Clinical trial results:
Prospective, open-label, monocenter, trial to investigate the efficacy and tolerability of Vagisan® a lactic acid containing vaginal suppository, in a panel of post-menopausal women suffering from vulvo vaginal atrophy (VVA)

Summary

EudraCT number	2019-002325-30
Trial protocol	DE
Global end of trial date	11 August 2020

Results information

Result version number	v1 (current)
This version publication date	12 November 2021
First version publication date	12 November 2021

Trial information

Trial identification

Sponsor protocol code	VMP-03/2018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04222647
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. August Wolff GmbH & Co. KG Arzneimittel
Sponsor organisation address	Sudbrackstr. 56, Bielefeld, Germany, 33611
Public contact	Clinical Trial Disclosures Office, Dr. August Wolff GmbH & Co. KG Arzneimittel, ClinicalTrialDisclosures@drwolffgroup.com
Scientific contact	Clinical Trial Disclosures Office, Dr. August Wolff GmbH & Co. KG Arzneimittel, ClinicalTrialDisclosures@drwolffgroup.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	16 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2020
Global end of trial reached?	Yes
Global end of trial date	11 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to investigate the changes in the Vaginal Maturation Index (VMI) during the course of the trial.

Protection of trial subjects:

This study was in compliance with the ethical principles of current applicable regulations, International Council for Harmonisation (ICH) of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements. All regulatory requirements relevant to the safety of the study participants were followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 2020
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: 43
Worldwide total number of subjects	43
EEA total number of subjects	43

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	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Post-menopausal women with the subjective symptoms of "vulvovaginal atrophy" were contacted and invited to the gynecological examination. If all the inclusion criteria were met, patients underwent the gynecological examination for the assessment of the VMI.

Pre-assignment

Screening details:

111 women were screened. 49 patients were eligible to participate and of those, 43 patients were enrolled in this study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Vagisan®
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Vagisan®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Vaginal use

Dosage and administration details:

During the first week, the suppository was applied intra-vaginally once daily (in the evening); during the following 5 weeks, the suppository was applied twice a week with a time period of at least 72 hours in between two consecutive applications. The total duration of application was 6 weeks. All applications were performed by the patients themselves at home.

Number of subjects in period 1	Vagisan®
Started	43
Completed	40
Not completed	3
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups	
Reporting group title	Vagisan®

Reporting group description: -

Reporting group values	Vagisan®	Total	
Number of subjects	43	43	
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Women (53-78 years)	43	43	
Gender categorical Units: Subjects			
Female	43	43	
Male	0	0	

Subject analysis sets	
Subject analysis set title	Vagisan® (SP)
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population (SP) for Vagisan®. The Safety Population (SP) includes all patients who were included to the trial according to protocol and who received at least one application of the investigational product, regardless of the number of further assessments.

Subject analysis set title	Vagisan® (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS) for Vagisan®. The Full Analysis Set (FAS) includes all patients of Safety Population for whom at least one post-Baseline assessment was performed (LOCF).

Subject analysis set title	Vagisan® (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol population (PP) for Vagisan®. The Per protocol population (PP) includes all patients of FAS who finished the trial in accordance with the CTP without major protocol deviations.

Reporting group values	Vagisan® (SP)	Vagisan® (FAS)	Vagisan® (PP)
Number of subjects	42	42	39

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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Women (53-78 years)	42	42	39
Gender categorical Units: Subjects			
Female	42	42	39
Male	0		

End points

End points reporting groups

Reporting group title	Vagisan®
Reporting group description: -	
Subject analysis set title	Vagisan® (SP)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population (SP) for Vagisan®. The Safety Population (SP) includes all patients who were included to the trial according to protocol and who received at least one application of the investigational product, regardless of the number of further assessments.	
Subject analysis set title	Vagisan® (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS) for Vagisan®. The Full Analysis Set (FAS) includes all patients of Safety Population for whom at least one post-Baseline assessment was performed (LOCF).	
Subject analysis set title	Vagisan® (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
Per protocol population (PP) for Vagisan®. The Per protocol population (PP) includes all patients of FAS who finished the trial in accordance with the CTP without major protocol deviations.	

Primary: Change of Vaginal Maturation Index (VMI) from Day 1 to Day 43

End point title	Change of Vaginal Maturation Index (VMI) from Day 1 to Day 43[1]
End point description:	
Full Analysis Set. The VMI quantifies the relative proportion of the vaginal parabasal, intermediate, and superficial cells in the vaginal epithelium. The Vaginal Maturation Index is calculated as follows: Vaginal Maturation Index = 1.0 x % superficial cells + 0.5 x % intermediate cells + 0.0 x % parabasal cells	
End point type	Primary
End point timeframe:	
Day 1 to Day 43	

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: Since there was no comparison group, mean VMI between Day 1 and Day 43 was compared. A paired t-test (one-sided) with a significance level of p = 0.05 was conducted, showing a statistically significant improvement of the VMI

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Index				
arithmetic mean (standard deviation)				
Day 1 Day 43	8.3 (± 12.2) 34.9 (± 19.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of VMI from Day 1 to Day 8 and from Day 8 to Day 43

End point title	Change of VMI from Day 1 to Day 8 and from Day 8 to Day 43

End point description:

Full Analysis Set.
The VMI quantifies the relative proportion of the vaginal parabasal, intermediate, and superficial cells in the vaginal epithelium. The Maturation Index is calculated as follows:

Maturation Index =
1.0 x % superficial cells +
0.5 x % intermediate cells +
0.0 x % parabasal cells

End point type	Secondary

End point timeframe:

Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	8.3 (± 12.2)			
Day 8	29.5 (± 18.0)			
Day 43	34.9 (± 19.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vaginal Health Index (VHI) parameter: Elasticity

End point title	Vaginal Health Index (VHI) parameter: Elasticity

End point description:

Full Analysis Set.
1 (none) to 5 (excellent)

End point type	Secondary

End point timeframe:

Day 1, Day, 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	2.4 (± 0.9)			
Day 8	3.1 (± 0.7)			
Day 43	3.6 (± 0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vaginal Health Index (VHI) parameter: Fluid secretion type and consistency

End point title	Vaginal Health Index (VHI) parameter: Fluid secretion type and consistency
End point description: Full Analysis Set. 1 (none) to 5 (normal, white flocculent).	
End point type	Secondary
End point timeframe: Day 1, Day 8, Day 43	

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	1.4 (± 0.6)			
Day 8	2.2 (± 1.0)			
Day 43	3.2 (± 1.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vaginal Health Index (VHI) parameter: Vaginal pH

End point title	Vaginal Health Index (VHI) parameter: Vaginal pH
End point description: Full Analysis Set. pH ≥ 6.1 (vaginal pH score 1) to pH 5.6 – 6.0 (vaginal pH score 2).	
End point type	Secondary

End point timeframe:
Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: pH Score				
arithmetic mean (standard deviation)				
Day 1	1.1 (± 0.5)			
Day 8	1.6 (± 1.1)			
Day 43	2.2 (± 1.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vaginal Health Index (VHI) parameter: Condition epithelial mucosa

End point title	Vaginal Health Index (VHI) parameter: Condition epithelial mucosa

End point description:
Full Analysis Set.
1 (Petechiae noted before contact) to 5 (Not friable, normal mucosa).

End point type	Secondary

End point timeframe:
Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	2.9 (± 1.1)			
Day 8	3.6 (± 1.0)			
Day 43	3.7 (± 1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vaginal Health Index (VHI) parameter: Moisture

End point title	Vaginal Health Index (VHI) parameter: Moisture

End point description:
Full Analysis Set. 1 (None, mucosa inflamed) to 5 (Normal).

End point type	Secondary

End point timeframe:
Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	2.0 (± 0.7)			
Day 8	2.9 (± 0.9)			
Day 43	3.7 (± 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Sum Score of Vaginal Health Index (VHI)

End point title	Total Sum Score of Vaginal Health Index (VHI)

End point description:
Full Analysis Set. Each of the five criteria - elasticity, fluid secretion, pH, epithelial mucosa and moisture - was graded from 1 (worst) to 5 (best) and then summed up, so that the minimum score is 5 (worst) and the maximum score is 25 (best).

End point type	Secondary

End point timeframe:
Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	9.9 (± 2.5)			
Day 8	13.5 (± 3.5)			
Day 43	16.5 (± 5.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective Symptoms of vulvovaginal atrophy - Dryness

End point title	Subjective Symptoms of vulvovaginal atrophy - Dryness
End point description: Full Analysis Set. 0=none to 4=very severe	
End point type	Secondary
End point timeframe: Day 1, Day 8, Day 43	

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	2.5 (± 0.7)			
Day 8	1.2 (± 0.7)			
Day 43	0.8 (± 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective Symptoms of vulvovaginal atrophy - Itching

End point title	Subjective Symptoms of vulvovaginal atrophy - Itching
End point description: Full Analysis Set. 0=none to 4=very severe	
End point type	Secondary
End point timeframe: Day 1, Day 8, Day 43	

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	1.7 (± 0.8)			
Day 8	0.7 (± 0.8)			
Day 43	0.6 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective Symptoms of vulvovaginal atrophy - Burning

End point title	Subjective Symptoms of vulvovaginal atrophy - Burning
End point description: Full Analysis Set. 0=none to 4=very severe.	
End point type	Secondary
End point timeframe: Day 1, Day 8, Day 43	

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	1.4 (± 0.9)			
Day 8	0.7 (± 1.0)			
Day 43	0.5 (± 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective Symptoms of vulvovaginal atrophy - Pain unrelated to sexual intercourse

End point title	Subjective Symptoms of vulvovaginal atrophy - Pain unrelated to sexual intercourse
End point description: Full Analysis Set. 0=none to 4=very severe.	
End point type	Secondary
End point timeframe: Day 1, Day 8, Day 43	

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	0.4 (± 0.8)			
Day 8	0.3 (± 0.8)			
Day 43	0.2 (± 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective Symptoms of vulvovaginal atrophy - Sum Score

End point title	Subjective Symptoms of vulvovaginal atrophy - Sum Score

End point description:

Full Analysis Set.
The sum score for subjective symptoms of vulvovaginal atrophy is calculated as the sum of the severity scores of each subjective symptom of VVA, dryness, itching, burning and pain unrelated to sexual intercourse. (sum score ranging from 0 – 16).

End point type	Secondary

End point timeframe:

Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	6.0 (± 2.0)			
Day 8	2.9 (± 2.7)			
Day 43	2.0 (± 2.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dyspareunia

End point title	Dyspareunia

End point description:

Only women of the FAS with continuous sexual activity over the course of the study were included in the analysis.
0=none to 4=very severe.

End point type	Secondary

End point timeframe:
Day 1, Day 8 Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	2.8 (± 1.6)			
Day 8	1.0 (± 1.2)			
Day 43	0.8 (± 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with normal Lactobacillus Flora Status

End point title	Number of patients with normal Lactobacillus Flora Status

End point description:
Full Analysis Set.
Normal Lactobacillus flora status: 5 x 10^7 – 1 x 10^9 CFU.

End point type	Secondary

End point timeframe:
Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Number of patients				
Day 1	1			
Day 8	2			
Day 43	5			

Statistical analyses

No statistical analyses for this end point

Secondary: DIVA Domain Score Part A - Daily Activity

End point title	DIVA Domain Score Part A - Daily Activity

End point description:
Full Analysis Set.

Evaluation of Impact of Vaginal Aging on Daily Activities (0=not at all to 4=extremely)

End point type	Secondary

End point timeframe:

Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42[2]			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	1.1 (± 0.69)			
Day 8	0.87 (± 0.86)			
Day 43	0.51 (± 0.67)			

Notes:

[2] - Day 1: 41 subjects
Day 8 and Day 43: 42 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: DIVA Domain Score Part B - Emotional Well-Being

End point title	DIVA Domain Score Part B - Emotional Well-Being

End point description:

Full Analysis Set.
Evaluation of Impact of Vaginal Aging on Emotional Well-Being (0=not at all to 4=extremely)

End point type	Secondary

End point timeframe:

Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	0.96 (± 0.80)			
Day 8	0.68 (± 0.65)			
Day 43	0.36 (± 0.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: DIVA Domain Score Part C - Sexual Functioning

End point title	DIVA Domain Score Part C - Sexual Functioning

End point description:

Full Analysis Set.
Evaluation of Impact of Vaginal Aging on Sexual Functioning (0=not at all to 4=extremely). In case of varying sexual activity of the patient during the course of the trial the domain subscale Part C, namely questions 12, 13, 14, and 15 are influenced. Therefore, these questions were not included into the calculation of the DIVA domain scores.

End point type	Secondary

End point timeframe:

Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42[3]			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	1.52 (± 1.07)			
Day 8	1.31 (± 1.06)			
Day 43	0.88 (± 0.81)			

Notes:

[3] - Day 1: 41 subjects
Day 8 and Day 43: 42 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: DIVA Domain Score Part D - Self-Concept and Body Image

End point title	DIVA Domain Score Part D - Self-Concept and Body Image

End point description:

Full Analysis Set.
Evaluation of Impact of Vaginal Aging on Self-Concept and Body Image (0=not at all to 4=extremely)

End point type	Secondary

End point timeframe:

Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	1.78 (± 1.1)			
Day 8	1.19 (± 1.04)			
Day 43	0.81 (± 0.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total DIVA Score

End point title	Total DIVA Score

End point description:

Full Analysis Set. The DIVA questionnaire addressed the impact of vaginal symptoms such as vaginal dryness, soreness, irritation and itching on the day-today life regarding the patient's activities, relationships, and feelings by any of these symptoms calculated as the sum of the DIVA Domain Scores A,B,C and D (0-16).

End point type	Secondary

End point timeframe:

Day 1, Day 8, Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42[4]			
Units: Score				
arithmetic mean (standard deviation)				
Day 1	5.45 (± 2.8)			
Day 8	4.05 (± 2.88)			
Day 43	2.57 (± 1.97)			

Notes:

[4] - Day 1: 40 subjects
Day 8 and Day 43: 42 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Global Judgement of Tolerability by the Investigator

End point title	Global Judgement of Tolerability by the Investigator

End point description:

Safety Population.
The global judgement of tolerability was assessed by the Investigator on Day 43 according to the following scale: 1=very good to 4=poor.

End point type	Secondary

End point timeframe:

Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Score				
arithmetic mean (standard deviation)				
Day 43	1.8 (± 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Global Judgement of Tolerability by the Patient

End point title	Global Judgement of Tolerability by the Patient

End point description:

Safety Population.
The global judgement of tolerability was assessed by the patient on Day 43 according to the following scale: 1=very good to 4=poor.

End point type	Secondary

End point timeframe:

Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Score				
arithmetic mean (standard deviation)				
Day 43	1.7 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety parameters: number of changes in concomitant medication

End point title	Safety parameters: number of changes in concomitant medication

End point description:

Full Analysis Set

End point type	Secondary

End point timeframe:

Screening - Day 43

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42[5]			
Units: Number of changes				
Screening - Day 43	25			

Notes:

[5] - changes in concomitant therapies were observed in 10 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Safety parameters: number of patients with clinically relevant change of blood pressure

End point title	Safety parameters: number of patients with clinically relevant change of blood pressure
End point description: Full Analysis Set	
End point type	Secondary
End point timeframe: Screening -Day 43	

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Number of patients				
Screening -Day 43	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety parameters: number of patients with clinically relevant change of pulse rate

End point title	Safety parameters: number of patients with clinically relevant change of pulse rate
End point description: Full Analysis Set	
End point type	Secondary
End point timeframe: Screening - Day 43	

End point values	Vagisan®			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Number of patients				
Screening - Day 43	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screening - Day 43	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	Vagisan®

Reporting group description: -

Serious adverse events	Vagisan®		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Vagisan®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 42 (59.52%)		
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	8		
Migraine			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	14 / 42 (33.33%)		
occurrences (all)	17		
Instillation site warmth			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	10 / 42 (23.81%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Renal and urinary disorders			
Bladder irritation			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		

Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Sjogren's syndrome			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2019	The content of L-lactic acid was updated, taking into account the Ph. Eur. specification for content. According to Ph. Eur, the content of anhydrous L-lactic acid is 90% w/w (range between 88.0% - 92.0% (w/w). Therefore, 167 mg L-lactic acid equal to 150 mg anhydrous L-lactic acid. In combination with 50 mg sodium L-lactate solution, which equals to 40 mg anhydrous L-lactic acid, this results in a total of 190 mg of anhydrous L-lactic acid. The primary packaging of the vaginal suppositories was changed from PVC/PVDC/PE blisters to Alu/PE blisters.
25 March 2020	Temporary halt of the study due to Covid-19 on 25MAR2020
27 April 2020	Re-start of the study (June 2020)
04 June 2020	Addition to the Risk Benefit Analysis of the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 March 2020	Temporary halt of the study due to Covid-19	04 June 2020

Notes:

Limitations and caveats

None reported