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 ≥3 documented UTIs/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 a mean 6.8 UTIs/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 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 the 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.[1-4] Short- and long-term side effects of the most effective therapy, antibiotics, can be severe and even devastating.[5,6] Management of rUTI results in significant direct and indirect cost to society and the medical system,[7] while promoting significant personal patient and population-wide antibiotic resistance — an evolving medical crisis.[8]

Uncomplicated rUTI, defined as ≥3 UTIs in 12 months (or ≥2 in six months),[9] is one of the most common infections occurring in women. Eleven percent of women develop a UTI each year,[10] with over 25% reporting a second UTI within six months,[11] resulting in a reported rUTI yearly incidence rate in women of 3%.[9] While some patients can be successfully managed with non-antibiotic practices,[12,13] the only Canadian Urological Association/American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (CUA/AUA/SUFU) guideline-recommended alternative therapies for UTI prevention include cranberry prophylaxis and vaginal estrogen in peri- and post-menopausal women.[14] Increasing water intake may also be helpful;[15] however North American guidelines recommend antibiotic prophylaxis as the most effective preventative therapy

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.

(conditional recommendation; evidence level grade B).[9] The European Association of Urology guidelines recommend consideration of UTI vaccines;[16] 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[17] identified five observational studies[18-22] 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 1400 women treated with the vaccine. The analysis reported UTI-free rates among those women treated with the vaccine of 32–90%.

A recently published European, multicenter, randomized, double-blind, placebo-controlled, parallel-group, one-year trial (NCT02543827) in which 240 women with rUTI were allocated to receive MV140 for three or six months, or placebo for six months, in a 1:1:1 ratio, showed both efficacy and safety for the vaccine.[23] MV140, either for three- or six-month administration, significantly decreased the number of UTI episodes from a median of 3.0 to 0.0 compared to placebo in the nine-month efficacy period (i.e., following three months of intervention). A significant increase in the UTI-free rate of over two-fold was found, being 55.7% and 58.0% in subjects receiving MV140 for three or six 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 Inmunotek 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 ≥3 episodes of uncomplicated cystitis in the previous year, with ≥1 episode requiring culture confirmation (≥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 immunologic diseases. Enrollment was initiated in October 2019 but temporarily suspended due to COVID-19 clinical research protocol mandates from 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 a clinic nurse to administer MV140. MV140 (Inmunotek 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 four 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 two sprays of 100 µL each sublingually for three months. All subjects were followed up every three months for 12 additional months (whole study period: 12 months from first dose; three-month vaccination period, nine-month 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 questionnaire (Medical Outcomes Short Form-12-Item Health Survey [12-SF]) 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 one-year post-vaccination efficacy and safety data, an amendment (December 2020) allowed subject volunteers, after further consent, to continue in the study for another three 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.[9] 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 nine months following the three-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 nine-month study period, after the first three months of intervention (Figure 1). Further secondary outcomes included the SF-12,[24] seven-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, or 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, and 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 AEs — 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 Inmunotek 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 [IQR], minimum and maximum) episodes of UTI period during each three-month study period (Mann-Whitney-Wilcoxon

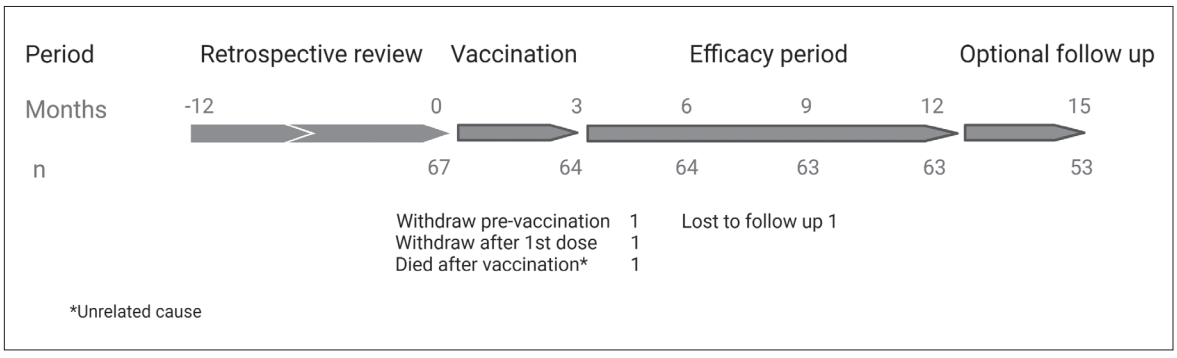

Figure 1. Trial profile: Trial design and analysis group.

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 nine vs. 12 months, prospective vs. retrospective data collection, and the inclusion criteria that ≥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-squared analysis). Evaluable subjects for the efficacy analyses (intention to treat [ITT]) consisted of all subjects who had ≥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 followup 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 12–15-month optional followup) consisted of all subjects who were administered at least one dose of MV140. Potential ARs to the study intervention were determined by the study team, with final decision by the principal investigator (similar to real-life clinical practice by the treatment physician).

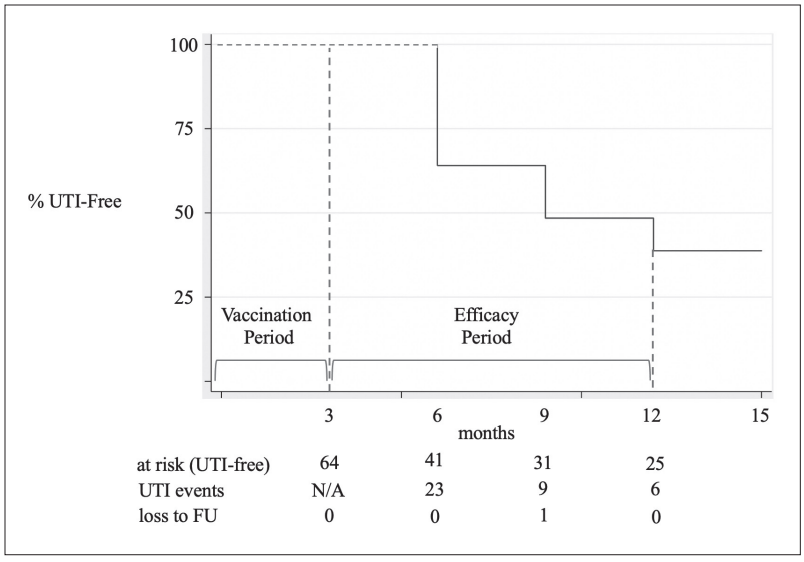

Figure 2. Subjects remaining urinary tract infection (UTI)-free during the 9-month efficacy period. FU: followup.

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 three-month vaccination period and at least one post-vaccination assessment (ITT population) (Table 1). One subject was lost to followup after the six-month efficacy visit. Fifty-four subjects elected to take part in the optional followup period. (Figure 1).

Prior to vaccination, subjects reported a mean 6.8 (median 5.0, range 3–20) UTIs/year. *E. coli* (60%), *Klebsiella sp.* (19%), and *Enterococcus sp.* (14%) were the predominant causative bacterial species. The UTI-free rate for the nine-month post-vaccination efficacy period was 40.6% (41.3% per-protocol analysis) (Figure 2). Compared to the UTI rate in the year prior

Table 1. Baseline characteristics of the subjects in the intent-to-treat 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 ± standard deviation	
Heat rate (bpm)	74.4±10.3
Systolic blood pressure (mmHg)	126.6±16.6
Diastolic blood pressure (mmHg)	74.1±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)

to vaccination (0.58 UTIs/subject/month), there was a 75.9% reduction for the nine-month efficacy period (0.14 UTIs/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 three-month followup period, including the optional extra three-month followup (Table 2). In the per-protocol population, the median UTI episodes/three-month period decreased from 1.25 (IQR 1.0–2.37) pre-vaccination to 0.0 (IQR 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 AEs were reported in 45 subjects. Fourteen AEs in nine subjects were potentially related to vaccine (AR). These included skin rash/sensitivity (4), mucosal burning/sensitivity (5), upper gastrointestinal discomfort (4), and fatigue (1); all were mild and resolved by three 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 three-month dosing period with no AEs and suffered a cardiac event that was not unexpected by the 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 the vaccine (Table 3).

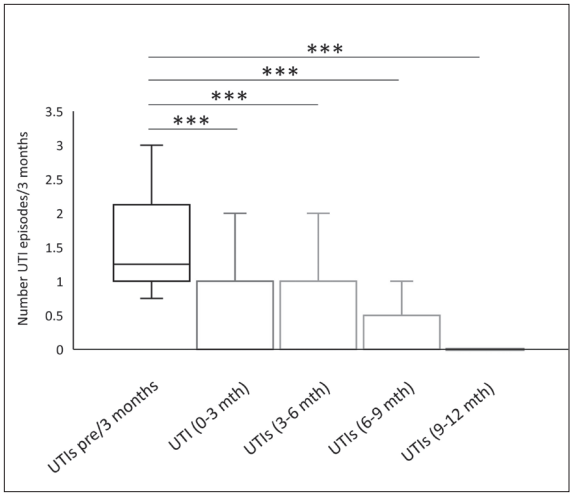

Figure 3. Episodes of urinary tract infection (UTI) period are shown as box plots, indicating the median, interquartile range, minimum, and maximum. ***p=0.001, Mann-Whitney-Wilcoxon test comparing the number UTIs/3 months before treatment and the number of UTIs during the 3-month treatment, and each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

Table 2. 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 followup 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[a]

[a]Intention-to-treat analysis (UTI-free rate in per protocol analysis – 41.3%). UTI: urinary tract infection.

Table 3. AEs and ARs (possibly associated with vaccine administration) in the safety population (n=66)

Event	Number	Percentage
AEs		
Number of AEs	98	–
Subjects with AEs[a]	45	68.2
Serious AEs[b]	13	16.9
AEs leading withdrawal[b]	1	1.3
ARs		
Number of ARs	14	–
Subjects with ARs[a]	9	13.6
ARs leading withdrawal[c]	0	0.0

None of the serious AEs were related to vaccine. All ARs were mild and all resolved by 3-month visit. [a]Percentages based on total subjects in safety population. [b]Percentages based on total number of AEs. [c]Percentages based on total number of ARs. AE: adverse event; AR: adverse reaction.

DISCUSSION

All the published series, including the single, pivotal, randomized controlled trial (RCT) demonstrating efficacy and safety of MV140 in reducing the risk of rUTI in women, involved clinical research sites in Spain and the U.K.[18-23] 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.[25] Regulatory authorities and clinical researchers recognize that real-world evidence is playing an increasing role in healthcare decisions,[26] including regulatory assessment of new and/or novel approaches to therapy (UA 21st 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) UTIs/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 three-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%)[23] 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 urologic infections.[16]

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, and 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 those reported in controlled trials; however, in our case, the safety identified in the RCT[23] was confirmed with our real-life, clinical practice experience. Only 14 mild and temporary ARs were identified in nine subjects and the only AE resulting in withdrawal was an anxiety/panic attack not related to the actual components of MV140.

Limitations

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 followup) 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 ≥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 overesti-

mated the clinical effectiveness of the vaccine, in reality, our case series observed lower UTI-free rates than those reported in the published RCT.[23]

Our experience illustrated the challenges with an investigator-initiated and primarily funded (MV140 was supplied by Inmunotek 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 pandemic-related amendments to allow virtual visits, timing of COVID-19 vaccine with MV140 vaccine, as well as difficulties obtaining urine cultures and subjects developing the virus 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 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.

COMPETING INTERESTS: Dr. Nickel is investigator and advisor for Inmunotek and Red Leaf Medical and a consultant for OM Pharma. Dr. Elterman is a consultant/investigator for Boston Scientific, Procept Biorobotics, Olympus, Urotronic, Prodeon, and Zenflow. Dr. Doiron is an investigator for Red Leaf Medical. All other authors do not report any competing personal or financial interests related to this work. MV140 was supplied at no cost by Inmunotek S.L.

This paper has been peer-reviewed.

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