Clinical trial results:
Assessment of therapeutical equivalence of a newly developed vaginal tablet containing 10 g of estradiol in comparison with a marketed reference product (Vagifem®) – a double-blind, double-dummy, multiple dose, parallel-group, placebo- and active-controlled trial with additional characterisation of systemic exposure in postmenopausal female volunteers suffering from vaginal atrophy

Summary

EudraCT number	2017-000142-22
Trial protocol	DE
Global end of trial date	17 January 2019

Results information

Result version number	v1 (current)
This version publication date	11 October 2020
First version publication date	11 October 2020

Trial information

Trial identification

Sponsor protocol code	148-2016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	1335esd16ct: CRO trial number

Notes:

Sponsors

Sponsor organisation name	Helm AG
Sponsor organisation address	Nordkanalstrasse 28, Hamburg, Germany, 20097
Public contact	Clinical Development, Helm AG, +49 40 2375 1798, Irina.Maslova@helmag.com
Scientific contact	Clinical Development, Helm AG, +49 40 2375 1798, Irina.Maslova@helmag.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	21 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Characterisation and comparison of efficacy of Test vs. Reference with regard to pharmacodynamic (PD) surrogate parameters (primary endpoints: change from baseline of vaginal maturation value after 2 weeks of treatment and change from baseline of vaginal pH after 6 weeks of treatment)

- Assessment of superiority of Test vs. Placebo with regard to PD primary endpoints

- Assessment of therapeutic equivalence of Test vs. Reference with regard to PD primary endpoints

- Characterisation of systemic exposure by means of AUC- and Cmax–values of Test and Reference vaginal tablets containing 10 µg estradiol on Day 14 after multiple dose vaginal application (PK group)

- Descriptive characterisation of safety and tolerability of the Test and Reference treatments.

Protection of trial subjects:

Prior to recruitment of patients, all relevant documents of the clinical study were submitted and approved 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 patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient 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 patient 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 patient’s consent was obtained in writing before the start of the study. By signing the informed consent, the patient 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:

Any pre-existing long-term medication for treatment of existing disorders, which was not considered to interfere with absorption, efficacy, or safety of the IMP or is not listed in the restrictions was permitted.

Evidence for comparator:

Comparators were the following products:
a) Marketed reference product Vagifem® 10 µg vaginal tablets (Novo Nordisk, Denmark)
b) Placebo for Test (Aenova Holding GmbH, Germany on behalf of Helm AG, Germany)
c) Placebo for Reference (Aenova Holding GmbH, Germany on behalf of Helm AG, Germany)

Actual start date of recruitment	28 June 2017
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	Moldova, Republic of: 242
Country: Number of subjects enrolled	Bulgaria: 188
Country: Number of subjects enrolled	Germany: 44
Worldwide total number of subjects	474
EEA total number of subjects	232

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)	369
From 65 to 84 years	103
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

In total, 474 female subjects were enrolled in the study. The pharmacokinetic group included 27 subjects in total from Germany. The pharmacodynamic group included 17 subjects from Germany, 188 subjects from Bulgaria and 242 subjects from Moldova.

Pre-assignment

Screening details:

In total 1736 subjctes were screened for the study. From 56 subjects screened for the pharmacokinetic group, 27 subjects were randomised into this study group. From 1680 subjects screened for the pharmacodynamic group, 447 subjects were randomised into this study group.

Period 1

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

Blinding implementation details:

In order to avoid bias the study was realised with a double-blinded approach in the Pharmacodynamic group for assessment of efficacy, i.e. subjects and investigators as well as the laboratory have not been aware of the treatment administered.
Test and Reference vaginal tablets were visually similar but the difficulty for blinding arose from the different application devices. To overcome this drawback the study has been planned with a double-dummy approach for the Pharmacodynamic group.

Arms

Are arms mutually exclusive?	Yes
Arm title	Estradiol 10 µg - Test

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Estradiol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Intravaginal application of 1 tablet of Estradiol and 1 tablet of Placebo per day for 14 days (initial treatment period) followed by intravaginal application of 1 tablet of Estradiol and 1 tablet of Placebo-Reference twice a week for 4 weeks (maintenance treatment period).

Arm title	Vagifem 10 µg - Reference

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Vagifem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Intravaginal application of 1 tablet of Vagifem and 1 tablet of Placebo per day for 14 days (initial treatment period) followed by intravaginal application of 1 tablet of Vagifem and 1 tablet of Placebo-Test twice a week for 4 weeks (maintenance treatment period).

