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ORIGINAL ARTICLE

Sublingual MV140 for Prevention of Recurrent Urinary Tract Infections

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Abstract

BACKGROUND Recurrent urinary tract infections (UTIs), which consist of three or more episodes in 1 year or two or more infections in 6 months, affect 5% to 10% of women. MV140, a sublingual preparation of whole-cell inactivated bacteria, has shown clinical benefit in observational studies. This trial examined treatment with MV140 to prevent recurrent UTI.

METHODS In this multicenter, randomized, double-blind, placebo-controlled, parallel-group 1-year trial, 240 women 18 to 75 years of age from Spain and the United Kingdom with recurrent UTI were allocated to receive MV140 for 3 or 6 months or placebo for 6 months in a 1:1:1 ratio. The primary end point was the number of UTIs in the 9-month study period after 3 months of intervention. Key secondary end points were the percentage of women who were UTI free over the above period, time to UTI onset, and health-related quality of life.

RESULTS The median (interquartile range) of UTI episodes was 3.0 (0.5 to 6.0) for placebo compared with 0.0 (0.0 to 1.0) in both groups receiving MV140 ($P<0.001$). Among women treated with placebo, 25% (95% confidence interval [CI], 15% to 35%) were free of UTIs compared with 56% (95% CI, 44% to 67%) and 58% (95% CI, 44% to 67%) of women who received 3 and 6 months of MV140 treatment, respectively. A total of 205 AEs in 101 participants were registered (81, 76, and 48 in the placebo, 3-month MV140, and 6-month MV140 groups, respectively).

CONCLUSIONS 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. (Funded by Inmunotek S.L. and Syner-Med [Pharmaceutical Products] Ltd.; ClinicalTrials.gov number, NCT02543827.)

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Introduction

Urinary tract infections (UTIs) in women are associated with significant morbidity and substantial economic burden.[1] More than 50% of the female population experiences uncomplicated cystitis (the most common manifestation of UTIs) in their lifetime. Moreover, 5% to 10% of adult women suffer from recurrent UTI, defined as either three or more episodes in 1 year or two or more infections in 6 months.[1–5] *Escherichia coli* accounts for up to 80% of infections, followed by smaller rates of *Klebsiella pneumoniae*, *Enterococcus faecalis*, or *Proteus* spp.[6]

Antibiotic prophylaxis is currently the principal therapy for management of recurrent UTI,[4,5] but it is associated with a high incidence of side effects and notably contributes to antimicrobial resistance.[3] Thus, current guidelines on urologic infections,[4,5] as well as expert reports on infectious diseases,[2,7,8] encourage the development of nonantibiotic alternative approaches.

MV140 is a sublingual bacterial preparation of whole-cell inactivated bacteria, indicated for the prevention of recurrent UTI. MV140 has shown excellent long-term effectiveness in previous observational studies after 3-month daily administration.[9–13] A recent systematic review of these studies reported UTI-free rates ranging from 33% to 90% for a period of up to 24 months, without safety concerns.[14] The objective of this randomized, double-blind, placebo-controlled trial was to assess whether 3- or 6-month treatment with MV140 would reduce the risk of and/or prevent UTIs in women with recurrent UTI compared with placebo.

Methods

STUDY PARTICIPANTS AND TRIAL DESIGN

An international multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial was conducted in Spain and the United Kingdom to assess the safety and efficacy of MV140 from October 2015 to April 2019 (EUDRACT 2013-001838-17 and NCT02543827). The study included women (18 to 75 years of age) diagnosed with recurrent UTI. Inclusion criteria included participants suffering from at least five uncomplicated cystitis episodes in the previous year. This inclusion criterion of five UTIs per year was chosen based on the experience of women accessing the treatment outside North America in special access programs (named patient prescriptions), described in Table S8 in the Supplementary Appendix, and participants agreeing to enroll in the previous five observational studies.[14] This criterion was judged to include participants most likely to agree to enroll based on the expected benefits of the treatment. The exclusion criteria included complicated UTIs, comorbidities associated with the genitourinary tract, and/or immunologic diseases. Full inclusion and exclusion criteria can be found in section V.1.1 and Box S1 in the Supplementary Appendix.

Participants were allocated by means of a list generated with Epidat software (version 3.1) in a 1:1:1 ratio to receive either placebo for 6 months, MV140 for 3 months (plus 3 months of placebo), or MV140 for 6 months (Fig. 1A). The random list was stratified in blocks. Each block contained six treatments (two for placebo, two for 3 months of MV140, and two for 6 months of MV140). All centers received the treatments in blocks. Trial personnel and participants were masked to treatment assignments during recruitment and follow-up. The active product (MV140; Uromune, Inmunotek S.L., Alcalá de Henares, Madrid, Spain) consists of a suspension of whole-cell heat-inactivated bacteria (300 formazin turbidity units, equivalent to approximately 10^9 bacteria per milliliter) in glycerol, sodium chloride, artificial pineapple flavoring, and water. Selected strains of four bacterial species (O6:H49 V121 *E. coli*, capsular type 3 V113 *K. pneumoniae*, V125 *E. faecalis*, and V127 *P. vulgaris*) at equal percentages of formazin turbidity units are included. The placebo preparation contained all ingredients as in MV140 except for bacteria. The pineapple essence resulted in identical-tasting active and placebo preparations; the preparations were supplied in topaz-colored glass bottles. The assigned treatment was self-administered daily sublingually by spraying two sprays of 100 μl each under the tongue. All participants were followed for 6 additional months (whole study period: 12 months from randomization) (Fig. 1A). Clinic visits, without regard to UTI symptoms, were arranged every 3 months.

Patients could receive additional medication, including antibiotics for managing UTI episodes, as needed according to European Association of Urology guidelines.[4] Each participant was instructed on the use of a diary for recording symptoms and medications and was told to attend the health center on suspicion of infection, where they would provide a urine sample for culture analysis. Standardized UTI symptoms, including discomfort when urinating, urinating more often than normal, needing to urinate with no

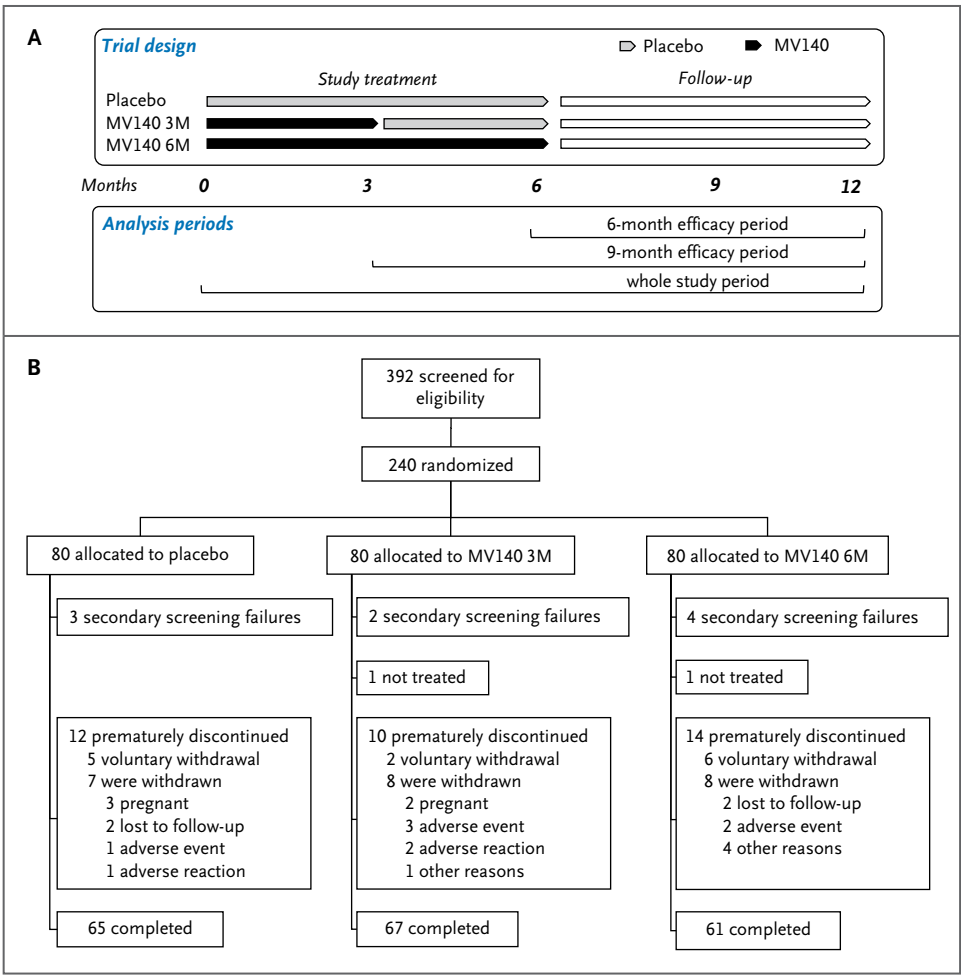

Figure 1. Trial Profile.

(A) Trial design. (B) Randomization and analysis groups. MV140 3M denotes the group receiving 3 months of active treatment, followed by 3 months of placebo; MV140 6M denotes the group receiving 6 months of active treatment.

urine in the bladder, fever (scored as the number of days with a temperature greater than 37°C), painful urination, and blood in urine, were collected using a diary. Attending physicians used this information as well as standard clinical assessment to determine a possible UTI case, obtain a urine culture, and initiate antibiotic therapy and follow-up according to recommendations of the European Association of Urology guidelines on urologic infections.[4] The type and duration of antibiotic therapy was recorded. Symptom and treatment diaries were reviewed with the participants at scheduled visits. Quality of life (QoL) was examined at scheduled visits by using the 36-Item Short-Form Questionnaire (SF-36).[15,16] The SF-36 score ranges from 0 to 100, with higher scores indicating better health status. Any adverse event (AE) was recorded and evaluated to assess severity and drug relationship. UTI symptom and urine culture data were reviewed in a blinded manner by the investigators who defined for each patient the initiation and the end of each UTI (defined as symptoms and a positive culture of at least 10^3 colony-forming units per milliliter of an accepted uropathogen).

Additional method details, including a full list of inclusion and exclusion criteria, are provided in Box S1 and the Supplementary Methods in the Supplementary Appendix. The full trial protocol is available at evidence.nejm.org.

STUDY OVERSIGHT

The trial was conducted in accordance with good clinical practice guidelines and the provisions of the Declaration of Helsinki. The protocol and amendments were approved

by the institutional review boards or independent ethics committees at each study site and national regulatory authorities. Written informed consent was obtained from all participants.

All of the data were collected by the investigators and associated site personnel and analyzed jointly with the sponsor. The first, second, and third authors prepared the manuscript draft with assistance of sponsor authors (no medical writer was involved). All authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at evidence.NEJM.org), provided input into the drafting of the manuscript, gave critical feedback, and gave final approval for submission, having access to the data (under confidentiality agreements). Additional details on study oversight are provided in the Supplementary Methods in the Supplementary Appendix.

STUDY OUTCOMES

The primary outcome was the number of UTI episodes in the 9-month study period, after the first 3 months of intervention (Fig. 1A). UTI episodes were defined by a combination of clinical features and required a positive urine culture according to European Association of Urology guidelines[4]; symptomatic cases without positive cultures, under 10^3 colony-forming units per milliliter, were not considered as UTI outcomes. The major secondary outcome was the proportion of participants remaining free of UTIs during that time. The evaluation of UTI episodes and UTI-free patients during the 6-month post-treatment efficacy (after 6 months of intervention) and the whole study period (Fig. 1A) were also secondary outcomes. Other secondary end points included the time to first UTI and the analysis of health-related QoL (SF-36 questionnaire). The minimal clinically important differences for patients suffering from recurrent UTI, to our knowledge, are not known.

Safety analyses included assessments of all AEs, which were examined individually to evaluate their severity, intensity (assessed by a blinded investigator), and outcome. UTIs, the objective of the study, were not considered AEs.

Details of the definition and recording of efficacy and safety outcomes are provided in section V.1 in the Supplementary Appendix.

STATISTICAL ANALYSIS

The null hypothesis was that MV140 would not reduce the UTI episodes after 3 months of treatment compared with placebo treatment. The SAS statistical package (version 9.4; SAS Institute Inc., Cary, NC) was used for statistical analysis. The sample size was calculated based on the reduction in UTI rate from a study by Lorenzo-Gómez et al.,[9] who found a mean difference of 2.99 for UTIs in the MV140 group compared with antibiotic prophylaxis. Accepting alpha and beta risks of 0.02 and 0.2, respectively, and assuming a SD of 1.28 and a dropout rate of 10%, 73 individuals would be needed per group. Efficacy analyses were carried out by protocol-defined primary analysis population (PDPA) (the population included all participants randomly assigned to treatment who completed week 12 according to the treatment assignment at randomization) and secondarily by per-protocol (PP) analysis, while safety analysis was performed on the safety population. Two post hoc analyses were conducted: a comparison of the mean monthly UTIs in the PDPA population and an intention-to-treat (ITT) population analysis (all patients that received at least one dose of the treatment assignment at randomization). A further comparison of the number of UTIs in each treatment group between Spain and the United Kingdom was undertaken.

According to the normal distribution analyzed, UTI episodes and UTI-free rates were analyzed by chi-square and Kruskal-Wallis nonparametric tests, respectively, comparing the two treatment groups to the placebo group. Post hoc tests with Bonferroni adjustments were subsequently conducted to evaluate pairwise differences. The number needed to treat (NNT) was calculated based on the number of patients to be treated to prevent one case of UTI during the study: NNT = 1/ARR, where ARR, the absolute risk reduction, is defined as the proportion of control events minus the proportion of treatment events. Risk ratios of active groups compared with placebo were calculated as the treatment events rate divided by the control events rate. Calculations of risk ratios and NNT are included in section V.1.6.2 in the Supplementary Appendix. Time to first UTI was analyzed with a Kaplan-Meier estimator and associated log-rank tests at the established time periods. Hazard ratios and their 95% confidence intervals (CIs) were estimated by Cox model. For the PDPA analysis of UTI outcomes, the data were imputed with the last observation carried forward. Repeated measures over time were analyzed with the Wilcoxon-signed ranked test (within a group) and mixed-effects models. For all hazard ratios or treatment differences other than the primary outcome, no adjustment has been made for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

Regarding the SF-36 data, the analysis was performed considering the difference versus the baseline data, that is (SF-36 value in months 3, 6, 9, and 12 post-treatment) minus (SF-36 value before the treatment/baseline). Therefore, the outcome of interest for this analysis was SF-36 month minus SF-36 baseline, where month could be 3, 6, 9, and 12.

No formal comparisons between the treatment duration groups will be presented. Further detail on sample size calculation, evaluable populations, and overall statistical analysis is provided in the Supplementary Appendix.

Results

TRIAL PARTICIPANTS

Of the 392 women screened, 240 participants were enrolled and underwent randomization (Fig. 1B). After secondary screening failures plus two patients who did not initiate treatment, a total of 229 participants (95%; 77, 77, and 75 in the placebo, 3-month MV140, and 6-month MV140 groups, respectively) initiated sublingual treatment and were subjected to safety analysis. The rate of completion of the 6-month treatment period was 87%, with no differences in adherence between groups. There were 215 patients (90%; 76, 70, and 69 in the placebo, 3-month MV140, and 6-month MV140 groups, respectively) included in the PDPA population, 229 in the ITT analysis (all patients who initiated treatment), and 193 (80%; 65, 67, and 61 in the placebo, 3-month MV140, and 6-month MV140 groups, respectively) in the PP analysis (Fig. 1B). No formal assessment of blinding success was determined. The demographic and clinical characteristics were balanced at baseline (Table 1). The median age (interquartile range) of participants in the PDPA population was 48.0 (34.0 to 61.5), 54.5 (38.0 to 66.0), and 47.0 (34.0 to 58.0) years for the placebo, 3-month MV140, and 6-month MV140 groups, respectively. The median number of UTIs for any study group in the year before the study was 6.0 (interquartile range, 5.0 to 6.0 or 5.0 to 7.0), depending on the group (Table 1). There were no differences between groups regarding epidemiologic data and risk factors (metabolic disorders, cardiovascular diseases, smoking status, and menopause) (Table 1).

EFFICACY

In the PDPA population, the total number of UTIs during the 9-month evaluation period was 399, with 249, 80, and 70 in the placebo, 3-month MV140, and 6-month MV140 groups, respectively. The median number (interquartile range) of UTI episodes per patient in the 9-month study efficacy period (i.e., following 3 months of intervention) was 3.0 (0.5 to 6.0) for the placebo group compared with 0.0 (0.0 to 1.0) in both groups receiving MV140 ($P < 0.001$ Kruskal-Wallis) (Fig. 2A and Table 2, which displays the median values and the comparison of each active group with placebo). In the placebo group, 42 patients experienced three or more UTIs versus 12 patients in the 3-month MV140 group and 9 in the 6-month MV140 group (Table 2). No differences between the results obtained in the number of UTIs of each treatment group between Spain and the United Kingdom were observed ($P=0.411$ for placebo, $P = 0.125$ for 3-month MV140, and $P=0.095$ for 6-month MV140).

The NNT to prevent one UTI was 3.26 in the 3-month MV140 group and 3.03 in the 6-month MV140 group. 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. The bacteria isolated in the urine cultures are shown in Table S1. Bacterial genera included in the treatment represented 61.8% and 75.8% of the positive urine cultures in the 3- and 6-month treatment groups, respectively, compared with 84.8% in the placebo group.

Of the women receiving MV140, 39 in the 3-month MV140 group (56%; 95% CI, 44% to 67%) and 40 in the 6-month MV140 group (58%; 95% CI, 44% to 67%) remained UTI free compared with 19 (25%; 95% CI, 15% to 35%) in the placebo-treated group (Fig. 2B and Table 2). Among the participants, the median time (interquartile range) until the appearance of the first UTI after 3 months of treatment was 275.0 days (87.0 to 275.0) in the 3-month MV140 group, 275.0 days (77.0 to 275.0) in the 6-month MV140 group, and 48.0 days (17.0 to 189.0) in the placebo group (Fig. 2C and Table 2). Hazard ratios for suffering a UTI were 0.36 (95% CI, 0.23 to 0.56) for 3-month MV140 and 0.33 (95% CI, 0.21 to 0.54) for 6-month MV140 versus placebo. The results on UTI incidence and recurrence obtained for the 6-month post-treatment efficacy period and during the whole study period (12 months) were very similar to those of the 9-month efficacy period (Table 2).

Median (interquartile range) SF-36 QoL scores were balanced at baseline (placebo, 65.7 [52.2 to 79.2]), after 3 months of MV140 treatment (67.5 [45.3 to 77.0]), and

Table 1. Baseline Characteristics of Participants, According to Treatment Group (PDPA Population).*

Characteristic	Placebo (n=76)	3-mo MV140 (n=70)	6-mo MV140 (n=69)	P value
Age — yr†	48.0 (34.0–61.5)	54.5 (38.0–66.0)	47.0 (34.0–58.0)	0.235‡
Race or ethnicity — no. (%)§				
Caucasian	72 (95)	68 (97)	66 (96)	0.840¶
Latino	2 (3)	2 (3)	3 (4)	0.897¶
Others	2 (3)	0 (0)	0 (0)	0.331¶
Body-mass index†,‖	24.1 (21.6–28.3)	25.0 (21.7–28.2)	23.9 (22.0–27.1)	0.945‡
Vital signs**				
Heart rate — bpm	78.2±11.8	81.8±13.5	82.1±13.2	0.134††
Systolic BP — mm Hg	122.5±16.9	125.2±14.5	120.0±15.1	0.174††
Diastolic BP — mm Hg	76.3±13.3	76.3±9.1	73.5±10.4	0.263††
Metabolic disorders according medical records — no. (%)				
None	58 (76)	54 (77)	49 (71)	0.663‡‡
Diabetes	3 (4)	2 (3)	6 (9)	0.310¶
Hypothyroidism	7 (9)	7 (10)	5 (7)	0.871¶
Dyslipidemia	5 (7)	6 (9)	8 (12)	0.600¶
Hypercholesterolemia	3 (4)	4 (6)	6 (9)	0.484¶
Obesity	1 (1)	0 (0)	2 (3)	0.420¶
Others	3 (4)	3 (4)	5 (7)	0.685¶
Cardiovascular diseases according medical records — no. (%)				
None	59 (78)	51 (73)	57 (83)	0.663‡‡
Arterial hypertension	11 (14)	12 (17)	7 (10)	0.485¶
Vascular dysfunction	1 (1)	3 (4)	4 (6)	0.321¶
Others	7 (9)	4 (6)	4 (6)	0.668¶
Self-reported smoking status — no. (%)				
Never smoked	74 (97)	65 (93)	66 (96)	0.432¶
Current smoker	0 (0)	1 (1)	2 (3)	0.209¶
Previous smoker	2 (3)	4 (6)	1 (1)	0.400¶
Self-reported menopause status — no. (%)				
Premenopausal	41 (54)	32 (46)	38 (55)	0.479‡‡
Postmenopausal	35 (46)	38 (54)	31 (45)	0.479‡‡
UTIs in previous year according medical records†	6.0 (5.0–6.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)	0.184‡

* The protocol-defined primary analysis population (PDPA) included all participants randomly assigned to treatment who completed week 12 according to the treatment assignment at randomization. No differences between groups were found. BP denotes blood pressure and UTI urinary tract infection.

† Values are shown as the median (interquartile range).

‡ Kruskal-Wallis nonparametric test.

§ Race and ethnicity were self-reported.

¶ Fisher test.

‖ The body-mass index is the weight in kilograms divided by the square of the height in meters.

** Values are means±SD.

†† Analysis of variance.

‡‡ Chi-square test.

after 6 months of MV140 treatment (67.7 [49.1 to 79.9]) (Fig. 2D). In contrast with the placebo group, which showed no change in QoL, both MV140-receiving groups noted an improvement in SF-36 scores over time. This improvement appeared as early as 3 months since initiation of the active treatment but reached maximum levels at the longest time period (12 months): 81.9 (65.5 to 89.4) and 85.8 points (71.2 to 91.7) for the 3-month MV140 and 6-month MV140 groups, respectively (Fig. 2 and Table S4).

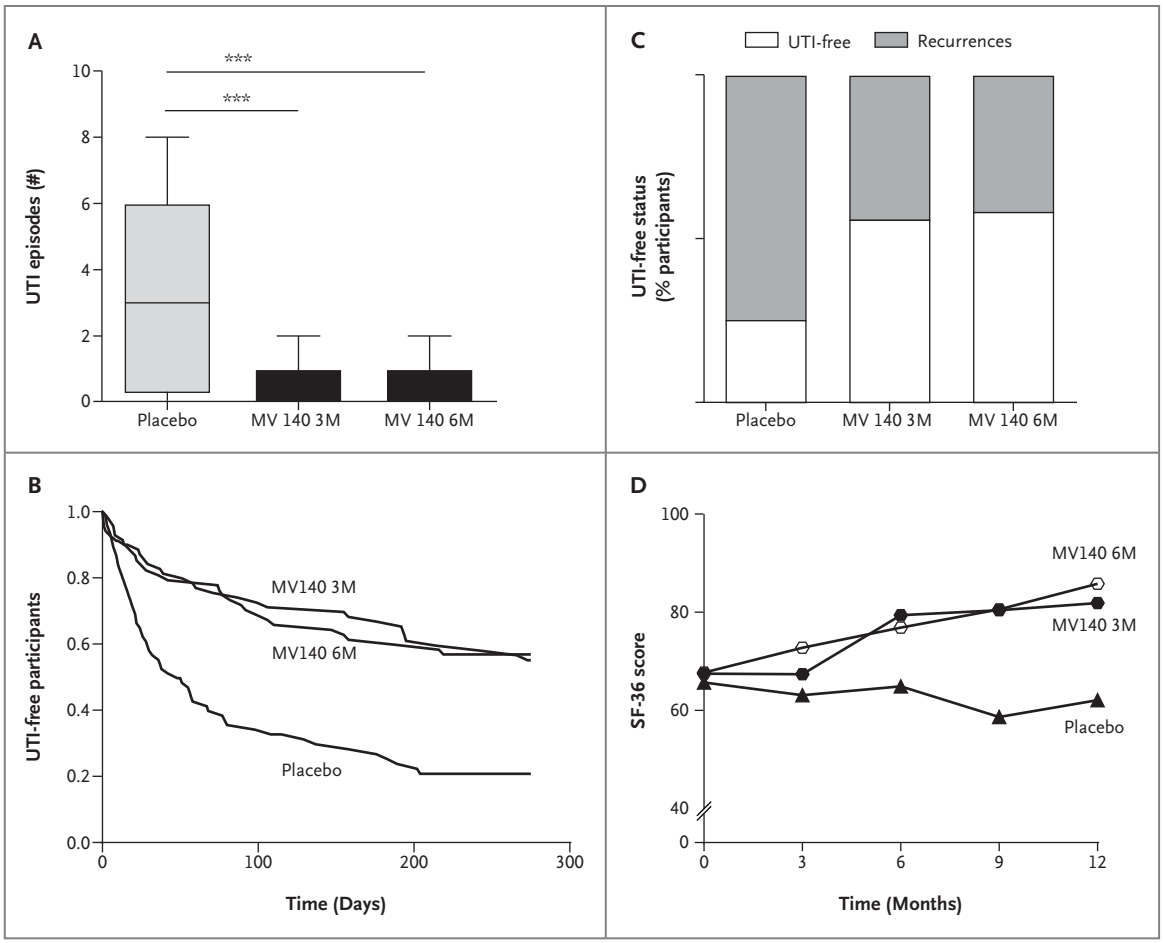

Figure 2. UTI Incidence in the 9-Month Efficacy Period: Primary and Additional Efficacy Outcomes.
(A) Episodes of urinary tract infection (UTI) are shown as box plots, indicating the median, interquartile range, minimum, and maximum according to the Tukey range. ***P<0.001, Mann-Whitney-Wilcoxon test comparing the placebo group with the 3-month MV140 (MV140 3M) and 6-month MV140 (MV140 6M) groups. (B) Kaplan-Meier estimator of time to UTI during the 9-month efficacy period. Results from the protocol-defined primary analysis population are shown. (C) Frequencies of UTI-free participants are shown as bars, indicating the rate of participants free of infection or suffering recurrences. (D) Quality of life throughout the whole study period. Scores are from the 36-Item Short-Form Questionnaire (SF-36) ranging from 0 to 100 points with higher scores indicating better health status. Medians at 3, 6, 9, and 12 months are shown.

The number of UTIs across the ITT population and PP was consistent with the PDPA results (Tables S2 and S3).

SAFETY

A total of 205 AEs in 101 participants were registered: 81 in the placebo group and 76 and 48 in the 3-month and 6-month MV140 groups, respectively. The most common AEs (5% or more of participants) were chest infection, candidiasis, and vaginitis (Table 3). Seven AEs in five participants were assessed as serious but not unexpected or logically related to MV140 (Tables 3 and S5). No deaths occurred during the trial. A description of the nine AEs considered as adverse reactions attributed to treatment by the investigators is provided in Table S6.

Discussion

In this randomized, double-blind, placebo-controlled trial conducted in Spain and the United Kingdom, MV140 for either a 3- or 6-month administration schedule significantly decreased UTI incidence and prevented recurrence over placebo (more than twofold), delaying the onset of a new UTI in active groups, for up to a year. In addition, women receiving MV140 experienced a sustained improvement in

Table 2. Primary and Additional Efficacy Outcomes: UTI Incidence at Different Study Periods (PDPA Population).*

Efficacy period	Placebo (n=76) No. (%)	3-mo MV140 (n=70) No. (%)	P value†	6-mo MV140 (n=69) No. (%)	P value†
9 mo					
UTI episodes‡	3.0 (0.5–6.0)	0.0 (0.0–1.0)	<0.001§	0.0 (0.0–1.0)	<0.001§
Monthly UTI episodes	0.3 (0.1–0.7)	0.0 (0.0–0.1)		0.0 (0.0–0.1)	
UTI-free participants — % [95% CI]	19 (25) [15–35]	39 (56) [44–67]		40 (58) [46–70]	
Days to first UTI‡	48.0 (17.0–89.0)	275 (87.0–275.0)		275.0 (77.0–275.0)	
Participants with ≥3 UTIs — % [95% CI]	42 (55) [44–66]	12 (17) [8–26]		9 (13) [5–21]	
6 mo					
UTI episodes‡	2.0 (0.0–4.0)	0.0 (0.0–1.0)	< 0.001§	0.0 (0.0–1.0)	< 0.001§
UTI-free participants — % [95% CI]	25 (33) [22–43]	46 (66) [55–77]		47 (68) [57–79]	
Days to first UTI‡	60.0 (21.0–180.0)	180.0 (104.0–180.0)		180.0 (98.0–180.0)	
Whole study					
UTI episodes‡	5.0 (1.0–7.0)	1.0 (0.0–2.0)		1.0 (0.0–2.0)	
UTI-free participants — % [95% CI]	16 (21) [12–30]	27 (39) [27–50]		30 (44) [32–55]	
Monthly UTI episodes	0.4 (0.1–0.6)	0.1 (0.0–0.2)		0.1 (0.0–0.2)	
Days to first UTI‡	73.5 (44.0–276.0)	183.0 (65.0–365.0)		189.0 (61.0–365.0)	
UTI difference‡,¶	−1.0 (−5.0 to 1.0)‖	−5.0 (−6.0 to −4.0)‖		−5.0 (−6.0 to −4.0)‖	

* The protocol-defined primary analysis population (PDPA) included all participants randomly assigned to treatment who completed week 12 according to the treatment assignment at randomization. UTI denotes urinary tract infection and CI confidence interval.

† Unless otherwise specified, comparison of each active group versus placebo group at the same timepoint.

‡ Values are shown as median (interquartile range).

§ Mann-Whitney-Wilcoxon test with Bonferroni correction.

¶ Difference between UTIs in the previous year and during the whole study period.

‖ Fisher test.

QoL. These results confirm previous evidence gained from retrospective or uncontrolled clinical studies performed with MV140, showing very similar results.[9–14]

We tested a heat-inactivated whole-cell bacterial preparation, administered sublingually, in this randomized controlled trial of prevention of recurrent UTI in women. The sublingual route was chosen for treatment delivery of MV140 because it has been shown to induce both systemic and mucosal immunity (including the genitourinary tract)[14,17,18]; similar results have been shown for other whole-cell bacterial formulations.[18–21] Since we do not report immunologic data herein, we speculate that by stimulating mucosal immunity, sublingual administration may impact infections affecting distant mucosal sites such as the lower urinary tract.[22,23] In our study, compared with placebo there was a reduction in the incidence of positive urine cultures seen across most species in the treatment groups, As expected, the difference in bacterial species associated with recurrent UTI post-treatment between the treated and placebo groups was more pronounced for the genera represented in the treatment.

Our results corroborate previous studies from other bacterial formulations to prevent recurrent UTI.[24,25] Efficacy evaluation in the short term (6 months or less) provided similar UTI-free rates between MV140 (more than 65%) and oral bacterial lysates (53% to 88%). In contrast with studies performed with other bacterial immunotherapies, which were carried out for short-term periods or failed to support longer clinical protection,[24] our current trial confirms that MV140 conferred durable protection for at least 1 year. The longer clinical benefits of MV140 once treatment is completed differ from management of recurrent UTI with antibiotic prophylaxis, which shows a rapid lack of efficacy following discontinuation as well as numerous side effects.[26,27]

Although no formal comparison was made between treatment groups, the data are consistent with the hypothesis that administration of MV140 for 6 months rather than 3 months did not appear to further impact clinical outcomes in regard to reducing recurrent UTI. While more data from larger and longer studies will be needed to determine the duration of treatment benefit, we do not think there is justification for extending the administration beyond 3 months.

Table 3. Safety Analysis (Safety Population).*				
AEs — n (%)	Placebo (n=78)	3-mo MV140 (n=77)	6-mo MV140 (n=75)	All groups (N=230)
Any				
Participants with any AE†	39 (50)	34 (44)	28 (37)	101 (44)
No. of AEs‡	81 (40)	76 (37)	48 (23)	205 (100)
AEs reported in ≥ 5% of participants‡				
Chest infection	7 (3)	3 (2)	3 (2)	13 (6)
Candidiasis	4 (2)	7 (3)	1 (1)	12 (6)
Vaginitis	5 (2)	4 (2)	2 (1)	11 (5)
Serious AEs	0 (0)	6 (3)	1 (1)	7 (3)

* Safety population included all participants randomly assigned to treatment who received at least one dose, excluded screening failures. AE denotes adverse event.

† Percentages based on total participants per group.

‡ Percentages based on total number of AEs.

Although the beneficial role of licensed or developing bacterial preparations for the prevention of recurrent UTI has been extensively evaluated,[24,25,28] the mechanisms of action to induce protective immunity in the bladder that mediates this protection are not fully understood.[28–30] Thus, for symptomatic UTIs, clinical outcomes are considered the most important factors in assessing efficacy.[28,31] Mechanistic studies have shown that sublingual MV140 induces antibody production[18] and activates human dendritic cells to generate T helper (Th) 1, Th17, and interleukin 10-producing anti-inflammatory T-cell responses in secondary lymphoid organs[17] and locally in the bladder.[17] The induction of adaptive immunity likely underlies the clinical protection observed following treatment discontinuation, although trained immunity could also play a role.[18,31]

In our trial, we did not observe clinically concerning side effects. Our data are similar to those reported from postmarketing surveillance of MV140,[14] in which safety data have been collected since 2017 (ClinicalTrials.gov NCT04173013) on almost 21,000 patients representing 1.5 million doses of MV140 in special access programs (Named Patient Programs, i.e., programs that provide patients and physicians access to medicines that are not available to them in their own country) outside North America; there were safety reports for 13 patients, most of which were mild and self-limited (Table S8 classified according to MedDRA).

This 12-month study has limitations when discussing the long-term implications of this preventative treatment for recurrent UTI in women. While we speculate that this nonantibiotic alternative could potentially decrease antibiotic side effects in patients with recurrent UTI while improving overall antibiotic stewardship over the long term, the 12-month duration of the study limits any such discussion beyond this time period. Discussion of longer-term efficacy and safety will have to await follow-up beyond 12 months, which may uncover the need for retreatment in the future. A further issue noted was that the number of UTIs in the placebo group in the 12-month study period was less than that reported for the year before baseline, while 25% were noted to be UTI free after placebo treatment. This placebo effect, reported in previous randomized controlled trials for recurrent UTI,[24,25] may be attributed, at least in part, to the fact that the prebaseline data were collected retrospectively. Nonetheless, the placebo group still experienced a median of three UTIs during the 9-month efficacy period, a number that would still define them as suffering from recurrent UTI (two or more UTIs per 6 months).[4,5] Finally, although we have postulated a potential mechanism of action, we have not provided accompanying immunologic measurements from this study to substantiate this. Ongoing studies will be required to provide this important corroborative information.

In our trial, MV140 demonstrated clinical efficacy and improved QoL, with a side effect profile that did not limit treatment acceptance. The duration of the treatment effect will need to be established through further research in women with recurrent UTI.

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Disclosures

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