Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain

Summary

EudraCT number	2011-004295-11
Trial protocol	GB CZ AT IT HU ES
Global end of trial date	19 December 2016

Results information

Result version number	v1 (current)
This version publication date	03 January 2018
First version publication date	03 January 2018

Trial information

Trial identification

Sponsor protocol code	M12-671

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01931670
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Paul M. Peloso, MD, MSc, AbbVie, 1 847-935-2233, paul.peloso@abbvie.com
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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	19 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability and efficacy of elagolix (ABT-620), administered once daily (QD) or twice daily (BID) for 6 months in the management of moderate to severe endometriosis-associated pain, and to evaluate the effect of elagolix treatment on analgesic use for endometriosis-associated pain.

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	09 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 147
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Czech Republic: 56
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	New Zealand: 16
Country: Number of subjects enrolled	South Africa: 20
Country: Number of subjects enrolled	United States: 402
Worldwide total number of subjects	815
EEA total number of subjects	325

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)	815
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Requirements for washout were to be completed before a subject entered the Screening Period or underwent any screening procedures. Subjects who were not taking exclusionary medications that required washout were entered directly into the Screening Period and provided written informed consent before any study-related procedures were performed.

Period 1

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

Blinding implementation details:

Each active 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	Placebo

Arm description:

Placebo twice daily (BID) for the 6-month Treatment Period

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken at approximately the same time every morning and every evening in order to promote compliance.

Arm title	Elagolix 150 mg QD

Arm description:

Elagolix 150 mg once daily (QD) for the 6-month Treatment Period plus

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

Dosage and administration details:

Study drug was taken at approximately the same time every morning and every evening in order to promote compliance. To maintain the blind, a matching 150 mg placebo tablet was also administered to allow for BID dosing.

Arm title	Elagolix 200 mg BID

Arm description:

Elagolix 200 mg BID for the 6-month Treatment Period

Arm type	Experimental

Investigational medicinal product name	elagolix
Investigational medicinal product code	ABT-620
Other name	elagolix sodium
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken at approximately the same time every morning and every evening in order to promote compliance.

Number of subjects in period 1	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID
Started	360	226	229
Completed	270	178	184
Not completed	90	48	45
Surgery/invasive intervention	4	2	-
Consent withdrawn by subject	17	12	7
Not specified	8	7	2
Pregnancy	7	2	-
Adverse event	19	8	21
Lost to follow-up	19	5	7
Subject noncompliant	4	9	5
Exclusionary medication received	1	1	1
Lack of efficacy	11	2	2

Period 2

Period 2 title	Post-Treatment Follow-Up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Each active 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	Placebo

Arm description:

Placebo BID for the 6-month Treatment Period

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Elagolix 150 mg QD

Arm description:	
Elagolix 150 mg QD for the 6-month Treatment Period	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Elagolix 200 mg BID
Arm description:	
Elagolix 200 mg BID for the 6-month Treatment Period	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2[1]	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID
Started	61	40	54
Completed PTFU Month 6	42	24 [2]	18 [3]
Completed PTFU Month 12	0 [4]	4 [5]	15 [6]
Completed	42	28	33
Not completed	19	12	21
Surgery/invasive intervention	4	4	2
Consent withdrawn by subject	6	3	13
Not specified	6	3	3
Adverse event	-	2	1
Lost to follow-up	-	-	2
Exclusionary medication received	3	-	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Milestone presents the number of subjects who completed PTFU period at given time points.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone presents the number of subjects who completed PTFU period at given time points.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone presents the number of subjects who completed PTFU period at given time points.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone presents the number of subjects who completed PTFU period at given time points.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone presents the number of subjects who completed PTFU period at given time points.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone presents the number of subjects who completed PTFU period at given time points.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo twice daily (BID) for the 6-month Treatment Period	
Reporting group title	Elagolix 150 mg QD
Reporting group description:	
Elagolix 150 mg once daily (QD) for the 6-month Treatment Period plus	
Reporting group title	Elagolix 200 mg BID
Reporting group description:	
Elagolix 200 mg BID for the 6-month Treatment Period	

Reporting group values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID
Number of subjects	360	226	229
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.1	33.1	33.4
standard deviation	± 6.69	± 6.80	± 6.67
Gender categorical Units: Subjects			
Female	360	226	229
Male	0	0	0

Reporting group values	Total		
Number of subjects	815		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	815		
Male	0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo twice daily (BID) for the 6-month Treatment Period	
Reporting group title	Elagolix 150 mg QD
Reporting group description:	
Elagolix 150 mg once daily (QD) for the 6-month Treatment Period plus	
Reporting group title	Elagolix 200 mg BID
Reporting group description:	
Elagolix 200 mg BID for the 6-month Treatment Period	
Reporting group title	Placebo
Reporting group description:	
Placebo BID for the 6-month Treatment Period	
Reporting group title	Elagolix 150 mg QD
Reporting group description:	
Elagolix 150 mg QD for the 6-month Treatment Period	
Reporting group title	Elagolix 200 mg BID
Reporting group description:	
Elagolix 200 mg BID for the 6-month Treatment Period	

Primary: Percentage of Responders at Month 3 Based on Daily Assessment of Dysmenorrhea (DYS)

End point title	Percentage of Responders at Month 3 Based on Daily Assessment of Dysmenorrhea (DYS)

End point description:

The DYS pain scale ranges from 0 (none) to 3 (severe). The criteria for a responder was based on a pre-defined threshold and accounted for analgesic use.

The modified intent-to-treat (mITT) analysis set; all randomized subjects who took at least 1 dose of randomized, double-blind study drug. Population included mITT subjects who either had data during the Month 3 35-day window or who prematurely discontinued prior to or at Month 3 and met the rules for last observation carried forward.

End point type	Primary

End point timeframe:

At Month 3 of the Treatment Period

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	221	225	
Units: percentage of subjects				
number (not applicable)	22.7	43.4	72.4	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Elagolix 150 mg QD
Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Elagolix 200 mg BID
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic

Primary: Percentage of Responders at Month 3 Based on Daily Assessment of Non-Menstrual Pelvic Pain (NMPP)

End point title	Percentage of Responders at Month 3 Based on Daily Assessment of Non-Menstrual Pelvic Pain (NMPP)

End point description:

The NMPP pain scale ranges from 0 (none) to 3 (severe). The criteria for a responder was based on a pre-defined threshold and accounted for analgesic use.

The mITT analysis set; all randomized subjects who took at least 1 dose of randomized, double-blind study drug. Population included mITT subjects who either had data during the Month 3 35-day window or who prematurely discontinued prior to or at Month 3 and met the rules for last observation carried forward.

End point type	Primary

End point timeframe:

At Month 3 of Treatment Period

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	221	225	
Units: percentage of subjects				
number (not applicable)	36.5	49.8	57.8	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Elagolix 150 mg QD v Placebo
Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Regression, Logistic

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Elagolix 200 mg BID
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic

Secondary: Change From Baseline to Month 3 in Numeric Rating Scale (NRS) Scores

End point title	Change From Baseline to Month 3 in Numeric Rating Scale (NRS) Scores

End point description:

The NRS for overall endometriosis-associated pain ranges 0 (none) to 10 (worst pain ever).

The mITT analysis set included all randomized participants who took at least 1 dose of randomized, double-blind study drug. Observed cases.

End point type	Secondary

End point timeframe:

Baseline, Month 3 of the Treatment Period

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	312	204	209	
Units: units on a scale				
least squares mean (standard error)	-1.33 (± 0.097)	-1.90 (± 0.122)	-2.55 (± 0.122)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Ranked secondary efficacy endpoint 1 of 7.

Comparison groups	Placebo v Elagolix 150 mg QD

Number of subjects included in analysis	516
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effects model

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Ranked secondary efficacy endpoint 1 of 7.	
Comparison groups	Placebo v Elagolix 200 mg BID
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effects model

Secondary: Change From Baseline to Month 6 in DYS

End point title	Change From Baseline to Month 6 in DYS
End point description: The DYS pain scale ranges from 0 (none) to 3 (severe). The mITT analysis set included all randomized subjects who took at least 1 dose of randomized, double-blind study drug. Observed cases.	
End point type	Secondary
End point timeframe: Baseline, Month 6 of Treatment Period	

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	273	185	187	
Units: units on a scale				
least squares mean (standard error)	-0.52 (± 0.047)	-1.06 (± 0.057)	-1.65 (± 0.057)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Ranked secondary efficacy endpoint 2 of 7.	
Comparison groups	Placebo v Elagolix 200 mg BID

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effects model

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Ranked secondary efficacy endpoint 2 of 7.	
Comparison groups	Placebo v Elagolix 150 mg QD
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effects model

Secondary: Change From Baseline to Month 6 in NMPP

End point title	Change From Baseline to Month 6 in NMPP
End point description: The NMPP pain scale ranges from 0 (none) to 3 (severe). The mITT analysis set included all randomized subjects who took at least 1 dose of randomized, double-blind study drug. Observed cases.	
End point type	Secondary
End point timeframe: Baseline, Month 6 of Treatment Period	

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	273	185	187	
Units: units on a scale				
least squares mean (standard error)	-0.48 (± 0.035)	-0.63 (± 0.044)	-0.80 (± 0.044)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Ranked secondary efficacy endpoint 3 of 7.	
Comparison groups	Placebo v Elagolix 150 mg QD

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	mixed-effects model

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Ranked secondary efficacy endpoint 3 of 7.

Comparison groups	Placebo v Elagolix 200 mg BID
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effects model

Secondary: Change From Baseline to Month 3 in Analgesic Use Across Both Classes of Rescue Analgesics

End point title	Change From Baseline to Month 3 in Analgesic Use Across Both Classes of Rescue Analgesics

End point description:

Permitted rescue medications included the nonsteroidal anti-inflammatory drug naproxen (500 or 550 mg), and one country-specific narcotic analgesic (5 mg hydrocodone + 300 or 325 mg acetaminophen, or 30 mg codeine + 500 mg acetaminophen, or 30 mg codeine, or 37.5 mg tramadol + 325 mg acetaminophen). Assessment was based on average pill counts.

The mITT analysis set included all randomized subjects who took at least 1 dose of randomized, double-blind study drug. Observed cases.

End point type	Secondary

End point timeframe:

Baseline, Month 3 of Treatment Period

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	312	204	209	
Units: number of pills				
least squares mean (standard error)	-0.31 (± 0.028)	-0.36 (± 0.035)	-0.49 (± 0.034)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Ranked secondary efficacy endpoint 4 of 7.	
Comparison groups	Placebo v Elagolix 200 mg BID
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effects model

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Ranked secondary efficacy endpoint 4 of 7.	
Comparison groups	Elagolix 150 mg QD v Placebo
Number of subjects included in analysis	516
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	mixed-effects model

Secondary: Change From Baseline to Month 6 in Analgesic Use Across Both Classes of Rescue Analgesics

End point title	Change From Baseline to Month 6 in Analgesic Use Across Both Classes of Rescue Analgesics

End point description:

Permitted rescue medications included the nonsteroidal anti-inflammatory drug naproxen (500 or 550 mg), and one country-specific narcotic analgesic (5 mg hydrocodone + 300 or 325 mg acetaminophen, or 30 mg codeine + 500 mg acetaminophen, or 30 mg codeine, or 37.5 mg tramadol + 325 mg acetaminophen). Assessment was based on average pill counts.

The mITT analysis set included all randomized subjects who took at least 1 dose of randomized, double-blind study drug. Observed cases.

End point type	Secondary

End point timeframe:

Baseline, Month 6 of Treatment Period

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	273	185	187	
Units: number of pills				
least squares mean (standard error)	-0.32 (± 0.030)	-0.40 (± 0.038)	-0.52 (± 0.037)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Ranked secondary efficacy endpoint 5 of 7.	
Comparison groups	Placebo v Elagolix 150 mg QD
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	mixed-effects model

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Ranked secondary efficacy endpoint 5 of 7.	
Comparison groups	Placebo v Elagolix 200 mg BID
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effects model

Secondary: Change From Baseline to Month 3 in Dyspareunia (DYSP)

End point title	Change From Baseline to Month 3 in Dyspareunia (DYSP)

End point description:

The DYSP pain scale ranges from 0 (absent) to 3 (severe).

The mITT analysis set included all randomized subjects who took at least 1 dose of randomized, double-blind study drug. Observed cases. Subjects who responded "not applicable" for the entire time point and at Baseline are excluded from the analysis.

End point type	Secondary

End point timeframe:

Baseline, Month 3 of Treatment Period

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226	145	150	
Units: units on a scale				
least squares mean (standard error)	-0.30 (± 0.042)	-0.39 (± 0.052)	-0.60 (± 0.052)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Ranked secondary efficacy endpoint 6 of 7.	
Comparison groups	Placebo v Elagolix 150 mg QD
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172
Method	mixed-effects model

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Ranked secondary efficacy endpoint 6 of 7.	
Comparison groups	Placebo v Elagolix 200 mg BID
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effects model

Secondary: Change From Baseline to Month 3 in Use of Narcotic Class of Medication (Opioids)

End point title	Change From Baseline to Month 3 in Use of Narcotic Class of Medication (Opioids)

End point description:

Permitted country-specific rescue narcotic analgesics included 5 mg hydrocodone + 300 or 325 mg acetaminophen, or 30 mg codeine + 500 mg acetaminophen, or 30 mg codeine, or 37.5 mg tramadol + 325 mg acetaminophen. Assessment was based on average pill counts.

The mITT analysis set included all randomized subjects who took at least 1 dose of randomized, double-blind study drug. Observed cases.

End point type	Secondary

End point timeframe:

Baseline, Month 3 of Treatment Period

End point values	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	312	204	209	
Units: number of pills				
least squares mean (standard error)	-0.12 (± 0.019)	-0.12 (± 0.024)	-0.21 (± 0.023)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Ranked secondary efficacy endpoint 7 of 7.	
Comparison groups	Placebo v Elagolix 200 mg BID
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	mixed-effects model

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Ranked secondary efficacy endpoint 7 of 7.	
Comparison groups	Placebo v Elagolix 150 mg QD
Number of subjects included in analysis	516
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.968
Method	mixed-effects model

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study treatment through 6 months of treatment plus up to 12 months of follow-up.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Elagolix 150 mg QD
Reporting group description: Elagolix 150 mg QD for the 6-month Treatment Period	
Reporting group title	Placebo
Reporting group description: Placebo BID for the 6-month Treatment Period	
Reporting group title	Elagolix 200 mg BID
Reporting group description: Elagolix 200 mg BID for the 6-month Treatment Period	

Serious adverse events	Elagolix 150 mg QD	Placebo	Elagolix 200 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 226 (5.31%)	12 / 360 (3.33%)	5 / 229 (2.18%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 226 (0.00%)	0 / 360 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCEDURAL PAIN			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (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
Vascular disorders			
BLOOD PRESSURE FLUCTUATION			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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	1 / 226 (0.44%)	1 / 360 (0.28%)	0 / 229 (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
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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
HEADACHE			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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
LUMBAR RADICULOPATHY			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (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
SYNCOPE			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABORTION SPONTANEOUS COMPLETE			
subjects affected / exposed	0 / 226 (0.00%)	2 / 360 (0.56%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			

subjects affected / exposed	2 / 226 (0.88%)	3 / 360 (0.83%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FREQUENT BOWEL MOVEMENTS			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (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
LARGE INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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
NAUSEA			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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			
ENDOMETRIOSIS			
subjects affected / exposed	2 / 226 (0.88%)	1 / 360 (0.28%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENORRHAGIA			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC PAIN			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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
PERINEAL PAIN			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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
UTERINE POLYP			

subjects affected / exposed	2 / 226 (0.88%)	0 / 360 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VAGINAL HAEMORRHAGE			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (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
Psychiatric disorders			
COMPLETED SUICIDE			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
RENAL COLIC			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (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
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	2 / 226 (0.88%)	0 / 360 (0.00%)	0 / 229 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (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
JAW CYST			
subjects affected / exposed	0 / 226 (0.00%)	0 / 360 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABSCESS ORAL			

subjects affected / exposed	1 / 226 (0.44%)	0 / 360 (0.00%)	0 / 229 (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
APPENDICITIS			
subjects affected / exposed	0 / 226 (0.00%)	0 / 360 (0.00%)	2 / 229 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHARYNGEAL ABSCESS			
subjects affected / exposed	0 / 226 (0.00%)	0 / 360 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE ABSCESS			
subjects affected / exposed	0 / 226 (0.00%)	0 / 360 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 226 (0.00%)	1 / 360 (0.28%)	0 / 229 (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

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

Non-serious adverse events	Elagolix 150 mg QD	Placebo	Elagolix 200 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	128 / 226 (56.64%)	158 / 360 (43.89%)	162 / 229 (70.74%)
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	51 / 226 (22.57%)	37 / 360 (10.28%)	109 / 229 (47.60%)
occurrences (all)	52	39	123
Nervous system disorders			
HEADACHE			
subjects affected / exposed	42 / 226 (18.58%)	50 / 360 (13.89%)	52 / 229 (22.71%)
occurrences (all)	62	75	68
Gastrointestinal disorders			

NAUSEA			
subjects affected / exposed	26 / 226 (11.50%)	40 / 360 (11.11%)	36 / 229 (15.72%)
occurrences (all)	28	44	42
Reproductive system and breast disorders			
AMENORRHOEA			
subjects affected / exposed	11 / 226 (4.87%)	1 / 360 (0.28%)	20 / 229 (8.73%)
occurrences (all)	15	1	21
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	13 / 226 (5.75%)	12 / 360 (3.33%)	24 / 229 (10.48%)
occurrences (all)	14	12	24
MOOD SWINGS			
subjects affected / exposed	13 / 226 (5.75%)	8 / 360 (2.22%)	6 / 229 (2.62%)
occurrences (all)	13	8	6
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	7 / 226 (3.10%)	11 / 360 (3.06%)	16 / 229 (6.99%)
occurrences (all)	7	12	19
BACK PAIN			
subjects affected / exposed	8 / 226 (3.54%)	15 / 360 (4.17%)	13 / 229 (5.68%)
occurrences (all)	9	18	13
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	15 / 226 (6.64%)	21 / 360 (5.83%)	16 / 229 (6.99%)
occurrences (all)	21	27	20
SINUSITIS			
subjects affected / exposed	10 / 226 (4.42%)	14 / 360 (3.89%)	15 / 229 (6.55%)
occurrences (all)	13	14	16
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	11 / 226 (4.87%)	16 / 360 (4.44%)	12 / 229 (5.24%)
occurrences (all)	12	18	13
URINARY TRACT INFECTION			
subjects affected / exposed	10 / 226 (4.42%)	26 / 360 (7.22%)	19 / 229 (8.30%)
occurrences (all)	12	32	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2013	• Modified the rescue therapy permitted for endometriosis-associated pain in Austria, Czech Republic, Hungary, and Spain to allow the use of a combination product containing tramadol 37.5 mg and acetaminophen 325 mg. • Revised the list of protocol signatories in Appendix B.
18 June 2013	• Updated the Overall Study Design and Plan section to reflect the revised approximate number of sites planned for the study, the clarification of pregnancy testing around timing of Day 1, and the expanded Screening Period based on cycle length changes. • Modified the following key inclusion criteria: Expanded the endometriosis clinical laparoscopic diagnosis window to 10 years. The menstrual cycle window was expanded, and only 1 menstrual cycle would be required to proceed to the Screening Period. Expanded the window during which 2 menstrual cycles were required to occur in order to proceed to the Treatment Period, Day 1. Clarified conditions that would interfere with obtaining adequate DXA measurements Defined which analgesics were to be used in each participating country • Modified the following key exclusion criteria: Clarified that the use of any known inducers of CYP3A was prohibited within 1 month prior to Day 1. Updated the description of major psychiatric disorders that would result in subject exclusion and expanded to include post-Traumatic stress disorder. • Updated the Table of Prohibited Medications to indicate that one time use of Cytotec was allowed with the endometrial biopsy procedure required for the study. • Updated the Table of Permitted Rescue Therapy for endometriosis-associated pain to allow the combination hydrocodone/acetaminophen with 300 mg of acetaminophen since the 300 mg and 325 mg formulations are considered to be equivalent and add the opioids analgesics used in Canada. • Revised rescue therapy to allow the use of both protocol allowed rescue analgesics simultaneously. • Updated the Study Procedures Section to describe the Pap test results required for enrollment in the study, and to clarify premedication use for the endometrial biopsy procedure. • Updated details related to the interim analysis based on the Sponsor's decision regarding the timing of the start of the second pivotal study.
18 June 2013	(continued) • Changed the purpose of the interim analysis based on internal decision to start the second pivotal study with the current elagolix data available at the time.
03 July 2014	• Updated the Overall Study Design Plan to clarify Month 6 Treatment visit was Day 1 of extension Study M12-821. • Revised entry criteria to: Clarified Screening criteria for documentation of menstrual cycles and intervals, malignancy, suicide, use of corticosteroids, and types of investigational studies and products; Updated Pap Test to include biopsy with colposcopy; Clarified use of QTcF or QTcB to evaluate QT interval of 12-lead ECG. • Added procedures required to be conducted if an additional study drug kit(s) was dispensed at Study Day 168 ± 5 days. • Updated ECG section to add QT interval correction formula.

13 July 2015	• Updated Screening, Treatment, and PTFU Period study activities to further describe physical examination and pregnancy testing requirements, as well as assessment of vital signs and ECGs. • Added criteria for consideration of clinically significant BMD changes as AEs • Updated Management of BMD Loss at Month 6 to capture < 8% BMD in the femoral neck as being eligible for participation in the extension study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported