Clinical trial results:
A Prospective, Randomized, Double-Blind, Placebo-controlled, Multicenter, Phase III Study Assessing Efficacy and Safety of the IMUNOR® Therapy Versus Placebo in Patients with Recurrent Vulvovaginitis Episodes

Summary

EudraCT number	2015-001472-22
Trial protocol	SK CZ
Global end of trial date	08 April 2019

Results information

Result version number	v1
This version publication date	18 July 2025
First version publication date	18 July 2025
Summary attachment (see zip file)	Synopsis (Synopsis_IMUNOR-201501_final_02.07.2025.pdf)

Trial information

Trial identification

Sponsor protocol code	IMUNOR-201501

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ImunomedicA, a.s.
Sponsor organisation address	Chuderov 118, Ústí nad Labem, Czechia, 400 11
Public contact	Ing. Zdeňka Svobodová, ImunomedicA, a.s., 00420 777872 067, imunomedica@iol.cz
Scientific contact	Ing. Zdeňka Svobodová, ImunomedicA, a.s., 00420 777872 067, imunomedica@iol.cz

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	01 July 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2019
Global end of trial reached?	Yes
Global end of trial date	08 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm efficacy of IMUNOR® based on reduction of the number of documented mycotic and bacterial vulvovaginitis episodes during 12 months observation, compared to patients receiving placebo.

Protection of trial subjects:

The study was conducted in accordance with the approved version of the Study Protocol, the ICH Guideline for Good Clinical Practice (ICH-GCP E6(R2)), the Declaration of Helsinki, the General Data Protection Regulation (Regulation (EU) 2016/679), as well as applicable national and international legislation and Standard Operating Procedures (SOPs) related to the conduct of clinical trials. Prior planning or performing of any study-related procedure, a written informed consent had to be obtained from patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	Czechia: 110
Worldwide total number of subjects	137
EEA total number of subjects	137

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)	137
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At Visit 1 (Screening, Day -21 to -7), written ICF had to be obtained prior performing of any Study related procedure. Patients considered eligible based on past medical history and clinical examination and those willing to provide written ICF, had to undergo further assessment of their eligibility based on defined inclusion and exclusion criteria.

Period 1

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

Blinding implementation details:

Blinding of the IMP was done centrally by the sponsor.

Arms

Are arms mutually exclusive?	Yes
Arm title	IMUNOR group

Arm description:

Administration of IMUNOR® - active treatment.

Arm type	Experimental
Investigational medicinal product name	IMUNOR®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Oral use

Dosage and administration details:

IMUNOR® was administered as 1 dose/week, orally for a total period of 3 months within treatment period 1.
Prior each administration, re-constitution of the IMP was performed. The content of a vial had to be dissolved under gently shaking in approximately 3 mL of drinking water (up to the vial neck). Upon complete dissolution of the lyophilizate, the solution could be administered.

Arm title	Placebo group

Arm description:

Administration of placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as 1 dose/week, orally for a total period of 3 months within treatment period 1.
Prior each administration, re-constitution of the IMP was performed. The content of a vial had to be dissolved under gently shaking in approximately 3 mL of drinking water (up to the vial neck). Upon complete dissolution of the lyophilizate, the solution could be administered.

Number of subjects in period 1	IMUNOR group	Placebo group
Started	91	46
Completed	90	46
Not completed	1	0
Randomized by mistake, no IMP dose used	1	-

Period 2	
Period 2 title	Observation period 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Blinding of the IMP was done centrally by the sponsor.

Arms	
Are arms mutually exclusive?	Yes
Arm title	IMUNOR group - SOC

Arm description:

Standard of care without intervention.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo group - SOC

Arm description:

Standard of care without intervention.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	IMUNOR group - SOC	Placebo group - SOC
Started	90	46
Completed	85	45
Not completed	5	1
Consent withdrawn by subject	3	-
Adverse event, non-fatal	1	-
Need of systemic antifungal medication	-	1
Used prohibited medication - systemic corticoid	1	-

Period 3

Period 3 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Blinding of the IMP was done centrally by the sponsor.

Arms

Are arms mutually exclusive?	Yes
Arm title	IMUNOR group

Arm description:

Administration of IMUNOR® - active treatment.

Arm type	Experimental
Investigational medicinal product name	IMUNOR®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Oral use

Dosage and administration details:

IMUNOR® was administered as 1 dose/week, orally for a total period of 3 months within treatment period 2.
Prior each administration, re-constitution of the IMP was performed. The content of a vial had to be dissolved under gently shaking in approximately 3 mL of drinking water (up to the vial neck). Upon complete dissolution of the lyophilizate, the solution could be administered.

Arm title	Placebo group

Arm description:

Administration of placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as 1 dose/week, orally for a total period of 3 months within treatment period 2.
Prior each administration, re-constitution of the IMP was performed. The content of a vial had to be dissolved under gently shaking in approximately 3 mL of drinking water (up to the vial neck). Upon complete dissolution of the lyophilizate, the solution could be administered.

Number of subjects in period 3	IMUNOR group	Placebo group
Started	85	45
Completed	83	42
Not completed	2	3
Consent withdrawn by subject	-	1
Pregnancy	-	1
Need of systemic antifungal medication	1	-
Used prohibited medication - Fluco Sandoz	1	-
Protocol deviation	-	1

Period 4	
Period 4 title	Observation period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor
Blinding implementation details: Blinding of the IMP was done centrally by the sponsor.	

Arms	
Are arms mutually exclusive?	Yes
Arm title	IMUNOR group - SOC
Arm description: Standard of care without intervention.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Placebo group - SOC
Arm description: Standard of care without intervention.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	IMUNOR group - SOC	Placebo group - SOC
Started	83	42
Completed	78	42
Not completed	5	0
Consent withdrawn by subject	2	-
Withdrawal due to need of systemic antifungal th	1	-
Oncological disease unrelated to study drug	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	IMUNOR group
Reporting group description: Administration of IMUNOR® - active treatment.	
Reporting group title	Placebo group
Reporting group description: Administration of placebo.	

Reporting group values	IMUNOR group	Placebo group	Total
Number of subjects	91	46	137
Age categorical			
Age at randomization			
Units: Subjects			
Adults (18-50 years)	91	46	137
Age continuous			
Age at randomization			
Units: years			
arithmetic mean	34.7	33.5	
standard deviation	± 8.25	± 8.33	-
Gender categorical			
Female			
Units: Subjects			
Female	91	46	137
Race			
White (Caucasian)			
Units: Subjects			
White (Caucasian)	91	46	137
Prevailing etiology			
Bacterial, Mycotic, Not specified			
Units: Subjects			
Bacterial	11	1	12
Mycotic	51	26	77
Not specified	29	19	48
Height			
Height [cm]			
Units: centimetre			
arithmetic mean	168.1	168.6	
standard deviation	± 5.49	± 6.73	-
Weight			
Weight [kg]			
Units: kilogram(s)			
arithmetic mean	65.0	61.5	
standard deviation	± 12.60	± 8.92	-
BMI			
BMI [kg/m2]			
Units: kilogram(s)/square metre			
arithmetic mean	22.98	21.60	

standard deviation	± 4.128	± 2.815	-

Subject analysis sets

Subject analysis set title	Full Analysis Set - IMUNOR
Subject analysis set type	Full analysis

Subject analysis set description:

IMUNOR group: All patients of the safety set and have at least one measurement after baseline.

Subject analysis set title	Full Analysis Set - Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo group: All patients of the safety set and have at least one measurement after baseline.

Subject analysis set title	Per-Protocol Set - IMUNOR
Subject analysis set type	Per protocol

Subject analysis set description:

IMUNOR group: All patients of the Full Analysis Set without any relevant protocol violations (major protocol deviations) and complete data for the primary efficacy variable.

Subject analysis set title	Per-Protocol Set - Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Placebo group: All patients of the Full Analysis Set without any relevant protocol violations (major protocol deviations) and complete data for the primary efficacy variable.

Reporting group values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR
Number of subjects	90	46	52
Age categorical			
Age at randomization			
Units: Subjects			
Adults (18-50 years)	90	46	52
Age continuous			
Age at randomization			
Units: years			
arithmetic mean	34.7	33.5	33.6
standard deviation	± 8.25	± 8.33	± 8.39
Gender categorical			
Female			
Units: Subjects			
Female	90	46	52
Race			
White (Caucasian)			
Units: Subjects			
White (Caucasian)	90	46	52
Prevailing etiology			
Bacterial, Mycotic, Not specified			
Units: Subjects			
Bacterial	11	1	7
Mycotic	51	26	42
Not specified	28	19	3

Height			
Height [cm]			
Units: centimetre			
arithmetic mean	168.1	168.6	168.5
standard deviation	± 5.49	± 6.73	± 5.29
Weight			
Weight [kg]			
Units: kilogram(s)			
arithmetic mean	65.0	61.5	64.1
standard deviation	± 12.60	± 8.92	± 11.86
BMI			
BMI [kg/m2]			
Units: kilogram(s)/square metre			
arithmetic mean	22.98	21.60	22.56
standard deviation	± 4.128	± 2.815	± 3.986

Reporting group values	Per-Protocol Set - Placebo		
Number of subjects	21		
Age categorical			
Age at randomization			
Units: Subjects			
Adults (18-50 years)	21		
Age continuous			
Age at randomization			
Units: years			
arithmetic mean	31.5		
standard deviation	± 7.54		
Gender categorical			
Female			
Units: Subjects			
Female	21		
Race			
White (Caucasian)			
Units: Subjects			
White (Caucasian)	21		
Prevailing etiology			
Bacterial, Mycotic, Not specified			
Units: Subjects			
Bacterial	1		
Mycotic	18		
Not specified	2		
Height			
Height [cm]			
Units: centimetre			
arithmetic mean	167.0		
standard deviation	± 6.67		
Weight			
Weight [kg]			
Units: kilogram(s)			
arithmetic mean	61.1		
standard deviation	± 9.87		

BMI			
BMI [kg/m2]			
Units: kilogram(s)/square metre			
arithmetic mean	21.85		
standard deviation	± 3.069		

End points

End points reporting groups

Reporting group title	IMUNOR group
Reporting group description: Administration of IMUNOR® - active treatment.	
Reporting group title	Placebo group
Reporting group description: Administration of placebo.	
Reporting group title	IMUNOR group - SOC
Reporting group description: Standard of care without intervention.	
Reporting group title	Placebo group - SOC
Reporting group description: Standard of care without intervention.	
Reporting group title	IMUNOR group
Reporting group description: Administration of IMUNOR® - active treatment.	
Reporting group title	Placebo group
Reporting group description: Administration of placebo.	
Reporting group title	IMUNOR group - SOC
Reporting group description: Standard of care without intervention.	
Reporting group title	Placebo group - SOC
Reporting group description: Standard of care without intervention.	
Subject analysis set title	Full Analysis Set - IMUNOR
Subject analysis set type	Full analysis
Subject analysis set description: IMUNOR group: All patients of the safety set and have at least one measurement after baseline.	
Subject analysis set title	Full Analysis Set - Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Placebo group: All patients of the safety set and have at least one measurement after baseline.	
Subject analysis set title	Per-Protocol Set - IMUNOR
Subject analysis set type	Per protocol
Subject analysis set description: IMUNOR group: All patients of the Full Analysis Set without any relevant protocol violations (major protocol deviations) and complete data for the primary efficacy variable.	
Subject analysis set title	Per-Protocol Set - Placebo
Subject analysis set type	Per protocol
Subject analysis set description: Placebo group: All patients of the Full Analysis Set without any relevant protocol violations (major protocol deviations) and complete data for the primary efficacy variable.	

Primary: Primary endpoint - number of vulvovaginitis episodes during 12 months

End point title	Primary endpoint - number of vulvovaginitis episodes during 12 months
End point description: Number of vulvovaginitis episodes, irrespective of their etiology, during the complete study duration (12-month period) were compared between the IMUNOR® group and the placebo group.	

End point type	Primary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	46	52	21
Units: number				
0 episodes	45	13	27	4
1 episode	25	15	12	5
2 episodes	13	7	9	6
3 episodes	3	4	2	3
4 episodes	3	7	1	3
6 episodes	1	0	1	0

Attachments (see zip file)	Primary endpoint - statistical results/14.2.1 Primary endpoint -

Statistical analyses

Statistical analysis title	Statistical analysis - Primary endpoint - PPS

Statistical analysis description:

The primary endpoint was tested on the PPS. Only vulvovaginitis episodes that started after randomization, and before / during EOS, were considered for this analysis.
The following null hypothesis was tested against the alternative hypothesis:

- Null hypothesis H0: The number of episodes during the study duration is equal to or higher under IMUNOR® than that for placebo.
- Alternative hypothesis H1: The number of episodes during the study duration is smaller under IMUNOR® than that for placeb

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0069 [2]
Method	Regression, Linear
Parameter estimate	Ratio of mean counts
Point estimate	0.489
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.291
upper limit	0.822

Notes:

[1] - To test the hypothesis, a generalized linear model with negative binomial distribution with natural logarithm link function was used. The use of negative binomial regression is suitable for cases where the dependent variable is the count and accounts for cases where overdispersion is present.
Generalized linear model with number of vulvovaginitis episodes as dependent variable and treatment group as independent class variable was fitted in SAS.

[2] - P-value obtained for parameter estimate for the IMUNOR® group was used as the hypothesis test for difference between treatments.

Statistical analysis title	Statistical analysis - Primary endpoint - FAS

Statistical analysis description:

The same analysis as for the PPS was performed on the FAS as sensitivity analysis.
The following null hypothesis was tested against the alternative hypothesis:
- Null hypothesis H0: The number of episodes during the study duration is equal to or higher under IMUNOR® than that for placebo.
- Alternative hypothesis H1: The number of episodes during the study duration is smaller under IMUNOR® than that for placebo.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0067 [4]
Method	Regression, Linear
Parameter estimate	Ratio of mean counts
Point estimate	0.578
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.389
upper limit	0.859

Notes:

[3] - To test the hypothesis, a generalized linear model with negative binomial distribution with natural logarithm link function was used. The use of negative binomial regression is suitable for cases where the dependent variable is the count and accounts for cases where overdispersion is present.
Generalized linear model with number of vulvovaginitis episodes as dependent variable and treatment group as independent class variable was fitted in SAS.
[4] - P-value obtained for parameter estimate for the IMUNOR® group was used as the hypothesis test for difference between treatments.

Secondary: Secondary endpoint 1 - number of vulvovaginitis episodes during 6 months

End point title	Secondary endpoint 1 - number of vulvovaginitis episodes during 6 months

End point description:

Efficacy of IMUNOR® based on reduction of the number of mycotic or bacterial vulvovaginitis episodes during 6 months of treatment as compared to placebo.

End point type	Secondary

End point timeframe:

initial 6-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	27	49	19
Units: number				
0 episodes	32	6	27	4
1 episode	16	8	11	5

2 episodes	10	7	8	6
3 episodes	1	2	1	2
4 episodes	2	4	1	2
6 episodes	1	0	1	0

Attachments (see zip file)	Secondary endpoint 1 - statistical results/14.2.2.1 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 1 - PPS
Statistical analysis description:	
The same methodology as for the primary endpoint was used.	
Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.019 [6]
Method	Regression, Linear
Parameter estimate	Ratio of mean counts
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.892

Notes:

[5] - To test the hypothesis, a generalized linear model with negative binomial distribution with natural logarithm link function was used. The use of negative binomial regression is suitable for cases where the dependent variable is the count and accounts for cases where overdispersion is present.
Generalized linear model with number of vulvovaginitis episodes as dependent variable and treatment group as independent class variable was fitted in SAS.

[6] - P-value obtained for parameter estimate for the IMUNOR® group was used as the hypothesis test for difference between treatments.

Statistical analysis title	Statistical analysis - Secondary endpoint 1 - FAS
Statistical analysis description:	
The same methodology as for the primary endpoint was used.	
Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.009 [8]
Method	Regression, Linear
Parameter estimate	Ratio of mean counts
Point estimate	0.525
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.323
upper limit	0.851

Notes:

[7] - To test the hypothesis, a generalized linear model with negative binomial distribution with natural logarithm link function was used. The use of negative binomial regression is suitable for cases where the dependent variable is the count and accounts for cases where overdispersion is present.
Generalized linear model with number of vulvovaginitis episodes as dependent variable and treatment group as independent class variable was fitted in SAS.
[8] - P-value obtained for parameter estimate for the IMUNOR® group was used as the hypothesis test for difference between treatments.

Secondary: Secondary endpoint 2 - number of vulvovaginitis episodes during 12 months - prevailing bacterial etiology

End point title	Secondary endpoint 2 - number of vulvovaginitis episodes during 12 months - prevailing bacterial etiology

End point description:

Efficacy of IMUNOR® based on reduction of the number of vulvovaginitis episodes during 12 months observation, as compared to placebo, in patients with prevailing bacterial etiology.

End point type	Secondary

End point timeframe:

12 months

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	1	7	1
Units: number				
0 episodes	7	1	4	1
1 episode	1	0	1	0
2 episodes	2	0	1	0
3 episodes	1	0	1	0

Attachments (see zip file)	Secondary endpoint 2 - statistical results/14.2.2.2 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 2 - PPS

Statistical analysis description:

The same methodology as for the primary endpoint was used. The analysis was performed on subset of patients with confirmed prevailing bacterial etiology of vulvovaginitis episodes (documented prior randomization). Vulvovaginitis episodes that started after randomization and before / during EOS were considered.

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0 [10]
Method	Regression, Linear

Notes:

[9] - To test the hypothesis, a generalized linear model with negative binomial distribution with natural logarithm link function was used. The use of negative binomial regression is suitable for cases where the dependent variable is the count and accounts for cases where overdispersion is present.
Generalized linear model with number of vulvovaginitis episodes as dependent variable and treatment

group as independent class variable was fitted in SAS.

[10] - The comparison between treatments was not performed due to low number of patients in the placebo group. P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 2 - FAS

Statistical analysis description:

The same methodology as for the primary endpoint was used. The analysis was performed on subset of patients with confirmed prevailing bacterial etiology of vulvovaginitis episodes (documented prior randomization). Vulvovaginitis episodes that started after randomization and before / during EOS were considered.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0 [12]
Method	Regression, Linear

Notes:

[11] - To test the hypothesis, a generalized linear model with negative binomial distribution with natural logarithm link function was used. The use of negative binomial regression is suitable for cases where the dependent variable is the count and accounts for cases where overdispersion is present.
Generalized linear model with number of vulvovaginitis episodes as dependent variable and treatment group as independent class variable was fitted in SAS.
[12] - The comparison between treatments was not performed due to low number of patients in the placebo group. P-value was not calculated.

Secondary: Secondary endpoint 3 - number of vulvovaginitis episodes during 12 months - prevailing mycotic etiology

End point title	Secondary endpoint 3 - number of vulvovaginitis episodes during 12 months - prevailing mycotic etiology

End point description:

Efficacy of IMUNOR® based on reduction of the number of vulvovaginitis episodes during 12 months observation, as compared to placebo, in patients with prevailing mycotic etiology.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	51	26	42	18
Units: number				
0 episodes	25	5	23	3
1 episode	15	8	10	5
2 episodes	8	7	7	6
3 episodes	0	2	0	2
4 episodes	2	4	1	2
6 episodes	1	0	1	0

Attachments (see zip file)	Secondary endpoint 3 - statistical results/14.2.2.3 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 3 - PPS

Statistical analysis description:

For analysis of this endpoint the same methodology as for the primary endpoint was used. The analysis was performed on subset of patients with confirmed prevailing mycotic etiology of vulvovaginitis episodes (documented prior randomization). Vulvovaginitis episodes that started after randomization and before / during EOS were considered.

Comparison groups	Per-Protocol Set - Placebo v Per-Protocol Set - IMUNOR
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0106 [14]
Method	Regression, Linear
Parameter estimate	Ratio of mean counts
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.263
upper limit	0.839

Notes:

[13] - To test the hypothesis, a generalized linear model with negative binomial distribution with natural logarithm link function was used. The use of negative binomial regression is suitable for cases where the dependent variable is the count and accounts for cases where overdispersion is present.
Generalized linear model with number of vulvovaginitis episodes as dependent variable and treatment group as independent class variable was fitted in SAS.

[14] - P-value obtained for parameter estimate for the IMUNOR® group was used as the hypothesis test for difference between treatments.

Statistical analysis title	Statistical analysis - Secondary endpoint 3 - FAS

Statistical analysis description:

For analysis of this endpoint the same methodology as for the primary endpoint was used. The analysis was performed on subset of patients with confirmed prevailing mycotic etiology of vulvovaginitis episodes (documented prior randomization). Vulvovaginitis episodes that started after randomization and before / during EOS were considered.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0086 [16]
Method	Regression, Linear
Parameter estimate	Ratio of mean counts
Point estimate	0.521
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.321
upper limit	0.847

Notes:

[15] - To test the hypothesis, a generalized linear model with negative binomial distribution with natural logarithm link function was used. The use of negative binomial regression is suitable for cases where the dependent variable is the count and accounts for cases where overdispersion is present.

Generalized linear model with number of vulvovaginitis episodes as dependent variable and treatment group as independent class variable was fitted in SAS.
[16] - P-value obtained for parameter estimate for the IMUNOR® group was used as the hypothesis test for difference between treatments.

Secondary: Secondary endpoint 4 - mean duration of vulvovaginitis episodes

End point title	Secondary endpoint 4 - mean duration of vulvovaginitis episodes

End point description:

Comparison of the mean duration of vulvovaginitis episodes.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	46	52	21
Units: number				
Number of vulvovaginitis episodes with known durat	34	27	20	13

Attachments (see zip file)	Secondary endpoint 4 - statistical results/14.2.2.4 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 4 - PPS

Statistical analysis description:

For all vulvovaginitis episodes, their duration was reported in the study database as part of AE data. If the duration was unavailable after DB lock for any reason, the sponsor provided the available information on duration via a note-to-file (when retrievable).

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0951 [18]
Method	Regression, Linear
Parameter estimate	Ratio of mean durations
Point estimate	1.701
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.898
upper limit	3.221

Notes:

[17] - The duration of VV episode was expected to be lognormally distributed, therefore logarithmically transformed values of duration were used for the analysis. The difference in mean duration of VV episodes was analysed using a mixed effects model accounting for repeated VV episodes in the same patient using patient as random effect. SAS procedure proc mixed was used for the model. Least square estimates were back transformed by exponentiation and presented as mean duration for each treatment

group.

[18] - Corresponding p-value for difference in least square means was presented.
The presented results should be interpreted with caution due to the limited availability of data on episode duration.

Statistical analysis title	Statistical analysis - Secondary endpoint 4 - FAS

Statistical analysis description:

For all vulvovaginitis episodes, their duration was reported in the study database as part of AE data. If the duration was unavailable after DB lock for any reason, the sponsor provided the available information on duration via a note-to-file (when retrievable).

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0447 [20]
Method	Regression, Linear
Parameter estimate	Ratio of mean durations
Point estimate	1.593
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.012
upper limit	2.507

Notes:

[19] - The duration of VV episode was expected to be lognormally distributed, therefore logarithmically transformed values of duration were used for the analysis. The difference in mean duration of VV episodes was analysed using a mixed effects model accounting for repeated VV episodes in the same patient using patient as random effect. SAS procedure proc mixed was used for the model. Least square estimates were back transformed by exponentiation and presented as mean duration for each treatment group.
[20] - Corresponding p-value for difference in least square means was presented.
The presented results should be interpreted with caution due to the limited availability of data on episode duration.

Secondary: Secondary endpoint 5 - proportion of patients withdrawn from the study due to the need of use of oral antifungal medication

End point title	Secondary endpoint 5 - proportion of patients withdrawn from the study due to the need of use of oral antifungal medication

End point description:

Comparison of proportion of patients withdrawn from the study due to the need of use of oral antifungal medication.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	46	52	21
Units: percent				
number (not applicable)				
Number of patients withdrawn due to need of th	2	1	0	1

Percentage of patients withdrawn due to need of th	2.2	2.2	0	4.8

Attachments (see zip file)	Secondary endpoint 5 - statistical results/14.2.2.5 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 5 - PPS

Statistical analysis description:

For each treatment group, the number of patients withdrawn due to the need of use of oral antifungal medication, along with percentage out of total number of patients in the treatment group, was reported. Comparison between treatments was not performed due to low number of patients.

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0 [22]
Method	Descriptive Summary

Notes:

[21] - Descriptive Summary

[22] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 5 - FAS

Statistical analysis description:

For each treatment group, the number of patients withdrawn due to the need of use of oral antifungal medication, along with percentage out of total number of patients in the treatment group, was reported. Comparison between treatments was not performed due to low number of patients.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0 [24]
Method	Descriptive Summary

Notes:

[23] - Descriptive Summary

[24] - Descriptive Summary.
P-value was not calculated.

Secondary: Secondary endpoint 6 - use of local symptomatic and/or topical antifungal/antibacterial treatment

End point title	Secondary endpoint 6 - use of local symptomatic and/or topical antifungal/antibacterial treatment

End point description:

Comparison of the use of local symptomatic and/or topical antifungal/antibacterial treatment.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	46	52	21
Units: number				
G01AC05 / Dequalinium	8	5	6	3
D01AC20 / Imidazoles/triazoles in combination with	7	4	5	2
G01AF12 / Fenticonazole	5	2	4	1
G01AF20 / Combinations of imidazole derivatives	7	5	3	2
G01AX05 / Nifuratel	4	0	4	0
G01AX / Other antiinfectives and antiseptics	6	4	2	1
D03AX / Other cicatrizants	8	5	2	0
G01AA10 / Clindamycin	2	1	1	1
G01AF15 / Butoconazole	5	3	2	0
G02CC03 / Benzydamine	3	1	2	0
J01FA10 / Azithromycin	1	1	1	1
J01XE01 / Nitrofurantoin	2	0	2	0
D07AC13 / Mometasone	1	0	1	0
D07CA01 / Hydrocortisone and antibiotics	5	4	1	0
G01AX12 / Ciclopirox	0	1	0	1
G04BD04 / Oxybutynin	1	0	1	0
J01AA02 / Doxycycline	1	0	1	0
J01CA04 / Amoxicillin	0	1	0	1
J01FF01 / Clindamycin	1	0	1	0
J01MA06 / Norfloxacin	1	0	1	0
J01XX01 / Fosfomycin	1	0	1	0
J02AC01 / Fluconazole	2	2	1	0
P01AB01 / Metronidazole	0	2	0	1
V07AB / Solvents and diluting agents	1	0	1	0
M01AB05 / Diclofenac	1	0	0	0
J01CR04 / Sultamicillin	1	0	0	0
J01XX / Other antibacterials	0	1	0	0
D08AD / Boric acid products	1	0	0	0
J01MA01 / Ofloxacin	1	0	0	0
G01AA51 / Nystatin, combinations	17	12	10	7
G01AA01 / Nystatin	1	0	0	0
D01AA01 / Nystatin	3	2	1	1
G01AA02 / Natamycin	2	1	2	1
D01AA02 / Natamycin	1	1	1	1
G01AF02 / Clotrimazole	25	20	17	12
D01AC01 / Clotrimazole	7	6	3	4
G01AF05 / Econazole	3	3	2	2
D01AC03 / Econazole	0	1	0	0

Attachments (see zip file)	Secondary endpoint 6 - statistical results/14.2.2.6 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 6 - PPS
Statistical analysis description: Descriptive Summary	
Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0 [26]
Method	Descriptive Summary

Notes:

[25] - Descriptive Summary

[26] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 6 - FAS
Statistical analysis description: Descriptive Summary	
Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0 [28]
Method	Descriptive Summary

Notes:

[27] - Descriptive Summary

[28] - Descriptive Summary.
P-value was not calculated.

Secondary: Secondary endpoint 7a - QoL - EQ-5D dimensions - by visit

End point title	Secondary endpoint 7a - QoL - EQ-5D dimensions - by visit
End point description: Summary of EQ-5D dimensions by scheduled visit and treatment group.	
End point type	Secondary
End point timeframe: 12-month period	

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	46	52	21
Units: number of subjects				
Mobility - EOS - I have no problems	79	43	47	18
Mobility - EOS - I have slight problems	5	1	3	1
Mobility - EOS - I have moderate problems	0	1	0	1
Mobility - EOS - Missing	6	1	2	1
Self-care - EOS - I have no problems	84	44	50	19
Self-care - EOS - I have slight problems	0	1	0	1
Self-care - EOS - Missing	6	1	2	1
Usual activities - EOS - I have no problems	79	40	47	17
Usual activities - EOS - I have slight problems	4	5	3	3
Usual activities - EOS - I have moderate problems	1	0	0	0
Usual activities - EOS - Missing	6	1	2	1
Pain/discomfort - EOS - I have no pain/discomfort	62	34	39	17
Pain/discomfort - EOS - I have slight pain/discom	18	10	8	3
Pain/discomfort - EOS - I have moderate pain/disco	3	1	3	0
Pain/discomfort - EOS - I have severe pain or disc	1	0	0	0
Pain/discomfort - EOS - Missing	6	1	2	1
Anxiety/depression - EOS - I am not A/D	70	39	43	17
Anxiety/depression - EOS - I am slightly A/D	11	3	6	0
Anxiety/depression - EOS - I am moderately A/D	0	3	0	3
Anxiety/depression - EOS - I am severely A/D	3	0	1	0
Anxiety/depression - EOS - Missing	6	1	2	1

Attachments (see zip file)	Secondary endpoint 7a - statistical results/14.2.2.7 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 7a - PPS

Statistical analysis description:

The results of the EQ-5D-5L questionnaire were presented descriptively and stratified by the scheduled visit and treatment group. Individual items were presented by category.

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0 [30]
Method	Descriptive Summary

Notes:

[29] - Descriptive Summary

[30] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 7a - FAS

Statistical analysis description:

The results of the EQ-5D-5L questionnaire were presented descriptively and stratified by the scheduled visit and treatment group. Individual items were presented by category.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0 [32]
Method	Descriptive Summary

Notes:

[31] - Descriptive Summary

[32] - Descriptive Summary.
P-value was not calculated.

Secondary: Secondary endpoint 7b - QoL - EQ-5D summary index and EQ-VAS - by visit

End point title	Secondary endpoint 7b - QoL - EQ-5D summary index and EQ-VAS - by visit

End point description:

Summary of EQ-5D summary index and EQ-VAS by scheduled visit and treatment group.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	84	45	50	20
Units: value				
arithmetic mean (standard deviation)				
EQ-5D Summary Index - EOS	0.953 (± 0.0986)	0.962 (± 0.0717)	0.963 (± 0.0739)	0.958 (± 0.0909)
EQ Overall Health (VAS) - EOS	85.9 (± 15.76)	88.0 (± 12.65)	85.0 (± 16.19)	87.6 (± 16.31)

Attachments (see zip file)	Secondary endpoint 7b - statistical results/14.2.2.7 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 7b - PPS

Statistical analysis description:

The results of the EQ-5D-5L questionnaire were presented descriptively and stratified by the scheduled visit and treatment group. Overall score and VAS were presented as continuous variables.

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0 [34]
Method	Descriptive Summary

Notes:

[33] - Descriptive Summary

[34] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 7b - FAS

Statistical analysis description:

The results of the EQ-5D-5L questionnaire were presented descriptively and stratified by the scheduled visit and treatment group. Overall score and VAS were presented as continuous variables.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0 [36]
Method	Descriptive Summary

Notes:

[35] - Descriptive Summary

[36] - Descriptive Summary.
P-value was not calculated.

Secondary: Secondary endpoint 7c - QoL - study specific QoL questionnaire - by visit

End point title	Secondary endpoint 7c - QoL - study specific QoL questionnaire - by visit

End point description:

Summary of study specific quality of life questionnaire by scheduled visit and treatment group.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	44	48	20
Units: value				
arithmetic mean (standard deviation)				
No. of days unable to work/study due to VV -EOS	0.1 (± 0.37)	0.0 (± 0.15)	0.0 (± 0.20)	0.0 (± 0.00)
No. of days of partial work/study due to VV -EOS	0.4 (± 1.28)	0.0 (± 0.21)	0.1 (± 0.55)	0.0 (± 0.00)
Quality of Life during actual episode/visit -EOS	6.2 (± 2.29)	6.3 (± 2.38)	6.4 (± 1.94)	6.2 (± 2.30)

Attachments (see zip file)	Secondary endpoint 7c - statistical results/14.2.2.7 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 7c - PPS

Statistical analysis description:

Study specific QoL questions were summarized descriptively and stratified by scheduled visit and treatment group.

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0 [38]
Method	Descriptive Summary

Notes:

[37] - Descriptive Summary

[38] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 7c - FAS

Statistical analysis description:

Study specific QoL questions were summarized descriptively and stratified by scheduled visit and treatment group.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0 [40]
Method	Descriptive Summary

Notes:

[39] - Descriptive Summary

[40] - Descriptive Summary.
P-value was not calculated.

Secondary: Secondary endpoint 7d - QoL - EQ-5D dimensions - by episode order

End point title	Secondary endpoint 7d - QoL - EQ-5D dimensions - by episode order

End point description:

Summary of EQ-5D dimensions by order of vulvovaginitis episode and treatment group.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	33	25	17
Units: number of subjects				
Mobility - E1 - I have no problems	39	20	21	9
Mobility - E1 - I have slight problems	3	3	2	1
Mobility - E1 - Missing	3	10	2	7
Self-care - E1 - I have no problems	42	20	23	9
Self-care - E1 - I have slight problems	0	3	0	1
Self-care - E1 - Missing	3	10	2	7
Usual activities - E1 - I have no problems	38	18	21	8
Usual activities - E1 - I have slight problems	3	5	2	2
Usual activities - E1 - I have moderate problems	1	0	0	0
Usual activities - E1 - Missing	3	10	2	7
Pain/discomfort - E1 - I have no pain/discomfort	18	12	12	6
Pain/discomfort - E1 - I have slight pain/discom	17	7	9	2
Pain/discomfort - E1 - I have moderate pain/disco	7	4	2	2
Pain/discomfort - E1 - Missing	3	10	2	7
Anxiety/depression - E1 - I am not A/D	34	14	20	7
Anxiety/depression - E1 - I am slightly A/D	7	6	2	1
Anxiety/depression - E1 - I am moderately A/D	0	3	0	2
Anxiety/depression - E1 - I am severely A/D	1	0	1	0
Anxiety/depression - E1 - Missing	3	10	2	7

Attachments (see zip file)	Secondary endpoint 7d - statistical results/14.2.2.7 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 7d - PPS

Statistical analysis description:

The results of the EQ-5D-5L questionnaire were presented descriptively and stratified by vulvovaginitis episode order and treatment group. Individual items were presented by category.

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0 [42]
Method	Descriptive Summary

Notes:

[41] - Descriptive Summary

[42] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 7d - FAS

Statistical analysis description:

The results of the EQ-5D-5L questionnaire were presented descriptively and stratified by vulvovaginitis episode order and treatment group. Individual items were presented by category.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0 [44]
Method	Descriptive Summary

Notes:

[43] - Descriptive Summary

[44] - Descriptive Summary.
P-value was not calculated.

Secondary: Secondary endpoint 7e - QoL - EQ-5D summary index and EQ-VAS - by episode order

End point title	Secondary endpoint 7e - QoL - EQ-5D summary index and EQ-VAS - by episode order

End point description:

Summary of EQ-5D summary index and EQ-VAS by order of vulvovaginitis episode and treatment group.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	23	23	10
Units: value				
arithmetic mean (standard deviation)				
EQ-5D Summary Index - E1	0.932 (± 0.0700)	0.907 (± 0.1013)	0.939 (± 0.0733)	0.921 (± 0.1113)
EQ Overall Health (VAS) - E1	69.5 (± 17.56)	63.9 (± 16.37)	69.3 (± 16.55)	66.0 (± 12.87)

Attachments (see zip file)	Secondary endpoint 7e - statistical results/14.2.2.7 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 7e - PPS

Statistical analysis description:

The results of the EQ-5D-5L questionnaire were presented descriptively and stratified by vulvovaginitis episode order and treatment group. Overall score and VAS were presented as continuous variables.

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0 [46]
Method	Descriptive Summary

Notes:

[45] - Descriptive Summary

[46] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 7e - FAS

Statistical analysis description:

The results of the EQ-5D-5L questionnaire were presented descriptively and stratified by vulvovaginitis episode order and treatment group. Overall score and VAS were presented as continuous variables.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0 [48]
Method	Descriptive Summary

Notes:

[47] - Descriptive Summary

[48] - Descriptive Summary.
P-value was not calculated.

Secondary: Secondary endpoint 7f - QoL - mean EQ-5D summary index and EQ-VAS

End point title	Secondary endpoint 7f - QoL - mean EQ-5D summary index and EQ-VAS

End point description:

Mean EQ-5D summary index and EQ-VAS assessment during vulvovaginitis episodes between treatments.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	46	52	21
Units: value				
number (not applicable)				
Mean EQ-5D Summary Index	0.92	0.90	0.95	0.90
Mean EQ Overall Health (VAS)	68.75	66.94	69.68	66.82

Attachments (see zip file)	Secondary endpoint 7f - statistical results/14.2.2.7 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis-Mean EQ-5D Summary Index -PPS
Statistical analysis description:	
Difference in mean EQ-5D summary index during vulvovaginitis episodes between treatments.	
Comparison groups	Per-Protocol Set - Placebo v Per-Protocol Set - IMUNOR
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.0724
Method	Regression, Linear
Parameter estimate	Difference in mean
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.107

Notes:

[49] - The presented results should be interpreted with caution due to the limited availability of data on episode duration.

Statistical analysis title	Statistical analysis-Mean EQ-5D Summary Index -FAS
Statistical analysis description:	
Difference in mean EQ-5D summary index during vulvovaginitis episodes between treatments.	
Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.2794
Method	Regression, Linear
Parameter estimate	Difference in mean
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.069

Notes:

[50] - The presented results should be interpreted with caution due to the limited availability of data on episode duration.

Statistical analysis title	Statistical analysis-Mean EQ-VAS -PPS
Statistical analysis description:	
Difference in mean EQ-VAS assessment during vulvovaginitis episodes between treatments.	
Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.5295
Method	Regression, Linear
Parameter estimate	Difference in mean
Point estimate	2.861

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.298
upper limit	12.019

Notes:

[51] - The presented results should be interpreted with caution due to the limited availability of data on episode duration.

Statistical analysis title	Statistical analysis-Mean EQ-VAS -FAS

Statistical analysis description:

Difference in mean EQ-VAS assessment during vulvovaginitis episodes between treatments.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.6248
Method	Regression, Linear
Parameter estimate	Difference in mean
Point estimate	1.811
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.579
upper limit	9.2

Notes:

[52] - The presented results should be interpreted with caution due to the limited availability of data on episode duration.

Secondary: Secondary endpoint 7g - QoL - study specific QoL questionnaire - by episode order

End point title	Secondary endpoint 7g - QoL - study specific QoL questionnaire - by episode order

End point description:

Summary of study specific quality of life questionnaire by order of vulvovaginitis episode and treatment group.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	20	23	9
Units: value				
arithmetic mean (standard deviation)				
No. of days unable to work/study due to VV - E1	0.0 (± 0.00)	0.4 (± 1.09)	0.0 (± 0.00)	0.0 (± 0.00)
No. of days of partial work/study due to VV - E1	0.3 (± 1.28)	0.7 (± 1.59)	0.1 (± 0.42)	0.4 (± 1.33)
Quality of Life during actual episode/visit - E1	5.4 (± 2.03)	4.4 (± 2.06)	5.0 (± 1.80)	4.3 (± 2.26)

Attachments (see zip file)	Secondary endpoint 7g - statistical results/14.2.2.7 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 7g - PPS

Statistical analysis description:

Study specific QoL questions were summarized descriptively and stratified by vulvovaginitis episode order and treatment group.

Comparison groups	Per-Protocol Set - IMUNOR v Per-Protocol Set - Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0 [54]
Method	Descriptive Summary

Notes:

[53] - Descriptive Summary

[54] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 7g - FAS

Statistical analysis description:

Study specific QoL questions were summarized descriptively and stratified by vulvovaginitis episode order and treatment group.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	= 0 [56]
Method	Descriptive Summary

Notes:

[55] - Descriptive Summary

[56] - Descriptive Summary.
P-value was not calculated.

Secondary: Secondary endpoint 8 - changes in vaginal biocenosis

End point title	Secondary endpoint 8 - changes in vaginal biocenosis

End point description:

Summary of evaluation of changes in vaginal biocenosis by scheduled visit and treatment group.

End point type	Secondary

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	46	52	21
Units: number of subjects				
Visit 2 - Yes	19	6	13	2
Visit 2 - No	70	39	39	18
Visit 2 - Not done/available	1	1	0	1
Visit 3 - Yes	7	2	3	1
Visit 3 - No	20	11	12	6
Visit 3 - Not done/available	61	33	36	14
Visit 4 - Yes	20	11	12	4
Visit 4 - No	58	31	36	15
Visit 4 - Not done/available	5	1	1	0
Visit 5 - Yes	8	3	3	0
Visit 5 - No	19	11	11	4
Visit 5 - Not done/available	52	28	33	15
EOS - Yes	22	13	16	6
EOS - No	59	32	32	14
EOS - Not done/available	9	1	4	1

Attachments (see zip file)	Secondary endpoint 8 - statistical results/14.2.2.8 Secondary

Statistical analyses

Statistical analysis title	Statistical analysis - Secondary endpoint 8 - PPS

Statistical analysis description:

Vaginal biocenosis findings were reported as Presence or Absence of Candida species in cultivation result. Relative and absolute counts of individual responses “Yes”, “No” and “Not done/available” were summarized descriptively and stratified by scheduled visit and treatment group. The “Yes” category was reported overall as well as by specific Candida species.

Comparison groups	Per-Protocol Set - Placebo v Per-Protocol Set - IMUNOR
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	= 0 [58]
Method	Descriptive Summary

Notes:

[57] - Descriptive Summary.
Data analysis was affected by the limited availability of cultivation results, e.g., due to non-performance of the examination during menstruation or in symptom-free patients with a negative objective finding.
[58] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Secondary endpoint 8 - FAS

Statistical analysis description:

Vaginal biocenosis findings were reported as Presence or Absence of Candida species in cultivation result. Relative and absolute counts of individual responses “Yes”, “No” and “Not done/available” were summarized descriptively and stratified by scheduled visit and treatment group. The “Yes” category was reported overall as well as by specific Candida species.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0 [60]
Method	Descriptive Summary

Notes:

[59] - Descriptive Summary.
Data analysis was affected by the limited availability of cultivation results, e.g., due to non-performance of the examination during menstruation or in symptom-free patients with a negative objective finding.
[60] - Descriptive Summary.
P-value was not calculated.

Other pre-specified: Exploratory endpoint

End point title	Exploratory endpoint

End point description:

Summary statistics, changes from baseline and frequencies of abnormal values of CD3+, CD4+, CD8+, CD16+/CD56+, CD19+, CD3+/HLA-DR3+ cell counts [109/], differential counts of CD3+, CD4+, CD8+, CD16+/CD56+, CD19+, CD3+/HLA-DR3+ cells [%], total IgG, total IgM, total IgA [g/L], anti-D-mannan IgM, anti-D-glucan IgG [U/mL], and phagocyte activity [%] stratified by scheduled visit and treatment group.

End point type	Other pre-specified

End point timeframe:

12-month period

End point values	Full Analysis Set - IMUNOR	Full Analysis Set - Placebo	Per-Protocol Set - IMUNOR	Per-Protocol Set - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78[61]	42[62]	46[63]	19[64]
Units: value				
arithmetic mean (standard deviation)				
Mean count of CD3+ cells [10^9/L] - Visit 5	1.494 (± 0.5214)	1.668 (± 0.5214)	1.513 (± 0.4905)	1.850 (± 0.5322)
Mean diff. count of CD3+ cells [%] - Visit 5	76.49 (± 5.970)	78.06 (± 5.840)	77.25 (± 5.601)	79.99 (± 3.235)
Mean count of CD4+ cells [10^9/L] - Visit 5	0.940 (± 0.3466)	1.096 (± 0.3384)	0.951 (± 0.3095)	1.199 (± 0.3240)
Mean diff. count of CD4+ cells [%] - Visit 5	48.16 (± 6.585)	51.44 (± 5.822)	48.86 (± 6.512)	52.16 (± 5.962)
Mean count of CD8+ cells [10^9/L] - Visit 5	0.492 (± 0.2208)	0.513 (± 0.2168)	0.496 (± 0.2002)	0.577 (± 0.2437)
Mean diff. count of CD8+ cells [%] - Visit 5	25.32 (± 6.574)	23.89 (± 6.234)	25.34 (± 5.413)	24.72 (± 5.781)
Mean count of CD16+/CD56+ cells [10^9/L] - Visit 5	0.226 (± 0.1151)	0.219 (± 0.0974)	0.234 (± 0.1238)	0.204 (± 0.0820)
Mean diff. count of CD16+/CD56+ cells [%] -Visit 5	11.98 (± 5.374)	10.44 (± 3.843)	11.90 (± 4.790)	8.86 (± 2.571)
Mean count of CD19+ cells [10^9/L] - Visit 5	0.199 (± 0.1009)	0.221 (± 0.0957)	0.183 (± 0.0852)	0.227 (± 0.0902)
Mean diff. count of CD19+ cells [%] - Visit 5	10.08 (± 3.393)	10.19 (± 3.375)	9.30 (± 3.063)	9.78 (± 3.273)
Mean count of CD3+/HLA-DR3+ cells [10^9/L]-Visit 5	0.082 (± 0.0559)	0.086 (± 0.0701)	0.081 (± 0.0555)	0.101 (± 0.0687)
Mean diff. count of CD3+/HLA-DR3+cells [%]-Visit 5	4.17 (± 2.605)	3.84 (± 2.537)	4.38 (± 2.739)	4.58 (± 2.573)
Mean level of total IgG [g/L] - Visit 5	11.123 (± 2.1822)	10.769 (± 2.3199)	11.244 (± 2.2239)	10.741 (± 2.0338)

Mean level of total IgM [g/L] - Visit 5	1.219 (± 0.4630)	1.480 (± 0.9116)	1.218 (± 0.4569)	1.402 (± 1.1996)
Mean level of total IgA [g/L] - Visit 5	1.982 (± 0.8195)	2.215 (± 0.7795)	1.985 (± 0.5897)	2.125 (± 0.6267)
Mean level of anti-D-mannan IgM [U/mL] - Visit 5	18.874 (± 16.4249)	20.926 (± 18.096)	17.268 (± 12.2924)	16.626 (± 14.7514)
Mean level of anti-D-mannan IgM [NTU] - Visit 5	4.639 (± 2.3915)	6.453 (± 4.7492)	0 (± 0)	0 (± 0)
Mean level of anti-D-glucan IgG [U/mL] - Visit 5	22.565 (± 23.4687)	19.809 (± 20.3833)	21.677 (± 21.2119)	23.000 (± 25.2827)
Mean level of anti-D-glucan IgG [NTU] - Visit 5	27.630 (± 7.7873)	26.117 (± 7.6006)	0 (± 0)	0 (± 0)
Mean value of phagocyte activity [%] - Visit 5	95.721 (± 7.3766)	95.892 (± 4.0825)	96.905 (± 3.1553)	95.721 (± 4.5385)

Notes:

[61] - Number of subjects with available values for each parameter is specified in the attached tables.

[62] - Number of subjects with available values for each parameter is specified in the attached tables.

[63] - Number of subjects with available values for each parameter is specified in the attached tables.

[64] - Number of subjects with available values for each parameter is specified in the attached tables.

Attachments (see zip file)	Exploratory endpoint - statistical results/14.2.3 Exploratory

Statistical analyses

Statistical analysis title	Statistical analysis - Exploratory endpoint - PPS

Statistical analysis description:

For all patients included in the sub-study, descriptive statistics were calculated for measured values at each scheduled timepoint and for changes from baseline. Additionally, geometric mean was also reported for measured values (not for change from baseline) as the variables of interest could have had log-normal distribution. Moreover, frequencies of normal and abnormal values were reported alongside descriptive statistics.

Comparison groups	Per-Protocol Set - Placebo v Per-Protocol Set - IMUNOR
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	= 0 [66]
Method	Descriptive Summary

Notes:

[65] - Descriptive Summary.
For the assessment of anti-D-mannan IgM and anti-D-glucan IgG antibody levels, patients from study sites 004 and 005 were not included in the PPS due to different measurement units. The data were analysed within the FAS and separately for each unit.

[66] - Descriptive Summary.
P-value was not calculated.

Statistical analysis title	Statistical analysis - Exploratory endpoint - FAS

Statistical analysis description:

For all patients included in the sub-study, descriptive statistics were calculated for measured values at each scheduled timepoint and for changes from baseline. Additionally, geometric mean was also reported for measured values (not for change from baseline) as the variables of interest could have had log-normal distribution. Moreover, frequencies of normal and abnormal values were reported alongside descriptive statistics.

Comparison groups	Full Analysis Set - IMUNOR v Full Analysis Set - Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	= 0 [68]
Method	Descriptive Summary

Notes:

[67] - Descriptive Summary.
For the assessment of anti-D-mannan IgM and anti-D-glucan IgG antibody levels, patients from study sites 004 and 005 were not included in the PPS due to different measurement units. The data were analysed within the FAS and separately for each unit.

[68] - Descriptive Summary.
P-value was not calculated.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12-month period per patient	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	IMUNOR group
Reporting group description:	
Administration of IMUNOR® as 1 dose/week, orally for a total of 3 months within treatment period 1 and treatment period 2. Each treatment period was followed by 3-month observation period. Total study duration was 12 months.	
Reporting group title	Placebo group
Reporting group description:	
Administration of placebo as 1 dose/week, orally for a total of 3 months within treatment period 1 and treatment period 2. Each treatment period was followed by 3-month observation period. Total study duration was 12 months.	

Serious adverse events	IMUNOR group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 90 (4.44%)	2 / 46 (4.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug ineffective	Additional description: Lack of efficacy of hormonal contraception. Pregnancy confirmed by urinal pregnancy tests and blood test (HCG = 537 IU/L) on 16-APR-2018. Pregnancy terminated upon subject's request on 23-APR-2018.		

subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goiter			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chondropathy			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
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: 0 %

Non-serious adverse events	IMUNOR group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 90 (86.67%)	43 / 46 (93.48%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			

Essential hypertension			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Antibiotic therapy			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 90 (1.11%)	1 / 46 (2.17%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 90 (1.11%)	1 / 46 (2.17%)	
occurrences (all)	1	1	
Food allergy			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Milk allergy			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Bacterial vaginosis			
subjects affected / exposed	19 / 90 (21.11%)	15 / 46 (32.61%)	
occurrences (all)	30	17	
Vulvovaginal discomfort			
subjects affected / exposed	6 / 90 (6.67%)	3 / 46 (6.52%)	
occurrences (all)	9	4	
Vaginal haemorrhage			

subjects affected / exposed	4 / 90 (4.44%)	0 / 46 (0.00%)	
occurrences (all)	5	0	
Cervical dysplasia			
subjects affected / exposed	0 / 90 (0.00%)	2 / 46 (4.35%)	
occurrences (all)	0	2	
Vaginal discharge			
subjects affected / exposed	2 / 90 (2.22%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Vulvovaginal pruritus			
subjects affected / exposed	2 / 90 (2.22%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Amenorrhoea			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Breast disorder			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Dyspareunia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Ovarian cyst			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Pruritus genital			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Unexpected vaginal bleeding on hormonal IUD			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	

Uterine inflammation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Uterine polyp			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 90 (1.11%)	1 / 46 (2.17%)	
occurrences (all)	1	1	
Affective disorder			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Traumatic haematoma			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 90 (1.11%)	1 / 46 (2.17%)	
occurrences (all)	3	2	
Anaesthesia			

subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 90 (1.11%)	1 / 46 (2.17%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Tinnitus auris			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 90 (0.00%)	2 / 46 (4.35%)	
occurrences (all)	0	2	
Anal fissure			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Duodenal ulcer			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Dermatitis atopic			

subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 90 (1.11%)	1 / 46 (2.17%)	
occurrences (all)	1	1	
Cystitis noninfective			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Urethral syndrome			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 90 (2.22%)	2 / 46 (4.35%)	
occurrences (all)	2	2	
Tendon disorder			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Tenosynovitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Vulvovaginal mycotic infection			
subjects affected / exposed	31 / 90 (34.44%)	23 / 46 (50.00%)	
occurrences (all)	50	42	
Vulvovaginitis			
subjects affected / exposed	9 / 90 (10.00%)	17 / 46 (36.96%)	
occurrences (all)	13	18	

Bacterial vaginosis			
subjects affected / exposed	17 / 90 (18.89%)	6 / 46 (13.04%)	
occurrences (all)	29	7	
Cystitis			
subjects affected / exposed	13 / 90 (14.44%)	9 / 46 (19.57%)	
occurrences (all)	20	11	
Bacterial vulvovaginitis			
subjects affected / exposed	13 / 90 (14.44%)	6 / 46 (13.04%)	
occurrences (all)	15	9	
Vulvitis			
subjects affected / exposed	13 / 90 (14.44%)	6 / 46 (13.04%)	
occurrences (all)	15	7	
Vulvovaginal candidiasis			
subjects affected / exposed	9 / 90 (10.00%)	8 / 46 (17.39%)	
occurrences (all)	9	8	
Lactobacillus infection			
subjects affected / exposed	12 / 90 (13.33%)	3 / 46 (6.52%)	
occurrences (all)	14	5	
Bronchitis			
subjects affected / exposed	7 / 90 (7.78%)	1 / 46 (2.17%)	
occurrences (all)	8	1	
Nasopharyngitis			
subjects affected / exposed	6 / 90 (6.67%)	2 / 46 (4.35%)	
occurrences (all)	7	2	
Urinary tract infection			
subjects affected / exposed	7 / 90 (7.78%)	0 / 46 (0.00%)	
occurrences (all)	10	0	
Tonsillitis			
subjects affected / exposed	3 / 90 (3.33%)	1 / 46 (2.17%)	
occurrences (all)	3	1	
Gastroenteritis			
subjects affected / exposed	1 / 90 (1.11%)	2 / 46 (4.35%)	
occurrences (all)	1	2	
Genital herpes			
subjects affected / exposed	1 / 90 (1.11%)	1 / 46 (2.17%)	
occurrences (all)	3	1	

Influenza			
subjects affected / exposed	2 / 90 (2.22%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Laryngitis			
subjects affected / exposed	2 / 90 (2.22%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	2 / 90 (2.22%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Viral infection			
subjects affected / exposed	2 / 90 (2.22%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Bacteriuria			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Cervicitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Tracheitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Ureaplasma cervicitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 90 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2015	Substantial Amendment No. 01 (Consolidated Study Protocol, final version 1.0, dated 27 July 2015) Approvals: MEC CZ 16.9.2015 / RA CZ 24.8.2015 / MEC SK 5.12.2015 / RA SK 17.8.2015 Main changes: • Postponement of the recruitment period to September 2015 – February 2016 (including FPLV to September 2016 and LPLV to March 2017); • Change of the CRO and electronic data capture system; • Simplification of the randomization process; • Change in packaging of the IMP.
13 January 2016	Substantial Amendment No. 02 (Consolidated Study Protocol, final version 2.0, dated 09 November 2015) Approvals: MEC CZ 9.12.2015 / RA CZ 4.12.2015 / MEC SK 14.12.2015 / LEC SK 16.12.2015 / RA SK 13.1.2016 Main changes: • Postponement of the recruitment period to January – June 2016 (including FPLV to January 2016 and LPLV to July 2017); • Implementation of the pharmacoeconomic sub-study; • Merge of Visit 6 and the Premature study withdrawal visit; • Update of the information about the source of Reference Safety Information; • QPS Netherlands responsible for data management (instead of QPS Austria GmbH).
01 August 2016	Substantial Amendment No. 03 (Consolidated Study Protocol, final version 4.0, dated 11 May 2016) Approvals: MEC CZ 8.6.2016 / RA CZ 3.6.2016 / MEC SK 19.7.2016 / LEC SK 1.8.2016 / RA SK 28.6.2016 Main changes: • Prolongation of the recruitment period to March 2017 (including postponement of the LPLV to April 2018); • Central evaluation of the reported results of immunology tests; • Prolongation of the screening period (enabling treatment of vulvovaginitis episodes recorded during screening); • Specification of requirements for reporting clinically significant deviations of evaluated laboratory parameters.
31 March 2017	Substantial Amendment No. 04 (Consolidated Study Protocol, final version 5.0, dated 15 February 2017) Approvals: MEC CZ 8.3.2017 (corrected vote received on 28.4.2017) / RA CZ 20.3.2017 / MEC SK 14.3.2017 / LEC SK 31.3.2017 / RA SK 15.3.2017 Main changes: • Prolongation of the recruitment period to December 2017 (including postponement of the LPLV to January 2019); • Clarification of the exclusion criterion No. 11 (in accordance with the list of prohibited and permitted treatments); • Specification of the procedure in the case of non-compliance detected at Visit 5 / after the end of IMP administration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

inclusion of inflammatory and non-inflammatory conditions for acute vaginitis (N 76.0); limited availability of data on episode duration and cultivation results; no comparison for prevailing bacterial etiology due to low no. of placebo patients

Notes: