

Summary of Uromune (MV140) Studies – September 2023.

Study	Design	Sample Information	Main Results and Conclusions
<p>1. Lorenzo-Gómez MF, Foley S, Nickel JC, García-Cenador MB, Padilla-Fernández B, González-Cascado I, Martínez-Huélamo M, Yang B, Blick C, Ferreira F, Caballero R, Saz-Leal P, Casanovas M. Sublingual MV140 for prevention of recurrent urinary tract infections. NEJM Evid 2022 Jan;1(4). doi:10.1056/EVIDoa2100018.</p>	<ul style="list-style-type: none"> - Multi-centre – Spain and UK. - Randomised (Epidat software) - Double-blind, placebo-controlled, parallel-group one-year trial. - Placebo prepared with all the same excipients as active, just without bacteria. - <u>Primary outcome</u> – number of UTIs in the 9-month study period following 3 months of intervention. - <u>Secondary outcomes</u> – percentage of women UTI-free over the above period and the time to UTI onset. - Patient reported UTI symptoms in a diary and attended a clinic for urine sample. 	<p>240 enrolled women (18 to 75 years of age) with recurrent UTIs allocated to receive MV140 for 3 or 6 months, or placebo in a 1:1:1 ratio.</p> <p>229 participants (balanced baseline statistics)– 77:77:75</p> <p>Inclusion:</p> <ul style="list-style-type: none"> - 5 episodes of uncomplicated cystitis episodes in the previous year. <p>Excluded:</p> <ul style="list-style-type: none"> - Complicated UTIs - Co-morbidities associated with genitourinary tract - Immunological diseases 	<p>Efficacy</p> <p>Median of UTI episodes was 3.0 (0.5 to 6.0) for placebo compared to 0.0 (0.0 to 1.0) in patients receiving MV140 (either for the 3 month or 6 month period) (p<0.001).</p> <p>25% (n=19) (95% CI, 15% to 35%) in placebo group were free from UTI.</p> <p>56% (n=39) (95% CI, 44% to 67%) in MV140 3-month group were free from UTI.</p> <p>58% (n=40) (95% CI, 44% to 67%) in MV140 6-month group were free from UTI.</p> <p>The NNT to prevent one UTI was 3.26 in the 3-month MV140 group and 3.03 in the 6-month MV140 group.</p> <p>Risk ratios for recurrence were 0.59 (95% CI, 0.44 to 0.79) and 0.56 (95% CI, 0.41 to 0.76) for groups receiving MV140 for 3 or 6 months, respectively, compared with placebo, while 0.95 (95% CI, 0.65 to 1.39) between active treatment schedules.</p> <p>The median time until the appearance of the first UTI after 3 months of treatment was 275.0 days [IQR, 87.0–275.0] in both the MV140 3-month and 6-month groups compared to 48.0 days in the placebo group.</p> <p>Safety</p> <p>81 adverse events in placebo group 76 adverse events in 3-month MV140 48 adverse events in 6-month MV140.</p> <p>The most common AEs (5% or more of participants) were chest infection, candidiasis, and vaginitis.</p> <p>Author’s Conclusion</p> <p>In this controlled trial of modest size and duration, MV140 showed promising clinical efficacy in reducing recurrent UTI in women suffering from this condition. Adverse effects were not clinically limiting.</p>

<p>2. Nickel JC, Saz-Leal P, Doiron RC. Could sublingual vaccination be a viable option for the prevention of recurrent urinary tract infection in Canada? A systematic review of the current literature and plans for the future. <i>Can Urol Assoc J.</i> 2020 Aug;14(8):281-287. doi: 10.5489/cuaj.6690. PMID: 33626320; PMCID: PMC7402698.</p>	<ul style="list-style-type: none"> - Systematic review - Peer-reviewed - Uromune as prophylaxis for uncomplicated recurrent UTI in women - <u>Primary Outcome</u> - UTI-free rate following initiation of the vaccine - <u>Secondary Outcomes</u> – safety, change in frequency of UTI, time to first UTI and comparator analyses. - 5 eligible studies included - Study quality evaluated using Newcastle-Ottawa Scale - None of the 5 included studies were randomised or placebo-controlled – non-blinded. 	<p>In total, the 5 studies included:</p> <p>1408 women treated with Uromune.</p> <p>499 with antibiotic prophylaxis.</p>	<p><u>Two retrospective, observational comparative cohort studies:</u></p> <p>Lorenzo-Gomez et al. (study 6 below) – 3 months of Uromune Vs. 6 months of antibiotic prophylaxis (co-trimoxazole).</p> <ul style="list-style-type: none"> - Uromune showed higher UTI-free rates at 15 months – 34.6% (n=55) Vs. 0% (p<0.001). <p>Lorenzo-Gomez et al. (study 5 below) – Uromune Vs. antibiotic prophylaxis.</p> <ul style="list-style-type: none"> - Uromune showed higher UTI-free rates at 12 months follow-up – 90.3% (n=325) Vs. 0% (p<0.001). <p><u>Three prospective, uncontrolled cohort studies –</u></p> <p>Yang et al. (study 4 below) – 78.7% (n=59) UTI-free rate at 12 months.</p> <p>Ramirez-Sevilla et al. (study 3 below)– 45.4% (n=294) UTI-free rate at three-month follow-up.</p> <p>Carrion-Lopez et al. (study 7 below) – 74.4% (n=212) UTI-free at 3 months, 68.1% (n=113) at 6 months, 52.4% (n=87) at 12 months and 44.5% (n=43) at 24 months.</p> <p>No major safety issues identified.</p> <p>Author’s Conclusion</p> <p>Analysis concludes Uromune “appears to be a safe and effective alternative to repeated or long-term dosing of antibiotics to prevent rUTI in Canadian women.”</p>
<p>3. Ramírez Sevilla C, Gómez Lanza E, Manzanera JL, Martín JAR, Sanz MÁB. Active immunoprophylaxis with uromune® decreases the recurrence of urinary tract infections at three and six months after treatment without relevant secondary effects. <i>BMC Infect Dis.</i> 2019 Oct 28;19(1):901. doi: 10.1186/s12879-</p>	<ul style="list-style-type: none"> - Prospective analysis - Uncomplicated recurrent urinary tract infections – review at 3 and 6 months - Spain 	<p>784 received Uromune.</p> <p>(Both men and women included)</p>	<p>Efficacy - All participants:</p> <ul style="list-style-type: none"> • 44.1% had 0 UTIs 3 months after Uromune, 32.3% 6 months after. • 27.6% had 1 UTI 3 months after Uromune, 32.4% 6 months after. <p>Efficacy - Women:</p> <ul style="list-style-type: none"> • 45.4% of women had 0 UTIs in the 3 months after Uromune, 32.7% 6 months after. • 28.5% of women had 1 UTI in the 3 months after Uromune, 33.2% 6 months after. <p>Safety</p>

<p>019-4541-y. PMID: 31660885; PMCID: PMC6819445.</p>			<p>Side effects local and rare – 8 patients with dry mouth, 4 with gastritis and 3 with sickness.</p> <p>Author's Conclusion</p> <p>Highly effective to reduce the number of episodes of urinary tract infections at 3 and 6 months of follow-up.</p> <p>Best results in women over 50 years old.</p>
<p>4. Yang B, Foley S. First experience in the UK of treating women with recurrent urinary tract infections with the bacterial vaccine Uromune®. <i>BJU Int.</i> 2018 Feb;121(2):289-292. doi: 10.1111/bju.14067. Epub 2017 Nov 23. PMID: 29171130.</p>	<ul style="list-style-type: none"> - Prospective study - Effectiveness of Uromune in preventing recurrent UTIs in women. - 12 month follow-up period - UK 	<p>77 women (microbiology-proven recurrent UTIs) – 75 completed treatment.</p> <p>100% of selected women had tried antibiotic prophylaxis and 50% had tried intravesical instillation therapies.</p>	<p>Efficacy</p> <ul style="list-style-type: none"> - 78% (n=59) no subsequent UTIs in the 12 month follow-up period. <p>Safety</p> <p>One serious adverse event (allergic reaction – participant withdrew) and seven minor adverse events (post-nasal drip, stinging around mouth, pruritus over old BCG scar, pruritus over abdomen, intermittent abdominal pain, mild nausea, and exacerbation of underlying asthma).</p> <p>Author's Conclusion</p> <p>Safe and effective at preventing UTIs in women.</p> <p>Larger groups for longer treatment times needed.</p>
<p>5. Lorenzo-Gómez MF, Padilla-Fernández B, García-Cenador MB, Virseda-Rodríguez AJ, Martín-García I, Sánchez-Escudero A, Vicente-Arroyo MJ, Mirón-Canelo JA. Comparison of sublingual therapeutic vaccine with antibiotics for the prophylaxis of recurrent urinary tract infections. <i>Front Cell Infect Microbiol.</i> 2015 Jun 3;5:50. doi:</p>	<ul style="list-style-type: none"> - Retrospective, cohort study - Evidence of power analysis in paper and details of statistical analysis. - No significant differences in baseline characteristics between groups. - 1 year follow-up. - Spain 	<p>669 women:</p> <ul style="list-style-type: none"> - 339 women receiving 6 months of antibiotic prophylaxis (co-trimoxazole). - 360 women receiving 3 months of Uromune. 	<p>Efficacy</p> <ul style="list-style-type: none"> - All women receiving antibiotics experienced a new UTI in the 12 month period. - Only 9.7% (n=35) who received Uromune experienced a UTI in the same period. - Statistically significant difference in disease-free time (p<0.0001). - ARR = 90.28% (95% CI, 87.18-93.38). - NNT = 1.1 <p>Safety - No reports of side effects.</p> <p>Author's Conclusion</p>

<p>10.3389/fcimb.2015.00050. PMID: 26090341; PMCID: PMC4452880.</p>			<p>Treatment with Uromune significantly reduces incidence of rUTIs – therefore an effective strategy (also reduces antibiotic consumption).</p> <p>Randomised, double-blind and placebo-controlled clinical trials are needed.</p>
<p>6. Lorenzo-Gómez MF, Padilla-Fernandez B, Garcia-Criado FJ, et al. Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections vs. prophylactic treatment with antibiotics. <i>Int Urogynecol J.</i> 2013;24:127–34. doi: 10.1007/s00192-012-1853-5.</p>	<ul style="list-style-type: none"> - Multi-centre, observational study. 	<ul style="list-style-type: none"> - 319 women (at least 2 episodes of UTI in past 6 months, or 3 in 12 months). - 159 received Uromune (3 months) - 160 received Co-trimoxazole (6 months) 	<p>Efficacy</p> <p>Mean number of infections at 3 months:</p> <ul style="list-style-type: none"> - 0.36 with Uromune - 1.60 with antibiotics (p<0.0001). <p>Mean number of infections at 9 months:</p> <ul style="list-style-type: none"> - 0.72 with Uromune - 3.71 with antibiotics (p<0.0001). <p>Significant difference also shown at 15 months.</p> <p>Safety</p> <p>None of the patients receiving Uromune reported any side effects, either local at the site of administration or systemic.</p> <p>Author’s Conclusions</p> <p>The results obtained in this study favor the use of this bacterial-based therapeutic vaccine as an effective strategy to reduce frequency, duration, severity, and costs of RUTIs.</p>
<p>7. Carillon Lopez - Carrión-López P., Martínez-Ruiz J., Librán-García L., Giménez-Bachs J.M., Pastor-Navarro H., Salinas-Sánchez A.S. Analysis of the Efficacy of a Sublingual Bacterial Vaccine in the Prophylaxis of Recurrent Urinary Tract Infection. <i>Urol. Int.</i> 2020;104:293–300. doi: 10.1159/000505162</p>	<ul style="list-style-type: none"> - Effectiveness of a sublingual bacterial vaccine for the prophylaxis of R-UTIs. - “Quasi-experimental”, pre-test post-test - 1-2 years after vaccination. 	<ul style="list-style-type: none"> - 166 women diagnosed with R-UTIs. 	<p>Efficacy</p> <ul style="list-style-type: none"> - After vaccination, there was a 54.6% reduction in episodes of UTI, and a 56.2% reduction in positive urine cultures. - At 3 months, 74.4% of the patients had no R-UTI, the rate falling to 68.1% at 6 months, 52.4% at 12 months, and 44.5% at 24 months. <p>Safety – 2 episodes of mild glossitis.</p> <p>Author’s Conclusions</p> <p>“The use of a sublingual bacterial vaccine for the prophylaxis of R-UTIs in women is an effective treatment that contributes to a reduction in the number of UTI episodes.”</p>