Clinical trial results:
A Phase 3, Randomized, Active-Comparator Controlled Clinical Trial to Study the Contraceptive Efficacy and Safety of the MK-8342B (Etonogestrel + 17-Estradiol) Vaginal Ring and the Levonorgestrel-Ethinyl Estradiol (LNG-EE) 150/30 g Combined Oral Contraceptive (COC) in Healthy Women 18 Years of Age and Older, at Risk for Pregnancy.

Summary

EudraCT number	2014-002208-26
Trial protocol	NO SE DE FI DK AT ES NL HU PL CZ IT
Global end of trial date	06 October 2016

Results information

Result version number	v1 (current)
This version publication date	28 September 2017
First version publication date	28 September 2017

Trial information

Trial identification

Sponsor protocol code	8342B-062

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02616146
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration: MK-8342B-062

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	06 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2016
Global end of trial reached?	Yes
Global end of trial date	06 October 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 contraceptive efficacy of the etonogestrel + 17β-estradiol (ENG-E2) vaginal ring in women between 18 and 35 years of age based on the number of in-treatment pregnancies as expressed by the Pearl Index (PI). The study will also assess the safety and tolerability of ENG-E2 vaginal ring. The levonorgestrelethinyl estradiol (LNG-EE) 150/30 µg combined oral contraceptive (COC) will be used as the active comparator.

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	01 December 2015
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	Austria: 6
Country: Number of subjects enrolled	Chile: 188
Country: Number of subjects enrolled	Colombia: 93
Country: Number of subjects enrolled	Costa Rica: 35
Country: Number of subjects enrolled	Czech Republic: 173
Country: Number of subjects enrolled	Denmark: 81
Country: Number of subjects enrolled	Finland: 168
Country: Number of subjects enrolled	Germany: 143
Country: Number of subjects enrolled	Hungary: 122
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Mexico: 118
Country: Number of subjects enrolled	Netherlands: 48
Country: Number of subjects enrolled	Norway: 175
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Poland: 225
Country: Number of subjects enrolled	Russian Federation: 224
Country: Number of subjects enrolled	South Africa: 97
Country: Number of subjects enrolled	Spain: 68

Country: Number of subjects enrolled	Sweden: 40
Worldwide total number of subjects	2016
EEA total number of subjects	1255

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)	1
Adults (18-64 years)	2015
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Note: One subject less than 18 years of age was inadvertently randomized and received study medication. She was discontinued from the study due to the major protocol violation.

Pre-assignment

Screening details:

This study enrolled in healthy, premenopausal women 18 years of age and older who were at risk of pregnancy. Additional inclusion and exclusion criteria applied.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

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

Arm description:

Participants received up to 13 cycles of ENG-E2 125 µg/300 µg. Each cycle consisted of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

Arm type	Experimental
Investigational medicinal product name	Etonogestrel + 17β-Estradiol Vaginal Ring
Investigational medicinal product code	
Other name	MK-8342B
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Up to 13 cycles of ENG-E2 125 µg/300 µg administered intravaginally, each cycle consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

Arm title	LNG-EE 150 µg/30 µg

Arm description:

Participants received up to 13 cycles of LNG-EE 150 µg/30 µg. Each cycle consisted of one tablet per day for 21 days, followed a 7-day tablet-free interval.

Arm type	Active comparator
Investigational medicinal product name	Levonorgestrel-Ethinyl Estradiol COC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Up to 13 cycles of LNG-EE 150 µg/30 µg administered orally, each cycle consisting of one tablet per day for 21 days, followed a 7-day tablet-free interval.

Number of subjects in period 1	ENG-E2 125 µg/300 µg	LNG-EE 150 µg/30 µg
Started	1512	504
Completed	0	0
Not completed	1512	504
Pregnancy Wish	3	-
Non-Compliance With Study Protocol	2	-
Withdrawal By Participant	30	24
Physician decision	2	1
Adverse event, non-fatal	64	24
Study Terminated By Sponsor	1372	432
Non-Compliance With Study Drug	4	2
Pregnancy	2	2
Participant Moved	4	3
Lost to follow-up	23	13
Protocol deviation	6	3

Baseline characteristics

Reporting groups	
Reporting group title	ENG-E2 125 µg/300 µg
Reporting group description:	
Participants received up to 13 cycles of ENG-E2 125 µg/300 µg. Each cycle consisted of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	
Reporting group title	LNG-EE 150 µg/30 µg
Reporting group description:	
Participants received up to 13 cycles of LNG-EE 150 µg/30 µg. Each cycle consisted of one tablet per day for 21 days, followed a 7-day tablet-free interval.	

Reporting group values	ENG-E2 125 µg/300 µg	LNG-EE 150 µg/30 µg	Total
Number of subjects	1512	504	2016
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	27.5	27.5	
standard deviation	± 6.3	± 6.3	-
Gender Categorical			
Units: Subjects			
Female	1512	504	2016
Male	0	0	0

End points

End points reporting groups

Reporting group title	ENG-E2 125 µg/300 µg

Reporting group description:

Participants received up to 13 cycles of ENG-E2 125 µg/300 µg. Each cycle consisted of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

Reporting group title	LNG-EE 150 µg/30 µg

Reporting group description:

Participants received up to 13 cycles of LNG-EE 150 µg/30 µg. Each cycle consisted of one tablet per day for 21 days, followed a 7-day tablet-free interval.

Primary: Number of In-Treatment Pregnancies per 100 Woman-Years of Exposure in Participants 18-35 Years of Age (Pearl Index)

End point title	Number of In-Treatment Pregnancies per 100 Woman-Years of Exposure in Participants 18-35 Years of Age (Pearl Index)[1]

End point description:

The Primary Efficacy Outcome Measure for this study was contraceptive efficacy, or the prevention of in-treatment pregnancy. The total incidence of in-treatment pregnancies was expressed as the Pearl Index, which is defined as the number of in-treatment pregnancies per 100 woman-years of exposure (one woman-year defined as a period of 365.25 days). This primary endpoint was based on the restricted Full Analysis Set (rFAS) population, defined as the population of women with at least one "at risk" treatment cycle without documented use of hormonal or nonhormonal backup contraception during the cycle, or participants with a treatment cycle (at risk or not) in which a pregnancy has occurred. These results should be interpreted with caution because the trial was terminated early and the subject diary data used for calculation of the Pearl Index were not verified.

End point type	Primary

End point timeframe:

Up to 1 year (13 28-day cycles)

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: No between-group statistical analyses were performed for Number of In-Treatment Pregnancies per 100 Woman-Years of Exposure in Participants 18-35 Years of Age (Pearl Index).

End point values	ENG-E2 125 µg/300 µg	LNG-EE 150 µg/30 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1266	404		
Units: Pregnancies per 100 woman years				
number (not applicable)	1.54	2.93		

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)[2]

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the Sponsor's product, is also an AE. This primary endpoint was based on all randomized participants in whom at least 1 vaginal ring was inserted or one comparator tablet was ingested.

End point type	Primary

End point timeframe:

Up to 1 year

Notes:

[2] - 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: No between-group statistical analyses were performed for Number of Participants Who Experienced an Adverse Event (AE)

End point values	ENG-E2 125 µg/300 µg	LNG-EE 150 µg/30 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1504	492		
Units: Participants	530	140		

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[3]

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the Sponsor's product, is also an AE. This primary endpoint was based on all randomized participants in whom at least 1 vaginal ring was inserted or one comparator tablet was ingested.