Arm title	Placebo

Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Intravaginal application of 1 tablet of Placebo-Reference and 1 tablet of Placebo-Test per day for 14 days (initial treatment period) followed by intravaginal application of 1 tablet of Placebo-Reference and 1 tablet of Placebo-Test twice a week for 4 weeks (maintenance treatment period).

Number of subjects in period 1[1]	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo
Started	203	179	60
Completed	196	163	56
Not completed	7	16	4
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	3	7	4
Adverse event, non-fatal	2	3	-
Protocol deviation	2	5	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The study consisted of two independent parts, a pharmacokinetic (PK)- and a pharmacodynamic (PD)- part. Due to presentation purposes, PD-group was definded as period 1 (baseline period). Different subjects were enrolled in PK- and PD-group. Thus, number of subjects in the baseline period 1 (PD-group) is not the same as the worldwide number enrolled in the trial (PD- + PK-group).

Period 2

Period 2 title	Pharmacokinetic Group
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

For the PK group, no blinding was necessary, since within this group the focus of the clinical trial was set on the characterisation of the systemic estradiol exposure as a surrogate safety parameter. Thus, for this group the trial was open for both, subjects and investigators but blinded with respect to the bioanalytical laboratory.

Arms

Are arms mutually exclusive?	Yes
Arm title	Estradiol 10 µg - Test

Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Estradiol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Intravaginal application of 1 tablet per day for 14 days.

Arm title	Vagifem 10 µg - Reference

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Vagifem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Intravaginal application of 1 tablet per day for 14 days.

Number of subjects in period 2[2]	Estradiol 10 µg - Test	Vagifem 10 µg - Reference
Started	13	14
Completed	13	14

Notes:

[2] - 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: The study consisted of two independent parts, a pharmacokinetic (PK)- and a pharmacodynamic (PD)- part. Different subjects were enrolled in PK- and PD-group. Due to presentation purposes, PD-group was definded as period 1 and PK-group was defined as period 2. Period 1 and period 2 were independent study parts and not subsequent study periods. Thus, numbers of subject starting the single periods are different.

Baseline characteristics

Reporting groups

Reporting group title	Pharmacodynamic Group

Reporting group description: -

Reporting group values	Pharmacodynamic Group	Total	
Number of subjects	442	442	
Age categorical Units: Subjects			
Adults (18-64 years)	350	350	
From 65-84 years	90	90	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	59.0		
full range (min-max)	45 to 96	-	
Gender categorical Units: Subjects			
Female	442	442	
Male	0	0	

Subject analysis sets

Subject analysis set title	PPS_PK
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS was defined as all subjects that:
- were randomised
- were included in the pharmacokinetic part of the clinical trial
- finished the pharmacokinetic part of the clinical trial with no major protocol deviations as defined in the trial protocol and the Statistical Analysis Plan, in particular:
  - randomized treatment not administered or wrong treatment administered
  - missing PK samples which result in insufficient profiling

Subject analysis set title	FAS_PK
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS was defined as all subjects randomised into the trial as subject of the pharmacokinetic arm.

Subject analysis set title	SAS_PK
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAS was defined as all subjects that:
- were randomised into the trial as subject of the pharmacokinetic arm
- received the investigational drug at least once.

Subject analysis set title	PPS_PD
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects that were randomized and finished the trial as defined in the protocol without major protocol deviations in particular regarding compliance with the treatment and, thus, being a complete case. The conventions for missed IMP applications apply:
- Initial treatment period: At least 80 % of the total IMP-dose had to be applied during the initial phase. Missing IMP applications on single days (but not on subsequent study days) were not considered

relevant, because the exposure to IMP was sufficient.
- Maintenance period: IMP application had to be performed on at least 7 out of 8 days and was not allowed to exceed a maximum of 9 application days to be compliant to the protocol.
- Duration of the maintenance phase was compliant to the protocol if visit 4 was held within 4 days after the last IMP application and within 28±4 days after visit 3.
- A complete case was defined as a subject for whom a result for maturation value was available on at least visits 01, 02 and 04.

Subject analysis set title	mFAS_PD
Subject analysis set type	Full analysis

Subject analysis set description:

The modified Full Analysis Sets were defined to include all subjects that:
- were randomised
- received the investigational drug at least once.
- fulfilled all major entry criteria
- provided at least one data value necessary post-baseline for the primary endpoints

All subjects for whom the mFAS definition was applicable and who were included in either evaluation of the first stage, evaluation of the second stage or the combined PD analysis, i.e. combining subjects from first stage (interim) analysis and second stage analysis.

Subject analysis set title	SAS_PD
Subject analysis set type	Safety analysis

Subject analysis set description:

The SASPD was defined as all subjects that:
- were randomised
- received the investigational drug at least once.

Reporting group values	PPS_PK	FAS_PK	SAS_PK
Number of subjects	27	27	27
Age categorical Units: Subjects			
Adults (18-64 years)	15	15	15
From 65-84 years	12	12	12
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61.9	61.9	61.9
full range (min-max)	49 to 78	49 to 78	49 to 78
Gender categorical Units: Subjects			
Female	27	27	27
Male	0	0	0

Reporting group values	PPS_PD	mFAS_PD	SAS_PD
Number of subjects	394	432	442
Age categorical Units: Subjects			
Adults (18-64 years)	315	342	350
From 65-84 years	77	88	90
85 years and over	2	2	2
Age continuous Units: years			
arithmetic mean	59.0	59.1	59.0
full range (min-max)	45 to 96	45 to 96	45 to 96
Gender categorical Units: Subjects			
Female	394	432	442

Male	0	0	0

End points

End points reporting groups

Reporting group title	Estradiol 10 µg - Test
Reporting group description: -	
Reporting group title	Vagifem 10 µg - Reference
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Estradiol 10 µg - Test
Reporting group description: -	
Reporting group title	Vagifem 10 µg - Reference
Reporting group description: -	
Subject analysis set title	PPS_PK
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS was defined as all subjects that:
- were randomised
- were included in the pharmacokinetic part of the clinical trial
- finished the pharmacokinetic part of the clinical trial with no major protocol deviations as defined in the trial protocol and the Statistical Analysis Plan, in particular:
  - randomized treatment not administered or wrong treatment administered
  - missing PK samples which result in insufficient profiling

Subject analysis set title	FAS_PK
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS was defined as all subjects randomised into the trial as subject of the pharmacokinetic arm.

Subject analysis set title	SAS_PK
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAS was defined as all subjects that:
- were randomised into the trial as subject of the pharmacokinetic arm
- received the investigational drug at least once.

Subject analysis set title	PPS_PD
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects that were randomized and finished the trial as defined in the protocol without major protocol deviations in particular regarding compliance with the treatment and, thus, being a complete case. The conventions for missed IMP applications apply:
- Initial treatment period: At least 80 % of the total IMP-dose had to be applied during the initial phase. Missing IMP applications on single days (but not on subsequent study days) were not considered relevant, because the exposure to IMP was sufficient.
- Maintenance period: IMP application had to be performed on at least 7 out of 8 days and was not allowed to exceed a maximum of 9 application days to be compliant to the protocol.
- Duration of the maintenance phase was compliant to the protocol if visit 4 was held within 4 days after the last IMP application and within 28±4 days after visit 3.
- A complete case was defined as a subject for whom a result for maturation value was available on at least visits 01, 02 and 04.

Subject analysis set title	mFAS_PD
Subject analysis set type	Full analysis

Subject analysis set description:

The modified Full Analysis Sets were defined to include all subjects that:
- were randomised
- received the investigational drug at least once.
- fulfilled all major entry criteria
- provided at least one data value necessary post-baseline for the primary endpoints

All subjects for whom the mFAS definition was applicable and who were included in either evaluation of

the first stage, evaluation of the second stage or the combined PD analysis, i.e. combining subjects from first stage (interim) analysis and second stage analysis.

Subject analysis set title	SAS_PD
Subject analysis set type	Safety analysis

Subject analysis set description:

The SASPD was defined as all subjects that:
- were randomised
- received the investigational drug at least once.

Primary: AUC0-TAU

End point title	AUC0-TAU[1]

End point description:

End point type	Primary

End point timeframe:

Baseline: 1 h, 0.5 h and immediately (within 5 minutes) prior to first IMP application
Post-dose: within 5 minutes prior to the 14th IMP application and 2 h, 4 h, 5 h, 6 h, 7 h, 8 h, 10 h, 12 h, 16 h and 24 h after the 14th IMP application.

