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 (with Optional Extension)

Summary

EudraCT number	2015-004325-14
Trial protocol	DE FI
Global end of trial date	07 September 2016

Results information

Result version number	v1 (current)
This version publication date	18 May 2018
First version publication date	18 May 2018

Trial information

Trial identification

Sponsor protocol code	8342B-059

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02668783
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-8342B-059

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, 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	07 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the etonogestrel (ENG) + 17β-estradiol (E2) vaginal ring's efficacy compared to a placebo vaginal ring in the treatment of dysmenorrhea at Treatment Cycle 2. In addition, this study will assess the safety and tolerability of the ENG-E2 vaginal rings. 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: -

Evidence for comparator: -

Actual start date of recruitment	11 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	Finland: 2
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	25
EEA total number of subjects	2

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)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 25 participants were randomized, with 24 participants receiving study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ENG-E2 125 µg/300 µg

Arm description:

Participants received 4 cycles (or 6 cycles if also participating in the extension) of ENG-E2 125 µg/300 µg. Each cycle consisted of 21 days of vaginal ring use followed by 7 ring-free days.

Arm type	Experimental
Investigational medicinal product name	Etonogestrel (ENG) 125µg + 17β-estradiol (E2) 300 µg vaginal ring
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Up to 4 cycles (or 6 cycles if also participating in the extension) of ENG-E2 125 µg/300 µg administered intravaginally. Each cycle will consist of 21 days of vaginal ring use followed by 7 ring-free days.

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

Dosage and administration details:

Ibuprofen tablets, to be taken orally, will be provided for use as rescue medication for dysmenorrhea treatment throughout the study. Participants may take 400 mg every 4 hours as needed for pelvic pain/cramping, or as instructed by their physician according to local labeling for relief of menstrual pain.

Arm title	Placebo

Arm description:

Participants received 4 cycles (or 6 cycles if also participating in the extension) of placebo. Each cycle consisted of 21 days of placebo vaginal ring use followed by 7 ring-free days.

Arm type	Placebo
Investigational medicinal product name	Placebo vaginal ring
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Up to 4 cycles (or 6 cycles if also participating in the extension) of placebo administered intravaginally. Each cycle will consist of 21 days of vaginal ring use followed by 7 ring-free days.

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

Dosage and administration details:

Ibuprofen tablets, to be taken orally, will be provided for use as rescue medication for dysmenorrhea treatment throughout the study. Participants may take 400 mg every 4 hours as needed for pelvic pain/cramping, or as instructed by their physician according to local labeling for relief of menstrual pain.

Number of subjects in period 1	ENG-E2 125 µg/300 µg	Placebo
Started	13	12
Treated	13	11
Completed	0	0
Not completed	13	12
Consent withdrawn by subject	1	-
Pregnancy	-	1
Study terminated by sponsor	9	10
Subject moved	1	-
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	ENG-E2 125 µg/300 µg
Reporting group description:	
Participants received 4 cycles (or 6 cycles if also participating in the extension) of ENG-E2 125 µg/300 µg. Each cycle consisted of 21 days of vaginal ring use followed by 7 ring-free days.	
Reporting group title	Placebo
Reporting group description:	
Participants received 4 cycles (or 6 cycles if also participating in the extension) of placebo. Each cycle consisted of 21 days of placebo vaginal ring use followed by 7 ring-free days.	

Reporting group values	ENG-E2 125 µg/300 µg	Placebo	Total
Number of subjects	13	12	25
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	12	25
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	27	29	
standard deviation	± 7	± 6	-
Sex: Female, Male Units: Subjects			
Female	13	12	25
Male	0	0	0

End points

End points reporting groups

Reporting group title	ENG-E2 125 µg/300 µg

Reporting group description:

Participants received 4 cycles (or 6 cycles if also participating in the extension) of ENG-E2 125 µg/300 µg. Each cycle consisted of 21 days of vaginal ring use followed by 7 ring-free days.

Reporting group title	Placebo

Reporting group description:

Participants received 4 cycles (or 6 cycles if also participating in the extension) of placebo. Each cycle consisted of 21 days of placebo vaginal ring use followed by 7 ring-free days.

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 rated pain/cramps in past 24 hours from 0 (none) to 10 (extreme) and reported number of ibuprofen tablets taken during 4-day cramping window. Peak pelvic pain score was defined as highest daily score in cycle cramping window. Baseline peak pelvic pain score (average of 2 scores) and baseline number (average) of ibuprofen tablets taken were defined during the cramping windows of 2 menstruations in screening period. Percentage of participants with reduction in peak pelvic pain score of ≥3 points and no increase in the use of ibuprofen at Cycle 2 compared to baseline was to be presented. Analysis Population: was to include all participants in whom a vaginal ring was inserted, with ≥1 day of diary entry in a 4-day cramping window during both a baseline & treatment cycle. Due to termination, a blinded independent committee to set cramping windows was not assembled, cramping windows were not determined & efficacy data could not be analyzed.

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-E2 125 µg/300 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Percentage of participants				

Notes:

[2] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

[3] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

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

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. Analysis Population: all randomized participants in whom a vaginal ring was inserted.

End point type	Primary

End point timeframe:

Up to approximately 158 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-E2 125 µg/300 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	11		
Units: Participants	1	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who discontinued treatment due to an AE

End point title	Number of participants who discontinued 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 to an AE is presented. Analysis Population: all randomized participants in whom a vaginal ring was inserted.

End point type	Primary

End point timeframe:

Up to approximately 128 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-E2 125 µg/300 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	11		
Units: Participants	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. Analysis Population: was to consist of all participants in whom a vaginal ring was inserted & who had ≥1 day of diary entry each within 4-day cramping window during a baseline & a treatment cycle. Due to termination, a blinded independent committee to determine cramping windows was not assembled, cramping windows were not determined & efficacy data could not be analyzed.

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-E2 125 µg/300 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Score on a scale				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[6] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

[7] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

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 indicated how much pain/cramps limited their physical, work/school and social/leisure activities 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 items, baseline was defined as mean value obtained from the 2 menstruations during the screening period. 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, and leisure/social activities. Analysis Population: was to include all participants in whom a vaginal ring was inserted & who had ≥1 day of diary entry each in a 4-day cramping window during a baseline & a treatment cycle. Due to termination, a blinded independent committee to determine cramping windows was not assembled, cramping windows were not determined & efficacy data could not be analyzed.

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-E2 125 µg/300 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Days				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[8] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

[9] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

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. Analysis 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 Treatment Cycle 2. Due to termination, a blinded independent committee to determine cramping windows was not assembled, cramping windows were not determined & efficacy data could not be analyzed.

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-E2 125 µg/300 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Percentage of participants				

Notes:

[10] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

[11] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

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 ibuprofen tablet intake 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 ibuprofen tablet intake at

	Treatment Cycle 2, compared to baseline

End point description:

Participants rated worst pain/cramps in past 24 hours from 0 (None) to 10 (Extreme) and indicated the number of ibuprofen tablets taken during the 4-day cramping window. Baseline peak pelvic pain score and number of ibuprofen tablets taken were respectively defined as mean value of the 2 peak pelvic pain scores and mean number of ibuprofen tablets taken during the cramping window of each of the 2 menstruations during screening period. 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. Analysis Population: was to include 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 & treatment cycle. Due to termination, a blinded independent committee to determine cramping windows was not assembled, cramping windows were not determined & efficacy data could not be analyzed.

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-E2 125 µg/300 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Percentage of participants				

Notes:

[12] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

[13] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean pelvic pain score at Treatment Cycle 2

End point title	Change from baseline in 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. Analysis 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 & a treatment cycle. Due to termination, a blinded independent committee to determine cramping windows was not assembled, cramping windows were not determined & efficacy data could not be analyzed.

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-E2 125 µg/300 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: Score on a scale				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[14] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

[15] - Trial terminated before determination of cramping windows; efficacy data could not be analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 158 days	
Adverse event reporting additional description:	
All randomized 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	Placebo
Reporting group description:	
Participants received 4 cycles (or 6 cycles if also participating in the extension) of placebo. Each cycle consisted of 21 days of placebo vaginal ring use followed by 7 ring-free days.	
Reporting group title	ENG-E2 125 microgram/300 microgram
Reporting group description:	
Participants received 4 cycles (or 6 cycles if also participating in the extension) of ENG-E2 125 µg/300 µg. Each cycle consisted of 21 days of vaginal ring use followed by 7 ring-free days.	

Serious adverse events	Placebo	ENG-E2 125 microgram/300 microgram	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (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	Placebo	ENG-E2 125 microgram/300 microgram	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 11 (18.18%)	1 / 13 (7.69%)	
Pregnancy, puerperium and perinatal conditions			
Vomiting in pregnancy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Vulvovaginal discomfort subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 13 (0.00%) 0	
Psychiatric disorders Mood swings subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 13 (7.69%) 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? Yes

Date	Interruption	Restart date
13 July 2016	Trial was terminated early.	-

Notes:

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: