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Efficacy and Safety of a Novel Gene Therapy (URO-902; pVAX/*hSlo*) in Female Patients With Overactive Bladder and Urge Urinary Incontinence: Results From a Phase 2a Trial

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Background

- URO-902 is an investigational gene therapy for overactive bladder (OAB)
  - URO-902 is a plasmid vector that expresses the α subunit of the human BK channel, a large-conductance Ca^{2+}-activated K^+ channel
  - The plasmid vector is injected directly into the detrusor under local anesthesia to increase the number of large K^+ channels and thereby reduce bladder hypercontractility
- In a small completed phase 1 trial (ION-03), women with OAB treated with URO-902 experienced significant reductions in urgency episodes and daily voids with no serious adverse events (SAEs) related to URO-902[1]

Objective

- To evaluate the safety and efficacy of URO-902 for the treatment of OAB

Methods

Study Design

- This was a prespecified, 12-week interim analysis of a 48-week multicenter, randomized, double-blind, placebo-controlled, dose-escalation study (NCT04211831)
- Women aged 40–79 years with OAB and urge urinary incontinence (UUI) who were not adequately managed with oral OAB medications were randomly assigned to receive single-dose URO-902 24 mg, URO-902 48 mg, or placebo administered by intradetrusor injection via cystoscopy under local anesthesia
- Patients were randomly assigned 2:1 to receive URO-902 (24 mg [cohort 1] or 48 mg [cohort 2]) or placebo
  - Each cohort was randomized separately, and enrollment was sequential starting with cohort 1 and followed by cohort 2
- Patients completed a 3-day bladder diary within 7 days before study visits to collect information on daily number of micturitions, urgency episodes, and UUI episodes
- Patients also completed the Overactive Bladder Questionnaire (OAB-q) on day 1 before receiving treatment and at week 12 and the Patient Global Impression of Change (PGI-C) at week 12

Endpoints and Statistical Analysis

- Exploratory endpoints were change from baseline to week 12 in mean daily micturitions, urgency episodes, and UUI episodes, as well as OAB-q and PGI-C scores
- Safety was assessed by AEs and postvoid residual (PVR) urine volume
- This exploratory study had no formal primary endpoint hypothesis
  - Nominal *P* values for each dose group relative to placebo are provided for descriptive purposes

Results

Patients

- Of the 80 patients randomized, 67 completed week 12, and 74 were included in the intent-to-treat population
  - 13 patients discontinued the study (placebo, n=4; URO-902 24 mg, n=4; URO-902 48 mg, n=5)
  - No patients discontinued due to treatment-emergent AE (TEAE)
- Mean (SD) age was 64.7 (7.1) years, and 13.5% had prior treatment with onabotulinumtoxinA (**Table 1**)

Table 1. Demographics and Baseline Characteristics (ITT-E Population*)

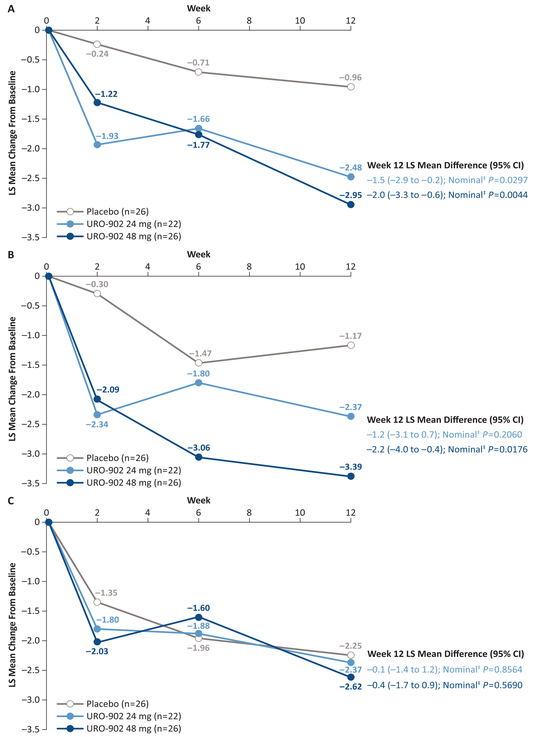
Characteristic	URO-902 24 mg (n=22)	URO-902 48 mg (n=26)	Placebo (n=26)	Overall (n=74)
Age, mean (SD) y	65.7 (7.4)	62.8 (6.8)	65.6 (7.1)	64.7 (7.1)
Age group, n (%)				
<65 y	8 (36.4)	18 (69.2)	12 (46.2)	38 (51.4)
≥65 y	14 (63.6)	8 (30.8)	14 (53.8)	36 (48.6)
UUI episodes per day, n (%)†				
≤3	4 (18.2)	6 (23.1)	7 (26.9)	17 (23.0)
>3	18 (81.8)	20 (76.9)	19 (73.1)	57 (77.0)
Use of onabotulinumtoxinA, n (%)†				
Naive	18 (81.8)	23 (88.5)	23 (88.5)	64 (86.5)
Prior use	4 (18.2)	3 (11.5)	3 (11.5)	10 (13.5)
Urodynamic detrusor overactivity, n (%)†				
Presence	11 (50.0)	19 (73.1)	13 (50.0)	43 (58.1)
Absence	11 (50.0)	7 (26.9)	13 (50.0)	31 (41.9)

ITT-E, intent-to-treat exposed; UUI, urinary urge incontinence.
*ITT-E population, defined as all patients who were randomized and treated. †As stratified.

Efficacy

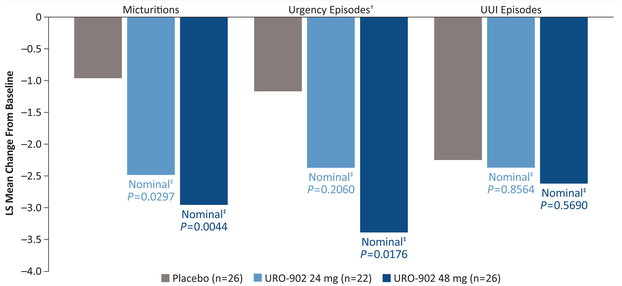
- At week 12, treatment with URO-902 24 and 48 mg was associated with clinically relevant improvement vs placebo in mean daily number of micturitions (least squares [LS] mean change from baseline, –2.5 and –3.0 vs –1.0, respectively), urgency episodes (LS mean change from baseline, –2.4 and –3.4 vs –1.2), and UUI episodes (LS mean change from baseline, –2.4 and –2.6 vs –2.3) (**Figures 1** and **2**)

Figure 1. Change From Baseline in Mean Daily Number of (A) Micturitions, (B) Urgency Episodes,* and (C) UUI Episodes (ITT-E Population†)



ITT-E, intent-to-treat exposed; LS, least squares; UUI, urge urinary incontinence.
*An urgency episode was defined as the "need to urinate immediately" as indicated in the bladder diary. †Defined as all patients who were randomized and treated. ‡This exploratory study has no formal primary endpoint hypothesis; thus, *P* values are considered nominal.

Figure 2. Change From Baseline at Week 12 in Average Daily Number of Micturitions, Urgency Episodes, and UUI Episodes (ITT-E Population*)



ITT-E, intent-to-treat exposed; LS, least squares; UUI, urge urinary incontinence.
*Defined as all patients who were randomized and treated. †An urgency episode was defined as the "need to urinate immediately" as indicated in the bladder diary. ‡This exploratory study has no formal primary endpoint hypothesis; thus, *P* values are considered nominal.

- At week 12, patients receiving URO-902 24 and 48 mg experienced greater improvement in the OAB-q symptom bother score vs placebo (LS mean change from baseline, –24.1 and –25.3 vs –11.2, respectively; **Table 2**)
- At week 12, a greater proportion of patients receiving URO-902 24 and 48 mg were considered responders on the PGI-C vs placebo (40.9% and 57.7% vs 30.8%, respectively; **Table 2**)

Table 2. Change From Baseline at Week 12 in QoL Endpoints (ITT-E Population*)

Outcome	URO-902 24 mg (n=22)	URO-902 48 mg (n=26)	Placebo (n=26)
OAB-q symptom bother score†			
Mean (SD) baseline	67.6 (20.9)	72.4 (16.6)	67.5 (22.9)
Mean (SD) week 12	42.7 (21.5)	42.4 (22.8)	58.0 (21.0)
LS mean (95% CI) change from baseline	−24.1 (−34.5 to −13.7)	−25.3 (−35.3 to −15.2)	−11.2 (−21.6 to −0.8)
LS mean difference (95% CI) vs placebo	−12.9 (−25.4 to −0.4)	−14.1 (−26.3 to −1.9)	–
Nominal *P* value vs placebo‡	0.0431	0.0246	–
PGI-C responders§			
Week 12 responders, n (%)	9 (40.9)	15 (57.7)	8 (30.8)
CMH difference (95% CI) vs placebo	11.2 (−15.4 to 37.9)	28.1 (3.4 to 52.8)	–
Nominal *P* value vs placebo‡	0.4093	0.0256	–

CMH, Cochran-Mantel-Haenszel; ITT-E, intent-to-treat exposed; OAB-q, overactive bladder questionnaire; PGI-C, Patient Global Impression of Change; QoL, quality of life.
*Defined as all patients who were randomized and treated. †Scored from 1–100. Decreases in score indicate improvement. ‡This exploratory study has no formal primary endpoint hypothesis; thus, *P* values are considered nominal. §Defined as a patient who answered "much better" or "moderately better" on the PGI-C. A patient with a missing PGI-C response was considered a nonresponder.

Safety

- 45.5% of patients receiving URO-902 24 mg, 46.2% receiving URO-902 48 mg, and 50.0% receiving placebo experienced ≥1 TEAE (**Table 3**)
- The most commonly occurring AE was urinary tract infection, occurring in 0%, 15.4%, and 3.8% of patients receiving URO-902 24 mg, URO-902 48 mg, and placebo, respectively

Table 3. Summary of Safety

Patients*, n (%)	URO-902 24 mg (n=22)	URO-902 48 mg (n=26)	Placebo (n=26)
≥1 TEAE	10 (45.5)	12 (46.2)	13 (50.0)
≥1 treatment-related TEAE	2 (9.1)	2 (7.7)	1 (3.8)
≥1 serious TEAE†	1 (4.5)	2 (7.7)	1 (3.8)
≥1 TEAE leading to study discontinuation	0	0	0
TEAEs occurring in ≥5% of patients in any treatment arm			
Urinary tract infection	0	4 (15.4)	1 (3.8)
Arthralgia	0	2 (7.7)	1 (3.8)
Bacteriuria	0	2 (7.7)	0
Hematuria	1 (4.5)	1 (3.8)	2 (7.7)
COVID-19 pneumonia	2 (9.1)	0	0
Hypertension	1 (4.5)	0	2 (7.7)
≥1 TEAE of special interest			
Urinary tract infection	0	4 (15.4)	1 (3.8)
Urinary retention	0	1 (3.8)‡	0

AE, adverse event; PVR, postvoid residual; TEAE, treatment-emergent AE.
*Patients may be counted in more than 1 category. †No serious AE resulted in death. ‡1 patient had asymptomatic elevated PVR urine volume (≥350 mL) at week 2 that resolved spontaneously by week 6 and did not require catheterization.

Conclusions

- In this prespecified 12-week analysis of a phase 2a trial of women with OAB and UUI, a single dose of URO-902 24 or 48 mg was associated with clinically relevant improvement in efficacy and quality-of-life endpoints
- URO-902 was also shown to be safe and well tolerated
  - Only 1 patient (48-mg arm) experienced an AE related to urinary retention; this AE resolved within 4 weeks and did not require catheterization
  - There were no reported TEAEs that led to discontinuation or SAEs that were related to URO-902
- Long-term follow-up (48 weeks postinjection) is ongoing

References **1**. Rovner E, et al. *Neurourol Urodyn*. 2020;39(2):744-753.

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