End point type	Primary

End point timeframe:

Up to 1 year

Notes:

[3] - 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: No between-group statistical analyses were performed for Number of Participants Who Discontinued Treatment Due to an AE

End point values	ENG-E2 125 µg/300 µg	LNG-EE 150 µg/30 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1504	492		
Units: Participants	61	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Breakthrough Bleeding/Spotting (BTB-S), by Cycle

End point title	Number of Participants With Breakthrough Bleeding/Spotting (BTB-S), by Cycle

End point description:

BTB-S was considered any bleeding/spotting that occurred during expected non-bleeding interval that was neither early nor continued withdrawal bleeding. BTB-S was classified as follows: Bleeding = any bloody vaginal discharge that required one or more sanitary pads or tampons per day; Spotting = any bloody vaginal discharge that required no sanitary pads or tampons per day. This secondary endpoint was based on the FAS Evaluable population, defined as a subset of the FAS population that met the following criteria: a) No more than 2 consecutive days with missing bleeding data on the Daily Diary unless there was at least one day with BTB-S during the ring-use interval; and b) Treatment cycle length (including the hormone-free interval) is between 22 and 35 days, inclusive. These results should be interpreted with caution because the trial was terminated early and the subject diary data used for calculation of these results were not verified. No hypothesis testing was performed.

End point type	Secondary

End point timeframe:

Up to 1 year

End point values	ENG-E2 125 µg/300 µg	LNG-EE 150 µg/30 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1504	492		
Units: Participants				
Cycle 2 (n=1263; n=375)	166	54		
Cycle 3 (n=1001; n=295)	112	36		
Cycle 4 (n=755; n=231)	79	20		
Cycle 5 (n=483; n=155)	42	13		
Cycle 6 (n=295; n=88)	29	8		
Cycle 7 (n=125 n=40)	13	7		
Cycle 8 (n=36; n=10)	8	2		
Cycle 9 (n=7; n=1)	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 1 year

Adverse event reporting additional description:

All randomized participants in whom at least 1 vaginal ring was inserted or one comparator tablet was ingested.

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: -	
Reporting group title	LNG-EE 150 µg/30 µg COC

Reporting group description: -

Serious adverse events	ENG-E2 125 µg/300 µg	LNG-EE 150 µg/30 µg COC	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 1504 (0.53%)	3 / 492 (0.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Foreign body			
subjects affected / exposed	1 / 1504 (0.07%)	0 / 492 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 1504 (0.00%)	1 / 492 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 1504 (0.07%)	0 / 492 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 1504 (0.07%)	0 / 492 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 1504 (0.00%)	1 / 492 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 1504 (0.00%)	1 / 492 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 1504 (0.07%)	0 / 492 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Dengue fever			
subjects affected / exposed	1 / 1504 (0.07%)	0 / 492 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 1504 (0.07%)	0 / 492 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 1504 (0.00%)	1 / 492 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 1504 (0.07%)	0 / 492 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device deployment issue			
subjects affected / exposed	1 / 1504 (0.07%)	0 / 492 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ENG-E2 125 µg/300 µg	LNG-EE 150 µg/30 µg COC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	116 / 1504 (7.71%)	40 / 492 (8.13%)	
Nervous system disorders			
Headache			
subjects affected / exposed	116 / 1504 (7.71%)	40 / 492 (8.13%)	
occurrences (all)	180	68	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2016	Amendment 1. The primary reasons for this amendment were: to emphasize that the discontinuation visit should be scheduled no sooner than 14 days and up to 17 days after discontinuation of study medication; to add a urine pregnancy test to be performed at home at the time of the safety follow-up phone visit if a discontinued participant refuses to return to clinic; and to clarify that safety labs (hematology, chemistry, and urinalysis) should be performed at discontinuation if not already performed at Visit 5 (i.e., participant discontinues prior to V5).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 July 2016	This 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. Results regarding the Pearl Index and BTB-S should be interpreted with caution because the trial was terminated early and the subject diary data used for these analyses were not verified.	-

Notes:

Limitations and caveats

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

This 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.

Notes: