

**MV140 sublingual vaccine reduces recurrent urinary tract infection in women: Results from the first North American clinical experience study**

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**ABSTRACT**

**Introduction:** This is the first North American clinical evidence for MV140, a novel bacterial sublingual vaccine, developed for prevention of recurrent urinary tract infection (UTI) in women.

**Methods:** Female subjects with  $\geq 3$  documented UTI/year underwent three-month vaccination treatment, nine-month efficacy period, and optional three-month followup (total 15 months). Primary outcome was no clinically diagnosed UTI following vaccination (UTI-free rate). Secondary outcomes included absolute, mean, and median overall reduction in UTI compared to pre-vaccination, quality of life, global response assessment, patient satisfaction, microbiology, and safety.

**Results:** Sixty-seven subjects (mean age 56 years; range 18–80) were enrolled; 64 completed the vaccination period and at least one post-vaccination assessment. Prior to vaccination, subjects reported mean 6.8 UTI/year. The UTI free rate for the nine-month efficacy period was 40.6%. Compared to the infection rate in the year prior to vaccination, the reduction was 75.3% for the nine-month efficacy period post-vaccination. At 12-month followup, 80.3% reported that they

**KEY MESSAGES**

- Recurrent UTI in women is a major healthcare issue.
- Antibiotic therapy results in personal and societal problems.
- This is first clinical report of MV140 in North American clinical practice.
- MV140 reduces recurrent UTI in women in “real-life clinical” practice.
- Case series provides further evidence of the safety of MV140 in clinical practice.

were moderately/markedly improved; 58.1% were mostly satisfied, pleased, or delighted, while mean quality of life score improved by 1.5 points. Fourteen of the adverse events in nine subjects were potentially related to vaccine — all mild and resolved by three months. None of the 13 serious adverse events were related to vaccine.

**Conclusions:** This first-in-North-America, prospective case series with the sublingual vaccine, MV140, adds further clinical evidence to its safety and effectiveness in reducing recurrent UTIs in women.

## INTRODUCTION

Recurrent urinary tract infections (rUTI) in women are associated with episodic bothersome symptoms that impact patients' life activities and quality of life<sup>1-4</sup>. Short- and long-term side effects of the most effective therapy, antibiotics, can be severe and even devastating<sup>5,6</sup>. Management of rUTI results in significant direct and indirect cost to society and the medical system<sup>7</sup> while promoting significant personal patient and population-wide antibiotic resistance, an evolving medical crisis<sup>8</sup>.

Uncomplicated rUTI, defined as  $\geq 3$  UTI in 12 months (or  $\geq 2$  in 6 months)<sup>9</sup> is one of the most common infections occurring in women. Eleven percent of women develop a UTI each year<sup>10</sup>, with over 25% reporting a second UTI within 6 months<sup>11</sup>, resulting in a reported rUTI yearly incidence rate in women of 3%<sup>9</sup>. While some patients can be successfully managed with non-antibiotic practices<sup>12,13</sup>, the only CUA/AUA/SUFU Guideline recommended alternative therapies for UTI prevention include cranberry prophylaxis and vaginal estrogen in peri- and post-menopausal women<sup>14</sup>. Increasing water intake may also be helpful<sup>15</sup>. However North American guidelines recommend antibiotic prophylaxis as the most effective preventative therapy (conditional recommendation; evidence level grade B)<sup>9</sup>. The European Association of Urology guidelines<sup>16</sup> recommend consideration of UTI vaccines, however such vaccines are not presently approved or available in North America.

A polyvalent bacterial whole cell-based sublingual vaccine, MV140, has been developed for prevention of UTI and is currently available under named patient (special access) programs and/or approved for use in 26 countries. A systematic review<sup>17</sup> identified 5 observational studies<sup>18-22</sup> evaluating the prevention of rUTI women with MV140 that met a unified criteria (standardized definition of rUTI, female subjects, at least one outcome parameter to include UTI-free rate after vaccination) and included 1,400 women treated with the vaccine. The analysis reported UTI-free rates amongst those women treated with the vaccine of 32-90%. A recently published European multicenter, randomized, double-blind, placebo-controlled, parallel-group one-year trial<sup>23</sup> (NCT02543827) in which 240 women with rUTI were allocated to receive MV140 for 3 or 6 months, or placebo for 6 months, in a 1:1:1 ratio, showed both efficacy and safety for the vaccine. MV140, either for 3- or 6-month administration, significantly decreased

the number of UTI episodes from a median of 3.0 to 0.0 compared to placebo in the 9-month efficacy period (i.e. following 3 months of intervention). A significant increase in the UTI-free rate of over 2-fold was found, being 55.7% and 58.0% in subjects receiving MV140 for 3 or 6 months, respectively compared to 25.0% in placebo group. The current study represents the first North American clinical evaluation of MV140 for the prevention of rUTI in women.

## METHODS

### Study subjects and trial design

A single center investigator initiated, Health Canada approved, prospective case series study was conducted in Kingston, Ontario (ClinicalTrials.gov: NCT04096820) to assess safety and efficacy of MV140 in women with rUTI. The MV140 was supplied in kind by Immunotek S.L. (Spain), but the study was designed, initiated, completed, and analyzed by the investigators. The study included women (18-80 years old) diagnosed with rUTI. defined as females suffering from  $\geq 3$  episodes of uncomplicated cystitis in the previous year with  $\geq 1$  episode requiring culture confirmation ( $\geq 10^8$  cfu/L with a traditionally accepted uropathogen). The most relevant exclusion criteria included complicated UTIs, comorbidities associated with the genitourinary tract, and/or immunological diseases. Enrollment was initiated in October 2019, but temporarily suspended due to Covid-19 clinical research protocol mandates March 2020 to July 2020. A second clinical research site (Toronto, Ontario) began enrollment in February 2021. Multiple amendments dated from March 2020 and beyond were required to conduct the clinical trial during the Covid-19 pandemic (e.g. virtual visits). The last subject completed in September 2022. The protocol was approved by Health Canada Biologics and Genetic Therapies Directorate while protocol and subsequent amendments were approved by the Queen's University institutional review board (#6026618).

Following pre-visit screening by study nurse, informed consent, and final eligibility screening, subjects were taught by clinic nurse to administer MV140. MV140 (Immunotek S.L., Spain) consists of a suspension of whole-cell heat-inactivated bacteria (300 Formazin Turbidity Units) in glycerol, sodium chloride, artificial pineapple flavoring and water. Selected strains of 4 bacterial species (*Escherichia coli* V121, *Klebsiella pneumoniae* V113, *Enterococcus faecalis* V125, *Proteus vulgaris* V127) at equal percentages are included. The treatment was administered daily by spraying 2 sprays of 100  $\mu$ L each sublingually for 3 months. All subjects were followed up every 3 months for 12 additional months (whole study period: 12 months from first dose; 3-month vaccination period, 9 months efficacy period). Midstream urine cultures were obtained at screening and 12-month visit. Adverse events were reviewed with the subjects at each scheduled visit. A quality of life (SF-12) questionnaire was administered at baseline and 12-month visit while Global Response Assessment (GRA) and Patient Satisfaction Questionnaires (PSQ) were administered at the end of the efficacy period (12 months). To obtain further 1 year post vaccination efficacy and safety data, an amendment (December 2020) allowed subject

volunteers, after further consent, to continue in the study for another 3 months (total 15 months after treatment initiated).

Subjects could receive additional medication, including antibiotics for managing UTI episodes, as needed according to the AUA guidelines<sup>9</sup>. Adverse events were reviewed with the subjects at scheduled visits. Any adverse event (AE) was recorded and evaluated to assess severity and relationship to MV140 administration.

### Study outcomes

The primary outcome was the proportion of subjects with no UTI reported during the 9 months following the 3-month vaccination period (Figure 1). The definition of a “clinical” UTI included acute cystitis-like symptoms requiring a physician prescription of antibiotics for resolution of the acute event. Patients were instructed to obtain a midstream urine culture prior to taking the antibiotic if possible. UTI symptom and culture data were reviewed by the research nurse and investigators who defined for each subject the presence of a symptomatic UTI. Asymptomatic bacteriuria detected at the time of mandatory culture at screening and/or 12-month efficacy visit were not included as a UTI event if the subject had no symptoms and had not received an antibiotic prescription.

The major secondary outcome was the number clinical UTI episodes in the 9-month study period, after the first 3 months of intervention (Figure 1). Further secondary outcomes included the Medical Outcomes Short Form-12 Item Health Survey -SF-12<sup>24</sup>, 7-point GRA and PSQ. For GRA, subjects were asked the following single question: “As compared to when you started the study, how would you rate your overall urinary symptoms now?” The seven potential answers included “markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, markedly improved”. A report of moderately or markedly improved was defined as a global responder. For PSQ, subjects were asked the following single question: “If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?” The seven potential answers included “delighted, pleased, mostly satisfied, mixed (about equally satisfied and dissatisfied), mostly dissatisfied, unhappy, terrible”.

Safety analyses included assessments of all AEs, which were individually examined to evaluate their severity, intensity, causality, and outcome. Likewise, adverse reactions (AR - intervention-related adverse events) were further evaluated based on location, timing of appearance, intensity, and outcome. UTI, the primary outcome of the study, was not considered an AE.

### Data analysis

The design of the trial was an investigator-initiated study with limited support (MV140 was supplied without cost by Immunotek S.L., Spain) and the planned sample size was determined by financial and time constraints (planned convenience sample size of 80). The analysis plan was descriptive, being proportion of subjects achieving primary outcome (UTI-free state). The major

secondary endpoint was the mean number of UTI episodes (overall and UTI/subject/month) as well as median (interquartile range, minimum and maximum) episodes of UTI) period during each 3-month study period (Mann-Whitney-Wilcoxon comparison of median values). This prospective secondary endpoint was descriptively compared to the number of UTIs reported by each subject in the 12 months pre-intervention. No statistical comparison was possible because of differences between the two groups including 9 vs 12 months, prospective vs retrospective data collection and the inclusion criteria that  $\geq 1$  UTI had to be documented by midstream urine culture in the pre-intervention period. The primary outcome in subjects reporting pre-menopausal status was compared to those reporting post-menopausal status, further stratified according to hormone supplementation (Chi-square analysis). Evaluable subjects for the efficacy analyses (intention to treat [ITT]) consisted of all subjects who had  $\geq 1$  efficacy visit. Per protocol analysis at each visit was also performed. Further efficacy data was obtained for months 12-15 for those subjects who elected to continue in the optional follow-up study period. The questionnaire surveys were tabulated as responders for the GRA and satisfied patients according to PSQ. Comparison of quality of life data at baseline and end of efficacy period was descriptive. Safety population during the entire study period (including the voluntary 12 to 15-month optional follow-up) consisted of all subjects who were administered at least one dose of MV140. Potential adverse reactions (AR) to the study intervention were determined by the study team with final decision by Principal Investigator (similar to real-life clinical practice by the treatment physician).

## RESULTS

Sixty-seven subjects met the eligibility criteria and signed informed consent. Two subjects withdrew from the study, and one died of an unrelated cardiac cause prior to first post vaccination efficacy visit (more detail provided in safety discussion). Sixty-six subjects were included in the safety population. Sixty-four subjects (mean age 56 years; range 18-80) completed the 3-month vaccination period and at least one post-vaccination assessment (ITT population; Table 1). One subject was lost to follow-up after the 6-month efficacy visit. Fifty-four subjects elected to take part in the optional follow-up period. (Figure 1).

Prior to vaccination, subjects reported mean 6.8 (median 5.0; range 3-20) UTI/year. *E. coli* (60%), *Klebsiella sp.* (19%) and *Enterococcus sp.* (14%) were the predominant causative bacterial species. The UTI free rate for the 9-month post vaccination efficacy period (Figure 2) was 40.6% (41.3% per protocol analysis). Compared to the UTI rate in the year prior to vaccination (0.58 UTI/subject/month), there was a 75.9% reduction for the 9-month efficacy period (0.14 UTI/subject/month) post-vaccination. The total number of UTIs, number of subjects reporting UTI and the UTI rate decreased substantially while the percentage of UTI-free subjects increased for each 3-month follow-up period, including the optional extra 3-month follow-up (Table 2). In the per protocol population, the median UTI episodes/3-month period decreased

from 1.25 (IQR, 1.0-2.37) pre-vaccination to 0.0 (Interquartile range, 0.0-1.0 to 0.0-0.0) during the efficacy period (Figure 3).

Culture evidence of a UTI during the efficacy period was available in 68.6% while the predominant bacterial strains post-vaccination remained *E. coli* (60%), *Klebsiella sp.* (18.2%) and *Enterococcus sp.* (11.9%). At the 12-month efficacy visit, 80.3% reported (GRA) that they were moderately/markedly improved; 58.1% were mostly satisfied, pleased, or delighted while mean SF-12 improved by 1.5 points on SF-12 quality of life assessment.

Pre-menopausal subjects had a greater UTI-free rate (14/22; 63.6%) than post-menopausal subjects (13/42; 33.3% [p=0.012]), however no difference was detected in the post-menopausal group for those on systemic and/or vaginal estrogen supplementation (9/27; 33.3%) compared to those who were not (4/15; 26.7% [p=0.654]).

Ninety-eight adverse events (AEs) were reported in 45 subjects. Fourteen AEs in 9 subjects were potentially related to vaccine (AR). These included skin rash/sensitivity (4), mucosal burning/sensitivity (5), Upper GI discomfort (4), and fatigue (1); all mild and resolved by 3 months. One subject was withdrawn from study following an anxiety/panic attack occurring at time of first vaccine dose. One subject died shortly after vaccination period of unrelated cardiovascular cause. A comprehensive safety report submitted to Health Canada described that the subject had completed the entire 3-month dosing period with no adverse events and suffered a cardiac event that was not unexpected by subject's cardiac condition and multi-pharmacy interaction (particularly treatment of chronic pain). The cardiac event did not follow any known or theoretical pattern of response to MV140. None of the other 12 Serious AEs were related to vaccine (Table 3).

## DISCUSSION

All the published series, including the single pivotal RCT demonstrating efficacy and safety of MV140 in reducing the risk of rUTI in women involved clinical research sites in Spain and the United Kingdom<sup>18-23</sup>. Although this vaccine has been available worldwide for over a decade, it has never been available for evaluation in North America, even though medical experts identify a large unmet need for such a preventative strategy<sup>25</sup>. Regulatory authorities and clinical researchers recognize that real-world evidence is playing an increasing role in health care decisions<sup>26</sup>, including regulatory assessment of new and/or novel approaches to therapy (UA 21<sup>st</sup> Century Cures Act, 2016). Collection and analysis of Canadian clinical evidence to further assess the potential benefits and risks of this MV140 vaccine option for this unmet need for UTI prevention was the primary reasons for this Health Canada approved, investigator-initiated simple, prospective, and pragmatic clinical trial.

We reported that women who were treated for an average of 6.8 (median 5.0) UTI/year had a UTI-free rate of approximately 40% associated with 75% reduction in UTI number overall. Furthermore, the risk of UTI decreased over time with an increase in proportion of subjects with UTI free status between each 3-month visit interval until at least 12 months after the vaccination

period. Most subjects believed they had achieved a global improvement and were generally satisfied with the results. Improvement in overall quality of life (SF-12) was minimal (and likely not clinically significant) and we believe that this was due to Covid-19 pandemic impact on general quality of life during most of the study period. The UTI-free rate in our case series was lower than in the pivotal MV140 RCT (56-58%)<sup>23</sup> despite similar vaccination and efficacy periods. The explanation likely lies in the fact that the latter trial had to follow strict regulatory definitions of a UTI with blinded adjudication based on culture proven recommendations of European Guidelines on Urological Infections<sup>16</sup>. Our study employed a more pragmatic clinical definition of UTI (cystitis symptoms in subjects with previous UTI documentation with resolution following antibiotic prescription with every attempt to obtain culture confirmation). The reality of clinical practice in North America is that many women with recurrent uncomplicated UTI are treated based on previous history of UTI, symptoms, urinalysis but not always with a confirming culture. As such, our analysis of UTI frequency would be higher than a study with a more rigorous UTI definition and therefore likely underestimates the true benefits of the vaccine. Our study will more closely represent the benefits of recommending the use of this vaccine to North American women suffering from rUTI. Similarly, the risks of interventions in real-life clinical practice can be different than that reported in controlled trials. However, in our case, the safety identified in the RCT<sup>23</sup> was confirmed with our real-life clinical practice experience. Only 14 mild and temporary ARs were identified in 9 subjects and the only AE resulting in withdrawal was an anxiety/panic attack not related to the actual components of MV140.

We have described some of the strengths of our prospective case series (pragmatic prospective clinical practice design, clinically practical definition of UTI, significant subject adherence to vaccine administration and follow-up) but this investigator-initiated study has real-world limitations and challenges as well. The obvious limitations include the fact that this was a non-randomized, unblinded study with no control group, pre-baseline UTI history was by retrospective recollection (although  $\geq 1$  culture documentation was required), and UTI outcome was not the standard culture-proven definition. While these methods are subject to biases and theoretically may have overestimated the clinical effectiveness of the vaccine, in reality our case series observed lower UTI-free rates than those reported in the published RCT<sup>23</sup>. Our experience illustrated the challenges with an investigator-initiated and primarily funded (MV140 was supplied by Immunotek S.L., Spain) study undertaken during the Covid-19 era. Our study team had to deal with mandated Covid-19 recruitment interruptions, development of the many Covid-19 related amendments to allow virtual visits, timing of Covid-19 vaccine with MV140 vaccine, as well as difficulties obtaining urine cultures and subjects developing Covid-19 during the efficacy period. Financial constraints of a self-funded, unsponsored study were already evident, but rising costs and delays secondary to Covid-19 further threatened the viability of continuing the study during the pandemic. Our study experience likely reflected that of many clinical research centers during the Covid-19 pandemic.

**CONCLUSIONS**

This real-life case series provides Canadian clinical experience to further support the safety and benefits of MV140 for the prevention of UTI in women suffering from rUTI.

DRAFT

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**Conflicts of interest:** Dr. Nickel declares that he is an investigator and advisor for Immunotek and Red Leaf Medical and a consultant for OM Pharma. Dr. Doiron declares that he is an investigator for Red Leaf Medical. The other authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript. MV140 was supplied at no cost by Immunotek S.L.

FIGURES AND TABLES

Figure 1. Trial profile: trial design and analysis group

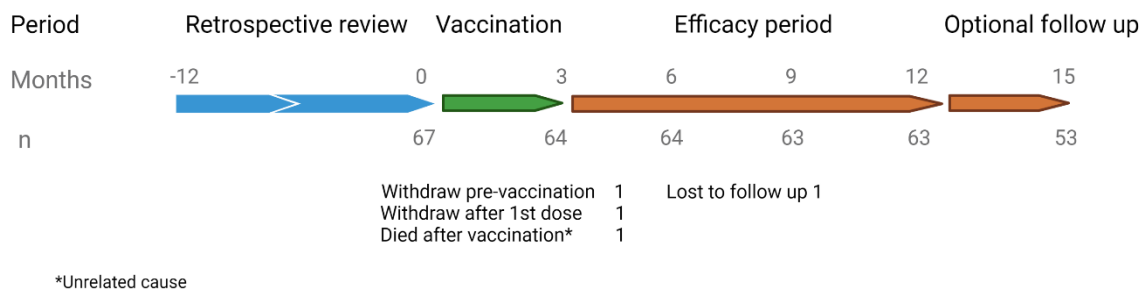
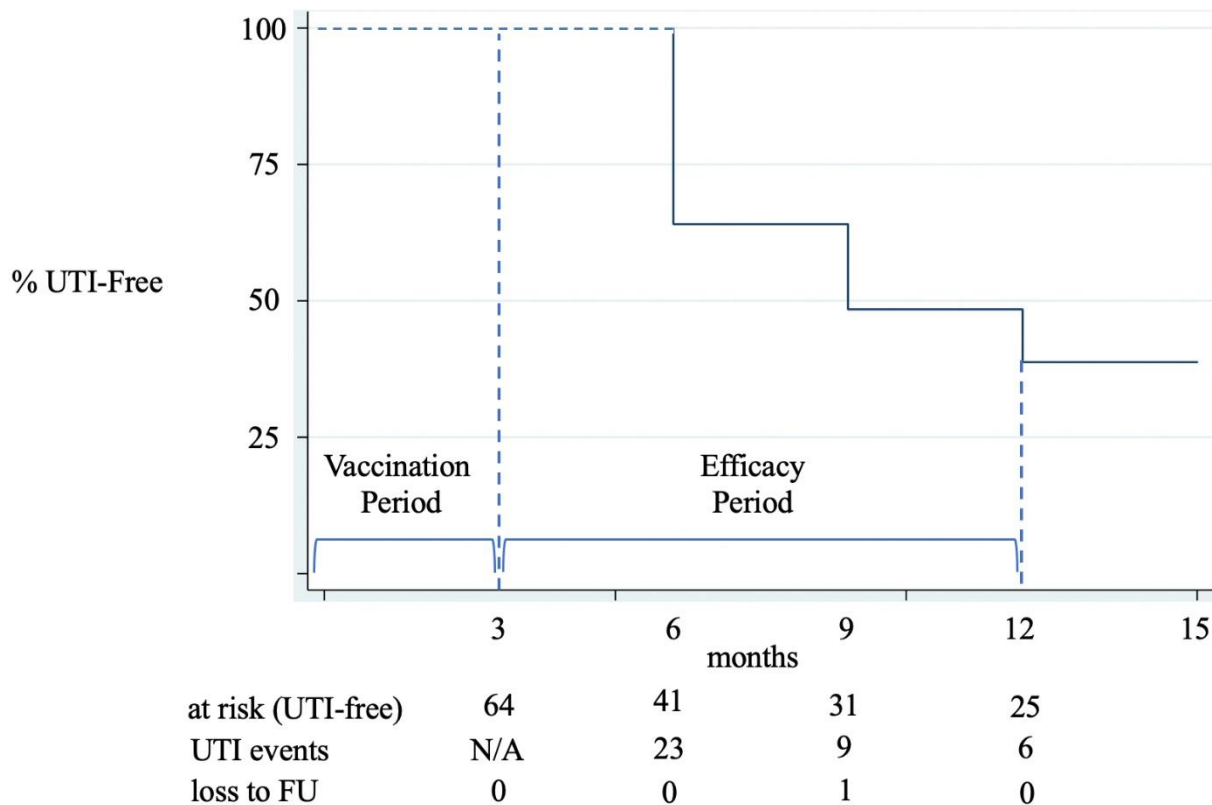
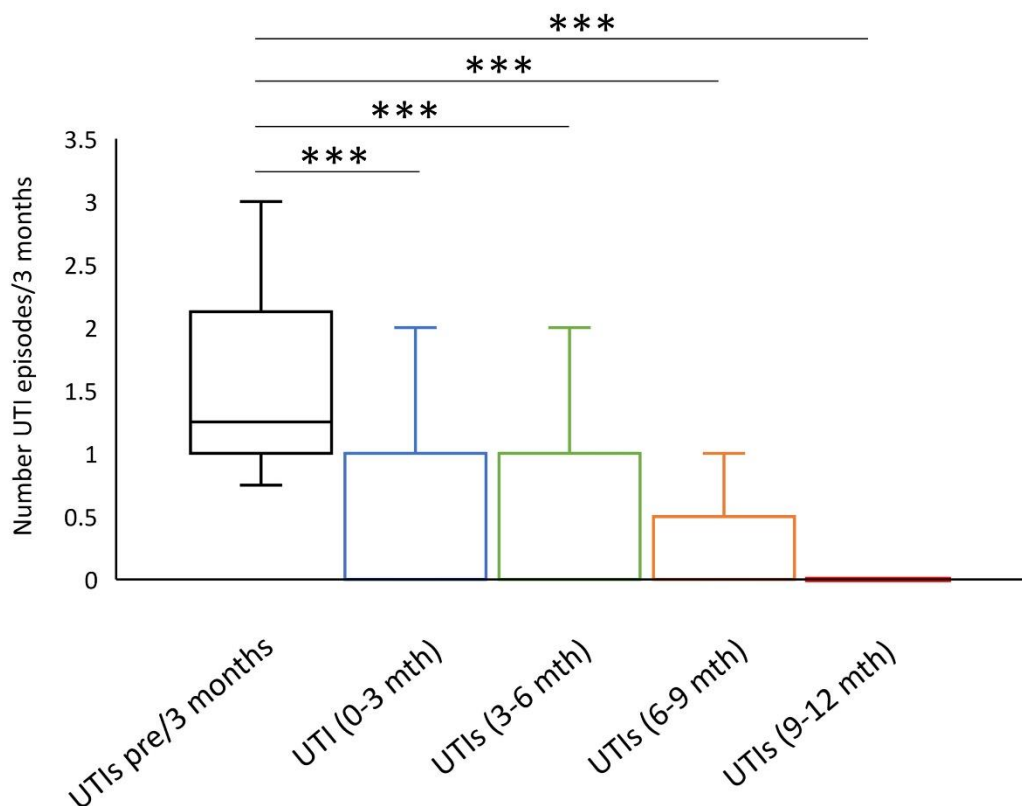


Figure 2. Subjects remaining urinary tract infection-free during the 9-month efficacy period.



**Figure 3.** Episodes of urinary tract infection (UTI) period are shown as box plots, indicating the median, interquartile range, minimum, and maximum. \*\*\*p=0.001, Mann-Whitney-Wilcoxon test comparing the number UTIs/3-months before treatment and the number of UTIs during the 3-months treatment and each 3-month follow up-during the efficacy period.



**Table 1. Baseline characteristics of the subjects in the ITT population (n=64).**

Age (years), median (interquartile range)	61 (43.5-70)
Race or ethnicity, n (%)	
Caucasian	57 (89.0)
Asian	3 (4.7)
Indigenous	1 (1.6)
Other	3 (4.7)
Body mass index, median (interquartile range)	25.5 (22-30)
Vital signs, means $\pm$ standard deviation	
Heart rate (bpm)	74.4 $\pm$ 10.3
Systolic blood pressure (mmHg)	126.6 $\pm$ 16.6
Diastolic blood pressure (mmHg)	74.1 $\pm$ 9.2

Hormone status, n (%)	
Premenstrual	22 (34.4)
Postmenstrual	42 (65.6)
Vaginal and/or oral hormone replacement	27 (64.3)
No hormone replacement	15 (35.7)
Metabolic disorders, n (%)	
None	37 (57.8)
Diabetes	4 (6.25)
Hypothyroidism	14 (21.9)
Hypercholesterolemia	4 (6.25)
Other	5 (7.8)
Cardiovascular disease, n (%)	
None	36 (56.25)
Hypertension	20 (31.25)
Vascular dysfunction	2 (3.1)
Other	6 (9.4)
Specified allergy history, n (%)	
Seasonal	6 (9.4)
Asthma	8 (12.5)
Antibiotics	25 (39.1)

Table 2. Urinary tract infection (UTI) data before and after MV140 vaccination							
	Pre-vaccination	Vaccination	Post-vaccination				
	-12–0 months n=64	Vaccination Period 0–3 months n=64	4–6 months n=64	7–9 months n=63	10–12 months n=63	Optional follow-up 13–15 months n=54	Efficacy period 4–12 months n=64
Subjects with UTI (%)	64 (100)	33 (51.6)	23 (35.9)	16 (23.8)	12 (19.0)	9 (15.1)	38 (59.4)
Total UTIs	438	61	39	25	17	13	81
UTIs/month	36.5	20.3	13.0	8.3	5.7	4.3	9.0
UTIs/subject/month	0.58	0.38	0.20	0.13	0.09	0.08	0.17
UTI free rate %	0.0	48.4	64.1	74.6	80.9	83.3	40.6 <sup>a</sup>

<sup>a</sup>Intention-to-treat analysis (UTI-free rate in per protocol analysis – 41.3%)

<b>Table 3. Adverse events (AE) and adverse reactions (AR - possibly associated with vaccine administration) in the safety population (n=66)</b>		
<b>Event</b>	<b>Number</b>	<b>Percentage</b>
Adverse event		
Number of A/Es	98	–
Subjects with AEs <sup>a</sup>	45	68.2
Serious AEs <sup>b</sup>	13	16.9
AEs leading withdrawal <sup>b</sup>	1	1.3
Adverse reactions (AR)		
Number of ARs	14	–
Subjects with ARs <sup>a</sup>	9	13.6
ARs leading withdrawal <sup>c</sup>	0	0.0

None of the serious AEs were related to vaccine. All ARs were mild and all resolved by 3 month visit. <sup>a</sup>Percentages based on total subjects in safety population. <sup>b</sup>Percentages based on total number of AEs. <sup>c</sup>Percentages based on total number of ARs.

DRAFT