	74.5	69.1	78.9
Month 3 (N = 88, 103, 131, 127)	63.6	70.9	67.9	77.2
Month 4 (N = 88, 101, 128, 123)	61.4	75.2	71.1	82.1
Month 5 (N = 82, 100, 124, 117)	67.1	81.0	71.8	82.1
Month 6 (N = 76, 93, 114, 106)	65.8	76.3	75.4	84.0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Endometriosis Health Profile-30 (EHP-30) Pain Dimension

End point title	Change From Baseline in Endometriosis Health Profile-30 (EHP-30) Pain Dimension

End point description:

The EHP-30 is an instrument to measure health-related quality of life in women with endometriosis. The EHP-30 consists of two parts: a core questionnaire containing 5 scales that are applicable to all women with endometriosis and includes pain, control and powerlessness, emotional well-being, social support, and self-image, and a modular part containing 6 scales which do not necessarily apply to all women with endometriosis.
Each question in the core questionnaire is scored on the following scale: 0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, 4 = Always.
The pain dimension consists of 11 questions. The dimension score ranges from 0 to 100, where 0 = best possible health status as measured by the questionnaire; 100 = worst possible health status. A negative change from baseline score indicates improvement in quality of life.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and months 1, 3, and 6

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	111	142	140
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1 (N = 98, 111, 136, 138)	-8.02 (± 17.828)	-12.18 (± 17.465)	-32.25 (± 21.235)	-36.45 (± 22.320)
Month 3 (N = 92, 104, 136, 129)	-11.12 (± 22.424)	-15.25 (± 21.467)	-32.00 (± 23.172)	-37.42 (± 21.492)
Month 6 (N = 74, 92, 110, 100)	-10.60 (± 20.827)	-15.61 (± 21.047)	-32.95 (± 23.674)	-38.48 (± 21.924)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Endometriosis Health Profile-30 (EHP-30) Sexual Intercourse Dimension

End point title	Change From Baseline in Endometriosis Health Profile-30 (EHP-30) Sexual Intercourse Dimension

End point description:

The EHP-30 is an instrument to measure health-related quality of life in women with endometriosis. The EHP-30 consists of two parts: a core questionnaire containing 5 scales that are applicable to all women with endometriosis and a modular part containing 6 scales which do not necessarily apply to all women with endometriosis; only 1 modular questionnaire (sexual intercourse [5 items]) was used in this study. The Sexual Intercourse dimension consists of 5 questions, each answered on the following scale: 0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, 4 = Always, or Not Applicable (not scored). The dimension score ranges from 0 to 100, where 0 = best possible health status as measured by the questionnaire; 100 = worst possible health status. A negative change from baseline score indicates improvement in quality of life.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal

study) and months 1, 3, and 6

End point values	Placebo/Elagoli x 150 mg QD	Placebo/Elagoli x 200 mg BID	Elagolix/Elagoli x 150 mg QD	Elagolix/Elagoli x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	97	109	111
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1 (N = 79, 71, 90, 98)	-3.29 (± 13.655)	-10.35 (± 16.846)	-24.17 (± 26.010)	-28.37 (± 29.886)
Month 3 (n = 68, 64, 90, 86)	-9.26 (± 20.264)	-12.50 (± 22.449)	-24.61 (± 26.986)	-28.66 (± 31.580)
Month 6 (N = 55, 63, 78, 67)	-9.36 (± 19.294)	-7.30 (± 22.963)	-23.21 (± 26.310)	-33.21 (± 31.988)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-Related Productivity Questionnaire (HRPQ): Hours of Work Lost in Workplace and Household

End point title	Change From Baseline in Health-Related Productivity Questionnaire (HRPQ): Hours of Work Lost in Workplace and Household

End point description:

The HRPQ consists of 9 questions measuring the impact of endometriosis-associated pain and its treatment on work productivity and daily activities in the home.

Absenteeism: Number of hours of intended work lost due to illness or treatment. Presenteeism: Number of hours of work where output was impacted by illness or treatments.

Total hours lost is the sum of hours missed due to absenteeism plus presenteeism.

