Clinical trial results:
A Phase 3 Randomized, Double-blind, Placebo-Controlled Trial to Study the Efficacy and Safety of MK-8342B (ENG-E2 vaginal ring) in Women with Moderate to Severe Primary Dysmenorrhea.

Summary

EudraCT number	2015-004326-34
Trial protocol	SE PL IT
Global end of trial date	12 September 2016

Results information

Result version number	v1 (current)
This version publication date	20 May 2018
First version publication date	20 May 2018

Trial information

Trial identification

Sponsor protocol code	8342B-060

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02668822
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Study Number: MK-8342B-060

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	ClinicalTrialsDisclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	ClinicalTrialsDisclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	12 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy of the etonogestrel (ENG) + 17β-estradiol (E2) (MK-8342B) vaginal ring compared to placebo vaginal ring in the treatment of dysmenorrhea at Treatment Cycle 2. This study was also to assess the safety and tolerability of the ENG-E2 vaginal rings over 4 treatment cycles. Primary hypothesis: Relative to the placebo ring, the ENG-E2 vaginal ring results in a greater proportion of participants with a ≥3-point reduction in peak pelvic pain score and no increase in the number of rescue pain relief (ibuprofen) tablets taken at Treatment Cycle 2 as compared to baseline

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Ibuprofen 400 mg every 4 hours as needed for pelvic pain/ cramping

Evidence for comparator: -

Actual start date of recruitment	09 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	18
EEA total number of subjects	4

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)	18
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was to involve 4 treatment cycles after a screening period. Each treatment cycle lasted 28 days (21 days of ring use followed by a 7-day ring-free interval). The study was terminated by the Sponsor as a result of a business decision to discontinue the development program for MK-8342B for reasons unrelated to safety or efficacy outcomes.

Pre-assignment

Screening details:

Post-menarcheal female participants aged 50 years and younger with moderate to severe primary dysmenorrhea were enrolled in this study. Other inclusion/exclusion criteria applied.

Period 1

Period 1 title	Treatment (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	ENG 125 µg + E2 300 µg (MK-8342B)

Arm description:

Participants received up to 4 cycles of etonogestrel-17β estradiol (ENG-E2) at a daily dose of 125 µg/300 µg via vaginal ring. Each cycle consisted of 21 days of MK-8342B vaginal ring use followed by 7 ring-free days.

Arm type	Experimental
Investigational medicinal product name	ENG-E2 vaginal ring
Investigational medicinal product code	
Other name	MK-8342B
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Vaginal ring inserted for 21 days then 7 days ring-free

Investigational medicinal product name	Ibuprofen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg as needed for cramps

Arm title	Placebo

Arm description:

Participants received up to 4 cycles of placebo via vaginal ring. Each cycle consisted of 21 days of placebo vaginal ring use followed by 7 ring-free days.

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

Dosage and administration details: 400 mg as needed for cramps	
Investigational medicinal product name	Placebo for ENG-E2 vaginal ring
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Vaginal ring inserted for 21 days then 7 days ring-free

Number of subjects in period 1	ENG 125 µg + E2 300 µg (MK-8342B)	Placebo
Started	9	9
Completed	0	0
Not completed	9	9
Study Terminated	7	9
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	ENG 125 µg + E2 300 µg (MK-8342B)
Reporting group description:	
Participants received up to 4 cycles of etonogestrel-17β estradiol (ENG-E2) at a daily dose of 125 µg/300 µg via vaginal ring. Each cycle consisted of 21 days of MK-8342B vaginal ring use followed by 7 ring-free days.	
Reporting group title	Placebo
Reporting group description:	
Participants received up to 4 cycles of placebo via vaginal ring. Each cycle consisted of 21 days of placebo vaginal ring use followed by 7 ring-free days.	

Reporting group values	ENG 125 µg + E2 300 µg (MK-8342B)	Placebo	Total
Number of subjects	9	9	18
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	31	28	
standard deviation	± 10	± 5	-
Gender Categorical Units: Subjects			
Female	9	9	18
Male	0	0	0

End points

End points reporting groups

Reporting group title	ENG 125 µg + E2 300 µg (MK-8342B)

Reporting group description:

Participants received up to 4 cycles of etonogestrel-17β estradiol (ENG-E2) at a daily dose of 125 µg/300 µg via vaginal ring. Each cycle consisted of 21 days of MK-8342B vaginal ring use followed by 7 ring-free days.

Reporting group title	Placebo

Reporting group description:

Participants received up to 4 cycles of placebo via vaginal ring. Each cycle consisted of 21 days of placebo vaginal ring use followed by 7 ring-free days.

Subject analysis set title	ENG 125 µg + E2 300 µg (MK-8342B)- Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants in whom a vaginal ring was inserted

Subject analysis set title	Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants in whom a vaginal ring was inserted

Subject analysis set title	ENG 125 µg + E2 300 µg (MK-8342B) - Efficacy
Subject analysis set type	Full analysis

Subject analysis set description:

The population was to consist of all participants in whom a vaginal ring was inserted & who had ≥1 day of diary entry each within a 4-day cramping window during a baseline cycle & a treatment cycle. Due to termination, the committee to determine cramping windows was not assembled, cramping windows were not determined & data could not be analyzed.

Subject analysis set title	Placebo - Efficacy
Subject analysis set type	Full analysis

Subject analysis set description:

The population was to consist of all participants in whom a vaginal ring was inserted & who had ≥1 day of diary entry each within a 4-day cramping window during a baseline cycle & a treatment cycle. Due to termination, the committee to determine cramping windows was not assembled, cramping windows were not determined & data could not be analyzed.

Primary: Percentage of Participants With ≥3 point Reduction in Peak Pelvic Pain Score and No Increase in Number of Ibuprofen Tablets Taken at Treatment Cycle 2, Compared to Baseline

End point title	Percentage of Participants With ≥3 point Reduction in Peak Pelvic Pain Score and No Increase in Number of Ibuprofen Tablets Taken at Treatment Cycle 2, Compared to Baseline[1]

End point description:

Participants were asked to rate their worst pain or cramps in the past 24 hours on a scale of 0 to 10 (0=No pain or cramps to 10=Extreme pain or cramps) and to indicate the number of ibuprofen tablets they took during the 4-day cramping window. The peak pelvic pain score was to be calculated as the highest (daily) pelvic pain score observed within the cramping window of the cycle and the total number of ibuprofen tablets taken was to be based on the 4-day cramping window. The baseline peak pelvic pain score and number of ibuprofen tablets taken were to be defined as the mean value of the 2 peak pelvic pain scores and the mean value of the total number of ibuprofen tablets taken during the cramping window of each of the 2 menstruations during the screening period, respectively. The percentage of participants with a reduction in peak pelvic pain score of ≥3 points and no increase in the use of ibuprofen at Treatment Cycle 2 as compared to baseline was to be presented.

End point type	Primary

End point timeframe:

Baseline 4-day cramping window and Treatment Cycle 2 4-day cramping window, as determined by committee for each participant

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: Efficacy data could not be analyzed as cramping windows were not determined due to early trial termination

End point values	ENG 125 µg + E2 300 µg (MK-8342B) - Efficacy	Placebo - Efficacy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[2]	0[3]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[2] - Study terminated

[3] - Study terminated

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an Adverse Event (AE)

End point title	Number of Participants Who Experienced an Adverse Event (AE)[4]

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the
use of the study treatment, whether or not considered related to the use of study treatment. The number of participants who experienced an AE is presented.

End point type	Primary

End point timeframe:

Up to approximately 126 days

Notes:

[4] - 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 analyses were not conducted for this safety endpoint due to early trial termination

End point values	ENG 125 µg + E2 300 µg (MK-8342B)- Safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Participants				
number (not applicable)	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Study Treatment Due to an AE

End point title	Number of Participants Who Discontinued Study Treatment Due

	to an AE[5]

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study treatment, whether or not considered related to the use of study treatment. The number of participants who discontinued study treatment due an AE is presented.

End point type	Primary

End point timeframe:

Up to approximately 112 days

Notes:

[5] - 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 analyses were not conducted for this safety endpoint due to early trial termination

End point values	ENG 125 µg + E2 300 µg (MK-8342B)-Safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Peak Pelvic Pain Score at Treatment Cycle 2

End point title	Change From Baseline in Peak Pelvic Pain Score at Treatment Cycle 2

End point description:

Participants were asked to rate their worst pain or cramps in the past 24 hours on a scale of 0 to 10 (0=No pain or cramps to 10=Extreme pain or cramps). The peak pelvic pain score was to be calculated as the highest (daily) pelvic pain score observed within the 4-day cramping window of the cycle. The baseline peak pelvic pain score was to be defined as the mean value of the 2 peak pelvic pain scores during the cramping window of each of the 2 menstruations during the screening period. The change from baseline in peak pelvic pain score at Treatment Cycle 2 was to be presented.

End point type	Secondary

End point timeframe:

Baseline 4-day cramping window and Treatment Cycle 2 4-day cramping window, as determined by committee for each participant

End point values	ENG 125 µg + E2 300 µg (MK-8342B) - Efficacy	Placebo - Efficacy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[6]	0[7]		
Units: Score on a Scale				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[6] - Study terminated

[7] - Study terminated

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Number of Days with No Impact on Items of Physical, Work/School and Social/Leisure Activities at Treatment Cycle 2

End point title	Change From Baseline in the Number of Days with No Impact on Items of Physical, Work/School and Social/Leisure Activities at Treatment Cycle 2

End point description:

Participants were asked to indicate how much pain or cramps limited their physical, work/school and social/leisure activities and over the previous 24 hours. The level of negative impact of dysmenorrhea on daily life was scored on a 5-point scale (0=Not at all to 4=Extremely impacted). For each of the 3 impact items, the baseline score was to be defined as the mean value obtained from the 2 menstruations during the screening period. The change from baseline to Treatment Cycle 2 in the number of days during the cramping window with no impact of dysmenorrhea (score = 0) on each of the following items was to be presented: work/school, physical activities and leisure/social activities.

End point type	Secondary

End point timeframe:

Baseline 4-day cramping window and Treatment Cycle 2 4-day cramping window, as determined by committee for each participant

End point values	ENG 125 µg + E2 300 µg (MK-8342B) - Efficacy	Placebo - Efficacy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[8]	0[9]		
Units: Days				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[8] - Study terminated

[9] - Study terminated

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pelvic Pain Score of "0" or "1" and No Use of Ibuprofen Tablets at Treatment Cycle 2

End point title	Percentage of Participants With Pelvic Pain Score of "0" or "1" and No Use of Ibuprofen Tablets at Treatment Cycle 2

End point description:

Participants were asked to rate their worst pain or cramps on a scale of 0 to 10 (0=No pain or cramps to 10=Extreme pain or cramps) and to indicate the number of ibuprofen tablets they took during the 4-day cramping window. The percentage of participants with no or minimal pelvic pain (score of "0" or "1") and no use of ibuprofen at Treatment Cycle 2 was to be presented.

End point type	Secondary

End point timeframe:

Treatment Cycle 2 4-day cramping window, as determined by committee for each participant

End point values	ENG 125 µg + E2 300 µg (MK-8342B) - Efficacy	Placebo - Efficacy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[10]	0[11]		
Units: Percentage of Participants				
number (not applicable)				

Notes:

[10] - Study terminated

[11] - Study terminated

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ≥3-point Reduction in Peak Pelvic Pain Score and a Decrease in Number of Ibuprofen Tablets Taken at Treatment Cycle 2, Compared to Baseline

End point title	Percentage of Participants With ≥3-point Reduction in Peak Pelvic Pain Score and a Decrease in Number of Ibuprofen Tablets Taken at Treatment Cycle 2, Compared to Baseline

End point description:

Participants were asked to rate their worst pain or cramps in the past 24 hours on a scale of 0 to 10 (0=No pain or cramps to 10=Extreme pain or cramps) and to indicate the number of ibuprofen tablets they took during the 4-day cramping window. The baseline peak pelvic pain score and number of ibuprofen tablets taken were to be defined as the mean value of the 2 peak pelvic pain scores and the mean value of the total number of ibuprofen tablets taken during the cramping window of each of the 2 menstruations during the screening period, respectively. The percentage of participants with a reduction in peak pelvic pain score of ≥3 points and a decrease in the use of ibuprofen at Treatment Cycle 2 as compared to baseline was to be presented.

End point type	Secondary

End point timeframe:

Baseline 4-day cramping window and Treatment Cycle 2 4-day cramping window, as determined by committee for each participant

End point values	ENG 125 µg + E2 300 µg (MK-8342B) - Efficacy	Placebo - Efficacy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[12]	0[13]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[12] - Study terminated

[13] - Study terminated

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Mean Pelvic Pain Score at Treatment Cycle 2

End point title	Change From Baseline in the Mean Pelvic Pain Score at Treatment Cycle 2

End point description:

The mean pelvic pain score was to be calculated as the mean of the highest scores for pelvic pain observed within the 4-day cramping window of the screening or treatment cycle. The baseline mean pelvic pain score was to be defined as the mean value of the 2 mean pelvic pain scores of the 2 menstruations during the screening period. The change from baseline in mean pelvic pain score at Treatment Cycle 2 was to be presented.

End point type	Secondary

End point timeframe:

Baseline 4-day cramping window and Treatment Cycle 2 4-day cramping window, as determined by committee for each participant

End point values	ENG 125 µg + E2 300 µg (MK-8342B) - Efficacy	Placebo - Efficacy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[14]	0[15]		
Units: Score on a scale				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[14] - Study terminated

[15] - Study terminated

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 30 days after last dose of study treatment (Up to approximately 126 days)	
Adverse event reporting additional description:	
The population consisted of all participants in whom a vaginal ring was inserted.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	ENG-E2 125 µg/300 µg
Reporting group description:	
Participants received up to 4 cycles of ENGE2 at a daily dose of 125 µg/300 µg via vaginal ring. Each cycle consisted of 21 days of MK-8342B vaginal ring use followed by 7 ring-free days.	
Reporting group title	Placebo
Reporting group description:	
Participants received up to 4 cycles of placebo via vaginal ring. Each cycle consisted of 21 days of placebo vaginal ring use followed by 7 ring-free days.	

Serious adverse events	ENG-E2 125 µg/300 µg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	ENG-E2 125 µg/300 µg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study terminated by Sponsor as a result of a business decision to discontinue the development program for MK-8342B for reasons unrelated to safety or efficacy

Notes: