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Evaluating the safety and potential activity of URO-902 (hMaxi-K) gene transfer by intravesical instillation or direct injection into the bladder wall in female participants with idiopathic (non-neurogenic) overactive bladder syndrome and detrusor overactivity from two double-blind, imbalanced, placebo-controlled randomized phase 1 trials

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Abstract

Aims: Two phase 1 trials were performed in healthy women with the overactive bladder (OAB) syndrome and urodynamically demonstrated detrusor overactivity (DO), with the aim to demonstrate the safety and potential efficacy of URO-902, which comprises a gene therapy plasmid vector expressing the human big potassium channel α subunit.

Methods: ION-02 (intravesical instillation) and ION-03 (direct injection) were double-blind, placebo-controlled, multicenter studies without overlap in enrollment between studies. Active doses were administered and evaluated sequentially (lowest dose first) for safety. ION-02 participants received either 5000 μg or 10 000 μg URO-902, or placebo. ION-03 participants received either 16 000 or 24 000 μg URO-902, or placebo, injected directly into the bladder wall using cystoscopy. Primary outcome variables were safety parameters occurring subsequent to URO-902 administration; secondary efficacy variables also were evaluated.

George Christ and Arnold Melman are co-founders of Ion Channel Innovatons, LLC.

Results: Among the safety outcomes, there were no dose-limiting toxicities or significant adverse events (AEs) preventing dose escalation during either trial, and no participants withdrew due to AEs. For efficacy, in ION-02 ($N = 21$), involuntary detrusor contractions on urodynamics at 24 weeks in patients receiving URO-902 ($P < .0508$ vs placebo) and mean urgency incontinence episodes in the 5000 μg group ($P = .0812$ vs placebo) each showed a downward trend. In ION-03 ($N = 13$), significant reduction versus placebo in urgency episodes (16 000 μg, $P = .036$; 24 000 μg, $P = .046$) and number of voids (16 000 μg, −2.16, $P = .044$; 24 000 μg, −2.73, $P = .047$) were observed 1 week after injection.

Conclusion: Promising safety and efficacy results in these preliminary phase 1 studies suggest gene transfer may be a promising therapy for OAB/DO, warranting further investigation.

KEYWORDS

BK channel, gene therapy, incontinence, urinary urgency

1 | INTRODUCTION

Overactive bladder (OAB) is a syndrome defined as urinary urgency, with or without incontinence, with increased daytime frequency and nocturia, in the absence of infection or other obvious pathological features.[1] OAB is a common and significant problem that affects millions of men and women in the United States,[2-4] with a major negative impact on quality of life (QOL).[5] Estimates for total cost of care for symptoms of OAB are upwards of $36.5 billion in the United States alone.[6] OAB is a symptom diagnosis, which may or may not be associated with the urodynamic finding of detrusor overactivity (DO).[7]

Primary pharmacologic therapy for OAB consists of oral antimuscarinics or adrenergic β-3 receptor agonists.[8-10] However, these drugs lack bladder selectivity, and there remains an unmet need for some patients. In addition, significant side effects, such as dry mouth, constipation, and cognitive defects limit use of many antimuscarinic agents.[11,12] Lack of efficacy and side effects have resulted in low long-term treatment persistence (ranging from 5% to 47%).[13,14] Chemodenervation agents, such as botulinum toxin, may be limited by side effects, including urinary retention requiring catheterization.[15] Additional treatment options would be welcomed.

The large-conductance Ca^{2+}-activated K^+(also known as big potassium [BK], MaxiK$^+$, BK_{Ca}, $K_{Ca}1.1$) channel is highly expressed on urinary bladder smooth-muscle cells and regulates bladder detrusor muscle function.[16,17] BK channels are activated by changes in both voltage and cytoplasmic Ca^{2+} and control cellular excitability and, thus, degree of smooth-muscle contraction.[16,17] Activation of the BK channel reduces smooth-muscle cell excitability and may be a potential therapeutic option for treatment of OAB.[18] Gene therapy using a plasmid vector has demonstrated that overexpression of the human BK channel α subunit (pore forming unit) improved smooth-muscle function in both animal and human applications.[19-21]

Here we provide data from two phase 1 trials demonstrating safety and potential efficacy of URO-902, comprising a gene therapy plasmid vector expressing the human BK channel α subunit. In these studies, URO-902 was delivered either by a single intravesical instillation or by direct injections into bladder detrusor muscle.

2 | MATERIALS AND METHODS

These studies were conducted in compliance with Declaration of Helsinki, U.S. Title 21 Code of Federal Regulations, and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The protocol and subject informed consent documents were approved by the institutional review committee and institutional biohazard committee of the Biomedical Research Alliance of New York. In addition, a data safety monitoring board reviewed all the data during the course of the trials.

URO-902 is a nonviral, double-stranded, naked plasmid DNA molecule (6880 base pair) derived from a pVAX (Invitrogen) backbone and *hSlo* complementary DNA. Expression of *hSlo* is driven by the cytomegalovirus promoter, and transcript maturation is supported with the bovine growth hormone poly(A) site. The construct also contains the kanamycin resistance gene and the pUC origin of replication.[22]

2.1 | Study design

Both the intravesical instillation (ION-02, NCT00495053) and direct injection (ION-03, NCT01870037) studies were double-blind, placebo-controlled, multicenter, sequential active-dose, phase 1 studies in healthy females of ≥18 years and non-childbearing potential, with moderate OAB of ≥6 months' duration with associated DO and at least one of the following: micturitions ≥8 times per day, symptoms of urinary urgency (sudden compelling desire to urinate) or nocturia (waking at night ≥2 times to void), urgency incontinence (≥5 incontinence episodes per week), and DO with ≥1 uncontrolled phasic contraction(s) of at least 5 cm/H_2O pressure documented on cystometrogram. Additional inclusion criteria were residual volume of ≤200 mL, nonresponse and/or poor tolerance to previous OAB treatments (eg, antimuscarinic/anticholinergic agents, β-3 agonists, or onabotulinumtoxin A), and did not wish to continue these treatments. Exclusion criteria included a positive serum (HCG) pregnancy test or lactating, history of three or more urinary tract infections/year, and any significant genitourinary disorder, except incontinence. There was no overlap in time in subject enrollment between the two sequentially performed studies.

In both studies, active doses were administered and evaluated sequentially (lowest dose first) for safety. Enrollment of the first four participants in each cohort was managed by the study sites with a 2-day waiting period following each participant's dosing. The next participant was enrolled only after the site had contacted the previously dosed participant on day 3 following transfer to determine if a clinically significant adverse event (AE) had occurred. If a clinically significant AE was reported, the medical monitor was to contact all the sites, and no further enrollment was to be done until the medical monitor or sponsor gave permission. Participants in the intravesical instillation (ION-02) study received a single administration of either 5000 μg or 10 000 μg URO-902, or placebo in phosphate-buffered saline (PBS)-20% sucrose solution (each dose was 90 mL total volume). Up to 13 female participants were to be enrolled per dose level (10 on active treatment, 3 on placebo). Patients in the direct injection study (ION-03) received a single administration of URO-902 in PBS-20% sucrose of either 16 000 μg (4 mL total as 20 distributed 0.2 mL injections) or 24 000 μg (6 mL total as 30 distributed 0.2 mL injections), or placebo (either 20 or 30 distributed injections) directly into the bladder wall using cystoscopy. Up to nine female participants were to be enrolled per dose level (6 on active treatment, 3 placebo).

Study periods for both ION-02 and ION-03 were 6 months following treatment with URO-902. Posttreatment visits occurred at weeks 1, 2, 4, 8, 16, and 24. At pre-specified intervals, physical examinations, electrocardiogram (including chemistry, hematology, and urine laboratory samples, cystometry, daily voiding diary information, pad test results, and bladder scans) were performed and reviewed. Urine samples for detection of *hSlo* DNA were collected at each visit in both studies. Blood samples for detection of *hSlo* DNA were collected at 2 hours postinjection. All participants who received the study drug were surveyed post-study to monitor for delayed AEs at 6, 12, and 18 months after completing the initial 6-month study period.

2.2 | Intravesical instillation and direct injection procedures

ION-02, intravesical instillation procedure: Each 90 mL dose was instilled through a small diameter catheter into the lumen of the bladder. Participants were requested to retain the solution in the bladder for at least 2 hours (dwell time).

ION-03, direct injection procedure: treatments were administered without general or regional anesthesia through a rigid cystoscope 10 to 20 minutes after 40 mL of 2% lidocaine was instilled into the bladder and 10cc of 2% xylocaine gel was instilled into the urethra. URO-902 was injected with a Bonee needle into the detrusor muscle, avoiding the trigone. The needle was inserted approximately 2 mm into the detrusor and 20 injections of either 0.2 mL (16 000 μg dose) or 30 injections of 0.2 mL (24 000 μg dose) each were spaced approximately 1 cm apart.

2.3 | Safety and efficacy assessment

The primary outcome variables for both ION-02 and ION-03 included all safety parameters occurring subsequent to administration of URO-902 compared with placebo, including all AEs, change from baseline for all clinical laboratory tests, measurements for the presence of *hSlo* in urine and/or blood, electrocardiograms (rate, rhythm, PR, QT, QT interval by Fredericia, QT interval by Bazett formula, QRS), and physical examinations. Urinary tract infection was defined as a positive urine culture (≥1000 colonies/mL) of a urinary pathogen from a catheterized urine. Urinary retention was defined as ≥400 mL of urine measured by bladder scan. Only treatment-emergent adverse events (TEAEs) were evaluated.

Secondary outcome variables were measured to determine efficacy and potential activity of URO-902, including changes in mean scores for detrusor contractions, urgency incontinence episodes, urgency episodes, and number of voids, from baseline to weeks 1, 2, 4, 8, 12, and 24 after the single administration of URO-902, and also diary variables, such as the number

of daily micturitions, urgency incontinence episodes, and urgency episodes (daily volume voided per micturition also was recorded in the ION-03 study). Also included were the change in the mean rating from baseline of QOL scores from the King's health questionnaire (KHQ). Cystometry was performed at baseline and at weeks 4 and 24 to assess involuntary detrusor contractions and other urodynamic variables, including post-residual volume. These results were interpreted by a blinded central reader.

2.4 | Data analysis

Both safety and efficacy data were summarized using summary descriptive statistics by treatment group (combined placebo versus two active treatment groups and combined placebo vs combined treatment groups) and the total study population. Linear mixed effect models were used to estimate difference of changes from baseline between placebo and active treatment and to test whether there was dose-response for different outcomes. Generalized estimating equation model was used to estimate effects for the binary endpoints.

For exploratory analysis, analysis of variance or analysis of covariance with baseline measure as covariate was applied to test for treatment difference at each separate week. χ^2 was used to test for difference in treatment versus placebo in participants' perception of response to treatment. Given the small sample size and exploratory nature of the efficacy data, no adjustment was made for multiple comparisons. All the *P* values presented were nominal.

3 | RESULTS

3.1 | Patient demographics

Forty-one participants were screened for ION-02 (intravesical instillation); 20 were excluded because they did not meet inclusion/exclusion criteria. In ION-3, 24 patients were assessed, and nine were excluded. The full CONSORT diagrams for both studies can be seen in Figure 1. All the participants in both studies had unsuccessful prior treatment with anticholinergics, and four had issues with onabotulinumtoxin A therapy in ION-03. Patient demographics and baseline characteristics were generally comparable between treatment groups in both studies (Table 1).

3.2 | Safety results

There was no detectable evidence of URO-902 in the urine of any participant during ION-02. In ION-03,

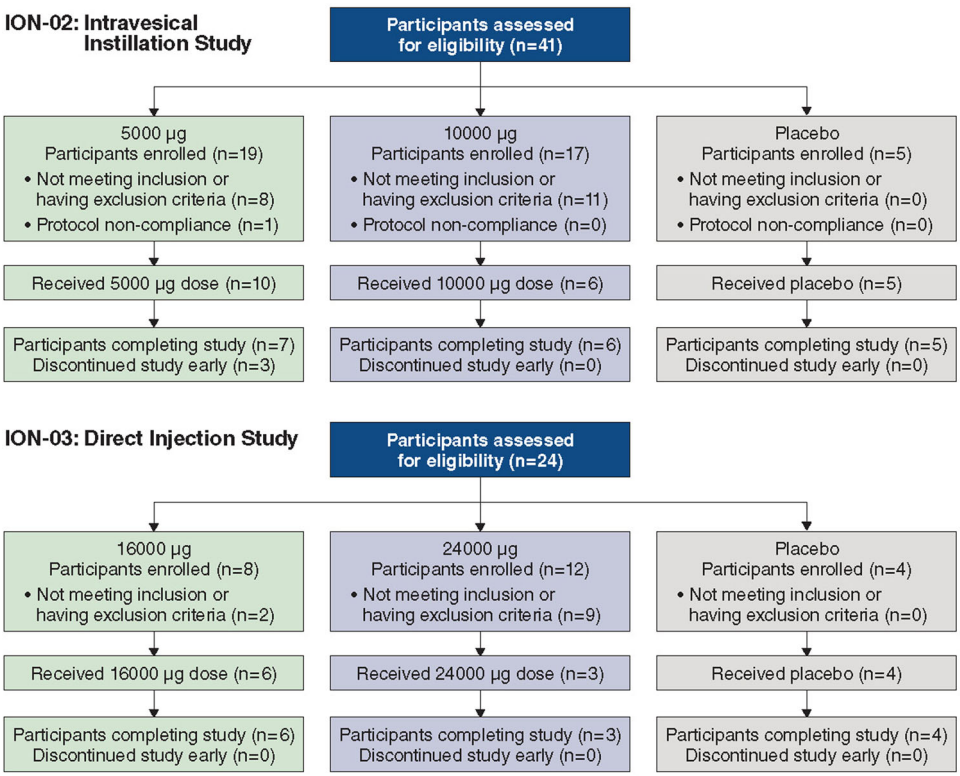

FIGURE 1 CONSORT diagrams. CONSORT, Consolidated Standards of Reporting Trials

TABLE 1 Patient demographics from ION-02 and ION-03

A. ION-02: patient demographics from the intravesical instillation study				
		URO-902 5000 μg	**URO-902 10 000 μg**	**Placebo**
N		10	6	5
Age, y	Mean (SD) Min, Max	62.6 (15.2) 45, 93	65.8 (14.4) 47, 80	69.8 (9.8) 56, 83
Race	White Black/African American	9 1	6 0	4 0
Ethnicity	Latino/Hispanic Not Latino/Hispanic	0 10	0 6	1 4
Height, cm	Mean (SD) Min, Max	162.0 (6.36) 147.3, 167.6	154.6 (4.9) 154.9, 167.6	163.6 (12.6) 152.4, 172.7
Weight, Kg	Mean (SD) Min, Max	81.5 (27.8) 50.3, 123.8	69.5 (13.0) 54, 81.6	81.5 (22.0) 63.5, 115.7
BMI, kg/m^2	Mean (SD) Min, Max	31.9 (8.36) 23.3, 44.1	27.7 (4.9) 21.8, 34.0	31.1 (7.6) 21.8, 38.8
Baseline mean number of urgency episodes (24 hr)	Mean (SD)	11.5 (3.2)	11.2 (4.7)	10.1 (3.2)
Baseline micturition frequency (24 hr)	Mean (SD)	11.5 (3.4)	11.2 (4.7)	10.1 (3.2)
Baseline mean number of urgency incontinence episodes (24 hr)	Mean (SD)	2.7 (2.3)	2.2 (2.2)	5.3 (3.6)
B. ION-03: patient demographics from the direct injection study				
		URO-902 16000 μg	**URO-902 24000 μg**	**Placebo**
N		6	3	4
Age, y	Mean (SD) Min, Max	55.8 (4.6) 50.2, 62.9	65.1 (9.2) 57.8, 75.5	57.0 (6.8) 51.0, 66.7
Race	White Black/African American	2 4	2 1	4 0
Ethnicity	Latino/Hispanic Not Latino/Hispanic	0 6	1 2	0 4
Height, cm	Mean (SD) Min, Max	25.3 (0.9) 24.4, 26.6	24.5 (0.8) 23.6, 25.2	26.0 (0.9) 24.8, 26.8
Weight, kg	Mean (SD) Min, Max	86.4 (29.8) 49.5, 120.0	62.6 (14.7) 52.7, 79.5	78.6 (23.4) 57.3, 109.1
BMI, kg/m^2	Mean (SD) Min, Max	32.7 (12.6) 19.6, 48.3	24.9 (5.6) 19.9, 31.0	27.7 (7.0) 21.9, 36.5
Baseline mean number of urgency episodes (24 hr)	Mean (SD)	10.21 (3.55)	17.19 (7.07)	9.82 (5.17)
Baseline micturition frequency (24 hr)	Mean (SD)	11.26 (2.70)	17.19 (7.07)	10.18 (4.78)
Baseline mean number of urgency incontinence episodes (24 hr)	Mean (SD)	1.91 (0.83)	3.81 (3.30)	1.82 (1.52)

Abbreviations: BMI, body mass index; max, maximum; min, minimum.

one participant had URO-902 detected in the blood, and four participants had URO-902 detected in the urine immediately after dosing (subsequent assays were negative). No dose-limiting toxicities or significant AEs occurred to prevent escalation to the next higher dose during either trial. Only one serious AE, unrelated to study drug, was reported in ION-03, in a woman with pre-existing asthma who had an exacerbation of her condition due to cold weather that required treatment (Table 2A,B). Three participants in ION-02 had TEAEs considered related or possibly related to study treatment. One, in the 5000 μg group with a history of first degree atrioventricular (AV) block, was a Mobitz type II second degree AV block at 170 days posttreatment that resolved in 1 day. The second was fatigue, headache, shaking chills, and insomnia (all possibly related; mild-moderate severity; 13-76 days posttreatment). The third was heart palpitations, which occurred in a patient with placebo.

TABLE 2A ION-02 summary of treatment-emergent adverse events

System organ class/AE (%)	URO-902 5000 μg (n = 10)	URO-902 10 000 μg (n = 6)	Placebo (n = 5)
Total number of TEAEs	36	11	7
Participants with TEAEs related to study treatment	2	0	1
Participants with serious TEAEs	0	0	0
Participants with TEAE leading to early withdrawal	0	0	0
Total participants with at least 1 AE	6 (60.0)	5 (83.3)	3 (60.0)
Gastrointestinal disorders	6	1	0
Total participants with at least 1 AE	3 (30.0)	1 (16.7)	0
Gastroesophageal reflux disease	2 (20.0)	0	0
Constipation	1 (10.0)	1 (16.7)	0
Diarrhea	1 (10.0)	0	0
Infections and infestations	7	3	2
Total participants with at least 1 AE	3 (30.0)	3 (50.0)	2 (40.0)
Urinary tract infection	5 (50.0)	1 (16.7)	2 (40.0)
Hepatitis C	0	1 (16.7)	0
Nasopharyngitis	0	1 (16.7)	0
Renal and urinary disorders	3	2	0
Total participants with at least 1 AE	1 (10.0)	2 (33.3)	0
Dysuria	0	1 (16.7)	0
Hypertensive nephropathy	1 (10.0)	0	0
Urinary retention	0	0	0
Musculoskeletal and connective tissue disorders	1	1	0
Total participants with at least 1 AE	1 (10.0)	1 (16.7)	0
Back pain	0	1 (16.7)	0
Tendonitis	1 (10.0)	0	0
Investigations	4	2	0
Total participants with at least 1 AE	2 (20.0)	2 (33.3)	0
Mobitz type 11 s block	1(10)	0	0
Blood creatinine phosphokinase increased	1 (10.0)	0	0
Blood pressure increased	0	1 (16.7)	0
Blood creatinine increased	1 (10.0)	0	0

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

No participants withdrew from either study due to adverse events. No deaths occurred during the studies. The majority of AEs reported were mild in severity and unrelated to treatment. No medical problems were reported during the post-study 18-month long-term follow-up. Urinary retention was not seen in any participants on active treatment. In addition, there were no participants on active treatment with worsening of symptoms of OAB as measured by diary, KHQ, or deterioration on urodynamics.

3.3 | Efficacy in ION-02

Although these were escalating-dose safety studies, secondary efficacy endpoints were evaluated. In ION-02 there was a trend in the overall mean difference in the number of decreased detrusor contractions from baseline at 24 weeks after transfer (5000 μg, −3.6; 1000 μg, −1.0; treatment effect, $P < .0508$). At week 8, there was also a trend in the 5000 μg dose group with an observed >40% mean decrease of 1.3 from baseline urgency incontinence episodes (treatment effect, $P = .0812$).

3.4 | Efficacy in ION-03

The utility of URO-902 as a viable treatment for OAB was more apparent when the plasmid was injected directly into the detrusor. Despite the small number of subjects, the ION-03 study demonstrated rapid and sustained improvements in multiple secondary efficacy endpoints. Significant improvements were observed in the mean reduction in number of urgency episodes/24 hours at 1 week compared with placebo (placebo, mean at 1 week: 11.27, mean change from baseline: +1.45; 16 000 μg, mean at 1 week: 7.89, mean change from baseline: −2.31, $P = .036$; 24 000 μg, mean at 1 week: 14.46, mean change from baseline: −2.73, $P = .046$) (Figure 2A). Significant improvements in at least one dose group were maintained at weeks 2, 4, 12, and 24 after

TABLE 2B ION-03 summary of treatment-emergent adverse events

System organ class/AE (%)	URO-902 160 00 μg (n = 6)	URO-902 24 000 μg (n = 3)	Placebo (n = 4)
Total number of TEAEs	13	8	17
Participants with TEAEs related to study treatment	0	0	0
Participants with one or more serious TEAEs	1	0	0
Participants with TEAE leading to early withdrawal	0	0	0
Total participants with at least 1 AE	4 (66.7)	3 (100.0)	4 (100.0)
Gastrointestinal disorders	1	1	1
Abdominal pain	1(16.7)	1(33.3)	1 (25.0)
Infections and Infestations	2	1	0
Urinary tract infection	1 (16.7)	1 (33.3)	0
Upper respiratory tract infection	1 (16.7)	0	0
Renal and urinary disorders	2	2	3
Hematuria	2 (33.3)	1 (33.3)	2 (50.0)
Bladder pain	0	1 (33.3)	0
Dysuria	0	1 (33.3)	1 (25.0)
Urinary retention	0	0	0
Musculoskeletal and connective tissue disorders	0	1	0
Arthralgia	0	1 (33.3)	0
Investigations	2	0	2
Antinuclear antibody positive	1 (16.7)	0	0
Blood creatine phosphokinase increased	1 (16.7)	0	1 (25.0)
Electrocardiogram QT prolonged	0	0	1 (25.0)
Hematocrit decreased	0	0	1 (25.0)
Hemoglobin decreased	0	0	1 (25.0)
Metabolism and nutrition disorders	4	2	4
Hyperglycemia	3 (50.0)	2 (66.7)	4 (100.0)
Hypoglycemia	1 (16.7)	0	0
Respiratory, thoracic, and mediastinal disorders	1	0	0
Asthma	1 (16.7)	0	0

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

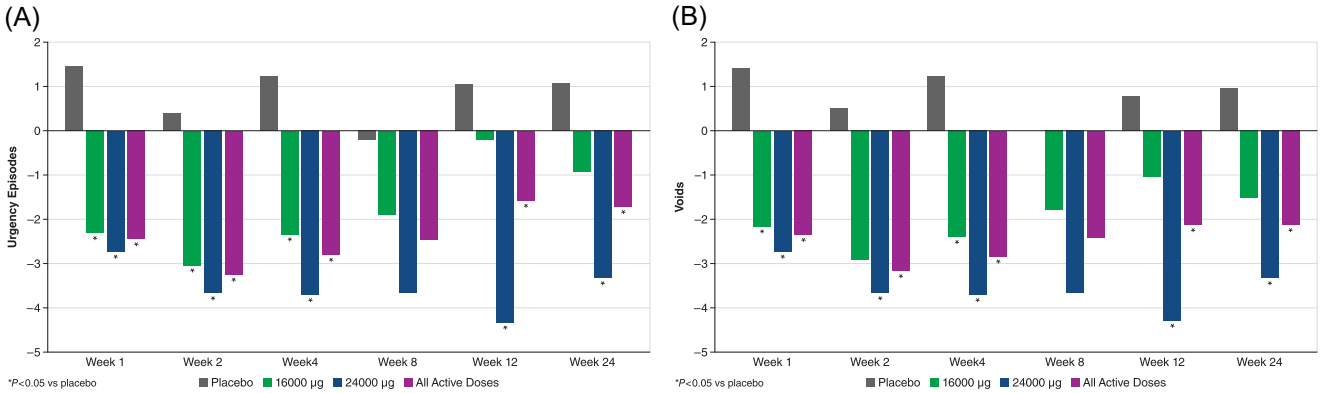

FIGURE 2 A, Change from baseline in mean number of urgency episodes/24 hours in ION-03. B, Change from baseline in mean number of voids/24 h in ION-03. Figure 2A footnote: *P* values are derived from a linear mixed model with the number of urgency episodes as dependent variables, treatments (placebo, 16 000 μg, 24 000 μg, total URO-902) time point and interaction of time and treatment. Figure 2B footnote: *P* values are derived from a linear mixed model with the number of voids as dependent variables, treatments (placebo, 16 000 μg, 24 000 μg, total URO-902) time point and interaction of time and treatment

administration. Significant improvements also were observed in the mean number of voids/24 hours compared with placebo 1 week after injection for both active doses (placebo, mean: 11.59 at 1 week, mean change from baseline: +1.41; 16 000 μg, mean: 9.10 at 1 week, mean change from baseline: −2.16, $P = .044$; 24 000 μg, mean:14.46 at 1 week, mean change from baseline: −2.73, $P = .047$) (Figure 2B). These improvements were maintained in all testing weeks except week 8. For both urgency episodes and voids, there were no significant differences between the two active treatments, possibly because of the small number of participants. However, there was a trend toward a longer duration of effect in the 24 000 μg dose group (Figure 2A,B).

Significant reductions in the number of urgency incontinence episodes compared with placebo were not observed. However, significant reductions from baseline in urgency incontinence episodes were seen at weeks 2, 4, 8, and 12 in at least one of the active treatment doses, and at week 24 both active doses had significant mean reductions from baseline (16 000 μg, −1.29, $P = .015$; 24 000 μg, −2.29, $P = .005$). In the placebo group, no significant reductions from baseline in urgency incontinence episodes were observed at any timepoint.

Participant perception of response to treatment also was improved significantly in the combined active treatment dose group versus placebo at weeks 1 ($P = .019$) and 4 ($P = .0126$) posttreatment. At week 1, roughly 44% of the participants administered URO-902 reported *a little benefit*, and another 44% reported *very much benefit*. Only 25% of the participants administered placebo at week 1 reported *a little benefit*, and none reported *very much benefit*.

QOL parameters as assessed with KHQ showed statistically significant mean improvements for the individual active treatments and for the combined active treatment groups versus baseline and versus placebo in many of the domains (including domain 2: *Impact on Life*, domain 3: *Role Limitations*, domain 4: *Physical Limitations*, domain 5: *Social Limitations*, and domain 8: *Sleep Energy*). Significant improvements in *Role Limitations* scores from baseline and significant improvements relative to placebo were observed at all of the assessed timepoints (weeks 4, 8, 12, and 24) (Table 3).

There were no significant increases in post-residual volume compared with placebo at any time point (Supplemental Table).

4 | DISCUSSION

Additional approaches to treatment of OAB are needed. The BK channel is an important regulator of detrusor muscle cell excitability, and modulation of this channel's activity using gene therapy is one such novel approach. URO-902 may represent a localized gene therapy approach to treating a benign bladder condition of OAB/urgency incontinence. Instillation of vectors designed to overexpress the BK channel significantly decreases hypercontractility of the bladder of rat models, and preclinical studies have shown that the tissue overexpression lasts for up to 6 months.[20] Modulating the expression levels of BK channels with URO-902 may possibly treat OAB/DO by reducing the excitability of the detrusor smooth-muscle. This makes *hSlo* gene transfer using URO-902 a potentially attractive gene therapy option for OAB.

In these studies, persistent exposure to URO-902 as measured by serial urine, blood, and EKG studies was minimal, supporting a local organ effect with little risk of systemic implications. Moreover, there were no

TABLE 3 ION-03 KHQ: domain 3, *role limitations*

			URO-902		
		Placebo	**16 000 μg**	**24 000 μg**	**Both active doses**
		(n = 4)	**(n = 6)**	**(n = 3)**	**(n = 9)**
Week 4	Mean change from baseline (SD)	8.33 (21.52)	−33.33 (33.33)	−38.89 (19.25)	−35.19 (28.19)
	P value change from BL	.675	.004	.015	<.001
	P value change from BL vs placebo		.030	.035	.015
Week 8	Mean change from baseline (SD)	8.33 (28.87)	−25.00 (22.97)	−38.89 (19.25)	−29.63 (21.70)
	P value change from BL	.476	.023	.014	.001
	P value change from BL vs placebo		.047	.020	.014
Week 12	Mean change from baseline (SD)	4.17 (28.46)	−27.78 (29.19)	−38.89 (19.25)	−31.48 (25.61)
	P value change from BL	.694	.012	.014	<.001
	P value change from BL vs placebo		.056	.032	.021
Week 24	Mean change from baseline (SD)	16.67 (23.57)	−16.67 (27.89)	−38.89 (9.62)	−24.07 (25.15)
	P value change from BL	.181	.118	.014	.005
	P value change from BL vs placebo		.047	.007	.007

Abbreviations: BL, baseline; KHQ, King's health questionnaire.

organ-specific safety signals, such as urinary retention. Urinary retention and the need for subsequent urinary catheterization can limit the application of other therapies, such as chemodenervation, in the treatment of OAB.

Significant reductions in the number of voids and urgency episodes were observed when URO-902 was injected directly into the detrusor (ION-03). Lesser efficacy was noted with the lower dose intravesical instillation (ION-02). This difference may be dose related or because of the relative potential difficulty in URO-902 crossing the urothelial barrier with intravesical instillation compared with direct injection. It is thought that direct injection into the bladder wall, relative to bladder instillation, will be a more definitive way to deliver the gene transfer product for optimal effect.

Overall, no significant difference between the 16 000 μg and 24 000 μg doses were observed, possibly due to the small number of participants in the 24 000 μg group. Such data argue against a dose-response effect; however, the number of treated participants was small, and importantly, there was a signal that the duration of effect may have been longer for the 24 000 μg group than for the 16 000 μg group.

The efficacy results from the diary variables were mirrored when participants were assessed using the KHQ. Multiple post dose visits throughout the study reported statistically significant improvements in many of the domains assessing QOL parameters (*Impact on Life*, *Role Limitations*, *Physical Limitations*, *Social Limitations*, and *Sleep*).

There are limitations to these phase 1 studies. Importantly, there were only a small number of participants enrolled (designed as a safety study where the efficacy parameters were secondary variables); thus, the possibility of a spurious statistical effect is possible. Also, the placebo group may have had less severe OAB/DO than the active treatment groups.

Although levels of the BK channel gene expression resulting from gene transfer of the plasmid were not determined, data from this and other studies suggest that enough gene is expressed to modulate smooth-muscle tone and that it lasts for up to 6 months.[21-25] Gap junctions (connexin 43) connecting urinary bladder smooth-muscle cells create a syncytium throughout the detrusor that allows for the rapid passage of ions and second messenger signals along the entire structure, and thus could enable functional effects even with relatively small changes in BK expression levels. As such, even limited uptake of URO-902 into a fraction of bladder cells might be expected to have a robust effect on overall bladder function.

5 | CONCLUSION

The safety and efficacy demonstrated in these two phase 1 studies suggest that modulation of BK channel expression levels using gene transfer may be a promising therapy and warrants further investigation. Overall, possible advantages of intravesical gene therapy include a minimally invasive, organ-specific direct injection approach with little risk of untoward collateral effects elsewhere in the body, as well as the potential for a long duration of activity. Since OAB/DO affects both sexes, future studies with URO-902 should include men as well. Additionally, the present study was limited to patients nonresponsive to or unable to tolerate prior oral OAB therapy. Its effects in newly diagnosed patients will require further elucidation.

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DISCLOSURES

Rovner reports relationships with Ion Channel Innovations, LLC, during the conduct of the study and with Urovant Sciences in the form of consulting honoraria. Chai reports a relationship with Ion Channel Innovations, LLC, in the form of consulting honoraria. Dr. Jacobs reports grants from NIH-NIA and personal fees from Ion Channel Innovations, LLC. Christ is cofounder, director, and shareholder of Ion Channel Innovations. Andersson has nothing to disclose. Mitchel Efros has nothing to disclose. Nitti reports relationships with Allergan, Astellas, and Medtronic in the form of clinical trials. Davies has nothing to disclose. McCullough has nothing to disclose. Melman reports an NIH grant for Ion Channel Innovations, LLC, and consultant relationship with Urovant Sciences; he was cofounder of Ion Channel Innovations, LLC.

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REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21(2):167-178.
2. Andersson KE. Mechanisms of disease: central nervous system involvement in overactive bladder syndrome. *NatClinPract Urol*. 2004;1(2):103-108.
3. Hashim H, Abrams P. Pharmacological management of women with mixed urinary incontinence. *Drugs*. 2006;66(5):591-606.
4. Subak LL, Brown JS, Kraus SR, et al. The "costs" of urinary incontinence for women. *Obstet Gynecol*. 2006;107(4):908-916.
5. Stewart W, Van Rooyen J, Cundiff G, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20(6):327-336.
6. Reynolds WS, Fowke J, Dmochowski R. The burden of overactive bladder on US public health. *Curr Bladder Dysfunct Rep*. 2016;11(1):8-13.
7. Digesu GA, Khullar V, Cardozo L, Salvatore S. Overactive bladder symptoms: do we need urodynamics? *Neurourol Urodyn*. 2003;22(2):105-108.
8. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019. *J Urol*. 2019;202:558-563. 101097JU0000000000000309.
9. Maman K, Aballea S, Nazir J, et al. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. *Eur Urol*. 2014;65(4):755-765.
10. Warren K, Burden H, Abrams P. Mirabegron in overactive bladder patients: efficacy review and update on drug safety. *Ther Adv Drug Saf*. 2016;7(5):204-216.
11. Yamada S, Ito Y, Nishijima S, Kadekawa K, Sugaya K. Basic and clinical aspects of antimuscarinic agents used to treat overactive bladder. *Pharmacol Ther*. 2018;189:130-148.
12. Coupland CA, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia: anested case-control study [published online ahead of print June 24. *JAMA Intern Med*. 2019;179:1084. https://doi.org/10.1001/jamainternmed.2019.0677
13. Chancellor M, Migliaccio-Walle K, Bramley TJ, Chaudhari SL, Corbell C, Globe D. Long-term patterns of use and treatment failure with anticholinergic agents for overactive bladder. *Clin Ther*. 2013;35(11):1744-1751.
14. Yeowell G, Smith P, Nazir J, Hakimi Z, Siddiqui E, Fatoye F. Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB): a systematic literature review. *BMJ Open*. 2018;8(11):e021889.
15. Moga MA, Dimienescu OG, Balan A, Scarneciu I, Barabas B, Ples L. Therapeutic approaches of botulinum toxin in gynecology. *Toxins*. 2018;10(4):169.
16. Petkov GV. Central role of the BK channel in urinary bladder smooth muscle physiology and pathophysiology. *Am J Physiol*. 2014;307(6):R571-R584.
17. Latorre R, Castillo K, Carrasquel-Ursulaez W, et al. Molecular determinants of BK channel functional diversity and functioning. *Physiol Rev*. 2017;97(1):39-87.
18. Hristov KL, Parajuli SP, Soder RP, Cheng Q, Rovner ES, Petkov GV. Suppression of human detrusor smooth muscle excitability and contractility via pharmacological activation of large conductance Ca2+-activated K+ channels. *Am J Physiol Cell Physiol*. 2012;302(11):C1632-C1641.
19. Christ GJ, Andersson KE, Williams K, et al. Smooth-muscle-specific gene transfer with the human maxi-k channel improves erectile function and enhances sexual behavior in atherosclerotic cynomolgus monkeys. *Eur Urol*. 2009;56(6):1055-1066.
20. Christ GJ, Day NS, Santizo C, et al. Bladder instillation of "naked" hSlo/pcDNA3 ameliorates detrusor hyperactivity in obstructed rats in vivo. *Urology*. 2001;57(6 Suppl 1):111.
21. Melman A, Bar-Chama N, McCullough A, Davies K, Christ G. Plasmid-based gene transfer for treatment of erectile dysfunction and overactive bladder: results of a phase I trial. *Isr Med Assoc J*. 2007;9(3):143-146.
22. Melman A, Bar-Chama N, McCullough A, Davies K, Christ G. hMaxi-K gene transfer in males with erectile dysfunction: results of the first human trial. *Hum Gene Ther*. 2006;17(12):1165-1176.
23. Christ GJ, Rehman J, Day N, et al. Intracorporal injection of hSlo cDNA in rats produces physiologically relevant alterations in penile function. *Am J Physiol*. 1998;275(2):H600-H608.
24. Melman A, Zhao W, Davies KP, Bakal R, Christ GJ. The successful long-term treatment of age related erectile dysfunction with hSlo cDNA in rats in vivo. *J Urol*. 2003;170(1):285-290.
25. Melman A, Zhao W, Davies KP, Bakal R, Christ GJ. The successful long-term treatment of age related erectile dysfunction with hSlo cDNA in rats in vivo. *J Urol*. 2003;170(1):285-290.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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