End point type	Secondary

End point timeframe:

Baseline (defined as baseline of Study M12-671 for participants who received elagolix in the pivotal study and baseline of the extension study M12-821 for participants who received placebo in the pivotal study) and Month 6

End point values	Placebo/Elagoli x 150 mg QD	Placebo/Elagoli x 200 mg BID	Elagolix/Elagoli x 150 mg QD	Elagolix/Elagoli x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	102	126	130
Units: hours				
arithmetic mean (standard deviation)				
Absenteeism from workplace (N = 49, 67, 77, 72)	-2.82 (± 5.648)	-1.33 (± 8.945)	-1.25 (± 4.377)	-1.73 (± 4.133)
Presenteeism from workplace (N = 48, 67, 76, 68)	-10.31 (± 15.902)	-8.37 (± 9.675)	-8.38 (± 12.489)	-10.63 (± 9.837)

Total hours lost from workplace (N=49, 67, 77, 72)	-13.22 (± 16.663)	-9.70 (± 13.683)	-9.36 (± 13.365)	-12.02 (± 10.447)
Absenteeism from household (N = 58, 71, 88, 88)	-3.17 (± 6.241)	-2.68 (± 3.779)	-3.56 (± 4.924)	-3.50 (± 4.180)
Presenteeism from household (N = 58, 71, 86, 84)	-2.47 (± 6.581)	-2.19 (± 4.973)	-2.33 (± 5.182)	-2.74 (± 5.308)
Total hours lost from household (N=58, 71, 88, 88)	-5.64 (± 9.919)	-4.86 (± 7.185)	-5.84 (± 7.844)	-6.17 (± 7.930)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Non-study Health Visits During the Treatment Period

End point title	Number of Participants With Non-study Health Visits During the Treatment Period

End point description:

The Health Resource Use Questionnaire (HRUQ) was used to collect information on non-study-related health visits that participants had during the study

End point type	Secondary

End point timeframe:

6 months

End point values	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD	Elagolix/Elagolix 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	111	142	140
Units: participants	48	65	76	76

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days in Hospital During the Treatment Period

End point title	Number of Days in Hospital During the Treatment Period

End point description:

The Health Resource Use Questionnaire (HRUQ) was used to collect information on non-study-related health visits that participants had during the study, including physician visits, hospitalizations and types of procedures received.

End point type	Secondary

End point timeframe:

6 months

End point values	Placebo/Elagoli x 150 mg QD	Placebo/Elagoli x 200 mg BID	Elagolix/Elagoli x 150 mg QD	Elagolix/Elagoli x 200 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[35]	11[36]	10[37]	13[38]
Units: days				
median (full range (min-max))	2.0 (1 to 6)	4.0 (2 to 13)	3.0 (1 to 7)	3.0 (1 to 7)

Notes:

[35] - Subjects who received at least 1 dose of study drug in Study M12-821 and underwent hospitalization

[36] - Subjects who received at least 1 dose of study drug in Study M12-821 and underwent hospitalization

[37] - Subjects who received at least 1 dose of study drug in Study M12-821 and underwent hospitalization

[38] - Subjects who received at least 1 dose of study drug in Study M12-821 and underwent hospitalization

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of the first dose of study drug in Study M12-821 through up to 30 days after the last dose of study drug (up to 7 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo/Elagolix 150 mg QD

Reporting group description:

Participants who received placebo in pivotal Study M12-671 and were randomized to elagolix 150 mg QD for 6 months in this extension Study M12-821.

Reporting group title	Placebo/Elagolix 200 mg BID

Reporting group description:

Participants who received placebo in pivotal Study M12-671 and were randomized to elagolix 200 mg BID for 6 months in this extension Study M12-821.

Reporting group title	Elagolix/Elagolix 150 mg QD

Reporting group description:

Participants were randomized to elagolix 150 mg QD in pivotal Study M12-671 and continued to receive elagolix 150 mg QD for 6 months in this extension Study M12-821.

Reporting group title	Elagolix/Elagolix 200 mg BID

Reporting group description:

Participants were randomized to elagolix 200 mg BID in pivotal Study M12-671 and continued to receive elagolix 200 mg BID for 6 months in this extension Study M12-821.

Serious adverse events	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 102 (3.92%)	8 / 111 (7.21%)	7 / 142 (4.93%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PELVIC NEOPLASM			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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
TERATOMA			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	1 / 142 (0.70%)
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			
CARBON MONOXIDE POISONING			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	0 / 142 (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
INCISIONAL HERNIA			
subjects affected / exposed	1 / 102 (0.98%)	0 / 111 (0.00%)	0 / 142 (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
LIGAMENT RUPTURE			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	0 / 142 (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
PROCEDURAL HYPERTENSION			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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
TIBIA FRACTURE			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	0 / 142 (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
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	2 / 142 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	0 / 142 (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
General disorders and administration site conditions			
PYREXIA			

subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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			
ABDOMINAL HERNIA			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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
ABDOMINAL PAIN			
subjects affected / exposed	2 / 102 (1.96%)	0 / 111 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN LOWER			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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 MOTILITY DISORDER			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IRRITABLE BOWEL SYNDROME			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
OVARIAN CYST			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC PAIN			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PERINEAL PAIN			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	0 / 142 (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
DYSPNOEA			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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
NASAL POLYPS			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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			
ARTHRALGIA			
subjects affected / exposed	1 / 102 (0.98%)	0 / 111 (0.00%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOCHONDROSIS			

subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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			
DENGUE FEVER			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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
DIVERTICULITIS			
subjects affected / exposed	0 / 102 (0.00%)	1 / 111 (0.90%)	0 / 142 (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
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 102 (0.00%)	0 / 111 (0.00%)	0 / 142 (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	Elagolix/Elagolix 200 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 140 (5.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PELVIC NEOPLASM			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
TERATOMA			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
CARBON MONOXIDE POISONING			

subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INCISIONAL HERNIA			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LIGAMENT RUPTURE			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PROCEDURAL HYPERTENSION			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
TIBIA FRACTURE			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
PYREXIA			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL HERNIA			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ABDOMINAL PAIN			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ABDOMINAL PAIN LOWER			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GASTROINTESTINAL MOTILITY DISORDER			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
IRRITABLE BOWEL SYNDROME			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
OVARIAN CYST			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PELVIC PAIN			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

PERINEAL PAIN			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DYSPNOEA			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
NASAL POLYPS			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
OSTEOCHONDROSIS			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
DENGUE FEVER			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DIVERTICULITIS			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo/Elagolix 150 mg QD	Placebo/Elagolix 200 mg BID	Elagolix/Elagolix 150 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 102 (48.04%)	74 / 111 (66.67%)	65 / 142 (45.77%)
Investigations			
BONE DENSITY DECREASED			
subjects affected / exposed	1 / 102 (0.98%)	2 / 111 (1.80%)	0 / 142 (0.00%)
occurrences (all)	1	2	0
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	15 / 102 (14.71%)	45 / 111 (40.54%)	7 / 142 (4.93%)
occurrences (all)	16	47	7
Nervous system disorders			
HEADACHE			
subjects affected / exposed	13 / 102 (12.75%)	18 / 111 (16.22%)	9 / 142 (6.34%)
occurrences (all)	15	20	11
General disorders and administration site conditions			

FATIGUE			
subjects affected / exposed	0 / 102 (0.00%)	6 / 111 (5.41%)	0 / 142 (0.00%)
occurrences (all)	0	6	0
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	6 / 102 (5.88%)	13 / 111 (11.71%)	14 / 142 (9.86%)
occurrences (all)	6	14	15
Reproductive system and breast disorders			
AMENORRHOEA			
subjects affected / exposed	4 / 102 (3.92%)	14 / 111 (12.61%)	4 / 142 (2.82%)
occurrences (all)	6	16	4
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	6 / 102 (5.88%)	6 / 111 (5.41%)	5 / 142 (3.52%)
occurrences (all)	6	6	6
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	3 / 102 (2.94%)	7 / 111 (6.31%)	4 / 142 (2.82%)
occurrences (all)	3	7	5
INSOMNIA			
subjects affected / exposed	4 / 102 (3.92%)	8 / 111 (7.21%)	4 / 142 (2.82%)
occurrences (all)	4	8	4
MOOD SWINGS			
subjects affected / exposed	7 / 102 (6.86%)	7 / 111 (6.31%)	3 / 142 (2.11%)
occurrences (all)	7	7	3
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	9 / 102 (8.82%)	12 / 111 (10.81%)	6 / 142 (4.23%)
occurrences (all)	10	13	6
BACK PAIN			
subjects affected / exposed	2 / 102 (1.96%)	6 / 111 (5.41%)	6 / 142 (4.23%)
occurrences (all)	2	7	6
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	6 / 102 (5.88%)	10 / 111 (9.01%)	6 / 142 (4.23%)
occurrences (all)	6	10	6
SINUSITIS			

subjects affected / exposed	6 / 102 (5.88%)	6 / 111 (5.41%)	8 / 142 (5.63%)
occurrences (all)	6	8	9
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 102 (4.90%)	6 / 111 (5.41%)	6 / 142 (4.23%)
occurrences (all)	6	7	8
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 102 (2.94%)	9 / 111 (8.11%)	10 / 142 (7.04%)
occurrences (all)	3	12	11

Non-serious adverse events	Elagolix/Elagolix 200 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 140 (50.00%)		
Investigations			
BONE DENSITY DECREASED			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences (all)	8		
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	11 / 140 (7.86%)		
occurrences (all)	11		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	9 / 140 (6.43%)		
occurrences (all)	9		
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences (all)	2		
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	5 / 140 (3.57%)		
occurrences (all)	5		
Reproductive system and breast disorders			
AMENORRHOEA			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences (all)	2		

Skin and subcutaneous tissue disorders ACNE subjects affected / exposed occurrences (all)	 2 / 140 (1.43%) 2		
Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all) INSOMNIA subjects affected / exposed occurrences (all) MOOD SWINGS subjects affected / exposed occurrences (all)	 2 / 140 (1.43%) 2 3 / 140 (2.14%) 3 2 / 140 (1.43%) 2		
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) BACK PAIN subjects affected / exposed occurrences (all)	 9 / 140 (6.43%) 10 10 / 140 (7.14%) 11		
Infections and infestations NASOPHARYNGITIS subjects affected / exposed occurrences (all) SINUSITIS subjects affected / exposed occurrences (all) UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all) URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	 9 / 140 (6.43%) 10 8 / 140 (5.71%) 8 6 / 140 (4.29%) 7 11 / 140 (7.86%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2014	The purpose of this amendment was to: ● Update the Treatment Period to add: "Prophylactic use of rescue analgesics (i.e., on a standing basis or for prevention of pain) for endometriosis-associated pain is not permitted during the study (from Day 1 of the Treatment Period through Month 6 of the Post-treatment Follow-up Period)." Subjects were allowed the use of permitted analgesic rescue therapy on an as needed basis. ● Update Selection of Study Population to split the combined Exclusion Criterion 6 into 2 separate criteria to clarify malignancy Criterion 6 and neuropsychiatric Criterion 7. ● Update Prohibited Therapy to remove prescription amphetamine, or amphetamine-like drugs, and to add cannabinoids inclusive of any marijuana use, as prohibited medications. ● Update Permitted Rescue Therapy to remove Tramadol 50 mg. ● Update Efficacy, Pharmacokinetic, Pharmacodynamic and Safety Assessments as follows: - Efficacy and Safety Measurements Assessed to provide clarifications and incorporate applicable changes within the body text of the protocol. - Increase the visit window from 4 to 5 days. - Update Medical/Social History to add a collection of documentation of drug abuse (licit or illicit) at Day 1. - Update Pap Test to add biopsy with colposcopy, and to clarify that both colposcopy and biopsy results should be discussed with the sponsor. - Update Study Procedures with a footnote to clarify 8-hour minimum fast for Clinical/Safety Laboratory Tests. - Update Clinical Laboratory Tests, to change "Any repeat testing must be approved" to "Any repeat testing should be approved by an AbbVie representative." - Update BMD to allow scans be performed within 5 days of scheduled visit ● Update Adverse Event Reporting to include a 24-hour hotline for the investigator to contact AbbVie on-call physician in emergency. ● Update Pregnancy to add "any" to clarify that outcome of any pregnancy should be collected ● Update Statistical Methods to clarify methods.

24 September 2015	The purpose of this amendment was to: ● Remove fasting requirement on study drug administration ● Add requirement on use of calcium and vitamin D daily during the PTFU Period. ● Clarify that a brief physical examination is conducted only if there are reported symptoms. ● Instruct on use of the same modality consistently to measure body temperature. ● Clarify that subjects with a Pap diagnosis of atypical squamous cells of undetermined significance (ASC-US) with high risk human papillomavirus (HPV) or low-grade squamous intraepithelial lesion (LSIL) should undergo additional evaluation with colposcopy and biopsy, if applicable per local guidelines. ● Clarify that pregnancy testing applies to all subjects, whether exempted from use of a dual barrier non-hormonal contraception or not, and request that subjects attest on use of allowable contraception methods at every visit. ● Add requirement for DXA Scan at Month 6 in the PTFU Period for all subjects. ● Change the capacity of the collection tubes and the amount of serum collected from 4 mL to 3 mL. ● Add change from baseline in ECG to the safety variables. ● Clarify that temperature must be recorded each business day to document proper temperature of clinical supplies. ● Clarify that changes in BMD may be considered an AE if resulting in discontinuation from the study. ● Instruct sites to complete an SAE on the non-CRF forms and provide guidance when access to RAVE® is unavailable. ● Add specifics on time windows for analyses, referencing the SAP. ● Replace "nominal day" with "reference study day," and clarify window calculation for Month 1. ● Clarify that sensitivity analyses are done for the proportion of DYS and NMPP responders at Month 6. ● Remove the statement on "Subjects who discontinue for other reasons will be categorized according to LOCF." ● Add that information on responders will be based on the ROC thresholds calculated in Study M12-671. ● Specify which variable will be analyzed at EOT.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported