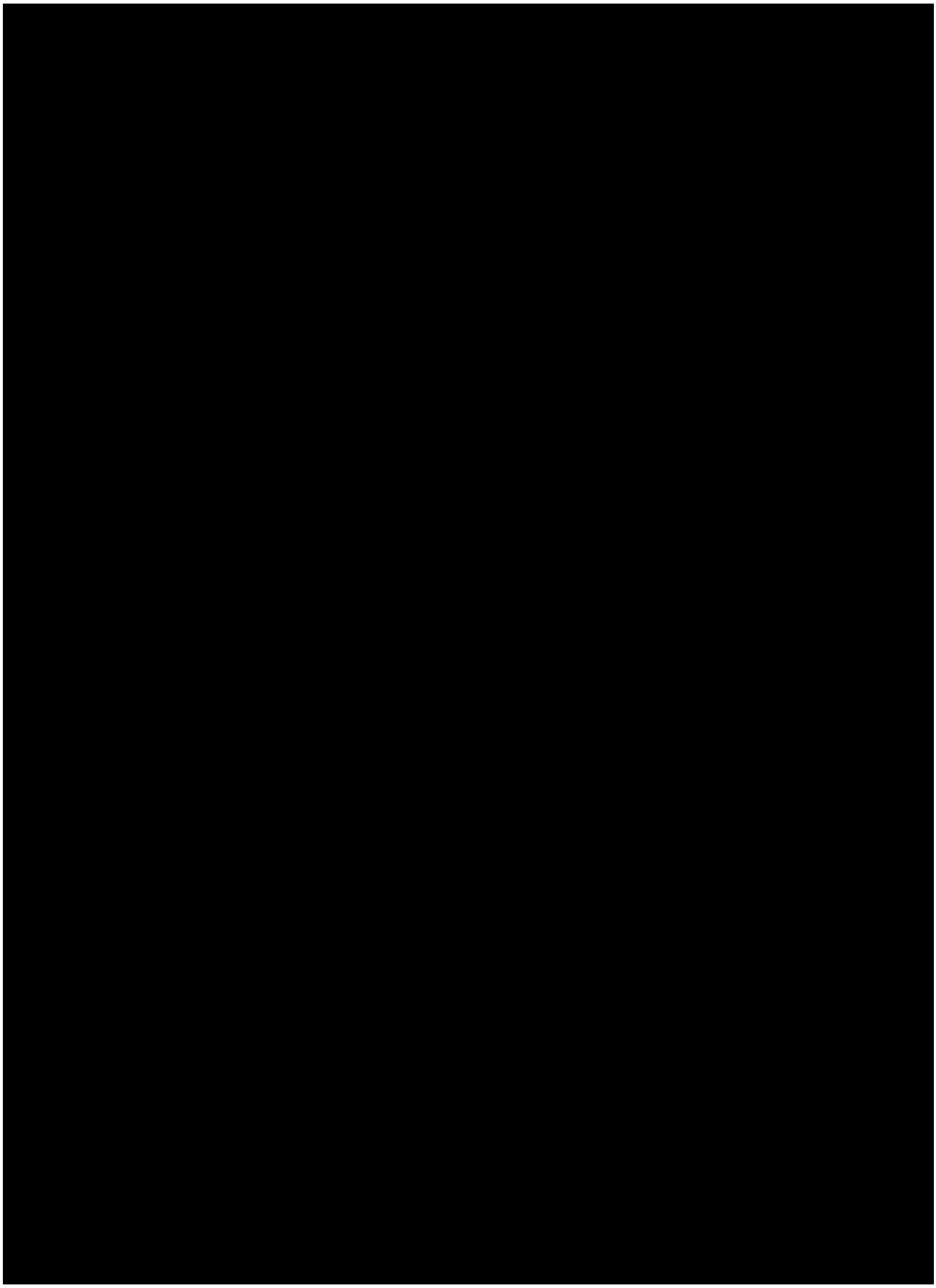
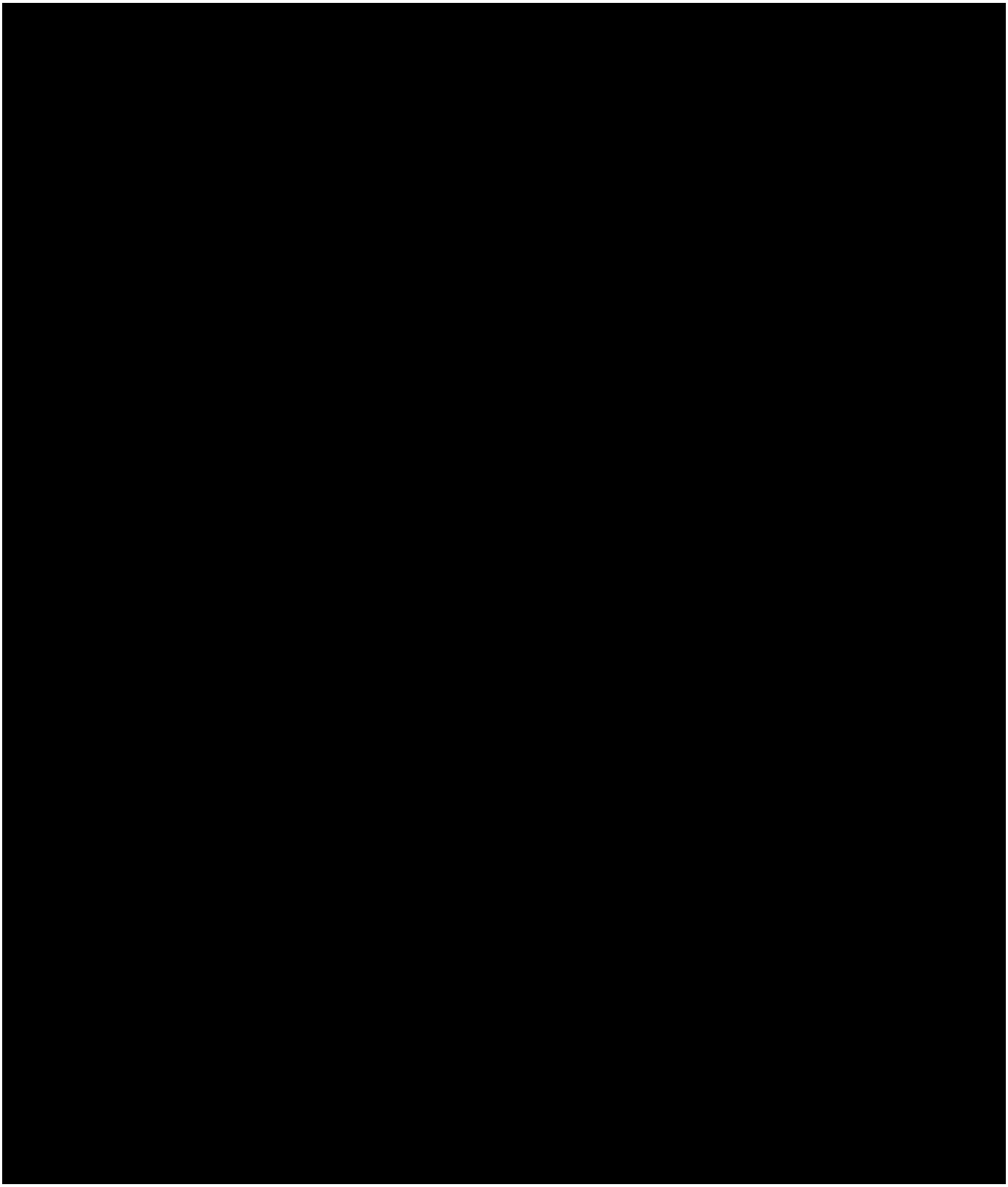
CLINICAL PROTOCOL

Protocol Title: An Exploratory Phase 2a Study Evaluating the Efficacy and Safety of URO-902 in Subjects with Overactive Bladder and Urge Urinary Incontinence

Protocol Number:	URO-902-2001
Version Number:	3.0 (Amendment 2.0) Replaces Version 2.0, dated 21 February 2020
Product Development Phase:	Phase 2a
Product:	URO-902, formerly known as *h*Maxi-K, pVAX/*hSlo*
Sponsor:	Urovant Sciences GmbH Viaduktstrasse 8 4051 Basel, Switzerland Telephone +41 (42) 2155999 **United States Contact:** [redacted] Senior Director, Clinical Development 5281 California Avenue, Suite 100 Irvine, CA 92617 USA Telephone: [redacted] Ext [redacted] Email: [redacted]
IND Number:	013208
EudraCT Number:	Not applicable
Emergency Contact Telephone Number:	**Refer to Study Contacts Page**
Contact for Serious Adverse Events (SAEs):	Email: PHV_Urovant@iqvia.com Phone: 1-866-599-1341/Fax: 1-866-599-1342
Approval Date:	19 February 2021
Sponsor Signatory:	[redacted] Chief Medical Officer





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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Exploratory Phase 2a Study Evaluating the Efficacy and Safety of URO-902 in Subjects with Overactive Bladder and Urge Urinary Incontinence

Protocol Number: URO-902-2001

Brief Title: URO-902 in Female Subjects with Overactive Bladder and Urge Urinary Incontinence

Study Rationale: There is a significant unmet need for treatment of overactive bladder (OAB) with agents with novel mechanisms of action and a well-tolerated safety profile, in particular, for patients who have been inadequately managed by pharmacologic therapy. URO-902 (pVAX/*hSlo*) is a GMP manufactured double-stranded deoxyribonucleic acid (DNA) plasmid (pVAX vector) containing a cDNA insert encoding the pore-forming α subunit of the human smooth muscle Maxi-K channel, *hSlo*. The Maxi-K channel is a prominent and well-studied potassium (K) channel subtype involved in smooth muscle relaxation. Because heightened smooth muscle tone may be a causative factor of OAB with detrusor overactivity (DO), increased numbers of Maxi-K channels in bladder smooth muscle cells associated with effective URO-902 treatment may improve this condition. Based on the well tolerated favorable safety profile demonstrated in the completed studies in subjects with OAB and erectile dysfunction (ED) and the preliminary signals of efficacy in the treatment of OAB observed in Study ION-03, the current exploratory study is designed to evaluate the efficacy and safety of a single treatment of URO-902 administered via intradetrusor injection in female subjects with OAB and urge urinary incontinence (UUI).

Objectives and Endpoints:

The study objectives are as follows:

- To evaluate the efficacy of a single dose of URO-902 24 mg and 48 mg (administered via intradetrusor injection), compared with placebo, in subjects with OAB and UUI up to 48 weeks post-dose

- To evaluate the safety and tolerability of a single dose of URO-902 24 mg and 48 mg (administered via intradetrusor injection), compared with placebo, in subjects with OAB and UUI up to 48 weeks post-dose

This exploratory study has no formal statistical primary endpoint hypothesis. Study endpoints are as follows:

Exploratory Efficacy Endpoints

- Change from baseline at Week 12 in average daily number of UUI episodes
- Change from baseline at Week 12 in average daily number of micturitions
- Change from baseline at Week 12 in average daily number of urinary incontinence (UI) episodes
- Change from baseline at Week 12 in the average daily number of urgency episodes
- Proportion of subjects achieving ≥ 50%, ≥ 75%, and 100% reduction from baseline at Week 12 in UUI episodes per day
- Change from baseline at Week 12 in average volume voided per micturition
- Health outcomes parameters:
    - Change from baseline at Week 12 in total summary score from the urinary Incontinence-Specific Quality-of-Life Instrument (I-QOL)
    - Change from baseline at Week 12 in OAB Questionnaire (OAB-q) scores
    - Overall change of bladder symptoms based on the Patient Global Impression of Change (PGI-C) scale score at Week 12
- Urodynamic parameters (read by an independent central reviewer):
    - Cystometric volume at 1st sensation to void (FSV)
    - Maximum cystometric capacity (MCC)
    - Maximum detrusor pressure during the storage phase (corrected $Pdet_{MaxStorage}$)
    - Presence/absence of the first involuntary detrusor contraction (IDC) and, if present:
        - Volume at first IDC (Vol@1stIDC)
        - Maximum detrusor pressure during the first IDC (corrected P_{det}@1stIDC)

Safety Endpoints

Safety endpoints include adverse events, serious adverse events, physical examination, vital signs (pulse rate, blood pressure, respiration rate, and body temperature), hematology and clinical chemistry, post-void residual (PVR) urine volume, electrocardiograms (ECGs), concomitant medications and concurrent procedures.

Other Endpoints

Other endpoints include *hSlo* cDNA concentrations (blood and urine)

Overall Study Design:

Structure: Multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2-cohort, dose-escalation

Study Treatment Groups: URO-902 (24 mg or 48 mg) administered as intradetrusor injections via cystoscopy. See Section 6.3 for details on treatment administration. A single treatment of URO-902 24 mg will be administered to subjects in Cohort 1. An independent Data and Safety Monitoring Board (DSMB) will make recommendations regarding dose escalation only after unblinded review of safety data from all subjects in Cohort 1 up to Week 6 (including subjects who prematurely exited the study prior to Week 6). Randomization into Cohort 2 will begin only after the DSMB has recommended it is safe to proceed.

- Cohort 1: URO-902 24 mg
- Cohort 2: URO-902 48 mg

Controls: Matching placebo (phosphate buffered saline with 20% sucrose [PBS-20%]) in Cohort 1 and Cohort 2 (see Section 1.2).

Dosage/Dose Regimen: For each subject in Cohort 1 or Cohort 2, a single treatment will be administered on Day 1 after fulfillment of the "day of treatment criteria" (see Section 6.2).

Randomization/Stratification: An estimated total of 78 subjects will receive treatment across 2 cohorts (Section 1.2), with approximately 39 subjects randomized into each cohort. In both cohorts, subjects will be randomized in a 2:1 ratio to receive either URO-902 (24 mg or 48 mg) or placebo. Each cohort will be randomized separately, and enrollment will be sequential, starting with Cohort 1 (URO-902 24 mg [n = 26] and placebo [n = 13]) and followed by Cohort 2 (URO-902 48 mg [n = 26] and placebo [n = 13]). At the Randomization Visit (Visit 2), subjects in both Cohort 1 and Cohort 2 will be randomized centrally to receive either a single treatment of URO-902 or matching placebo. In Cohort 1a, randomization will be stratified by baseline UUI episodes per day (ie, ≤ 3 vs. > 3 UUI episodes per day) and the presence or absence of DO (as determined by the investigator). In Cohort 1b and Cohort 2, randomization will be stratified by baseline UUI episodes per day and previous use of onabotulinumtoxinA (naïve vs. prior use). Enrollment for subjects with previous onabotulinumtoxinA use will be capped at 50% of the total subject population per cohort.

Visit Schedule: Study visits will be identical for Cohorts 1 and 2. A 5-week screening and randomization period (Days -35 to -1) will include screening subjects for eligibility (Visit 1) and randomization of eligible subjects (Visit 2). Subjects will be administered the study treatment via cystoscopy on Day 1 (Visit 3). All subjects will be evaluated at scheduled post-treatment visits at

Weeks 2, 6, 12, 18, and 24 (Visits 4 to 8, respectively), or until the subject exits the study. Afterwards, for subjects who complete the Week 24 Visit (Visit 8), 2 follow-up telephone (or other virtual technology) visits will be performed at Week 36 (Visit 9) and Week 48 (Visit 10).

Additional OAB treatment: Starting at Week 24 (Visit 8), subjects can request and receive additional OAB treatment(s) at the clinical discretion of the investigator. Subjects who receive additional OAB treatment(s) at Week 24 or after will only be followed to assess adverse events at any future telephone (or other virtual technology) visits (Week 36 and/or Week 48). No efficacy assessments will be performed once a subject receives additional OAB treatment (see Section 6.9.2).

Safety and efficacy assessments and study procedures are outlined in the study schema (Section 1.2) and the Schedule of Assessments (Section 1.3).

Diagnosis and Criteria for Inclusion and Exclusion:

Condition/Disease: OAB with UUI

Listed below are key inclusion and exclusion criteria for the study. See Section 5 for the complete list of inclusion and exclusion criteria.

Key Inclusion Criteria:

- Subject is female, aged 40 to 79 years old, at the Screening Visit (Visit 1).
- Subject has symptoms of OAB (frequency and urgency) with UUI for a period of at least 6 months prior to the Screening Visit (Visit 1), determined by documented subject history.
- Subject experiences an average of ≥ 1 episode of UUI per day (ie, a total of ≥ 3 UUI episodes over the 3-day subject Bladder Diary completed during the screening and randomization period).
- Subject experiences urinary frequency, defined as an average of ≥ 8 micturitions (toilet voids) per day (ie, a total of ≥ 24 micturitions over the 3-day subject Bladder Diary completed during the screening and randomization period).
- Subject has not been adequately managed with ≥ 1 oral or transdermal pharmacologic therapies for the treatment of their OAB symptoms (eg, anticholinergics, beta-3 agonist, etc), in the opinion of the investigator. Not adequately managed is defined as meeting one of the following:
    - an inadequate response after at least a 4-week period of pharmacologic therapy on a Food and Drug Administration (FDA)-approved dose(s) (ie, subject was still incontinent despite pharmacologic therapy), or

  - limiting side effects after at least a 2-week period of pharmacologic therapy on an FDA-approved dose(s)

- Subject is of non-childbearing potential. See Section 10.6 for criteria to be satisfied.

Key Exclusion Criteria:

- Subject has symptoms of OAB due to any known neurological reason (eg, spinal cord injury, multiple sclerosis, cerebrovascular accident, Alzheimer's disease, Parkinson's disease, etc).

- Subject has a predominance of stress incontinence in the opinion of the investigator, determined by subject history.

- Subject currently uses or plans to use medications or therapies to treat symptoms of OAB, including nocturia. Subjects previously receiving these medications must have discontinued their use to achieve sufficient washout prior to beginning recording of symptoms into the Screening Bladder Diary as follows:

  - for desmopressin, at least one day prior

  - for anticholinergic therapy, at least 14 days prior

  - for intravesical anticholinergic therapy, at least 4 weeks prior

  - for β_3 agonists, at least 14 days prior

- Subjects who have previously been treated with:

  - onabotulinumtoxinA for urological indications within 12 months of starting the Screening Bladder Diary (subjects treated with onabotulinumtoxinA or other toxins for non-urological indications are eligible, regardless of when treated).

  - any other toxin for urological indications, regardless of when treated

- Subject currently uses clean intermittent catheterization (CIC) or indwelling catheter to manage their urinary incontinence.

- Subject has a PVR urine volume of > 100 mL at any time during Screening (before randomization). The PVR measurement can be repeated once on the same day; the subject is to be excluded if the repeated measure is above 100 mL.

- Subject has had urinary retention or an elevated PVR urine volume that has been treated with an intervention (such as catheterization), within 6 months of the Screening Visit (Visit 1). Note: transient voiding difficulties as a result of surgical procedures that resolved within 24 hours are not exclusionary.

- Subject has a history of 3 or more urinary tract infections (UTIs) within 6 months of the Screening Visit (Visit 1) or is taking prophylactic antibiotics to prevent chronic UTIs. Subjects with a current acute UTI during screening can be treated appropriately and are eligible.

- Subject has current or previous uninvestigated hematuria. Subjects with investigated hematuria may enter the study if urological/renal pathology has been ruled out to the satisfaction of the investigator.

Number of Subjects: Approximately 78 adult female subjects will be randomized into the 2 cohorts, with approximately 39 subjects randomized into each cohort.

Approximate Number of Sites: Up to 25 sites in North America

Study Drug Groups and Study Duration:
Refer to section on Overall Study Design above for treatment group information.

Duration: Up to 53 weeks (5-week screening and randomization period, treatment administration on Day 1, and 48-week double-blind post-treatment/follow-up period)

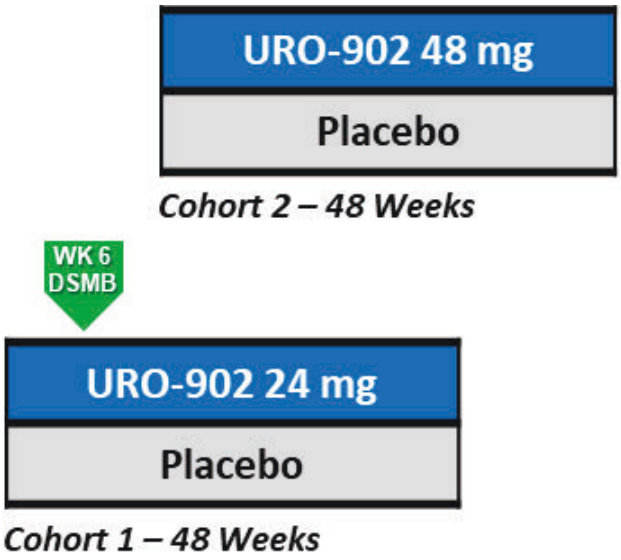
Statistical Methods:
The following analysis populations will be evaluated: safety, safety (modified), and intent-to-treat exposed (ITT-E). The safety population will consist of all subjects who received the study drug and will be used to assess treatment-emergent adverse events and other safety evaluations based on actual treatment received. A separate safety population, safety (modified), will be created to assess safety excluding subjects who received additional OAB medication at Week 24 or after. ITT-E will be used for demographics, baseline characteristics, and efficacy analyses. The ITT-E population will consist of all subjects randomized and treated from Cohorts 1 and 2.

Interim analyses may be conducted when ≥ 50% of subjects in Cohort 1 and/or when ≥ 50% of subjects in Cohort 2 have completed at least 12 weeks of follow-up post-randomization (or prematurely exited the study prior to Week 12) for future planning purposes. A planned interim analysis will be performed to evaluate the objectives of the protocol at Week 12, after all subjects in Cohorts 1 and 2 have completed the Week 12 Visit/Visit 6 (or prematurely exited the study prior to Week 12). The final analysis will be performed after all subjects have completed the study or exit the study prematurely. Details of the interim analyses and final analysis will be described in the Statistical Analysis Plan.
The study has no formal statistical primary endpoint hypothesis. Descriptive statistics will be used to evaluate the efficacy and safety endpoints. For continuous efficacy endpoints, estimates of least squares means, standard error, and 95% confidence intervals (CI) will be presented for each treatment group. Nominal p-values from comparisons to placebo may be provided for descriptive purposes.
The point estimate of the treatment difference and 95% confidence interval for the change from baseline at each visit for each continuous efficacy variable relative to placebo will be analyzed using a mixed-effect model for repeated measures (MMRM) method. The analysis model will include terms for baseline value as a covariate, in addition to the terms for treatment, visit, and treatment by visit interaction. For the urodynamic variables evaluated, only the independent central reviewer's interpretation will be analyzed.

The proportion of subjects who achieve ≥ 50% reduction from baseline UUI episodes at Week 12 will be calculated for each treatment group. In addition, responder analyses will also be calculated for subjects who achieve ≥ 75% and 100% decrease in episodes of UUI at Week 12 relative to baseline. The Cochran-Mantel-Haenszel (CMH) method will be utilized to compare the proportion of responders between the active and placebo groups by adjusting for the stratification factors. Data for all visits will also be presented.
For safety variables, data from all subjects in the 2 cohorts who received study drug will be included. The incidence of adverse events will be summarized. The change from baseline in PVR urine volume will be analyzed.
Sample Size Estimation: For this exploratory study, the sample size was empirically chosen. Please see Section 9.2 for details.

Data and Safety Monitoring Board (DSMB): A DSMB will be retained to assess, on an ongoing basis, all safety aspects of this study including unblinded review of safety data after all subjects reach Week 6 (or prematurely exited the study prior to Week 6) in Cohort 1 (URO-902 24 mg). Randomization into Cohort 2 will begin only after the DSMB has recommended it is safe to proceed to Cohort 2. This committee will be an external independent DSMB that monitors safety. The detailed activities including meeting plans will be described and documented in a separate DSMB Charter. A separate statistical analysis plan may also be prepared for the DSMB.

1.2. Schematic of Study Design: 2-Cohort, Dose-Escalation



Note:

1) Dose escalation to Cohort 2 is based on unblinded review of safety data by the Data and Safety Monitoring Board (DSMB) after all subjects reach Week 6 (or prematurely exited the study prior to Week 6) in Cohort 1. Randomization into Cohort 2 will begin only after the DSMB has recommended it is safe to proceed.
2) Starting at Week 24, subjects can request and receive additional overactive bladder (OAB) treatment(s) at the clinical discretion of the investigator. Subjects who receive additional OAB treatment(s) at Week 24 or after will only be followed to assess adverse events at any future telephone (or other virtual technology) visits (Week 36 and/or Week 48). No efficacy assessments will be performed once a subject receives additional OAB treatment (see Section 6.9.2).

1.3. Schedule of Assessments

Study Period	**Screening Visit Visit 1**	**Randomization Visit Visit 2**	**Day 1 (Treatment Administration Visit) Visit 3**	**Week 2 (Follow-Up Clinic Visit) Visit 4**	**Week 6 (Follow-Up Clinic Visit) Visit 5**	**Week 12 (Follow-Up Clinic Visit) Visit 6**	**Week 18 (Follow-Up Phone Visit[b]) Visit 7**	**Week 24 (Exit or EW Clinic Visit) Visit 8**	**Week 36 (Follow-Up Phone Visit)[b] Visit 9**	**Week 48 (Follow-Up Phone Visit)[b] Visit 10**
Protocol-defined Visit Windows	**-35 to -1 Days[a]**			**± 3 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
COVID-19 Mitigation Visit Windows*				**+ 10 Days**	**+ 4 Weeks**	**+ 4 Weeks**	**N/A**	**+ 4 Weeks**	**N/A**	**N/A**
Consent/Authorization	X									
Screening entry into IWRS	X									
Inclusion/Exclusion Criteria	X	X								
Subject Randomization		X								
Day of Treatment Criteria			X[c]							
Study Treatment Administration			X							
Medical History and Demographics	X									
Prior OAB Med Review	X									
Physical Examination	X							X		
Vital Signs	X	X	X[c]	X	X	X		X		
ECG	X			X		X		X		
Urodynamics		X[d]				X				
PVR Urine	X[e]			X	X	X		X		
Bladder and Kidney Ultrasound	X							X		

Study Period	**Screening Visit Visit 1**	**Randomization Visit Visit 2**	**Day 1 (Treatment Administration) Visit 3**	**Week 2 (Follow-Up Clinic Visit) Visit 4**	**Week 6 (Follow-Up Clinic Visit) Visit 5**	**Week 12 (Follow-Up Clinic Visit) Visit 6**	**Week 18 (Follow-Up Phone Visit)[b] Visit 7**	**Week 24 (Exit or EW Clinic Visit) Visit 8**	**Week 36 (Follow-Up Phone Visit)[b] Visit 9**	**Week 48 (Follow-Up Phone Visit)[b] Visit 10**
Protocol-defined Visit Windows	**-35 to -1 Days[a]**			**± 3 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
COVID-19 Mitigation Visit Windows*				**+ 10 Days**	**+ 4 Weeks**	**+ 4 Weeks**	**N/A**	**+ 4 Weeks**	**N/A**	**N/A**
Urine Dipstick[f]	X	X	X[c]	X	X	X		X		
Urine Cytology (local lab)	X									
Hematology and Clinical Chemistry	X				X			X		
Dispense Bladder Diary	X		X	X	X	X[g]		X[h]		
Review and data enter Bladder Diary[i]		X		X	X	X	X	X	X[h]	X[h]
Pharmacokinetic Assessment (urine and blood *hSlo* cDNA)			X[c]		X			X[j]		
Prophylactic Antibiotics			X[k]							
I-QOL and OAB-q Questionnaires			X[c]		X	X				
PGI-C Questionnaire						X				
Con Meds/Procedures	X[l]	X	X	X	X	X	X	X[m]	X[m]	X
AE/SAE Review	X	X	X	X	X	X	X	X[m]	X[m]	X
Optional Immunogenicity Sample[n]										
Immunogenicity Consent	X[o]									
Sample Collection			X[c]		X			X		

AE = adverse event; Con Meds = concomitant medication(s); COVID-19 =coronavirus disease 2019; ECG = electrocardiogram; eCRF = electronic case report form; EW = early withdrawal; I-QOL = Incontinence-Specific Quality of Life Instrument; IWRS = interactive web response system; lab = laboratory; Med = medication(s); N/A = not applicable; OAB = overactive bladder; OAB-q = Overactive Bladder Questionnaire; PGI-C = Patient Global Impression of Change; PVR = Post-void residual; SAE = serious adverse event

* To accommodate any COVID-19-related events that affect a subject's scheduled visit, the COVID-19 Mitigation Visit Window may be used instead of the protocol-defined visit schedule window. However, if safe and feasible, study visits should adhere to the scheduled visit window for the study. Note that the COVID-19 Mitigation Visit Window is separate from the protocol-defined visit window and the 2 visit windows may not be combined.

a The actual number of days (duration) between the Screening Visit (Visit 1), Randomization Visit (Visit 2), and Day 1 (Visit 3) are flexible as long as the subject undergoes the required protocol-defined assessments at each respective visit and is fully evaluated for eligibility based on the clinical judgment of the investigator. The maximum Screening and Randomization period should not exceed 35 days prior to Day 1.

b Visits at Weeks 18, 36, and 48 may be conducted by phone or other virtual technology. Follow-up visits at Week 36 and Week 48 are only conducted for subjects who have completed the Week 24 Visit (Visit 8) and are not applicable for early withdrawal (EW) subjects.

c Performed prior to treatment. Additionally, for pharmacokinetic assessments only, these will also be performed approximately 2 hours ± 1 hour post-treatment on Day 1.

d Urodynamic assessments at baseline should only be conducted after confirmation of subject eligibility during Visit 2 and must be performed prior to the actual randomization procedure. An historical urodynamic study, performed no more than 90 days prior to the first day of screening, may serve as the baseline urodynamic assessment if the criteria detailed in Section 8.2.3 are satisfied. At Week 12, all subjects will undergo a second urodynamic assessment. Note that the investigator does not need to wait for the results of the baseline urodynamic assessments to rule out bladder outlet obstruction if there are no other signs or symptoms of obstruction, in the investigator's assessment, including elevated PVR volume (see Exclusion Criterion 14).

e May be performed at any time during screening (before randomization), excluding diary data collection days.

f A sample for urinalysis and urine culture/sensitivity will be sent to the laboratory only if the urine dipstick (performed at the site) results are suggestive of a urinary tract infection (ie, positive for the presence of leukocytes, nitrites, or blood cells). The urinalysis sample should be sent to the central laboratory, and the urine culture and sensitivity sample should be sent to the local laboratory.

g Since the Week 18 visit (Visit 7) is a telephone (or other virtual technology) visit, sufficient diaries should be dispensed at Week 12 (Visit 6) to record data through Week 24.

h At the Week 24 exit clinic Visit (Visit 8), a sufficient number of bladder diaries will be provided to subjects in advance for the remaining follow-up phone or other virtual technology visits; bladder diaries completed for the Week 36 (Visit 9) and Week 48 (Visit 10) follow-up visits will need to be collected by mail prior to the scheduled visit and reviewed by phone or other virtual technology with the subject. Diaries will not be collected if subjects receive additional OAB treatment(s) at Week 24 (Visit 8) or after. See Section 6.9.2 for further details.

i Bladder diary must be completed by subjects for any 3 consecutive days in the 7 days prior to the protocol-defined visit timepoint. If a visit will be delayed per the COVID-19 mitigation window, the site should contact the subject to ensure that the diary completion occurs per the protocol-defined timepoints and not within the 7 days prior to the COVID-delayed visit. For screening only, the diary can be completed for 3 consecutive days at any time during the screening and randomization period. The total volume voided must be collected for one 24-hour period during the 3-day diary collection period.

j If specimen(s) is still positive at Week 24, per the clinical discretion of the investigator, a subject may be instructed to return at Week 36 (Visit 9) and, if necessary, Week 48 (Visit 10) until the specimen(s) result is negative for *hSlo* cDNA. Pharmacokinetic assessment is to be performed at the EW Visit for subjects who withdraw early from the study.

k All subjects must receive prophylactic antibiotics prior to treatment administration on Day 1 and for 1 additional day post-treatment at a minimum.

l Prohibited medication washout of pharmacologic therapy for OAB must be complete prior to beginning recording of symptoms into the Screening Bladder Diary.

m Starting at Week 24, subjects can request and receive additional OAB treatment(s) at the clinical discretion of the investigator. Subjects who receive additional OAB treatment(s) at Week 24 or after will only be followed to assess AEs at any future telephone (or other virtual technology) visits (Week 36 and/or Week 48). No efficacy assessments will be performed once a subject receives an additional OAB treatment. Any additional OAB concomitant medication used or procedure performed as well as any AEs reported must be recorded in the appropriate eCRF form. See Section 6.9.2 for further details.

n If the subject consents and a baseline sample can be obtained prior to study treatment administration, then blood will be collected at each specified visit (applies to Cohort 2 only). Note that the sample will be stored, and antibody testing may be performed at a later date (up to 5 years from date of collection).

o Consent may be obtained at any time before the sample is collected on Day 1.

2. INTRODUCTION

Urovant Sciences GmbH (Urovant) is developing URO-902 (formerly known as *h*Maxi-K or pVAX/*hSlo*) for the treatment of overactive bladder (OAB) and urge urinary incontinence (UUI) in adults who have been inadequately managed by pharmacologic therapy.

2.1. Background

Overactive Bladder

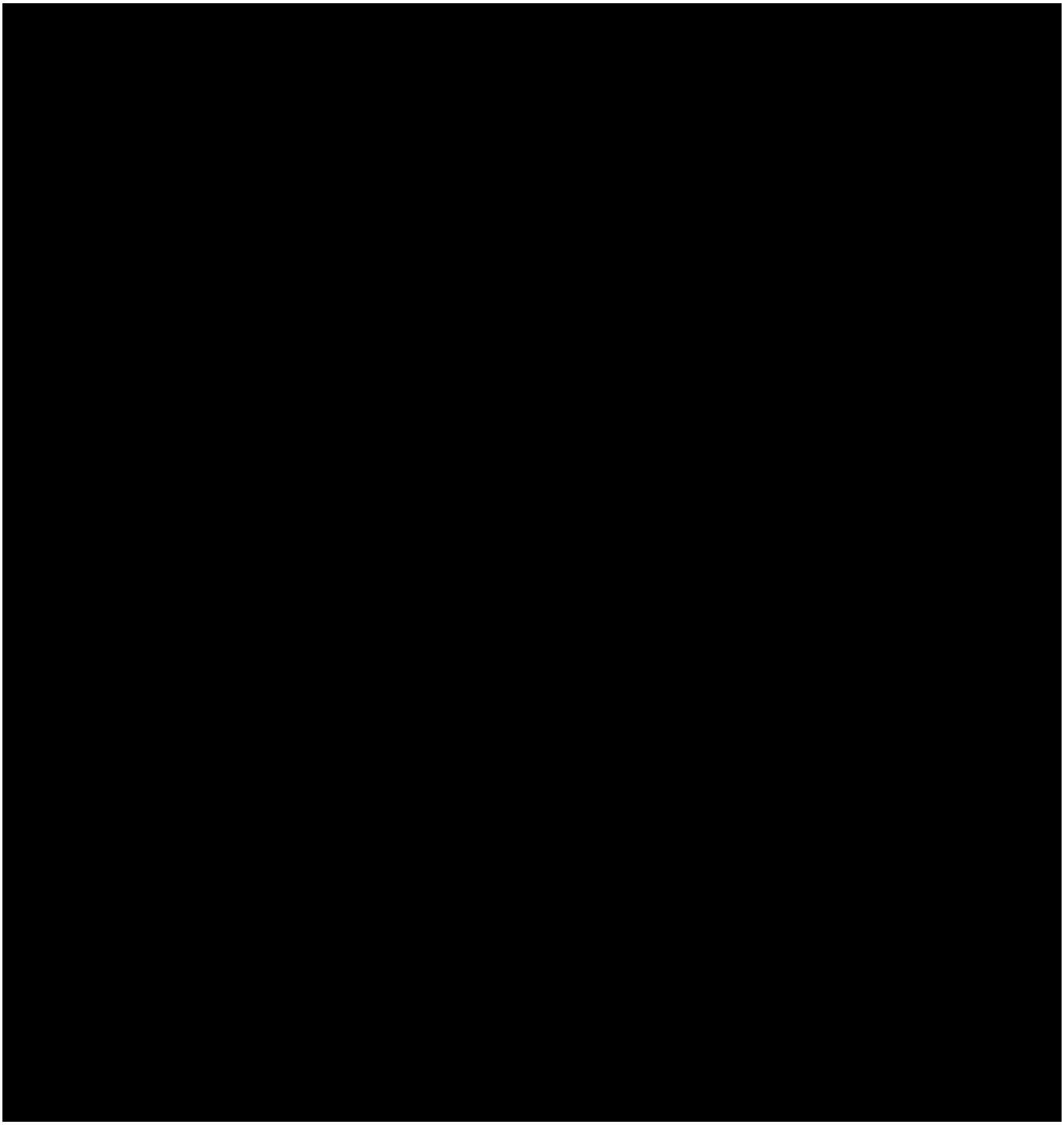
OAB is highly prevalent and affects approximately 16% of the population in the United States and Europe. Prevalence increases with age, affecting approximately a third of people 75 years and older [Stewart, 2003; Milsom, 2001]. The International Continence Society (ICS) defines OAB as urgency, with or without urge incontinence, usually associated with frequency and nocturia [Abrams, 2002]. Urgency is defined as a sudden compelling desire to void which is difficult to defer and, from the medical definition perspective, it is a necessary symptom for OAB. Urgency incontinence is the involuntary loss of urine accompanied by urgency (referred to as OAB Wet) and is present in approximately one-third of patients with OAB [Stewart, 2003; Milsom, 2001]. In the absence of incontinence, OAB is referred to as OAB Dry. OAB has been shown to negatively impact both social and medical well-being and represents a significant burden in terms of annual direct and indirect healthcare expenditures [Kelleher, 2002; Abrams, 2000; Reynolds, 2016].

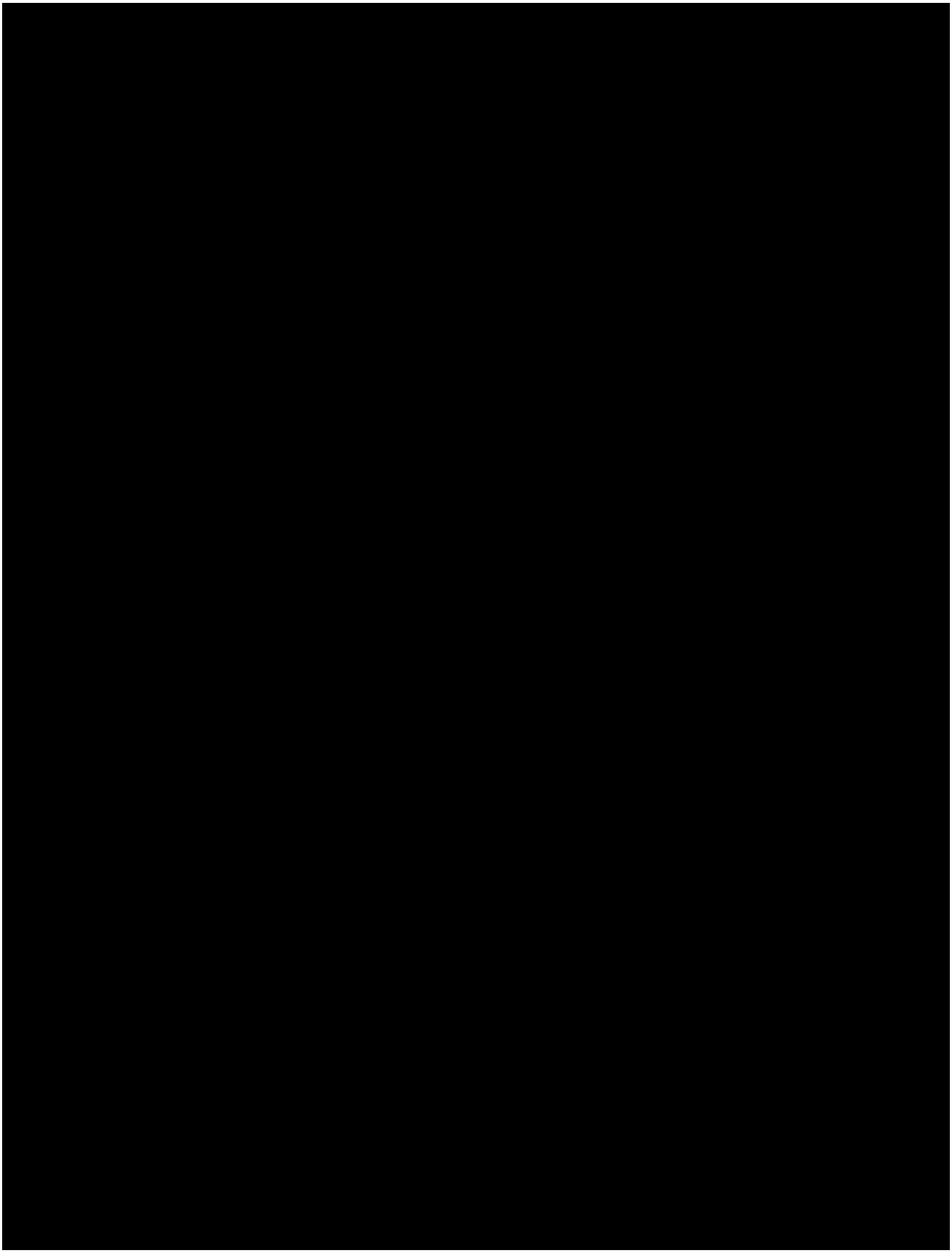
Currently, the predominant class of drugs used to treat OAB is antimuscarinics. The clinical utility of antimuscarinics is limited by their modest efficacy and poor tolerability due to mechanism-based side effects including dry mouth and constipation. In addition to poor tolerability and modest efficacy, a recent body of literature suggests that chronic use of anticholinergics is associated with cognitive impairment and dementia [Risacher, 2016; Gray, 2015]. Mirabegron (Myrbetriq®; Astellas Pharma US, Inc), a β3-agonist and smooth muscle relaxer, is currently approved in multiple countries for the treatment of OAB [Nitti, 2013]. The reported adverse effects with mirabegron were similar to antimuscarinics, but with a lower incidence of dry mouth compared with tolterodine, an antimuscarinic. However, the effects of mirabegron on the cardiovascular system, pharmacokinetic interactions with other drugs, and increased incidence of new malignant events will require careful evaluation in the near future [Sacco, 2012]. In addition, BOTOX® (onabotulinumtoxinA), a neurotoxin which inhibits muscle contraction by blocking neuromuscular transmission through decreased acetylcholine release, has been approved for the treatment of neurogenic and idiopathic OAB (since 2011and 2012, respectively). BOTOX is administered via multiple intradetrusor injections into the bladder wall about every 6 months. BOTOX has been associated with urinary tract infections (UTIs), dysuria, and urinary retention. Other side effects are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing

difficulties. These symptoms have been reported hours to weeks after injection [BOTOX Package Insert, 2018].

A major problem with currently available OAB treatments is that even when these drugs have documented efficacy, treatment is still limited by their side effects. There is a significant unmet need for the treatment of OAB with agents with novel mechanisms of action and a well-tolerated safety profile.

URO-902





[redacted]

2.2. Study Rationale

Overactive bladder is a highly prevalent disease shown to negatively impact both the social and medical well-being of patients. Many of the existing treatments are limited by their side effects. Thus, there is a significant unmet need for the treatment of OAB with agents with novel mechanisms of action and a well-tolerated safety profile, in particular, for patients who have been inadequately managed by pharmacologic therapy. URO-902 (pVAX/*hSlo*) is a GMP manufactured double-stranded DNA plasmid (pVAX vector) containing a cDNA insert encoding the pore-forming α subunit of the human smooth muscle Maxi-K channel, *hSlo*. The Maxi-K channel is a prominent and well-studied K channel subtype involved in smooth muscle relaxation. Because heightened smooth muscle tone may be a causative factor of OAB with DO, increased numbers of Maxi-K channels in the bladder smooth muscle cells associated with effective URO-902 treatment may improve this condition. Based on the favorable safety profile demonstrated in the completed clinical studies in subjects with OAB [redacted] the current exploratory study is designed to evaluate the efficacy and safety of a single treatment of URO-902 administered via intradetrusor injection in subjects with OAB and UUI.

2.3. Benefit/Risk Assessment

2.3.1. Potential Benefits

URO-902's mechanism of action has the potential to demonstrate significant therapeutic benefit in the treatment of OAB and UUI. Nonclinical studies conducted with URO-902 have demonstrated no toxicity and no off-target effects in safety pharmacology studies. URO-902 has demonstrated a favorable safety profile in completed clinical studies [redacted]

2.3.2. Potential Risks

Nonclinical studies evaluating URO-902 support the safety of the doses being evaluated in this study. Data from URO-902 nonclinical studies are summarized in the IB. See Section 4.3 for justification of dose selection.

URO-902 at doses of up to 24 mg (which is the starting dose being evaluated in the current study) administered by direct injections into the bladder wall/detrusor muscle has been evaluated in a previous clinical study ION-03. No clinical safety signals (including no urinary retention), were identified in the studies. More detailed information about the known and reasonably expected adverse events of URO-902 administered via intradetrusor injections can be found in the IB.

The risk to subjects in the current study will be minimized by compliance with the eligibility criteria, proper study design, close monitoring, and an independent Data and Safety Monitoring Board (DSMB). The study follows a dose-escalation design. The DSMB will make recommendations regarding dose escalation only after unblinded review of safety data from all subjects in Cohort 1 up to Week 6.

URO-902 is an investigational drug and should only be used as specified in the clinical study protocol. Subjects should be excluded from treatment with URO-902 in accordance with inclusion/exclusion criteria of the protocol.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

The objectives of this study are as follows:

- To evaluate the efficacy of a single dose of URO-902 24 mg and 48 mg (administered via intradetrusor injection), compared with placebo, in subjects with OAB and UUI up to 48 weeks post-dose
- To evaluate the safety and tolerability of a single dose of URO-902 24 mg and 48 mg (administered via intradetrusor injection), compared with placebo, in subjects with OAB and UUI up to 48 weeks post-dose

3.2. Endpoints

This exploratory study has no formal statistical primary endpoint hypothesis. Study endpoints are as follows:

3.2.1. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include the following:

- Change from baseline at Week 12 in average daily number of UUI episodes
- Change from baseline at Week 12 in average daily number of micturitions
- Change from baseline at Week 12 in average daily number of urinary incontinence (UI) episodes
- Change from baseline at Week 12 in average daily number of urgency episodes
- Proportion of subjects achieving ≥ 50%, ≥ 75%, and 100% reduction from baseline at Week 12 in UUI episodes per day
- Change from baseline at Week 12 in average volume voided per micturition
- Health outcomes parameters:
    - Change from baseline at Week 12 in total summary score from the urinary Incontinence-Specific Quality-of-Life Instrument (I-QOL)
    - Change from baseline at Week 12 in OAB Questionnaire (OAB-q) scores
    - Overall change of bladder symptoms based on the Patient Global Impression of Change (PGI-C) scale score at Week 12

- Urodynamic parameters (read by an independent central reviewer):
    - Cystometric volume at 1st sensation to void (FSV)
    - Maximum cystometric capacity (MCC)
    - Maximum detrusor pressure during the storage phase (corrected $Pdet_{MaxStorage}$)
    - Presence/absence of the first involuntary detrusor contraction (IDC) and, if present:
        - Volume at first IDC (Vol@1stIDC)
        - Maximum detrusor pressure during the first IDC (corrected P_{det}@1stIDC)

3.2.2. Safety Endpoints

Safety endpoints include adverse events, serious adverse events, physical examination, vital signs (pulse rate, blood pressure, respiration rate, and body temperature), hematology and clinical chemistry, post-void residual (PVR) urine volume, electrocardiograms (ECGs), concomitant medications and concurrent procedures.

3.2.3. Other Endpoints

Other endpoints include *hSlo* cDNA concentrations (blood and urine).

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2 cohort, dose-escalation study evaluating the efficacy and safety of URO-902 (24 mg or 48 mg) in the treatment of OAB and UUI in female subjects aged 40 to 79 years old. Subjects must complete all screening procedures and must meet all eligibility requirements to qualify for enrollment and randomization.

Safety and efficacy assessments and study procedures are outlined in the study schema (Section 1.2) and the Schedule of Assessments (Section 1.3).

The total duration of the study is up to 53 weeks including a 5-week screening and randomization period (Days -35 to -1); treatment on Day 1, and a 48-week double-blind post-treatment/follow-up period. Study visits will be identical for Cohorts 1 and 2. Subjects will be evaluated at the Screening Visit (Visit 1) for eligibility. Eligible subjects will be randomized to treatment within each cohort at the Randomization Visit (Visit 2); however, subjects will be administered study treatment via cystoscopy on Day 1 (Visit 3). All subjects will be evaluated at scheduled post-treatment visits at Weeks 2, 6, 12, 18 (phone/virtual), and 24 (Visits 4 to 8, respectively), or until the subject exits the study. Afterwards, for subjects who have completed the Week 24 Visit (Visit 8), 2 follow-up telephone visits (or other virtual technology visits) for assessment of safety will be performed at Week 36 (Visit 9) and Week 48 (Visit 10).

An estimated total of 78 subjects will receive treatment across 2 cohorts (Section 1.2), with approximately 39 subjects randomized into each cohort. In both cohorts, subjects will be randomized in a 2:1 ratio to receive either URO-902 (24 mg or 48 mg) or placebo. Each cohort will be randomized separately, and enrollment will be sequential, starting with Cohort 1 (URO-902 24 mg [n = 26] and placebo [n = 13]) and followed by Cohort 2 (URO-902 48 mg [n = 26] and placebo [n = 13]). Subjects in both Cohort 1 and Cohort 2 will be randomized centrally to receive either a single treatment of URO-902 or matching placebo.

In Cohort 1a, randomization will be stratified by baseline UUI episodes per day (ie, ≤ 3 vs. > 3 UUI episodes per day) and presence or absence of DO (as determined by the investigator) at Visit 2. In Cohort 1b and Cohort 2, randomization will be stratified by baseline UUI episodes per day and previous use of onabotulinumtoxinA (naïve vs. prior use). OnabotulinumtoxinA treatment for urological indications must have occurred at least 12 months prior to starting the Screening Bladder Diary. Enrollment for subjects with previous onabotulinumtoxinA use will be capped at 50% of the total subject population per cohort. See details on stratification factors in Section 6.5.

