



Clinical trial results:

Characterization of ovulation inhibition of a new vaginal delivery system (EVE 112, Evestra/Germany) containing etonogestrel and ethinylestradiol – an open label, single centre, comparative, parallel-group study in healthy females of childbearing potential

Summary

EudraCT number	2016-000115-32
Trial protocol	DE
Global end of trial date	17 January 2017

Results information

Result version number	v1 (current)
This version publication date	09 May 2020
First version publication date	09 May 2020

Trial information

Trial identification

Sponsor protocol code	EVE112-CT02-2015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CRO number: 1319ee15ct

Notes:

Sponsors

Sponsor organisation name	Evestra GmbH
Sponsor organisation address	Britzer Strasse 26 , Berlin, Germany, 12439
Public contact	Dr. Maika Friedrich, Evestra GmbH, +49 3066509643, mfriedrich@evestra.com
Scientific contact	Dr. Maika Friedrich, Evestra GmbH, +49 3066509643, mfriedrich@evestra.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	11 April 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of this clinical trial is:

- To show the non-inferior efficacy of the Test Product (EVE112) compared to the Reference Product (NuvaRing®) in terms of ovulation inhibition rate based on Hoogland score

Protection of trial subjects:

Prior to recruitment of subjects, all relevant documents of the clinical study were submitted and proved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and subject information sheet described the planned and permitted uses, transfers and disclosures of the subject's personal data and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every subject was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The subject's consent was obtained in writing before the start of the study. By signing the informed consent, the subject declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 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	Germany: 87
Worldwide total number of subjects	87
EEA total number of subjects	87

Notes:

Subjects enrolled per age group

In utero	0
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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)	87
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Assessments of screening examination was performed within 6 weeks prior to start of pre-treatment cycle to evaluate eligibility for the study. A total of 132 healthy female subjects was screened for enrolment and of them 87 subjects were randomised into the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Test - EVE 112

Arm description: -

Arm type	Experimental
Investigational medicinal product name	EVE 112
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

2 treatment cycles of 28 days each with vaginal application of 1 vaginal ring of Test with a nominal delivery rate of 120 µg/d etonogestrel (ENG) and 15 µg/d ethinylestradiol (EE) applied for 21 days per cycle separated by 7 treatment-free days

Arm title	Reference - NuvaRing®
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	NuvaRing®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

2 treatment cycles of 28 days each with vaginal application of 1 vaginal ring of Reference with a nominal delivery rate of 120 µg/d etonogestrel (ENG) and 15 µg/d ethinylestradiol (EE) for 21 days per cycle separated by 7 treatment-free days.

Number of subjects in period 1	Test - EVE 112	Reference - NuvaRing®
Started	44	43
Completed	40	40
Not completed	4	3
Consent withdrawn by subject	3	2
Pregnancy	1	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
Reporting group description: -	

Reporting group values	Overall Trial	Total	
Number of subjects	87	87	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	87	87	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	29		
standard deviation	± 4	-	
Gender categorical			
Units: Subjects			
Female	87	87	

Subject analysis sets

Subject analysis set title	SAS
Subject analysis set type	Safety analysis
Subject analysis set description: The SAS was defined as all subjects randomised.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all subjects of the SAS, who after randomisation, completed at least one treatment cycle of 28 days, or in whom a Hoogland score >5 was observed in any cycle during randomised treatment.	
Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS was defined as all subjects randomised

- who completely passed the pre-defined treatment regimen and
- whose relevant trial variables were available in all treatment cycles, and
- who finished the clinical trial without major protocol deviations.

PPS was the primary population for the analysis of efficacy endpoints.

Reporting group values	SAS	FAS	PPS
Number of subjects	87	81	78
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)	87	81	78
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	29	29	29
standard deviation	± 4	± 4	± 4
Gender categorical Units: Subjects			
Female	87	81	78

End points

End points reporting groups

Reporting group title	Test - EVE 112
Reporting group description: -	
Reporting group title	Reference - NuvaRing®
Reporting group description: -	
Subject analysis set title	SAS
Subject analysis set type	Safety analysis
Subject analysis set description: The SAS was defined as all subjects randomised.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all subjects of the SAS, who after randomisation, completed at least one treatment cycle of 28 days, or in whom a Hoogland score >5 was observed in any cycle during randomised treatment.	
Subject analysis set title	PPS
Subject analysis set type	Per protocol
Subject analysis set description: The PPS was defined as all subjects randomised • who completely passed the pre-defined treatment regimen and • whose relevant trial variables were available in all treatment cycles, and • who finished the clinical trial without major protocol deviations. PPS was the primary population for the analysis of efficacy endpoints.	

Primary: Ovulation inhibition rate - Hoogland and Skouby score

End point title	Ovulation inhibition rate - Hoogland and Skouby score
End point description:	
End point type	Primary
End point timeframe: The ovulation inhibition rate (defined as the proportion of subjects with a Hoogland and Skouby score $\leq$ 5) in treatment cycle 2 was calculated.	

End point values	Test - EVE 112	Reference - NuvaRing®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: percent				
number (not applicable)	100	100		

Statistical analyses

Statistical analysis title	Ovulation inhibition rate
Statistical analysis description: The ovulation inhibition rate (defined as the proportion of subjects with a Hoogland score less than or	

equal to 5) in treatment cycle 2 was calculated in both treatment arms.

Comparison groups	Test - EVE 112 v Reference - NuvaRing®
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.025
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0897
upper limit	0.0897

Notes:

[1] - The estimated difference between test and reference proportions and the two-sided 95% Wilson score confidence interval of the difference was calculated.

If the confidence interval of the difference between proportions is entirely above -10 % (the non-inferiority margin) then Test was considered non-inferior to Reference.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The observation phase for AEs began with start of the treatment and ended with the discharge of the subject from the clinical trial.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Test - EVE 112
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Reporting group description: -

Reporting group title	Reference - NuvaRing®
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Reporting group description: -

Serious adverse events	Test - EVE 112	Reference - NuvaRing®	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 44 (4.55%)	1 / 43 (2.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Cerebral vasoconstriction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (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			
Peritonsillar abscess			

subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Test - EVE 112	Reference - NuvaRing®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 44 (93.18%)	41 / 43 (95.35%)	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 44 (45.45%)	17 / 43 (39.53%)	
occurrences (all)	32	30	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 44 (11.36%)	6 / 43 (13.95%)	
occurrences (all)	7	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 44 (25.00%)	4 / 43 (9.30%)	
occurrences (all)	16	4	
Abdominal pain lower			
subjects affected / exposed	13 / 44 (29.55%)	2 / 43 (4.65%)	
occurrences (all)	14	2	
Vomiting			
subjects affected / exposed	6 / 44 (13.64%)	1 / 43 (2.33%)	
occurrences (all)	7	1	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	25 / 44 (56.82%)	20 / 43 (46.51%)	
occurrences (all)	39	31	
Dysmenorrhoea			
subjects affected / exposed	6 / 44 (13.64%)	3 / 43 (6.98%)	
occurrences (all)	6	3	
Skin and subcutaneous tissue disorders			

Acne subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 8	6 / 43 (13.95%) 7	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	17 / 44 (38.64%) 19	22 / 43 (51.16%) 25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2016	Amendment 01 of the final Clinical trial protocol became necessary due to changes requested by the Ethics Committee. An additional withdrawal criterion ("Venous and/or arterial thromboembolism after inclusion") considering the known side effects of the Reference product was added in the protocol.
01 April 2016	The substantial Amendment 02 of final clinical trial protocol became necessary due to planned changes in the conduct of the trial. Following the Sponsor's decision, the study objectives were changed in such that the nature of the evaluation was changed from a descriptive level to a confirmative assessment. This change led to an increase of the sample size needed to achieve the study objectives, adaptation of the statistical evaluation description, amendment of the definition of FAS. Furthermore, in order to improve retrospective control of treatment compliance, retrospective determination of the active ingredients ethinylestradiol (EE) and/or etonogestrel (ENG) in serum samples already available for progesterone determination in subjects for whom an ovulation has been observed by TVUS, was added. In addition, according to the SmPC of the reference product, definition of day of first insertion of IMP was adapted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported