SYNOPSIS

NAME OF COMPANY Inmunotek, S.L.	INDIVIDUAL STUDY TABULAR FORMAT
NAME OF FINISHED PRODUCT: Uromune	
NAME OF INVESTIGATIONAL PRODUCT SUBSTANCE(S): Uromune-MV140	
TITLE OF THE STUDY A multicentre, prospective, randomized, double-blind, parallel-group placebo-controlled clinical study for the assessment of the immunomodulatory efficacy, safety and clinical impact after three and six months treatment with a sublingual polyvalent bacterial vaccine (in oral mucosa) in women with recurrent urinary tract infections (rUTIs).	
PRINCIPAL INVESTIGATORS: María-Fernanda Lorenzo-Gómez (coordinating investigator), MD, PhD. Stephen Foley, MBBS, FRCS (principal investigator from UK study arm)	
STUDY CENTRE(S) 1.- University Hospital of Salamanca. Salamanca, Spain, 37007. 2.- Primary Health Care Centre "Universidad Centro". Salamanca, Spain, 37001. 3.- Primary Health Care Centre "Peñaranda". Salamanca, Spain, 37300. 4.- Primary Health Care Centre "Capuchinos". Salamanca, Spain, 37006 5.- Royal Berkshire Hospital NHS Foundation Trust. Reading, London, United Kingdom. RG1 5AN	
PUBLICATION (reference): N/A	
STUDY PERIOD: 12 months per subject **DATE OF FIRST ENROLMENT:** October 2015 **DATE OF LAST COMPLETED:** April 2019	**PHASE OF DEVELOPMENT:** III
OBJECTIVES Determine if immunization with the bacterial vaccine MV140 would reduce the risk of and/or prevent urinary tract infections (UTI) compared to placebo in women with recurrent UTIs.	
METHODOLOGY A multicentre, prospective, randomized, double-blind, parallel-group, placebo-controlled phase III clinical study. The study included 6 visits: a baseline visit (BV) and 5 programmed visits. The baseline visits took place between October 2015 and April 2018. The study lasted 12 months per subject. In the first 6 months, each subject received the treatment (active, placebo or active and placebo) through the sublingual route as follows, applying two sprays daily. The last 6 months correspond to the follow-up period. • Subjects in Group I received active treatment consisting of a bacterial vaccine sublingually for 6 months (*i.e.* MV140 6M). • Subjects in Group II received placebo sublingually for 6 months • Subjects in Group III received 3 months of active treatment and then 3 months of placebo sublingually (*i.e.* MV140 3M). Ratio between groups was 1:1:1. In all the visits, except for visit 5, the subject's diaries were given for the evaluation of symptoms, annotation of concomitant medication and consumption of healthcare resources. In visits 2 to 5, subject's diaries were collected.	
NUMBER OF SUBJECTS The number of subjects that were included in the study was 240. The number of subjects who received treatment (excluded screening failures) were 230 and those who finished were 195. Analysed sets: - Efficacy evaluable population (Intention-to-treat): 215	

- Efficacy evaluable population (per-protocol): 193
- Safety evaluable population: 230
- Immunological study: 45

DIAGNOSIS

Recurrent UTIs with the diagnosis of non-complicated UTIs

CRITERIA FOR INCLUSION

- Women who gave their informed consent.
- Age between 18 and 75 years.
- Must be able to meet the dosage regimen.
- Subjects who had had at least 5 episodes of cystitis in the last 12 months.
- Subjects who had not responded to hygienic-sanitary measures and / or suppressive treatment and / or postcoital prophylaxis.
- Subjects who were free of urinary tract infections at the time of inclusion in the study.

CRITERIA FOR EXCLUSION

- Could not offer cooperation and/or had severe psychiatric disorders.
- Presented with a pathologic post-micturition residue.
- Presented with moderate to severe incontinence.
- Presented with genital tumours.
- Presented with urinary tract tumours.
- Presented with lithiasis.
- Presented with alterations in the immune system.
- Presented with complicated UTIs.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NO.

The trial medication was a polyvalent bacterial vaccine; the pharmaceutical form was a glycerinated suspension containing a mixture of four inactivated non-lysated bacterial concentrates (*Escherichia coli* 25%, *Klebsiella pneumoniae* 25%, *Enterococcus faecalis* 25%, *Proteus vulgaris* 25%) as active substance. As excipients, it contains 0.63 g of glycerol, pineapple artificial flavouring (0.01 mL), sodium chloride (9 mg/mL) and water (q.s. for 1 mL). The trial medication was administered through the sublingual route, applying two sprays daily.

The strength and batches tested were as follows:

- EC0201G15F (SLG-003-01-01). 300 FTU (Formazin Turbidity Units, equivalent to 10^9 bacteria/mL).
- EC0501G16J (SLG-003-02-01). 300 FTU (Formazin Turbidity Units, equivalent to 10^9 bacteria/mL).

DURATION OF TREATMENT

Subjects received daily sublingual treatment for 6 months, either active, placebo or active and placebo as stated above (*See Methodology section*).

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, BATCH NO.

The control product was placebo.

It contained an identical solution to the test product but no active substance (without the inactivated non-lysate bacterial concentrates), and was administrated through the sublingual route, applying two sprays daily.

The composition was 0.63 g of glycerol, pineapple artificial flavouring 0.01 mL, sodium chloride 9 mg/mL and water (q.s. for 1 mL).

The batches tested were as follows:

- EC0202G15F (SLG-003-01-01).
- EC0502G16J (SLG-003-02-01)

CRITERIA FOR EVALUATION

EFFICACY

Primary outcome variable: mean number of episodes of urinary tract infections

The comparison of the number of episodes of UTIs in the three study groups in the 9 months study period following 3 months of intervention (placebo or immunization).

Major Secondary variable Outcome: infection free rates

The comparison of the proportion of subjects who remained infection free (no UTIs) in the three study groups in the 9-month study period following 3 months of intervention (placebo or immunization).

Other Secondary efficacy endpoints/analyses: Comparison of:

- Number of episodes of UTIs in the three study groups in the 6-month study period following 6 months of intervention (placebo and/or immunization).
- Number of episodes of UTIs in the three study groups in the 12-month study period following initiation of intervention (placebo and/or immunization).
- Proportion of subjects who remained infection free (no UTIs) in the three study groups in the 6-month study period following 6 months of intervention (placebo and/or immunization).
- Proportion of subjects who remained infection free (no UTIs) in the three study groups in the 12-month study period following initiation of intervention (placebo and/or immunization).
- Time to first UTI in the three study groups.
- Healthcare utilization and cost in the three study groups.
- Use of antibiotics for treatment of UTIs in the three study groups.
- Quality of life measured with the questionnaire SF-36.
- Family Resources (absenteeism).
- Other analyses: Symptoms and visual analogue scales.
- Immunological parameters

SAFETY

- Overall rate, severity and relationship of any adverse event (AE) per administration and per subject (*i.e.* number and percentage of subjects with AE and number of AE themselves and by type of event, seriousness, severity/grading, causality, action taken and outcome).
- Evaluation of tolerance. In essence, number and percentage of subjects with Adverse Reaction (AR), number of AR and its percentage, themselves and by location, timing of appearance, severity, outcome, withdrawal and by doses administered (extent of exposure).

STATISTICAL METHODS

The Clinical Research Organization (CRO) Bioclever, jointly with the Medical Department of INMUNOTEK S.L. carried out the statistical analysis.

Efficacy analyses were carried out by intention-to-treat (ITT) and per protocol. Safety analysis was performed on randomized subjects who received at least one dose of treatment (evaluable safety population).

Descriptive analysis of the collected variables was carried out. Depending on the variable nature, the following results were presented:

- Categorical variables were summarized by frequencies and percentages.

- Continuous variables were summarized by means of central tendency and dispersion measures: median, 25% and 75% (Q1 and Q3) percentiles, mean, standard deviation and extreme values (minimum and maximum).

Comparative statistics were performed as follows:

- For two categorical variables, contingency tables with the frequency in each category and the percentage by columns were presented. To evaluate the possible association Chi-square tests or Fisher's exact test were performed.
- For a numerical variable with a categorical, descriptive statistics were presented by groups. To evaluate the possible association, ANOVA and Kruskal-Wallis nonparametric test were performed, in accordance with the variable probability distribution.

Post hoc analysis were also conducted to evaluate pairwise differences, once the null hypothesis was rejected.

- Time-to-event data was analysed by the Kaplan-Meier estimator, and the median and the 25th and 75th percentiles were presented along with their 95% CI, comparing the three curves using the Log Rank test.
- Repeated measures over time including previous and post data were analysed by Wilcoxon-signed ranked test and Mixed-effects models.

SUMMARY CONCLUSIONS

EFFICACY RESULTS

As primary outcome of the study, the number of UTI episodes were significantly reduced in the 9-month efficacy period (*i.e.* following 3 months of intervention) in subjects receiving MV140 compared to placebo. The median of UTI episodes was 3.0 in placebo group [IQR, 0.5-6.0] compared to 0.0 [IQR, 0.0-1.0] in both groups receiving MV140 (P<0.001).

A significant increase in the UTI-free rate (major secondary outcome) was found in subjects receiving active treatment compared to placebo (25.0% in placebo, 55.7% in MV130 3M and 58.0% in MV140 6M groups; P<0.001). The median time until the appearance of the first UTI was significantly delayed in MV140-receiving individuals.

The results were similar when the 6-month efficacy period (*i.e.* following 6 months of intervention) and the whole study period (12 months after initiation of intervention) were evaluated.

A significant reduction in the symptom score (78.0-78.6% decrease) as well as days with symptoms were observed in both groups of subjects that received MV140 when compared to placebo (both P<0.001). A significant reduction in medication consumption (77.8% decrease), in the score of antibiotics needed, was observed in the subjects that received MV140 when compared to placebo (both P<0.001). A similar trend was observed regarding days on antibiotics.

Healthcare and workplace resources were also evaluated. A significant reduction (75.0-100.0% decrease) in the need for healthcare resources was observed in the subjects that received the bacterial vaccine when compared to placebo mainly due to non-programmed visits to the urologists, as well as the complementary tests carried out.

During the evaluation of all these parameters, no significant differences between active treatments (different schedules) were found, with subjects treated with 3 or 6 months active dosing schedules showing very similar results.

Health-perceived status and satisfaction were evaluated by means of different questionnaires and scales. Both MV140-receiving groups reported a significant improvement in their QoL as measured by SF-36. This improvement was noted as early as 3 months after initiation of the treatment and continued to improve during the study period (being significantly better than placebo from 6 months onwards). All groups (active and placebo) noted a significant improvement in their perceived health status visual analogue scale, both performed by subject or investigator. Additional questionnaires reflected a remarkable acceptance and overall satisfaction with the investigation medicinal product, as well as limited side effects or difficulties during administration. No differences in treatment compliance were observed between groups.

Regarding the immunological evaluation in a small subset of subjects, there was an increased change in serum IgM antibodies against MV140-containing bacteria at 12 months in MV140-receiving individuals compared to placebo. Likewise, increased and sustained systemic production of Th17-derived IL-17 cytokine was observed during the whole study period in MV140-receiving individuals compared to placebo. These figures showed notable statistical significance in the MV140 3M group.

SAFETY RESULTS

Sublingual MV140 treatment at a dose of 300 FTU/mL, administered to 230 subjects with recurrent urinary tract infections, daily either for 3 or 6 months was noted to be safe and has an excellent tolerability.

The majority of subjects (87.4%) completed the treatment phase, without experiencing dose reduction or variations in the treatment schedule. Temporary discontinuations of the IMP (referred as dose reduction, ≤ 14 days) due to an AE occurred in 3 subjects and were not related to the medication.

One hundred and one subjects (43.9%) experienced a total of 205 adverse events. Thirty nine (50.0%) belonged to the placebo group and 34 (44.2%) and 28 (37.3%) to individuals receiving MV140 for 3 and 6 months, respectively, with no differences between groups. Nine of these event descriptions (in 6 subjects), related or not to the medication, led to withdrawal from the trial. No deaths occurred during the trial and no significant or serious adverse events were related to the medication. The most common adverse events (> 5% of participants) were chest infection, candidiasis and vaginitis.

According to the investigators, only 9 events were definitely related to the medication and thus classified as adverse reactions. None of them were SARs or SUSARs. These 9 adverse reactions were experienced by 5 subjects (6.5%), all delayed (appearing later than 30 min) and with recovery. Two of these adverse reactions were reported in 2 subjects (2.6%) from the placebo group. Seven ARs (77.8%), in a total of 4 ICSRs, were experienced by 3 subjects (3.9%) from the MV140 3-month group while receiving active treatment. Noteworthy, no ARs were reported in the individuals receiving MV140 for 6 months. No significant difference between treatment groups was observed. Finally, ARs occurring in 3 out of the 5 subjects mentioned above eventually resulted in trial discontinuation.

Regarding location, most adverse reactions were assessed as local [6 (66.7%) out of 9 ARs: 1 in placebo (11.1%); 5 in MV140 3M (55.6%)] and mild [4 (44.4%) out of 6 local ARs, all in MV140 3M group]. The event description was as follows: urticaria and thickened mucus in the placebo group; itchy mouth, (3 cases), sore mouth, gastric discomfort and general malaise and itching in the MV140 3-month group. Most of these reactions have been previously reported and were already included in the Product Leaflet (PL) and in the Summary of Product Characteristics (SmPC). No remarkable differences were found in the features of the adverse reactions between groups.

CONCLUSION

In this study, MV140 demonstrated clinically meaningful efficacy for the treatment of female subjects with rUTI, as well as reduction in healthcare burden and antibiotic consumption. The trial also confirmed the excellent safety profile of MV140, either daily administration for 3 or 6 months, in women suffering rUTI. In terms of clinical outcomes, virtually no differences between administration schedules of 3 or 6 months were observed. This study predicts that the availability of this effective long-lasting non-antibiotic alternative for rUTI patients could minimize morbidity of these infections, reduce antibiotic-related side effects, improve patient's quality of life, and reduce overall costs.