In Cohort 1, an unblinded review of safety data by the DSMB will be performed after all subjects reach Week 6 (or prematurely exited the study prior to Week 6). Randomization into Cohort 2 will begin only after the DSMB has recommended it is safe to proceed. Details on tasks and

responsibilities and assessments of safety parameters will be provided in the DSMB Charter. The independent DSMB will review the safety data throughout the entire study.

For each subject in Cohort 1 or Cohort 2, a single treatment will be administered on Day 1 (Visit 3) after fulfillment of the "day of treatment criteria" (Section 6.2). Subjects will receive a single treatment of URO-902 or placebo administered by intradetrusor injections via cystoscopy. Details of the study treatment procedure are provided in Section 6.3.

Subjects will be instructed to contact the study site to report any adverse events that occur within 48 hours following administration of study treatment. A 3-day Bladder Diary will be used to collect information to assess exploratory efficacy endpoints related to the number of UUI, micturition, urgency, and UI episodes per day as well as one 24-hr volume voided of urine.

Medications prohibited before and during the study and the associated washout periods as well as permitted medications are described in Sections 6.9.1 and 6.9.2, respectively. Starting at Week 24, subjects can request and receive additional OAB treatment(s) at the clinical discretion of the investigator. Subjects who receive additional OAB treatment(s) at Week 24 or after will only be followed to assess adverse events at any future telephone (or other virtual technology) visits (Week 36 and/or Week 48). No efficacy assessments will be performed once a subject receives additional OAB treatment.

4.1.1. Clinical Hypothesis

Due to the exploratory nature of this trial, there is no formal hypothesis. Statistical testing will be performed to estimate the treatment effect of URO-902 relative to placebo in female subjects with OAB with UUI.

4.2. Scientific Rationale for Study Design

Study URO-902-2001 is a randomized, double-blind, placebo-controlled, single-treatment, 2 cohort, dose-escalation, exploratory efficacy and safety study.

The dose-escalation design, including interim safety analyses and DSMB review between each cohort, helps minimize the risk to subjects. Randomization into Cohort 2 (higher dose) will begin only after the DSMB has recommended it is safe to proceed.

Randomization will be stratified by baseline UUI episodes per day, presence or absence of DO (as determined by the investigator), and previous use of onabotulinumtoxinA (naïve vs. prior use) to ensure balance across the treatment groups. See details on stratification factors in Section 6.5.

This study is in the early stages of the development program for URO-902. There are no nonclinical studies that have investigated the genotoxic or reproductive effects of URO-902. Therefore, the study only includes female subjects of nonchildbearing potential. The study is randomized and double-blind to minimize investigator and subject bias and will provide a

placebo comparator for evaluating the safety and efficacy of the 2 doses of URO-902 being studied. In addition, relevant safety parameters including adverse events (AEs), SAEs, AEs of urinary retention and UTI as per protocol definition, physical examination, vital signs (pulse rate, blood pressure, respiration rate, and body temperature), urine dipstick reagent strip test, urinalysis/urine culture/sensitivity, as applicable, hematology and clinical chemistry, PVR urine volume, kidney and bladder ultrasound, concomitant medications and concurrent procedures will be closely monitored throughout the study.

4.3. Justification of Dose

An extensive series of *in vitro* and *in vivo* nonclinical studies evaluating the activity and safety of URO-902 have been conducted in OAB and ED animal models at doses up to 1 mg. The results of the nonclinical evaluations supported the initiation of URO-902 clinical studies. No toxicity was observed at any dose level in any of the preclinical studies at any dose in studies conducted to date, including multiple dosing in the ED rat model. Extensive data in the ED and OAB animal models has shown neither histopathological abnormality at any time point in any of 40 organs evaluated or expression of the gene in any other organ other than the organ that underwent transfer more than 1 week after that transfer, as well as in ED studies conducted up to 1 month after transfer.

The bladder preclinical studies evaluated single doses of 0.01, 0.03, 0.1, 0.3, and 1 mg based on an obstructed bladder surface area of 12.56 cm^2 and an average approximate bladder volume of 4 mL. The formula for surface area is $4\pi r^2$. Hence, human bladder surface area (average bladder volume of 400 mL) is 263.5 cm^2. Therefore, the approximate dose relationship of human to rat bladder is 20:1. In the completed OAB clinical studies, doses up to 25 mg by direct injection into the bladder wall/detrusor muscle were well-tolerated. Data from completed URO-902 nonclinical and clinical studies are summarized in the IB.

In the [redacted] No clinically meaningful safety signals were identified at either the 16 mg or 24 mg dose in [redacted] A starting dose of 24 mg will be initially tested in the planned Phase 2a clinical study URO-902-2001 to evaluate the safety and efficacy of URO-902 in subjects with OAB and UUI. Study URO-902-2001 has a dose-escalation design. Based on the unblinded review of observed safety data from all subjects in Cohort 1 (URO-902 24 mg) up to Week 6, the DSMB will make the recommendation to proceed with Cohort 2. Randomization into Cohort 2 (URO-902 48 mg) will begin only after the DSMB has recommended it is safe to proceed.

The dose equivalent to the 24 mg human dose and the 48 mg human dose in the rat is no more than 0.480 mg and 0.960 mg, respectively. As described above, the obstructed bladder preclinical studies in the rat evaluated single doses of up to 1 mg based on surface area of the bladder. In the rat ED model, doses up to 1 mg were administered by intracavernous injection. Thus, the starting

dose concentration of URO-902 at 24 mg as well as the highest dose to be evaluated in the planned clinical study (48 mg) are well within the range of doses investigated in the preclinical studies.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit or last scheduled procedure shown in the Schedule of Assessments (Section 1.3) for the last subject in the study.

A subject is considered to have completed the study if she was treated, has not been discontinued for any reason, and attends the scheduled exit visit (Week 24; Visit 8) of the cohort she is enrolled in.

5. STUDY POPULATION

The study is being conducted in female subjects with OAB and UUI. Specific inclusion and exclusion criteria are specified below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. For screen failure procedures, see Section 5.4.

5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria at the Screening Visit (Visit 1) and the Randomization Visit (Visit 2) to be eligible for participation in this study.

1. Capable of giving written informed consent, which includes compliance with the requirements and restriction listed in the consent form.
2. Subject is female, aged 40 to 79 years old, at the Screening Visit (Visit 1).
3. Subject has symptoms of OAB (frequency and urgency) with UUI for a period of at least 6 months prior to Screening Visit (Visit 1), determined by documented subject history.
4. Subject experiences an average of ≥ 1 episode of UUI per day (ie, a total of ≥ 3 UUI episodes over the 3-day subject Bladder Diary completed during the screening and randomization period).
5. Subject experiences urinary frequency, defined as an average of ≥ 8 micturitions (toilet voids) per day (ie, a total of ≥ 24 micturitions over the 3-day subject Bladder Diary completed during the screening and randomization period).
6. Subject has not been adequately managed with ≥ 1 oral or transdermal pharmacologic therapies for the treatment of their OAB symptoms (eg, anticholinergics, beta-3 agonist, etc), in the opinion of the investigator. Not adequately managed is defined as meeting one of the following:
    a an inadequate response after at least a 4-week period of pharmacologic therapy on a Food and Drug Administration (FDA)-approved dose(s) (ie, subject was still incontinent despite pharmacologic therapy), or
    b limiting side effects after at least a 2-week period of pharmacologic therapy on an FDA-approved dose(s)
7. Subject is willing to use clean intermittent catheterization (CIC) to empty the bladder at any time after receiving study treatment if it is determined to be necessary by the investigator.
8. Subject is of non-childbearing potential. See Section 10.6 for criteria to be satisfied.
9. In the opinion of the investigator, subject is able to: complete study requirements, including using the toilet without assistance; collect urine volume voided per micturition measurements over a 24-hour period; complete bladder diaries and questionnaires; and attend all study visits.

5.2. Exclusion Criteria

Subjects will be excluded from participating in the study for any one of the following criteria assessed during the Screening Visit (Visit 1) and at the Randomization Visit (Visit 2):

1. Subject has symptoms of OAB due to any known neurological reason (eg, spinal cord injury, multiple sclerosis, cerebrovascular accident, Alzheimer's disease, Parkinson's disease, etc).
2. Subject has a predominance of stress incontinence in the opinion of the investigator, determined by subject history.
3. Subject currently uses or plans to use medications or therapies to treat symptoms of OAB, including nocturia. Subjects previously receiving these medications must have discontinued their use to achieve sufficient washout prior to beginning recording of symptoms into the Screening Bladder Diary as follows:
    a for desmopressin, at least one day prior
    b for anticholinergic therapy, at least 14 days prior
    c for intravesical anticholinergic therapy, at least 4 weeks prior
    d for β_3 agonists, at least 14 days prior
4. Subjects who have previously been treated with:
    a onabotulinumtoxinA <u>for urological indications</u> within 12 months of starting the Screening Bladder Diary (subjects treated with onabotulinumtoxinA or other toxins for non-urological indications are eligible, regardless of when treated)
    b any other toxin <u>for urological indications</u>, regardless of when treated
5. Subject currently uses CIC or indwelling catheter to manage their urinary incontinence.
6. Subject has been treated with any intravesical pharmacologic agent (eg, capsaicin, resiniferatoxin) within 12 months of beginning recording of symptoms into the Screening Bladder Diary.
7. Subject has history or evidence of any pelvic or urological abnormalities, bladder surgery or disease, other than OAB, that may affect bladder function including but not limited to:
    a Bladder stones and/or bladder stone surgery at the time of screening or within 6 months prior to screening.
    b Surgery (including minimally invasive surgery) within 1 year of screening for: stress incontinence, uterine prolapse, rectocele, or cystocele.
    c Current or planned use of an implanted electrostimulation/neuromodulation device for treatment of urinary incontinence for the duration of the study. If a device is still implanted, it must be inactive 4 weeks prior to the Screening Visit (Visit 1) and for the duration of the study.
    d use of other non-implantable electrostimulatory devices for the duration of the study.
8. Subject has a history of interstitial cystitis/painful bladder syndrome, in the opinion of the investigator.
9. Subject has an active genital infection, other than genital warts, either concurrently or within 4 weeks prior to screening.

10. Subject has uterine prolapse of grade 3 or higher (ie, cervix descends outside of the introitus)
11. Subject has a history or current diagnosis of bladder cancer or other urothelial malignancy, and/or has un-investigated suspicious urine cytology results. Suspicious urine cytology abnormalities require that urothelial malignancy is ruled out to the satisfaction of the investigator according to local site practice.
12. Subject has evidence of bladder outlet obstruction, in the opinion of the investigator at screening or randomization.
13. Subject has evidence of urethral outlet obstruction or urethral injury or stricture, in the opinion of the investigator at screening or randomization.
14. Subject has a PVR urine volume of > 100 mL at any time during screening (before randomization). The PVR measurement can be repeated once on the same day; the subject is to be excluded if the repeated measure is above 100 mL.
15. Subject has had urinary retention or an elevated PVR urine volume that has been treated with an intervention (such as catheterization), within 6 months of the Screening Visit (Visit 1). Note: transient voiding difficulties as a result of surgical procedures that resolved within 24 hours are not exclusionary.
16. Subject has a 24-hour total volume of urine voided > 3000 mL, collected over 24 consecutive hours during the 3-day Bladder Diary collection period prior to randomization.
17. Subject has a history of 3 or more UTIs within 6 months of the Screening Visit (Visit 1) or is taking prophylactic antibiotics to prevent chronic UTIs. Subjects with a current acute UTI during screening can be treated appropriately and are eligible.
18. Subject has a serum creatinine level > 2 times the upper limit of normal at the Screening Visit (Visit 1).
19. Subject has current or previous uninvestigated hematuria. Subjects with investigated hematuria may enter the study if urological/renal pathology has been ruled out to the satisfaction of the investigator.
20. Subject has a known allergy or sensitivity to URO-902, anesthetics, or antibiotics to be used during the study.
21. Subject needs a walking aid on a permanent basis.
22. Subject is currently participating in or has previously participated in another therapeutic study within 30 days of screening (or longer if local requirements specify). Subject has been previously treated with URO-902 in clinical trials (formerly known as *h*Maxi-K or pVAX/*hSlo*).
23. Subject has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstances that might, in the opinion of the investigator, confound the results of the study, interfere with the subject's ability to comply with the study procedure, or make participation in the study not in the subject's best interest.

5.3. Lifestyle Considerations

Not applicable for this study.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized to treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened once upon consultation with, and approval by, the Sponsor or its designee. Rescreened subjects will be assigned a new subject number, and both subject numbers will be linked to the subject, and a new informed consent with the new subject number should be signed. Screening assessments specified in Section 1.3 should be repeated if subjects are rescreened. The following assessments would NOT need to be repeated if rescreening occurs within 2 to 8 weeks of the original screening date: Safety labs (if within 2 weeks); Urodynamics (if within 8 weeks). See Section 8.2.3 for information on valid historical urodynamic assessments.

