

SYNOPSIS

Name of Sponsor: Imunomedica, a.s. Chudrov 118 400 11 Ústí nad Labem Czech Republic	Individual Study Table Referring to Part of the Dossier Volume:	<i>(For National Authority Use only)</i>
Name of Finished Product: IMUNOR®		
Name of Active Ingredient: Porcine transfer factor	Page:	
Title of study: 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 Protocol No.: IMUNOR-201501 EudraCT No.: 2015-001472-22		
Coordinating Investigator: doc. MUDr. Vít Unzeitig, CSc. Principal Investigators: Czech Republic: MUDr. Vladimír Dvořák, PhD., MUDr. Alexandra Stará, MUDr. Jiří Dvořák, MUDr. Simona Motlová, MUDr. Hynek Kudělka, MBA, Slovakia: MUDr. Jozef Jendrušák, MUDr. Štefan Novysedlák		
Study centres: Czech Republic: 001, 002, 003, 006, 007 Slovakia: 004, 005		
Publication (reference):		
Studied period: Study initiation date (FPFV): 02.02.2016 Study completion date (LPLV): 08.04.2019	Phase of development: Phase III	
Objectives: Primary Objective: 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. Secondary Objectives: <ul style="list-style-type: none"> To confirm efficacy of IMUNOR® based on reduction of the number of documented mycotic and bacterial vulvovaginitis episodes during 6 months observation, as compared to placebo; To compare the mean duration of vulvovaginitis episodes; To evaluate safety of the IMUNOR® treatment based on the assessment of occurrence of adverse events and monitored laboratory parameters; To compare the use of local symptomatic and/or topical antifungal/antibacterial treatment; To evaluate efficacy of IMUNOR® based on reduction of the number of mycotic vulvovaginitis episodes during 12 months observation, as compared to placebo, in patients with prevailing mycotic etiology (within 12 months prior Screening); Comparison of the proportion of patients withdrawn from the study due to the need of systemic antifungal medication administration; To evaluate efficacy of IMUNOR® based on reduction of the number of bacterial vulvovaginitis episodes during 12 months observation, as compared to placebo, in patients with prevailing bacterial etiology (within 12 months prior Screening); To assess the quality of life of patients; To evaluate changes in vaginal biocenosis; To evaluate basic pharmacoeconomic parameters. Exploratory Objectives: To evaluate changes in selected immunological parameters during the course of IMUNOR®, or placebo, administration.		
Methodology: This was a prospective, randomized, double-blind, placebo-controlled, multicenter, phase III, confirmatory study assessing efficacy and safety of the IMUNOR® therapy versus placebo in female patients suffering from recurrent (mycotic and bacterial) vulvovaginitis episodes. In order to minimize potential risks for participants, all patients were allowed to receive local symptomatic and/or topic antifungal (or antibacterial) treatment in accordance with routine clinical practice of participating sites.		

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<p>In total, 140 female patients from 5 study sites in the Czech Republic and 2 study sites in Slovakia were screened. Enrolment of patients was competitive and performed between January 2016 and February 2018. 137 patients were included in the study based on the pre-defined inclusion/exclusion criteria. At Visit 2, they were randomized in a ratio of 2:1 to receive either IMUNOR®, or placebo, respectively. 136 patients were treated, 120 completed the study, and 73 patients were included in the PPS.</p> <p>The end of the entire study was defined as the date of the Last Visit of the Last Patient.</p> <p>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. The study was assessed by the respective Ethics Committees and approved by the corresponding National Regulatory Authorities.</p>		
Number of patients (planned and analysed): Planned: 135 Analysed: 140		
Diagnosis and main criteria for inclusion: Female patients aged between 18–50 years of age, with documented recurrent mycotic and/or bacterial vulvovaginitis episodes during the last 12 months prior their entry into the study, were included based on the pre-defined inclusion and exclusion criteria.		
Inclusion criteria: Only patients meeting all of the below mentioned inclusion criteria could be included: <ol style="list-style-type: none"> 1. Females aged 18–50 years, without signs of menopause-related oestrogen deficiency; 2. Suspected secondary immune deficiency based on presence of recurrent, symptomatic mycotic and/or bacterial vulvovaginitis episodes documented by a gynaecologist (4 or more episodes during the last 12 months prior randomization, with the exception of mycotic episodes accompanying systemic administration of antibiotics); 3. Patients willing and able to sign the informed consent, cooperate and participate on prescribed study visits; 4. Stable sexual relationships 12 months prior signature of the informed consent and a prerequisite for maintaining them for the next 12 months; 5. Documented use of an effective contraception method, Pearl index ≤ 1. 		
Exclusion criteria: Patients meeting one or more of the below mentioned exclusion criteria could not be included: <ol style="list-style-type: none"> 1. Subjects with known hypersensitivity to any ingredient of the study medication; 2. Pregnant or breast feeding females; 3. Females planning to get pregnant during the course of the next 12 months; 4. Known personal history of hypothyreosis (or suspected); 5. Known personal history of elevated anti-thyroidal antibodies; 6. Known personal history of an autoimmune or malignant disease; 7. Known personal history of HIV positivity, tuberculosis or intake of treatment lowering the function(s) of the immune system (e.g., immunosuppressants, chemotherapy), with the exception of treatment of bronchial asthma, or allergies (nasal or inhaled corticosteroids); 8. Acute vulvovaginitis with presence of herpetic viruses or gonorrhoea; 9. Evidence of chlamydia, trichomonads or another sexually transmitted disease within 30 days prior the first study visit; 10. Use of immune modulation therapy (transfer factor, bacterial lysates, systemic enzymatic therapy, immunoglobulins) during the last 12 months prior the first study visit, or planned initiation of such treatment during the course of the study; 11. Use of vaginal probiotics, or antibiotics (systemic), completed less than 30 days prior the first study visit; 12. Participation in another clinical trial within 30 days prior the first study visit; 13. Any clinically significant condition or disease, which in the opinion of the investigator, could affect safety of the patient or evaluation of this study. 		

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Test product, dose and mode of administration: <p>The investigational medicinal product (IMP) was IMUNOR® (active treatment) or placebo. Both were supplied, free of charge, by Imunomedica, a.s. Each vial of IMUNOR® contained 10 mg of porcine transfer factor as the active ingredient. Placebo was supplied in identical vial containing maltodextrin with brown caramel. The sponsor ensured that the placebo was identical with the provided IMUNOR® in terms of appearance, taste, colour, weight and smell. Both IMUNOR® and placebo were supplied in 3 mL glass vials sealed with a rubber lyophilizing stopper and a plastic screw cap, being packed in an outer paper box containing four vials. Three boxes containing the IMP were packed in an outer paper container (containing 12 glass vials), referred as to the medication kit. At Visit 2, two medication kits, with identical patient numbers, were allocated to a single patient. Each patient was provided only with vials from allocated medication kits throughout the entire study participation (at Visits 2 and 4). All supplied boxes and vials were labelled in compliance with the labelling requirements of the Good Manufacturing Practice Guideline (Volume 4, Annex 13) and the applicable laws and regulations of the Czech Republic and Slovakia. Dosing and handling instructions were provided to patients verbally as well as in printed form.</p> <p>Before administration of the IMP, the content of a vial had to be dissolved in approximately 3 mL of drinking water (under gently shaking). Upon complete dissolution of the lyophilizate, the solution was taken orally on an empty stomach approximately half an hour before breakfast. The IMP was administered by patients as 1 oral dose/week for a total of 3 months within both treatment periods.</p>		
Duration of treatment: <p>For each patient, study participation lasted approximately 12 months. The study was divided into two consecutive phases, each consisting of a 3-month IMP administration period (treatment period) followed by a 3 month observation period (follow-up period). During the study, all patients were asked to come for 6 site visits (and additional unscheduled visits in case of acute vulvovaginitis episodes).</p> <p><i>Study visits:</i></p> <p>Visit 1: Screening (Day -21 to -7)</p> <p>Visit 2: Randomization (Day 0)</p> <p>Visit 3: After completion of the initial treatment cycle (Day 90 ±7 days)</p> <p>Visit 4: Prior the second treatment cycle (Day 180 ±14 days)</p> <p>Visit 5: After the second treatment cycle (Day 270 ±14 days)</p> <p>Visit 6: End of Study Visit (Day 360 ±14 days or Premature study withdrawal)</p>		
Criteria for evaluation: Efficacy <p>The primary endpoint was defined in the study as follows: Assessment of IMUNOR®'s efficacy based on reduction of the number of vulvovaginitis episodes, with confirmed mycotic or bacterial etiology, during 12 months observation time, compared to patients receiving placebo. Episodes starting prior to the first IMP administration had to be documented, but not used for the analysis. All episodes starting during the second Observation Phase and being, or not, resolved after the EOS visit had to be included in the analysis.</p> Safety <p>All AEs occurring during the study (from the timepoint of signing of the ICF until completion of the patient's study participation or premature withdrawal), observed by the Investigator or reported by patients, whether or not attributed to the IMP, had to be recorded in patients' medical records and on the eCRF.</p> <p>AEs were coded using the MedDRA dictionary version 27.0 (most recent version available). Reconciliation of SAEs (i.e., a comparison of the number of SAEs in the clinical database and the number of SAEs reported to sponsor) was done before DB lock. Treatment-emergent AE means any AE that starts after the day of randomization (including the day of randomization).</p> <p>The number of AEs and proportion of patients reporting each treatment-emergent AE were summarized by the primary system organ class (SOC) and preferred term (PT) by treatment group. Percentages were based on the</p>		

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number of patients in the SAF for each treatment group. Additionally, AEs were reported by seriousness, leading to study discontinuation, intensity, relationship to treatment, outcome and action taken.

All AEs (including non-treatment emergent) were listed. No formal statistical tests were performed.

Summary tables with descriptive statistics were created for each laboratory parameter and its change from baseline by treatment group and visit.

Using the external reference ranges for laboratory data, provided by the sponsor, abnormal values below and above the corresponding reference range were classified as “Low” or “High”. Shift tables presenting the number and percentage of patients with low, normal and high values and changes (shifts) with respect to baseline were presented for each laboratory parameter by treatment group and study visit.

Vital signs data and their changes from baseline were summarized descriptively by scheduled visit and treatment group. Descriptive statistics and changes from baseline of heart rate, systolic blood pressure and diastolic blood pressure were summarized.

Statistical methods:

The statistical methods were planned in accordance with the approved version of the Study Protocol with several exceptions (section *Planned changes from study protocol*), and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials, CPMP/ICH/363/96. The Statistical Analysis Plan described statistical methodologies in detail. Main parts of the SAP included definition of study endpoints and analysis sets, definition of major and minor protocol deviations, description of statistical methodology used for the analysis, and preliminary list of tables, listings and figures to be produced.

Statistical package SAS (version 9.4) was used for the analysis and for generation of TFL.

For categorical and ordinal data, the standard set of summary statistics included counts and percentages. Missing values were not used for calculating the percentages. For continuous and ordinal data, the following descriptive statistics were presented: number of available (non-missing) observations, number of missing observations, mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), interquartile range, minimum, and maximum. Results were presented by treatment groups as well as overall, when applicable. All statistical tests were done as one-sided at the $\alpha=0.025$ level of significance. This situation was equivalent to a two-sided statistical test with $\alpha=0.05$, which was performed instead, but only result in direction corresponding to one-sided hypothesis was regarded as significant when interpreting the results. All presented confidence intervals were two-sided at the 95% level. The p-values were reported only if the number of patients included in the respective analysis was considered high enough for meaningful statistical testing. If this condition was not fulfilled, only descriptive statistics were reported. Only the test of the primary parameter was considered confirmatory. All other statistical tests were considered descriptive, therefore no adjustment due to multiple hypothesis testing was necessary.

Demographic and baseline characteristics were described using the standard sets of summary statistics by treatment for the SAF, FAS and PPS. The primary endpoint was tested on the PPS. Additionally, the same analysis as performed on the FAS as sensitivity analysis. Analyses of secondary and exploratory endpoints were performed on both PPS and FAS. Safety analyses were done on the SAF analysis set.

All tables were stratified by treatment group. All recorded data in the study database and all external data used for the analysis were presented in patients’ data listings which were sorted according to patient ID. Where applicable, the treatment group was reported along with patient’s ID.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS

In total, 140 patients were screened (Screening set). Of them, 137 were included in the study and randomized in a 2:1 ratio into the treatment groups (91:46 patients for the IMUNOR® group and placebo group, respectively) (SAF). 136 patients were treated (FAS and SAF), 120 completed the study, and 73 patients were included in the PPS. 16 premature withdrawals were recorded for the FAS.

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Table 1. Disposition of patients (Screening Set)

Patient group	Overall	IMUNOR	Placebo
Screened	N = 140		
Randomized	137 (97.9%)		
Screening failure	3 (2.1%)		
Randomized	N = 137	N = 91	N = 46
Treated (SAF)	136 (99.3%)	90 (98.9%)	46 (100%)
Other	1 (0.7%)	1 (1.1%)	
Treated (SAF)	N = 136	N = 90	N = 46
FAS	136 (100%)	90 (100%)	46 (100%)
PPS	73 (53.7%)	52 (57.8%)	21 (45.7%)
Completed study	120 (88.2%)	78 (86.7%)	42 (91.3%)
Premature withdrawals (FAS)	N = 16	N = 12	N = 4
Adverse event	1 (6.3%)	1 (8.3%)	
Lost to follow-up	1 (6.3%)	1 (8.3%)	
Withdrawal by subject	6 (37.5%)	5 (41.7%)	1 (25.0%)
Withdrawal due to the need of systemic antifungal medication administration	3 (18.8%)	2 (16.7%)	1 (25.0%)
Protocol violation	1 (6.3%)		1 (25.0%)
Other	4 (25.0%)	3 (25.0%)	1 (25.0%)

% is calculated out of corresponding N.

FAS = Full Analysis Set; PPS = Per-Protocol Set; SAF = Safety set.

BASELINE CHARACTERISTICS

The FAS population consisted of 136 patients in total, with 90 in the IMUNOR® group and 46 in the placebo group. All patients were white (Caucasian). The mean (\pm SD) age at randomization was 34.3 ± 8.26 years across both treatment groups. The mean (\pm SD) height, weight, and BMI were 168.2 ± 5.91 cm, 63.8 ± 11.57 kg, and 22.52 ± 3.79 kg/m², respectively. Prevailing mycotic etiology of documented vulvovaginitis episodes was identified in 56.7% of patients (N = 51) in the IMUNOR® group and 56.5% (N = 26) in the placebo group, and prevailing bacterial etiology was found in 12.2% (N = 11) and 2.2% (N = 1), respectively. An unspecified etiology was recorded in 31.1% of patients (N = 28) in the IMUNOR® group and 41.3% (N = 19) in the placebo group.

The PPS population comprised 52 patients in the IMUNOR® group and 21 patients in the placebo group. All patients were white (Caucasian). The mean (\pm SD) age at randomization was 33.0 ± 8.16 years overall. The mean (\pm SD) height, weight and BMI was 168.1 ± 5.71 cm, 63.2 ± 11.33 kg, and 22.35 ± 3.74 kg/m², respectively. Prevailing mycotic etiology was reported in 80.8% of patients (N = 42) in the IMUNOR® group and 85.7% (N = 18) in the placebo group, prevailing bacterial etiology in 13.5% (N = 7) and 4.8% (N = 1), and an unspecified etiology in 5.8% (N = 3) and 9.5% (N = 2), respectively.

Table 2. Demographic and baseline characteristics (FAS)

Characteristic	Statistics	IMUNOR	Placebo	Overall
Full analysis set	N	90	46	136
Sex	Female, n (%)	90 (100)	46 (100)	136 (100)
Age at randomization [years]	n / missing	90 / 0	46 / 0	136 / 0
	Mean (SD)	34.7 (8.25)	33.5 (8.33)	34.3 (8.26)
	Median	37.0	36.0	36.0
	IQR	13.0	14.0	14.0
	Q1 / Q3	28.0 / 41.0	26.0 / 40.0	26.5 / 40.5
	Min / Max	19 / 50	19 / 48	19 / 50
Race	White, n (%)	90 (100)	46 (100)	136 (100)

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Characteristic	Statistics	IMUNOR	Placebo	Overall
Height [cm]	n / missing	90 / 0	45 / 1	135 / 1
	Mean (SD)	168.1 (5.49)	168.6 (6.73)	168.2 (5.91)
	Median	168.5	170.0	169.0
	IQR	7.0	7.0	7.0
	Q1 / Q3	165.0 / 172.0	165.0 / 172.0	165.0 / 172.0
	Min / Max	154 / 182	147 / 192	147 / 192
Weight [kg]	n / missing	90 / 0	46 / 0	136 / 0
	Mean (SD)	65.0 (12.60)	61.5 (8.92)	63.8 (11.57)
	Median	62.0	61.0	62.0
	IQR	14.0	12.0	12.0
	Q1 / Q3	56.0 / 70.0	56.0 / 68.0	56.0 / 68.0
	Min / Max	47 / 113	36 / 82	36 / 113
BMI [kg/m²]	n / missing	90 / 0	45 / 1	135 / 1
	Mean (SD)	22.98 (4.128)	21.60 (2.815)	22.52 (3.788)
	Median	22.33	21.48	21.71
	IQR	4.17	3.11	4.14
	Q1 / Q3	20.07 / 24.24	19.72 / 22.84	19.95 / 24.09
	Min / Max	17.9 / 40.0	16.7 / 29.1	16.7 / 40.0
Prevailing etiology	Bacterial, n (%)	11 (12.2)	1 (2.2)	12 (8.8)
	Mycotic, n (%)	51 (56.7)	26 (56.5)	77 (56.6)
	Not specified, n (%)	28 (31.1)	19 (41.3)	47 (34.6)

% = Percentage of patients out of corresponding N; FAS = Full Analysis Set; IQR = Interquartile range; Max = Maximum; Min = Minimum; n = Number of patients; Q1 = lower quartile (25th percentile); Q3 = upper quartile (75th percentile); SD = Standard deviation.

Table 3. Demographic and baseline characteristics (PPS)

Characteristic	Statistics	IMUNOR	Placebo	Overall
Per-protocol set	N	52	21	73
Sex	Female, n (%)	52 (100)	21 (100)	73 (100)
Age at randomization [years]	n / missing	52 / 0	21 / 0	73 / 0
	Mean (SD)	33.6 (8.39)	31.5 (7.54)	33.0 (8.16)
	Median	35.0	31.0	34.0
	IQR	15.0	13.0	14.0
	Q1 / Q3	25.0 / 40.0	25.0 / 38.0	25.0 / 39.0
	Min / Max	19 / 49	19 / 45	19 / 49
Race	White, n (%)	52 (100)	21 (100)	73 (100)
Height [cm]	n / missing	52 / 0	21 / 0	73 / 0
	Mean (SD)	168.5 (5.29)	167.0 (6.67)	168.1 (5.71)
	Median	169.0	169.0	169.0
	IQR	7.0	7.0	7.0
	Q1 / Q3	165.0 / 172.0	165.0 / 172.0	165.0 / 172.0
	Min / Max	158 / 182	147 / 174	147 / 182
Weight [kg]	n / missing	52 / 0	21 / 0	73 / 0
	Mean (SD)	64.1 (11.86)	61.1 (9.87)	63.2 (11.33)
	Median	60.5	60.0	60.0
	IQR	12.5	9.0	12.0
	Q1 / Q3	56.0 / 68.5	57.0 / 66.0	56.0 / 68.0
	Min / Max	47 / 107	36 / 82	36 / 107

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Characteristic	Statistics	IMUNOR	Placebo	Overall
BMI [kg/m ²]	n / missing	52 / 0	21 / 0	73 / 0
	Mean (SD)	22.56 (3.986)	21.85 (3.069)	22.35 (3.738)
	Median	21.48	21.61	21.51
	IQR	4.69	2.81	3.99
	Q1 / Q3	19.69 / 24.38	19.83 / 22.65	19.82 / 23.81
	Min / Max	18.3 / 38.8	16.7 / 29.1	16.7 / 38.8
Prevailing etiology	Bacterial, n (%)	7 (13.5)	1 (4.8)	8 (11.0)
	Mycotic, n (%)	42 (80.8)	18 (85.7)	60 (82.2)
	Not specified, n (%)	3 (5.8)	2 (9.5)	5 (6.8)

% = Percentage of patients out of corresponding N; IQR = Interquartile range; Max = Maximum; Min = Minimum; n = Number of patients; PPS = Per-Protocol Set; Q1 = lower quartile (25th percentile); Q3 = upper quartile (75th percentile); SD = Standard deviation.

EFFICACY RESULTS

Analysing the primary endpoint, in the IMUNOR® treatment group, 51.9% of patients (N = 27) experienced no vulvovaginitis episodes during the 12-month study period (two 3-month treatment periods, each followed by a 3-month observation), while 19.0% of patients (N = 4) receiving placebo were episode-free (PPS). Four or more episodes per 12 months were reported in 14.3% of patients (N = 3) in the placebo group and in 3.8% of patients (N = 2) in the IMUNOR® group.

The mean number of vulvovaginitis episodes during the 12-month study period was lower in patients treated with IMUNOR® (0.88) compared to those receiving placebo (1.81), with the ratio of mean episode counts of 0.489 (95% CI, 0.291–0.822). A statistically significant difference between the treatment arms (p = 0.0069) was confirmed in the PPS. Similar results were achieved in the FAS, where the mean number of vulvovaginitis episodes per 12 months was 0.87 in the IMUNOR® group and 1.50 in the placebo group. The ratio of mean episode counts was 0.578 (95% CI, 0.389–0.859) and the difference statistically significant (p = 0.0067).

During the initial 6-month study period, 55.1% of patients (N = 27) in the IMUNOR® group and 21.1% of patients (N = 4) in the placebo group experienced no vulvovaginitis episodes (PPS). Four or more episodes per 6 months were documented in 10.5% of patients (N = 2) in the placebo group and in 4.0% of patients (N = 2) in the IMUNOR® group. Patients receiving IMUNOR® experienced a lower mean number of episodes (0.82) during the 6-month study period compared to placebo (1.63). The ratio of mean episode counts was 0.500 (95% CI, 0.280–0.892), and this difference was statistically significant (p = 0.0190).

The comparison of the mean number of vulvovaginitis episodes between treatments in patients with prevailing bacterial etiology during the 12-month study period was not performed due to the low number of patients in the placebo group (for PPS: N = 7 in the IMUNOR® group and N = 1 in the placebo group).

Among patients with prevailing mycotic etiology, 54.8% (N = 23) of those receiving IMUNOR® and 16.7% of patients (N = 3) receiving placebo remained free of vulvovaginitis episodes over the 12-month study period (PPS). Four or more episodes per 12 months were documented in 11.1% of patients (N = 2) in the placebo group and in 4.8% of patients (N = 2) in the IMUNOR® group. Patients in the IMUNOR® group demonstrated a lower mean number of vulvovaginitis episodes compared to placebo (0.81 vs. 1.72, respectively). The ratio of mean episode counts was estimated at 0.470 (95% CI, 0.263–0.839). This difference was found to be statistically significant (p = 0.0106).

In the PPS, the mean duration of vulvovaginitis episodes was 11.45 days in the IMUNOR® group and 6.73 days in the placebo group. The ratio of mean episode durations was 1.701 (95% CI, 0.898–3.221) and this difference was not statistically significant (p = 0.0951). The presented results should be interpreted with caution due to the limited availability of data on episode duration.

One patient (4.8%) in the placebo group and none in the IMUNOR® group were withdrawn from the study due to the need for systemic antifungal medication in PPS. In FAS, two patients (2.2%) in the IMUNOR® group and one patient (2.2%) in the placebo group were withdrawn for the same reason.

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In the PPS, the use of local symptomatic and/or topical antifungal/antibacterial treatment was reported in 50.0% of patients (N = 26) in the IMUNOR® group, and in 85.7% (N = 18) in the placebo group. In the FAS, 52.2% of patients (N = 47) in the IMUNOR® group and 73.9% (N = 34) in the placebo group received local symptomatic and/or topical antifungal/antibacterial medication indicated for vulvovaginitis.

During vulvovaginitis episodes, patients in the IMUNOR® group reported a mean EQ-5D Summary Index of 0.95, compared to 0.90 in the placebo group, with a between-group difference of 0.051 (95% CI, -0.005 to 0.107) which did not reach statistical significance (p = 0.0724). Similarly, the mean EQ Overall Health (VAS) was 69.68 in the IMUNOR® group and 66.82 in the placebo group, with a non-significant between-group difference of 2.861 (95% CI, -6.298 to 12.019; p = 0.5295).

Analysing the PPS, *Candida* species were present at Visit 2 in 25.0% of patients (N = 13) in the IMUNOR® group and 9.5% (N = 2) in the placebo group, with *C. albicans* identified in all isolates in both groups. At EOS, *Candida* species were detected in 30.8% of patients (N = 16) in the IMUNOR® group and 28.6% (N = 6) in the placebo group. Across both groups, *C. albicans* was identified in 20 patients, *C. glabrata* in 1 patient, and mixed *Candida* species in 1 patient at EOS. Microbiological cultivation was not performed or not available in one patient (4.8%) in the placebo group at Visit 2, and in four patients (7.7%) in the IMUNOR® group and one patient (4.8%) in the placebo group at EOS.

In addition, at EOS, 9.6% of patients (N = 5) in the IMUNOR® group and 4.8% (N = 1) in the placebo group demonstrated a shift from presence to absence of *Candida* species in cultivation result (Yes → No). A shift from absence to presence (No → Yes) occurred in 17.3% of patients (N = 9) in the IMUNOR® group and 23.8% (N = 5) in the placebo group. At EOS, assessment results were missing for four patients (7.7%) in the IMUNOR® group and two patients (9.5%) in the placebo group. 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.

Table 4. Primary endpoint: Comparison of the number of vulvovaginitis episodes between treatments during 12-month study period (PPS)

		IMUNOR N = 52	Placebo N = 21	Comparison
Number of vulvovaginitis episodes	0 episodes	27 (51.9%)	4 (19.0%)	
	1 episode	12 (23.1%)	5 (23.8%)	
	2 episodes	9 (17.3%)	6 (28.6%)	
	3 episodes	2 (3.8%)	3 (14.3%)	
	4 episodes	1 (1.9%)	3 (14.3%)	
	6 episodes	1 (1.9%)		
Comparison of number of vulvovaginitis episodes	Mean episode count	0.88	1.81	
	Ratio of mean episode counts (95% CI)			0.489 (0.291, 0.822)
	p-value			0.0069

% = Percentage of subjects out of N; CI = Confidence interval; N = Total number of subjects in the treatment arm; PPS = Per Protocol Set.

Mean episode estimates, ratio of mean episode counts with corresponding confidence interval and p-value were obtained from negative binomial regression model with number of episodes as dependent variable and treatment group as independent variable.

SAFETY RESULTS

In total, 458 AEs were reported in 127 patients (93.4%): 295 AEs in 82 patients (91.1%) in IMUNOR® group, 163 AEs in 45 patients (97.8%) in placebo group. Seven SAEs were reported in six patients during the study: four SAEs in the IMUNOR® group: biliary obstruction, joint injury, breast cancer, acute psychosis, and three SAEs in the placebo group: goiter, drug ineffective, chondropathy. No causal relationship between the administered investigational medicinal product (IMUNOR®) and the reported SAEs were assessed either by investigators or the sponsor.

Three AEs (two in the IMUNOR® group and one in the placebo group) led to premature study discontinuation, including one SAE (breast cancer) in the IMUNOR® group.

A total of two pregnancy cases were reported during the study (one in the IMUNOR® and one in the placebo group). The pregnancy in the IMUNOR® group had a favourable outcome. The pregnancy in the placebo group

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was terminated upon subject's request, with no abnormalities identified. The reported pregnancy cases did not contain any AE.

During the 12-month study period, no clinically significant changes were observed in routinely examined haematological, biochemical and immunological parameters, or vital signs in either treatment group.

No new risks which could affect the safety profile of IMUNOR® were identified.

Table 5. Treatment-emergent adverse events by treatment and primary system organ class (SAF)

System organ class	Preferred term	IMUNOR N = 90		Placebo N = 46		Overall N = 136	
		nAE	n (%)	nAE	n (%)	nAE	n (%)
Any		295	82 (91.1)	163	45 (97.8)	458	127 (93.4)
Infections and infestations	Any	199	70 (77.8)	118	43 (93.5)	317	113 (83.1)
Reproductive system and breast disorders	Any	59	36 (40.0)	23	18 (39.1)	82	54 (39.7)
Gastrointestinal disorders	Any	5	5 (5.6)	2	2 (4.3)	7	7 (5.1)
Musculoskeletal and connective tissue disorders	Any	3	3 (3.3)	4	3 (6.5)	7	6 (4.4)
Immune system disorders	Any	4	3 (3.3)	1	1 (2.2)	5	4 (2.9)
Injury, poisoning and procedural complications	Any	4	4 (4.4)			4	4 (2.9)
Nervous system disorders	Any	5	3 (3.3)	2	1 (2.2)	7	4 (2.9)
Psychiatric disorders	Any	2	2 (2.2)	2	2 (4.3)	4	4 (2.9)
Renal and urinary disorders	Any	3	3 (3.3)	1	1 (2.2)	4	4 (2.9)
Skin and subcutaneous tissue disorders	Any	1	1 (1.1)	3	2 (4.3)	4	3 (2.2)
Blood and lymphatic system disorders	Any	1	1 (1.1)	1	1 (2.2)	2	2 (1.5)
Endocrine disorders	Any	1	1 (1.1)	1	1 (2.2)	2	2 (1.5)
General disorders and administration site conditions	Any	1	1 (1.1)	1	1 (2.2)	2	2 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Any	2	2 (2.2)			2	2 (1.5)
Pregnancy, puerperium and perinatal conditions	Any	1	1 (1.1)	1	1 (2.2)	2	2 (1.5)
Ear and labyrinth disorders	Any			1	1 (2.2)	1	1 (0.7)
Hepatobiliary disorders	Any	1	1 (1.1)			1	1 (0.7)
Investigations	Any			1	1 (2.2)	1	1 (0.7)
Metabolism and nutrition disorders	Any			1	1 (2.2)	1	1 (0.7)
Respiratory, thoracic and mediastinal disorders	Any	1	1 (1.1)			1	1 (0.7)
Surgical and medical procedures	Any	1	1 (1.1)			1	1 (0.7)
Vascular disorders	Any	1	1 (1.1)			1	1 (0.7)

% = Percentage of subjects out of N; FAS = Full Analysis Set; N = Total number of subjects; n = Number of subjects with adverse event; nAE = Number of adverse events.

Coded using MedDRA version 27.0.

Table 6. Treatment-emergent serious adverse events by treatment and MedDRA preferred term within primary system organ class (SAF)

System organ class	Preferred term	IMUNOR N = 90		Placebo N = 46		Overall N = 136	
		nAE	n (%)	nAE	n (%)	nAE	n (%)
Any		4	4 (4.4)	3	2 (4.3)	7	6 (4.4)
Endocrine disorders	Goiter			1	1 (2.2)	1	1 (0.7)
General disorders and administration site conditions	Drug ineffective			1	1 (2.2)	1	1 (0.7)
Hepatobiliary disorders	Biliary obstruction	1	1 (1.1)			1	1 (0.7)
Injury, poisoning and procedural complications	Joint injury	1	1 (1.1)			1	1 (0.7)
Musculoskeletal and connective tissue disorders	Chondropathy			1	1 (2.2)	1	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	1	1 (1.1)			1	1 (0.7)
Psychiatric disorders	Acute psychosis	1	1 (1.1)			1	1 (0.7)

% = Percentage of subjects out of N; FAS = Full Analysis Set; N = Total number of subjects; n = Number of subjects with adverse event; nAE = Number of adverse events. Coded using MedDRA version 27.0.

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CONCLUSION

The results of this randomized, placebo-controlled trial confirm that IMUNOR®, porcine transfer factor, significantly reduced the frequency of vulvovaginitis episodes over the 12-month primary analysis period (two 3-month treatment periods, each followed by a 3-month observation). Notably, in the PPS, 51.9% of patients in the IMUNOR® group remained episode-free compared to 19.0% in the placebo group, and the mean number of episodes was significantly lower in the IMUNOR® group ($p = 0.0069$). A statistically significant difference was also observed after 6-month period (3 months of treatment, 3 months of observation). Specifically, among patients with prevailing mycotic etiology, 54.8% of those treated with IMUNOR® remained episode-free over 12 months, and the mean episode count was significantly lower compared to placebo ($p = 0.0190$).

These findings are consistent with results from a previously performed open-label study indicating the benefits of porcine transfer factor in the management of chronic gynaecological conditions. The study conducted by Unzeitig et al. demonstrated that 46% of women with chronic vulvovaginal discomfort reported significant improvement or even passing of their complaints following IMUNOR® administration over a 3-month period. The immunomodulatory effects of transfer factors, such as IMUNOR®, may enhance both innate and adaptive immune responses, leading to reduced susceptibility to infections. This is particularly relevant in the context of recurrent vulvovaginitis, where immune dysregulation plays a critical role.

Certain limitations should be acknowledged. The presented study faced a few challenges associated with the inclusion of inflammatory and non-inflammatory conditions under the ICD-10 code for acute vaginitis (N 76.0) and with the limited availability of data on episode duration and cultivation results. Future studies should aim to incorporate comprehensive microbiological and immunological evaluations to better understand the mechanisms underlying the observed clinical benefits.

Adverse events were reported in both treatment groups in the SAF. A total of seven serious adverse events were reported during the study, and none of them was assessed as related to the investigational medicinal product. In the IMUNOR® group, adverse events were predominantly mild to moderate, aligned with the expected safety characteristics of the medicinal product and did not raise new safety concerns.

The results of the study confirmed the absence of clinically significant changes in routinely examined haematological, biochemical and immunological parameters, or vital signs in either treatment group during 12-month study period. This observation supports the safety of IMUNOR® administration but at the same time points to the key role of functional changes in the immune system in the etiopathogenesis of recurrent vulvovaginitis.

Based on the assessment of all provided information, the overall safety profile of IMUNOR® remains favourable and supports its continued development in the treatment of recurrent vulvovaginitis. No new risks which could affect the safety profile of IMUNOR® were identified. The most common risks associated with IMUNOR® treatment are readily recognized and manageable, and all risks are adequately addressed in the SmPC. Overall, the benefit-risk ratio of IMUNOR® does not change and remains positive.

In conclusion, IMUNOR® administration significantly reduced the frequency of vulvovaginitis episodes in women with recurrent disease. The presented findings support the potential of IMUNOR® as an effective and safe immunomodulatory therapy for preventing recurrences of vulvovaginitis. Further research with detailed microbiological and immunological assessments is warranted to elucidate the underlying mechanisms.

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