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 formal statistial hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: h*pg/ml				
geometric mean (geometric coefficient of variation)	77.89 (± 62.63)	101.50 (± 32.16)		

Statistical analyses

No statistical analyses for this end point

Primary: Cmax

End point title	Cmax[2]

End point description:

End point type	Primary

End point timeframe:

Baseline samples: 1 h, 0.5 h and immediately (within 5 minutes) prior to first IMP application
Post-dose: within 5 minutes prior to the 14th IMP application and 2 h, 4 h, 5 h, 6 h, 7 h, 8 h, 10 h, 12 h, 16 h and 24 h after the 14th IMP application

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 formal statistial hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: pg/ml				
geometric mean (geometric coefficient of variation)	6.79 (± 68.30)	7.84 (± 37.16)		

Statistical analyses

No statistical analyses for this end point

Primary: Vaginal pH value

End point title	Vaginal pH value

End point description:

Statistical analysis (change from study day 1 to study day 43) is reported for the mFAS_PD.
Superiority (Test-Placebo) is reported for the mFAS_PD stage 1.
Numbers of subjects included in the analysis of endpoint values (vaginal pH value):
Period 1 Estradiol 10 µg - Test: 195
Period 1 Vagifem 10 µg - Reference: 167
Period 1 Placebo: 56

End point type	Primary

End point timeframe:

From study day 1 to study day 43.

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: unit(s)				
arithmetic mean (standard deviation)	-1.44 (± 0.97)	-1.48 (± 0.93)	-0.52 (± 0.73)	

Statistical analyses

Statistical analysis title	Superiority Test - Placebo
Comparison groups	Estradiol 10 µg - Test v Placebo
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	≤ 0.025
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.938406

Confidence interval	
level	95 %
sides	1-sided
lower limit	-1.19929
Variability estimate	Standard error of the mean
Dispersion value	0.131961

Notes:

[3] - Superiority with regard to Placebo had been demonstrated in the interim analysis of the trial and therefore the Placebo arm was omitted after the first stage of the trial.
Therfore the number of subjects calculated automatically for this statistical anaylsis is not correct.
The numbers of subjects in this analysis are the following:
Period 1 Estradiol 10 µg - Test: 104
Period 1 Placebo: 45

Statistical analysis title	Non-inferiority Theta0= ±0.4

Statistical analysis description:

Numbers of subjects included in the statistical analysis (non-inferitority, vaginal pH value): 362.

Comparison groups	Estradiol 10 µg - Test v Vagifem 10 µg - Reference
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.008673
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13082
upper limit	0.14816
Variability estimate	Standard error of the mean
Dispersion value	0.070929

Notes:

[4] - For the euqivalence tests (non-inferiority), the two one-sided tests procedure will be applied with one-sided tests performed at global level 0.05.

Primary: Vaginal maturation value

End point title	Vaginal maturation value

End point description:

Statistical analysis (change from study day 1 to study day 15) is reported for the mFAS_PD.
Superiority (Test - Placebo) is reported for the mFAS_PD stage 1.
Numbers of subjects included in the analysis of endpoint values (vaginal maturation value):
Period 1 Estradiol 10 µg - Test: 195
Period 1 Vagifem 10 µg - Reference: 169
Period 1 Placebo: 57

End point type	Primary

End point timeframe:

From study day 1 to study day 15.

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: percent				
arithmetic mean (standard deviation)	21.57 (± 20.28)	24.06 (± 20.39)	2.07 (± 14.15)	

Statistical analyses

Statistical analysis title	Superiority Test - Placebo
Comparison groups	Estradiol 10 µg - Test v Placebo
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	≤ 0.025
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	18.599367
Confidence interval	
level	95 %
sides	1-sided
lower limit	13.18557
Variability estimate	Standard error of the mean
Dispersion value	2.738069

Notes:

[5] - Superiority with regard to Placebo had been demonstrated in the interim analysis of the trial and therefore the Placebo arm was omitted after the first stage of the trial.
Therfore the number of subjects calculated automatically for this statistical anaylsis is not correct.
The numbers of subjects in this analysis are the following:
Period 1 Estradiol 10 µg - Test: 104
Period 1 Placebo: 45

Statistical analysis title	Non-inferiority (Theta0= ±6.5)
Statistical analysis description:	
Numbers of subjects included in the statistical analysis (non-inferitority, vaginal pH value): 369.	
Comparison groups	Estradiol 10 µg - Test v Vagifem 10 µg - Reference
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.862664
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.98559
upper limit	1.26026
Variability estimate	Standard error of the mean
Dispersion value	1.588064

Notes:

[6] - For the equivalence tests (non-inferiority), the two one-sided tests procedure will be applied with one-sided tests performed at global level 0.05.

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - dry vaginal mucosa

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - dry vaginal mucosa

End point description:

End point type	Secondary

End point timeframe:

study day 1 (visit 2)

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	2.1 (± 0.8)	2.1 (± 0.7)	2.1 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - flattening of folds

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - flattening of folds

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	2.0 (± 0.8)	2.0 (± 0.8)	2.1 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - pallor of the mucosa

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - pallor of the mucosa

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	1.9 (± 0.8)	1.8 (± 0.8)	1.8 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - fragility of the mucosa

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - fragility of the mucosa

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	1.8 (± 0.9)	1.7 (± 0.9)	1.7 (± 0.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - presence of petechiae

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - presence of petechiae

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	1.3 (± 1.0)	1.2 (± 1.0)	1.2 (± 1.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - dry vaginal mucosa

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - dry vaginal mucosa

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4)

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	195	167	56	
Units: units				
arithmetic mean (standard deviation)	0.6 (± 0.8)	0.6 (± 0.8)	1.0 (± 0.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - flattening of folds

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - flattening of folds

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	195	167	56	
Units: units				
arithmetic mean (standard deviation)	0.7 (± 0.8)	0.7 (± 0.7)	1.0 (± 0.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - pallor of the mucosa

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - pallor of the mucosa

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	195	167	58	
Units: units				
arithmetic mean (standard deviation)	0.6 (± 0.7)	0.5 (± 0.7)	0.9 (± 0.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - fragility of the mucosa

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - fragility of the mucosa

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	195	167	56	
Units: units				
arithmetic mean (standard deviation)	0.4 (± 0.7)	0.3 (± 0.5)	0.7 (± 0.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - presence of petechiae

End point title	Investigator assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - presence of petechiae

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	195	167	56	
Units: unit(s)				
arithmetic mean (standard deviation)	0.2 (± 0.5)	0.2 (± 0.5)	0.5 (± 0.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - vaginal dryness

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - vaginal dryness

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	2.0 (± 0.8)	2.1 (± 0.7)	1.9 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - vaginal and/or vulvar irritation/itching

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - vaginal and/or vulvar irritation/itching

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	1.6 (± 1.0)	1.5 (± 1.1)	1.5 (± 1.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - vaginal soreness

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - vaginal soreness

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	1.4 (± 1.0)	1.3 (± 1.0)	1.3 (± 1.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - dysuria

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - dysuria

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	1.3 (± 1.1)	1.3 (± 1.0)	1.2 (± 1.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - dyspareunia and vaginal bleeding associated with sexual activity

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 1 (visit 2) - dyspareunia and vaginal bleeding associated with sexual activity

End point description:

End point type	Secondary

End point timeframe:

Study day 1 (visit 2).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	174	58	
Units: units				
arithmetic mean (standard deviation)	1.4 (± 1.1)	1.3 (± 1.1)	1.2 (± 1.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - dysuria

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - dysuria

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196	167	56	
Units: units				
arithmetic mean (standard deviation)	0.3 (± 0.5)	0.3 (± 0.6)	0.4 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - vaginal soreness

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - vaginal soreness

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196	167	56	
Units: unis				
arithmetic mean (standard deviation)	0.3 (± 0.6)	0.3 (± 0.6)	0.4 (± 0.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - vaginal and/or vulvar irritation/itching

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - vaginal and/or vulvar irritation/itching

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196	167	56	
Units: units				
arithmetic mean (standard deviation)	0.3 (± 0.5)	0.3 (± 0.5)	0.4 (± 0.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - vaginal dryness

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - vaginal dryness

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196	167	56	
Units: units				
arithmetic mean (standard deviation)	0.5 (± 0.7)	0.5 (± 0.8)	0.7 (± 0.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - dyspareunia and vaginal bleeding associated with sexual activity

End point title	Subject assessment of vaginal health - signs of vaginal atrophy study day 43 (visit 4) - dyspareunia and vaginal bleeding associated with sexual activity

End point description:

End point type	Secondary

End point timeframe:

Study day 43 (visit 4).

End point values	Estradiol 10 µg - Test	Vagifem 10 µg - Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196	167	56	
Units: units				
arithmetic mean (standard deviation)	0.3 (± 0.5)	0.3 (± 0.6)	0.5 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Pharmacodynamic Group -Test-
Reporting group description: -	
Reporting group title	Pharmacokinetic Group -Test-
Reporting group description: -	
Reporting group title	Pharmacodynamic Group -Reference-
Reporting group description: -	
Reporting group title	Pharmacodynamic Group -Placebo-
Reporting group description: -	
Reporting group title	Pharmacokinetic Group -Reference-

Reporting group description: -

Serious adverse events	Pharmacodynamic Group -Test-	Pharmacokinetic Group -Test-	Pharmacodynamic Group -Reference-
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 203 (1.48%)	0 / 13 (0.00%)	1 / 179 (0.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 13 (0.00%)	0 / 179 (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
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 203 (0.00%)	0 / 13 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			

subjects affected / exposed	0 / 203 (0.00%)	0 / 13 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	1 / 203 (0.49%)	0 / 13 (0.00%)	0 / 179 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 13 (0.00%)	0 / 179 (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

Serious adverse events	Pharmacodynamic Group -Placebo-	Pharmacokinetic Group -Reference-	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Rotator cuff syndrome			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.68 %

Non-serious adverse events	Pharmacodynamic Group -Test-	Pharmacokinetic Group -Test-	Pharmacodynamic Group -Reference-
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 203 (5.42%)	6 / 13 (46.15%)	8 / 179 (4.47%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 203 (1.48%)	3 / 13 (23.08%)	2 / 179 (1.12%)
occurrences (all)	4	3	2
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 203 (0.00%)	0 / 13 (0.00%)	0 / 179 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	4 / 203 (1.97%)	0 / 13 (0.00%)	0 / 179 (0.00%)
occurrences (all)	4	0	0
Vaginal discharge			
subjects affected / exposed	0 / 203 (0.00%)	2 / 13 (15.38%)	2 / 179 (1.12%)
occurrences (all)	0	2	2
Menopausal symptoms			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 203 (0.00%)	1 / 13 (7.69%)	0 / 179 (0.00%)
occurrences (all)	0	1	0

Pelvic pain alternative dictionary used: MedDRA 20.0 subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	3 / 13 (23.08%) 3	0 / 179 (0.00%) 0
Breast discomfort subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	1 / 13 (7.69%) 1	0 / 179 (0.00%) 0
Uterine polyp subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	0 / 13 (0.00%) 0	1 / 179 (0.56%) 1
Ovarian cyst subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 13 (0.00%) 0	0 / 179 (0.00%) 0
Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	1 / 13 (7.69%) 1	1 / 179 (0.56%) 1
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 13 (0.00%) 0	1 / 179 (0.56%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	0 / 13 (0.00%) 0	1 / 179 (0.56%) 2
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain alternative dictionary used: MedDRA 20.0 subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 13 (7.69%) 1	0 / 179 (0.00%) 0

Non-serious adverse events	Pharmacodynamic Group -Placebo-	Pharmacokinetic Group -Reference-	
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 60 (5.00%)	6 / 14 (42.86%)	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	2 / 14 (14.29%) 6	

General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Vaginal discharge			
subjects affected / exposed	0 / 60 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Menopausal symptoms			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Pelvic pain			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Breast discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Uterine polyp			
subjects affected / exposed	0 / 60 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	0 / 60 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Vaginal haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	
occurrences (all)	4	3	
Nausea			
subjects affected / exposed	0 / 60 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 60 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2018	The substantial Amendment 04 (dated 2018-06-12) to the Amendment 03 of the clinical trial protocol became necessary due to the adaptive design of the clinical trial. It determined all necessary details about the continuation of trial procedures following the interim analysis. It was submitted to the Ethics Committees in Bulgaria and Moldova. For Germany Amendment 04 was not submitted to the Ethics Committee as the trial was not re-started in Germany after interim analysis. The substantial amendment 04 was submitted to the Ethics Committees in Bulgaria and Moldova and the members of the committees referred to above, confirmed that the given vote remained unchanged.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 March 2018	Temporary hold of the clinical trial for the duration of interim analysis due to adaptive design of the trial with sample size estimation.	16 July 2018

Notes:

Limitations and caveats

None reported