6. STUDY TREATMENTS

6.1. Study Drugs Administered

All eligible subjects enrolled into the study will receive a single double-blind treatment of either URO-902 or placebo based on the cohort they are enrolled in.

URO-902 (24 mg or 48 mg) or matching placebo will be administered as intradetrusor injections via cystoscopy.

For Cohort 1, a single treatment of URO-902 24 mg or placebo will be administered. Based on the unblinded review of observed safety data from all subjects in Cohort 1 up to Week 6 (including subjects who prematurely exited the study prior to Week 6), the DSMB will make the recommendation to proceed with Cohort 2. Randomization into Cohort 2 will begin only after the DSMB has recommended it is safe to proceed.

- Cohort 1: URO-902 24 mg or matching placebo (phosphate buffered saline with 20% sucrose [PBS-20%])
- Cohort 2: URO-902 48 mg or matching placebo (PBS-20%)

See Table 1 for a summary on study drugs.

Table 1: Summary of Study Drugs

Study Drug Name	URO-902	Matched Placebo
Identity of Formulation	URO-902 Drug Product	Phosphate Buffered Saline with 20% Sucrose (PBS-20%)
Dosage Formulation	[redacted]	
Dose	24 mg or 48 mg	Placebo
Route of Administration	Intradetrusor injection via cystoscopy	Intradetrusor injection via cystoscopy
Dosing Instructions	Single treatment administered by the investigators or study site personnel qualified to perform cystoscopy.	Single treatment administered by the investigators or study site personnel qualified to perform cystoscopy.
Packaging and Labeling	[redacted]	
Manufacturer		

6.2. Day of Treatment Criteria

For each subject in Cohort 1 or Cohort 2, a single treatment will be administered on Day 1 (Visit 3) after fulfillment of the following "day of treatment criteria":

- Negative urine dipstick reagent strip test (for nitrates and leukocyte esterase)
- If evaluated, negative urinalysis/urine culture/sensitivity results for a possible UTI have been reviewed
- Subject is asymptomatic for a UTI, in the opinion of the investigator
- No presence of bladder stones prior to or at cystoscopy
- Investigator continues to deem that no condition or situation exists which, in the investigator's opinion, puts the subject at significant risk from receiving URO-902

6.3. Treatment Administration

- If a subject is taking any anticoagulants or anti-platelet drugs, consult with the subject's primary care physician (or internist, cardiologist, etc), as deemed clinically necessary by the investigator, if the subject can discontinue these drugs for 2-3 days prior to the intradetrusor injections treatment and on the day of treatment. Subjects on an anticoagulant and/or anti-platelet therapy must be managed appropriately to decrease the risk of bleeding, per the clinical judgment of the investigator.

- All subjects must receive prophylactic antibiotics at a minimum on Day 1 prior to treatment administration and for 1 additional day post-treatment. At the investigator's discretion, subjects can receive prophylactic antibiotics up to 3 days prior to treatment per local site practice.

- Prior to administration of study treatment, subjects will be instructed to void their bladder and then assume a supine position.

- Use of anesthesia before treatment administration will be determined by the investigator. All study procedures are to be conducted using the appropriate antiseptic technique per local site practice for a cystoscopy. After disinfection of the urethral meatus, the following options are strongly recommended:

    - Lubricating gel, with or without local anesthetic, to facilitate insertion of the sterile, single-use transurethral catheter per local site practice

    - For all subjects, local anesthesia instillation in the bladder:

        - Instillation into the bladder of 1% to 4% lidocaine (or similar acting local anesthetic) prior to the procedure

        - Instillation solution should remain in the bladder for at least 15 minutes to achieve sufficient anesthesia; afterwards, the bladder will be drained of lidocaine, rinsed with saline, and drained again

- A flexible or rigid cystoscope will be used for administration of study treatment. Per local site practice lubricating gel will be used to insert the cystoscope. The bladder will be instilled with a sufficient amount of saline to visualize the study injections. One syringe of appropriate size to hold a minimum of 12 mL of study drug and one syringe of appropriate size to hold a minimum of 1 mL PBS-20% flushing solution will be prepared and ready for treatment administration (refer to Section 6.5 as needed). The injection needle will be primed with approximately 0.5 mL of study drug. The 12 mL of study drug should be administered as 20 injections, each approximately 0.6 mL. Under direct visualization via cystoscopy, injections will be distributed evenly across the detrusor wall and spaced approximately 1 cm apart, avoiding the bladder dome and trigone.

- To administer study drug from the syringe, the needle should be inserted approximately 2 mm into the detrusor for each injection. For the final injection site, a sufficient amount of PBS-20% (from the 1-mL syringe) will be pushed through the injection needle to ensure delivery of the remaining amount of study drug.

- After injections are administered, the saline used for visualization must not be drained from the bladder to allow subjects to demonstrate the ability to void prior to leaving the clinic. Subjects must remain in the clinic until a spontaneous void has occurred, and to complete post-treatment assessments including observation as well as pharmacokinetic sample collection.

- Subjects will be instructed to contact the study site to report any adverse events that occur within 48 hours following administration of study treatment.

6.4. Preparation/Handling/Storage/Accountability

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Refer to the appropriate study manual for the storage and handling of URO-902 and placebo. In the event a subject does not fulfill the day of treatment criteria (Section 6.2), likely due to a suspected UTI that requires antibiotic treatment, study drug (URO-902 or placebo) can remain in the refrigerator (2° to 8°C, in the original vial) as per instructions in the study manual to enable the subject to reschedule and return for the treatment visit (Day 1).

Receipt and dispensing of study treatment must be recorded by an authorized person at the study site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed and the amount remaining at the conclusion of the study. These records will be monitored throughout the study.

For all sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

6.5. Measures to Minimize Bias: Randomization and Blinding

To maintain blinding of the treatment groups, neither the investigator/physician subinvestigator (injector) nor site personnel who are involved in evaluating or injecting the subject should prepare the study drug. An additional individual (eg, unblinded pharmacist or nurse) with no subject evaluation or treatment involvement must be identified at each investigative site to prepare the study drug and the PBS-20% flushing solution. The responsibility of this individual will be to properly prepare the injection syringes with the accurate randomized study drug as per the volumes indicated by the Sponsor. They will draw the study drug into the syringes to be injected and dilute as needed as per instructions in the appropriate study manual. The study manual will be provided by the Sponsor/designee before the study start.

If an interim analysis(es) is/are performed (Section 9.8.1), the subject and the investigator or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will remain blinded to the treatment assignments. Limited personnel from the Sponsor will be unblinded (double-blind, sponsor-open design). Sponsor personnel/designees who are directly involved with site interactions and communications (eg, study data manager and site monitors) will remain blinded to subject level treatment assignment.

In both cohorts, subjects will be randomized in a 2:1 ratio to receive either URO-902 (24 mg or 48 mg) or placebo. Each cohort will be randomized separately, and enrollment will be sequential, starting with Cohort 1 and followed by Cohort 2. At the Randomization Visit (Visit 2), subjects in both Cohort 1 and Cohort 2 will be randomized centrally to receive either a single treatment of URO-902 or matching placebo.

In Cohort 1a, randomization will be stratified by baseline UUI episodes per day (≤ 3 vs. > 3 UUI episodes per day) and presence or absence of DO (as determined by the investigator) as per the original protocol. Subjects will be enrolled into Cohort 1b following implementation of Amendment 1 and updates to the interactive web response system (IWRS) system. In Cohort 1b and Cohort 2, randomization will be stratified by baseline UUI episodes per day and previous use of onabotulinumtoxinA (naïve vs. prior use).

For Cohorts 1a, 1b, and 2, stratification factor for baseline UUI episodes is based on the average number of UUI episodes per day recorded over the 3-day diary period at baseline (ie, ≤ 3 vs. > 3 UU1 episodes per day).

For Cohort 1a, the urodynamic assessment where an evaluation of the presence or absence of DO is performed to be used as a randomization factor, must be conducted at Visit 2 prior to performing the actual randomization procedure. For subjects with a valid historical urodynamic study (per protocol Section 8.2.3), the presence or absence of DO would already be known.

For Cohorts 1b and 2, onabotulinumtoxinA treatment for urological indications must have occurred at least 12 months prior to starting the Screening Bladder Diary. Enrollment for subjects with previous onabotulinumtoxinA use will be capped at 50% of the total subject population per cohort. Subjects randomized to Cohort 1a will be assigned to the onabotulinumtoxinA naïve stratum for all analyses.

Subjects will be centrally assigned to randomized study drug using an IWRS and the randomization schedule generated by the sponsor or designee. Before screening is initiated at each site, login information and directions for the IWRS will be provided.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator or designee has the sole responsibility for determining if unblinding of a subject's study drug assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor or designee prior to unblinding a

subject's study drug assignment unless this could delay emergency treatment of the subject. If a subject's study drug assignment is unblinded, the Sponsor or designee must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.6. Study Drug Compliance

Study treatment will be administered by the investigator or physician subinvestigator qualified to perform intradetrusor injections.

Study drug compliance will be closely monitored by counting the number of vials dispensed and returned. The study site personnel will make every effort to collect all unused study drug and empty vials.

The study site will keep an accurate drug disposition record that specifies the amount of study drug administered to each subject and the date of administration.

6.7. Dose Modification

No dose modification of study drug is permitted.

6.8. Drug After the End of the Study

Not applicable.

6.9. Prior and Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the subject's electronic case report form (eCRF) at each visit along with the reason the medication is taken, the dates of administration, and the dose.

6.9.1. Prohibited Drugs and Washout

Section 10.7 provides a list of medications prohibited before the study and during the study (until Week 24) and the associated washout periods. If there is a clinical indication for any therapy that is specifically prohibited during the study, discontinuation from the study may be required. The investigator should discuss any questions regarding this with the Sponsor's designated Medical Monitor. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject in the study requires the mutual agreement of the investigator and the Sponsor's designated Medical Monitor. Consult the Sponsor's designated Medical Monitor if there is any uncertainty regarding subject use of a particular drug or drug class.

Starting at Week 24 and after, the OAB treatments listed in Section 10.7 are no longer prohibited and can be prescribed to a subject upon her request and in accordance with the investigator's clinical judgment. See Section 6.9.2 for details.

6.9.2. Permitted Treatments

With the exception of the agents described in Section 10.7, any other concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If the permissibility of a specific medication/drug is in question, please contact the Sponsor's designated Medical Monitor. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment, start of screening, or receives during the study must be recorded in the eCRF.

Furthermore, starting at Week 24 and after (at clinic visit, phone [or other virtual technology] visits or between visits), subjects can request and receive additional OAB treatment(s) such as those listed in Section 10.7 (see Section 6.9.1) at the clinical discretion of the investigator. The following criteria should be followed in order for subjects to receive additional OAB treatment(s):

- Subject initiates a request for additional OAB treatment
- Ensure subject's last available OAB symptoms are recorded, as determined by the most recent 3-day patient Bladder Diary (if not already recorded)
- Investigator deems the additional OAB treatment is appropriate and that no condition or situation exists which, in the investigator's opinion, puts the subject at significant risk from treatment.

Subjects who receive additional OAB treatment(s) at Week 24 or after will only be followed to assess adverse events at any future telephone (or other virtual technology) visits (Week 36 and/or Week 48). No bladder diaries will be collected, and no efficacy assessments will be performed once a subject receives additional OAB treatment.

Additional OAB medications will not be provided by the Sponsor.

7. DISCONTINUATION OF STUDY AND SUBJECT DISCONTINUATION OR WITHDRAWAL

A premature discontinuation will occur if a subject who signs the informed consent form (ICF) and is randomized ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

7.1. Subject Discontinuation/Withdrawal from the Study

- A subject may choose to withdraw from the study at any time at her own request or may be withdrawn at any time at the discretion of the investigator or Sponsor for safety, behavioral, compliance, or administrative reasons.
- If a subject withdraws consent for disclosure of future information, the Sponsor or designee may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, she may request destruction of any blood or urine samples taken and not tested, and the investigator must document this in the site study records and communicate this request to the Sponsor study team so that appropriate measures may be taken to ensure destruction of the materials.
- Subjects who withdraw from the study will not be replaced (enrollment accounts for a predetermined dropout rate).

The Week 24/Exit Clinic Visit (Visit 8) assessments as specified in the Schedule of Assessments (Section 1.3) will be completed when a subject withdraws or is withdrawn from the study, if possible.

Reasons for discontinuation from the study include the following:

- AE
- Lack of efficacy
- Noncompliance
- Withdrawal of consent
- Lost to follow-up
- Physician decision
- Protocol deviation
- Pregnancy
- Death
- Administrative issues (eg, site closure)
- Other

7.2. Lost to Follow-Up

Should a subject fail to attend a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up", including at least three documented attempts to contact the subject (ie, phone, email, or certified letter). Efforts to establish the possible reason for discontinuation should be documented.

7.3. Early Study Termination

The Sponsor reserves the right to terminate the study for any reason. The study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study overall or at a particular study site may be stopped due to insufficient compliance with the protocol, Good Clinical Practice and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their scheduled timepoints are summarized in the Schedule of Assessments (Section 1.3). Site personnel should note the following:

- Protocol waivers or exemptions are not allowed; however, subjects who fail to meet eligibility criteria may be rescreened once, as appropriate (See Section 5.4). Any notable protocol deviations should be noted and raised to the Sponsor's or designee's attention.
- Immediate safety concerns should be discussed with the Sponsor's designated Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or be discontinued from the study.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.
- Evaluations should be performed by the same evaluator throughout the study whenever possible.

8.1. Screening Procedures

Screening procedures can commence once the informed consent and data authorization/protection form have been obtained. Screening will be considered to have started at the time of the first screening activity or procedure and completed when all the required inclusion/exclusion criteria have been met and the subject is randomized. Screening procedures should be completed as soon as possible, with a maximum of a 35-day window. There is no minimum duration for screening procedures and randomization as long as the subject undergoes the required protocol-defined assessments at each respective visit and is fully evaluated for eligibility based on the clinical judgment of the investigator.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Inclusion and exclusion criteria will be reviewed by the investigator or qualified designee at the Screening and Randomization Visits (Visits 1 and 2, respectively).

For screen failure procedures, see Section 5.4.

8.1.1. Informed Consent

Documented consent must be obtained from each potential subject prior to participating in any study procedures. Refer to Section 10.1.3 for a detailed description of the informed consent process, including the voluntary nature of clinical study participation and the subject's right to withdraw consent at any time.

8.1.2. Assignment of Subject Number

All subjects who sign the ICF will be assigned a unique subject number by IWRS. This number will be used to identify the subject throughout the study. Subjects who are rescreened will be assigned a new subject number. If a new subject number is assigned, the subject will be linked to both subject numbers.

8.1.3. Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all chronic and ongoing conditions, regardless of year diagnosed, surgical history, and substance abuse history. All events occurring after the subject signs the ICF will be recorded as adverse events.

8.1.4. Demographics

Demographic data collection will include sex, age, race, and ethnicity.

8.1.5. Prior and Concomitant Medications

Any prior OAB medications (over the past 3 years), any other prior medications used up to 6 months before the Screening Visit, as well as ongoing (concomitant) medications will be recorded beginning at the signing of the ICF and continuing until the Week 48 Safety Follow-up assessment.

If additional OAB medication(s) is used or procedures are performed at Week 24 or after (see Section 6.9.2), these must be recorded in the appropriate eCRF form.

8.2. Efficacy Assessments

Efficacy assessments will be collected as outlined in the Schedule of Assessments (Section 1.3) in the form of a 3-day Bladder Diary. Information collected in the diaries will be used for assessment of the exploratory efficacy endpoints related to the number of UUI episodes, micturitions, urgency episodes, and UI episodes per day as well as one 24-hr period to record volume voided of urine.

Subjects will complete questionnaires at the site during the study visits specified in the Schedule of Assessments (Section 1.3) before vital signs and blood draws to assess subject-perceived symptom relief and health-related quality of life. The patient-reported outcome (PRO) questionnaires are provided in Section 10.9. Urodynamic parameters will also be measured. Additional information on the Bladder Diary, questionnaires, and urodynamic parameters is provided below.

8.2.1. Bladder Diaries

The Bladder Diary is used by subjects to record the frequency of daily OAB symptoms including all micturitions, urgency, UUI, UI, and main reason for incontinence, and volume voided per micturition (over one 24-hour period) by selecting the respective box for each symptom/event occurring during the course of a given day and night.

Bladder diary must be completed by subjects for any 3 consecutive days in the 7 days prior to the visit (for screening only, it can be completed for 3 consecutive days at any time during the screening and randomization period); total volume voided must be collected for one 24-hour period during the 3-day diary collection period. Please refer to Section 10.7 for washout periods for prohibited medications. The Screening Bladder Diary should be started only after washout of prohibited medications is complete.

A "Diary Day" is defined as the time between when the subject gets up for the day each morning (ie, the time the subject got up for the day yesterday to the time the subject got up for the day today; approximately a 24-hour period).

To be eligible for the study, subjects must have a minimum of 3 consecutive Diary Days during the screening and randomization period (at any time during the period) and be capable in the investigator's opinion of maintaining compliance with the diary requirements, including the measurement and recording of urine volume, as required throughout the course of the study.

At all study visits, the site staff should inquire whether the subject had any difficulties with the diary and address any questions subjects may have. Instructions for proper completion of the diary should be re-reviewed. Subjects will be trained to enter data immediately following each event (in real time) and to input data from any "missed" events as soon as they are able. They will review and confirm that data from all events occurring within the preceding Diary Day (approximately 24 hours) have been entered at a consistent time each morning (eg, upon getting up for the day).

Responses to the Bladder Diary will be reviewed by the site staff to assess whether subjects are capable of completing the diary and if subjects meet eligibility criteria. The daily averages for micturitions, urgency episodes, UUI episodes, and UI episodes will be calculated as average of the total by the number of events on Diary Days. Subjects who do not meet the OAB entry criteria will be excluded from the study.

Note that diaries must be completed within 7 days prior to the protocol-defined timepoint regardless of any visit delay due to COVID-19. If a visit will be delayed per the COVID-19 mitigation window, the site should contact the subject to ensure that the diary completion occurs per the protocol-defined timepoints and not within the 7 days prior to the COVID-delayed visit.

More detailed instructions on the diary and instructions for use are provided in the appropriate study manual.

8.2.2. Patient-Reported Outcomes

The subject's perception of the level of impairment in functioning and well-being associated with the symptoms of OAB will be assessed using subject-completed questionnaires as specified below. Questionnaires should be administered prior to the subject undergoing any invasive procedure for any study visit, prior to vital signs measurement, and prior to study treatment at the Day 1 Visit. The versions of the questionnaires provided in the protocol are samples and will be replaced. Additional information on administering and completing these questionnaires is outlined in Section 10.9. These include the following questionnaires:

- Urinary Incontinence-Specific Quality-of-Life Instrument (I-QOL) total summary score
- OAB Questionnaire (OAB-q) score
- Patient Global Impression of Change (PGI-C) scale score

Examples of each of the PRO measures are provided in Section 10.9.

8.2.3. Urodynamic Parameters

Urodynamic assessments will only be performed at baseline after confirmation of subject eligibility during the Randomization Visit (Visit 2) prior to performing the actual randomization procedure. A historical urodynamic study, performed no more than 90 days prior to the first day of screening, may serve as the baseline urodynamic assessment if the criteria detailed below are satisfied.

Historical urodynamic study may be substituted for the baseline urodynamic assessment, if the following 3 criteria are met:

- Historical urodynamic study was obtained no more than 90 days prior to the first day of screening
- Historical urodynamic results are available for evaluation by the central reader
- Subject was not being treated with any OAB medication or had discontinued OAB treatment in accordance with Exclusion Criterion #3

In case of subjects being rescreened when a historical urodynamic assessment was used for the original screening, it will NOT need to be repeated if rescreening still occurs within 90 days of the valid historical urodynamic assessment. If rescreening occurs more than 90 days since the historical urodynamic assessment, a new urodynamic test will need to be performed prior to randomization as the baseline assessment.

At Week 12, all subjects will undergo a second urodynamic assessment.

Conduct of urodynamic testing will be standardized across all study sites and will be according to ICS standard guidelines [Homma 2002].

Urodynamic data will be reviewed by an independent central reviewer to determine final values for analysis purposes for the parameters listed below. The investigator, physician subinvestigator, or trained technician will perform urodynamic procedures on each subject, then interpret and record the results on the calculation worksheet. The worksheet and the tracings should be signed and dated by the investigator or physician subinvestigator. A test trace will be submitted by each site. A copy of the worksheet, along with the printed tracings will be submitted to the central reader. Only the central reader's interpretation of the results will be recorded in the eCRF for final analysis. Study sites will not typically be informed of any differences between their urodynamic values and the urodynamic values determined by the central reviewer. However, study sites may receive feedback if persistent methodological issues arise per the central urodynamic reader. Note that the investigator does not need to wait for the results of the baseline urodynamic assessment to rule out bladder outlet obstruction if there are no other signs or symptoms of obstruction, in the investigator's assessment, including elevated PVR volume (see Exclusion Criterion 13).

The following urodynamic parameters are to be measured:

- Cystometric volume at 1st sensation to void (FSV)
- Maximum cystometric capacity (MCC)
- Maximum detrusor pressure during the storage phase (corrected $Pdet_{MaxStorage}$)
- Presence/absence of the first involuntary detrusor contraction (IDC) and, if present:
    - Volume at first IDC (Vol@1stIDC)
    - Maximum detrusor pressure during the first IDC (corrected P_{det}@1stIDC)

Additional related instructions will be provided in the appropriate study manual.

8.3. Pharmacokinetic Assessments

Urine and blood samples for *hSlo* cDNA assessment will be collected pre-treatment from subjects on Day 1 (Visit 3; treatment administration), 2 hours (± 1 hour) post-treatment on Day 1, Week 6 follow-up clinic visit (Visit 5), and Week 24 follow-up clinic/exit visit (Visit 8). If a specimen(s) is still positive at Week 24, per the clinical discretion of the investigator, a subject may be instructed to return at Week 36 (Visit 9) and, if necessary, Week 48 (Visit 10) until the specimen(s) result is negative for *hSlo* cDNA. Pharmacokinetic assessment is to be performed at the Early Withdrawal Visit for subjects who withdraw early from the study. Information on procedures for collection, handling, storage, and shipping the samples will be provided in a separate study manual.

8.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the Schedule of Assessments (Section 1.3). Immediate safety concerns should be discussed with the Sponsor's designated Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.

8.4.1. Vital Signs

- Vital signs, including blood pressure (mmHg), heart rate (by pulse; beats per minute), respiration rate (breaths per minute), and body temperature (°C) will be assessed at the timepoints specified in the Schedule of Assessments (Section 1.3).
- Blood pressure and pulse will be measured after the subject has been resting in a seated position for 5 minutes, after questionnaires have been administered, and before blood draws.
- Blood pressure measurements will be taken on the same arm and by the same site staff throughout the study, if possible.
- The same method for assessing temperature should be used at all visits for a particular subject.
- Body weight will be measured with subjects in street clothing with jacket/coat and shoes removed, using the same scale throughout the study, if possible.
- Standing height will be measured at screening only.

8.4.2. Physical Examinations

Brief physical examinations will include examination of the heart, lungs, abdomen, and visual pelvic examination. In addition, any organ system in which a previous abnormality was noted during screening or a subject has a complaint or AE will be examined.

8.4.3. Electrocardiograms

A 12-lead ECG will be performed in the supine position at the visits specified in the Schedule of Assessments (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECGs will be read by trained personnel at the study site or appropriate delegates who are medically qualified.

8.4.4. Post-Void Residual Volume

The volume of urine that remains in the bladder after voiding (PVR) is an objective measurement that may serve as a proxy for impaired ability to void. The physician should assess subjects with an increase in PVR volume to determine whether an AE should be reported. (Refer to Section 8.5.6 for additional information on reporting AEs of urinary retention associated with increased PVR.)

The PVR assessment will be performed via ultrasound at the visits indicated in the Schedule of Assessments (Section 1.3). Note that since Visit 7 (Week 18) is a telephone (or other virtual technology) visit, subjects will not be seen in the clinic for 12 weeks between Visit 6 (Week 12) and Visit 8 (Week 24). Should the investigator identify a clinically relevant elevation in PVR volume at Visit 6, an unscheduled clinic visit should be performed at the investigator's discretion to repeat the urine PVR assessments and urine dipstick. All efforts should be made to ensure the same device and operator are used for all PVR volume measurements for individual subjects.

8.4.5. Clean Intermittent Catheterization

The following guidance should be used for the initiation of CIC in this study. Sterile, single-use intermittent catheters should be used. Indwelling catheters should not be used in this study.

Initiation of Clean Intermittent Catheterization

As described above in the PVR section, CIC should be initiated per protocol when one of the following criteria is fulfilled:

- PVR is ≥ 350 mL at any posttreatment visit, regardless of whether the subject reports associated symptoms
- PVR is ≥ 200 mL and < 350 mL and the subject spontaneously reports associated symptoms (ie, voiding difficulties, sensation of bladder fullness) that in the opinion of the investigator requires CIC.

The following will occur when initiating CIC (for elevated PVR as described above):

1. CIC is implemented and the subject should be instructed to perform CIC using sterile, single-use catheters (which will be provided to the subject)
2. An adverse event of urinary retention is recorded
3. Central laboratory urine analysis and culture/sensitivity are performed as per routine requirements at each study visit
4. The subject will be seen for a follow-up visit 1 week later where the PVR, associated symptoms, central laboratory urine analysis and culture/sensitivity will be reassessed. The investigator will determine whether the subject can then be followed per protocol scheduled study visits or whether additional follow-up visits should occur.

Once CIC is initiated, the status of CIC use should be documented in the subject record at each visit (ie, use/nonuse).

Cessation of Clean Intermittent Catheterization

CIC should be discontinued when the following criteria are fulfilled:

- the subject does not have any associated symptoms which in the opinion of the investigator require CIC AND

- the PVR is < 350 mL

The date of discontinuation of CIC should be documented. If the investigator deems that CIC should not be discontinued even though the above criteria are fulfilled, then this should be documented, and the reason given. Upon discontinuing CIC, the subject will be seen for a follow-up visit 1 week later where the PVR, associated symptoms, central laboratory urine analysis and culture/sensitivity will be reassessed. The investigator will determine whether the subject can then be followed at regularly scheduled study visits or whether additional follow-up visits should occur based on PVR and/or associated symptoms.

8.4.6. Clinical Safety Laboratory Assessments

All protocol-defined laboratory assessments must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Section 1.3). See Section 10.2 for the list of clinical laboratory tests to be performed and the Schedule of Assessments for the timing and frequency. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The clinical significance of test results will be evaluated as follows:

- At screening, the investigator or physician subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and subjects with abnormalities judged to be clinically significant will be excluded from the study.
- The investigator or physician subinvestigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Laboratory abnormalities associated with the underlying disease are not considered clinically significant unless judged by the investigator to have worsened or be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significant during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Sponsor's designated Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor's designated Medical Monitor notified.
  - If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

A urine dipstick will be performed at the study site at scheduled visits as noted in the Schedule of Assessments (Section 1.3) and when a subject presents with symptoms of a UTI at Unscheduled

Visits. If the urine dipstick is positive for leukocytes, nitrites, or blood cells, then a urinalysis and culture/sensitivity testing will be performed on the sample. The urinalysis should be performed at the central laboratory and the culture and sensitivity should be performed at the site's designated local laboratory.

If positive for nitrites and/or leukocyte esterase, indicating a possible infection, the subject should be treated with antibiotics per the clinical judgment of the investigator and in accordance with local site practice. Urine analysis, urine culture and sensitivity testing (performed from a sample collected on the same day as the dipstick) will be used to confirm the presence or absence of a UTI. If UTI is present, sensitivity testing will provide additional information to the investigator regarding pathogen susceptibility to the antibiotic selected for treatment based on the positive dipstick.

- Screening urine dipstick reagent strip test results: If positive, the screening and randomization period can be extended to a total maximum of 35 days prior to randomization) in order to accommodate the additional time required for antibiotic treatment. Some of the screening procedures may be repeated, as deemed clinically necessary, at the discretion of the investigator (eg, repeat the Screening Bladder Diary if subject had a symptomatic UTI during initial diary collection).
- Day 1 (treatment administration) urine dipstick reagent strip test results: Subjects with a dipstick positive for nitrites and/or leukocyte esterase on Day 1 (Visit 3) do not meet "day of treatment criteria" and therefore must not receive study treatment. The subject should be treated with antibiotics per the clinical judgment of the investigator and in accordance with local site practice and may then return for a rescheduled treatment Day 1 Visit within 10 days (but within a total maximum of 35 days of starting screening procedures). If the dipstick obtained at the rescheduled Day 1/treatment administration visit is negative for nitrites and leukocyte esterase and all "day of treatment criteria" are fulfilled, the subject can be treated.

Urine cytology: Urine cytology is performed at the Screening Visit (Visit 1) only. Abnormal urine cytology suspicious for a urothelial malignancy should be investigated by the investigator according to local site practice, and only if such malignancy is ruled out should the subject be enrolled. Results of the investigation will be recorded in the source documents.

8.4.7. Bladder and Kidney Ultrasound

Abdominal ultrasound of the bladder and kidneys will be performed with the bladder at least half full. Subjects are excluded from this study if the screening ultrasound demonstrates the presence of bladder stones and/or intra-luminal filling defects of the bladder suggestive of malignancy. In the case of unclear new findings identified at the exit visit, an ultrasound which may be suggestive of stones (kidney, ureter, or bladder), other diagnostic measures must be performed in order to confirm the presence of stones, rule out bladder malignancy (eg, x-ray with or without contrast, urogram, computed tomography (CT) scan, magnetic resonance imaging (MRI) or cystoscopy and histopathological confirmation).

8.4.8. Immunogenicity Blood Sample (Optional)

If the subject consents, blood samples for potential future immunogenicity testing will be collected at the timepoints specified in the Schedule of Assessments (Section 1.3) and stored for up to 5 years. If testing is not performed within 5 years of collection, the subject's sample will be appropriately discarded. Sample collection is limited to subjects who are able to provide a blood sample prior to administration of study treatment on Day 1 (Visit 3) (Cohort 2 only).

8.5. Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Section 10.3.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue the study drug or the study (see Section 7).

8.5.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the signing of the ICF through 30 days after the end of the study at the timepoints specified in the Schedule of Assessments (Section 1.3), and as observed or reported spontaneously by study subjects. Medical occurrences that begin before the start of study drug, but after obtaining informed consent will be recorded in the AE section of the eCRF.

All SAEs (including serious adverse events of special interest [AESIs]) will be recorded and reported on the eCRF within 24 hours of the study site personnel's knowledge of the event. Marking the event as "serious" will automatically send required notifications for Sponsor or designee review. The investigator will also submit any updated SAE data within 24 hours of receipt of the information.

Nonserious AESIs will be reported on the eCRF within **72 hours** of the site's knowledge of the information.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.5.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.2). If a subject dies during participation in the study, the investigator will provide the Sponsor or designee with a copy of any available postmortem findings including an autopsy report with histopathology.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF. As noted above, the investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

8.5.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification of an SAE by the investigator to the Sponsor or designee is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor or designee will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

No disease-related events or outcomes are excluded from AE reporting.

8.5.6. Adverse Events of Special Interest

Selected nonserious and SAEs will be reported as AESIs. AESIs that also meet the definition of an SAE must be reported as described in Section 10.3.

AESIs for this study include:

- Adverse events consistent with urinary retention

- An AE of urinary retention should only be recorded when a subject has a raised PVR that requires intervention with CIC or temporary placement of a urinary catheter according to the following criteria:

a) subject has a PVR of ≥ 350 mL (regardless of symptoms), OR

b) subject has a PVR ≥ 200 mL and < 350 mL and the subject reports associated symptoms, ie, sensation of bladder fullness or inability to void despite persistent effort, that in the investigator's opinion require CIC.

Note: An AE of residual urine volume should be recorded if, in the investigator's opinion, the raised PVR is clinically significant but does not fulfill the above definition for urinary retention.

- Adverse events suggestive of cystitis or UTI

- An AE of UTI will be recorded if both the following criteria are fulfilled, regardless of subject symptoms:

a) a positive urine culture result with a bacteriuria count of ≥ 10^5 CFU/mL
(ie, 100×10^3 CFU/mL)

b) leukocyturia of ≥ 5/hpf

If a subject meets the criteria for the definition of a UTI, the investigator will record whether the UTI was "symptomatic" or "asymptomatic" on the AE eCRF.

Note: If urinalysis/culture results are reported which, in the opinion of the investigator, are considered clinically significant but do not fulfill the above definition of a UTI, the findings should be recorded as AEs (eg, bacteriuria, leukocyturia).

8.5.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study drug as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong subject (ie, not administered to the intended subject)

Medication errors include occurrences of overdose and underdose of the study drug.

Overdose: Unintentional administration of a quantity of the study drug given per administration or per day that is above the maximum recommended dose according to the protocol. This also takes into account cumulative effects due to overdose (see Section 8.6 for treatment and reporting of overdose). For this study, any dose of URO-902 ≥ 20% higher than the dose that the subject has been randomized to is an overdose. There is no known antidote for an overdose.

Underdose: No underdose is defined for this study.

8.6. Treatment of Overdose

In the event of an overdose (any dose of URO-902 ≥ 20% higher than the dose that the subject has been randomized to), the investigator or treating physician should:

- Contact Sponsor's designated Medical Monitor immediately
- Closely monitor the subject for any AEs, SAEs, and laboratory abnormalities
- Report all overdose events within 24 hours of awareness by the study site, in the eCRF according to Section 10.3, whether or not the overdose is associated with an AE
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor's designated Medical Monitor based on the clinical evaluation of the subject.

9. STATISTICAL CONSIDERATIONS

This section contains a brief summary of the statistical analyses for this study; full details will be provided in the Statistical Analysis Plan (SAP).

The randomized allocation schedule will be generated by the Sponsor or designee and implemented by the vendor of the study. Stratification will be performed across the study (not per site). The statistical analysis of the data obtained from this study will be the responsibility of the Sponsor or designee. At the end of the study, the official, final database will be frozen and unblinded after medical/scientific review has been performed, and data have been declared final and complete. The SAP will be approved prior to the final database lock.

A subject is considered enrolled in the study at randomization.

9.1. Statistical Hypotheses

The study has no formal statistical primary endpoint hypothesis. The intent is to estimate the treatment effect of each dose group relative to placebo. For analysis of Cohort 1, subjects from Cohorts 1a and 1b will be combined. The primary analysis adjusted for randomization stratification will use the baseline UUI (≤ 3 vs. > 3 UUI episodes per day) and previous onabotulinumtoxinA use (naïve vs. prior use). Subjects in Cohort 1a will be assigned to the onabotulinumtoxinA naïve stratum. For the final analysis, the subjects receiving placebo from Cohort 1 and Cohort 2 will be pooled.

9.2. Sample Size Determination

For this exploratory study, the sample size was empirically chosen. With a total of 23 evaluable female subjects in each of the URO-902 treatment groups and 23 evaluable female subjects in the placebo group, this study would have approximately 55% power to detect a between-group difference of 1.8 episodes in the mean change from baseline to Week 12 in the number of UUI episodes per day between the URO-902 and placebo treatment groups (based on a 2-sample t-test with a 2-sided type I error rate of 0.05 and standard deviation [SD] of 2.86). Furthermore, the half-width of the confidence interval would be the following for different SD assumptions:

SD	N per Group	Half-Width of Confidence Interval	Lower Limit	Upper Limit
2.86	23	1.70	0.10	3.50
3.00	23	1.78	0.02	3.58
2.50	23	1.49	0.31	3.29

In order to account for subject attrition (approximately 10%), the sample size was increased to 26 subjects for each treatment group, amounting to a total of 78 randomized subjects required for exploratory efficacy analyses in both Cohort 1 (n = 39) and Cohort 2 (n = 39).

9.3. Analyses Populations

The following analysis populations will be evaluated: safety, safety (modified), and intent-to-treat exposed (ITT-E).

ITT-E will be used for demographics, baseline characteristics, and efficacy analyses. The ITT-E population will consist of all subjects randomized and treated from Cohorts 1 and 2.

The safety population will consist of all subjects from Cohorts 1 and 2 who were randomized and received study drug and will be used to analyze all safety endpoints based on actual treatment received. A separate safety population, safety (modified), will be created to assess safety excluding subjects who received additional OAB medication at Week 24 or after.

Other populations, such as Intent-To-Treat and All Subjects Screened populations, will be defined in the SAP.

9.4. Analysis Endpoints

The exploratory study has no formal statistical primary analysis endpoint.

9.4.1. Efficacy, Health Outcome, and Urodynamics Endpoints

For the purposes of this study, the number of UUI episodes will be defined as the number of times a subject has marked “urge” as the main reason for the leakage as indicated on the Bladder Diary; regardless of whether more than one reason for leakage in addition to “urge” is checked. Average daily number of UUI episodes is calculated using the daily entries in the Bladder Diary, which is completed prior to each study visit. Average daily number of UUI episodes will be calculated as the total number of UUI episodes that occur on a Diary Day divided by the number of Diary Days in the Bladder Diary.

A micturition is defined as “Urinated in Toilet” as indicated on the Bladder Diary. Average daily micturitions at each study visit will be calculated in the same manner as described above for UUI episodes.

Urinary incontinence is defined as having any reason for leakage or “Accidental Urine Leakage” as indicated on the Bladder Diary.

An urgency episode is defined as the “Need to Urinate Immediately” as indicated on the Bladder Diary.

Exploratory Efficacy Endpoints are listed in Section 3.2.1.

9.4.2. Safety Endpoints

Safety will be assessed via clinical review of all relevant safety parameters including AEs, clinical laboratory assessments, vital sign assessments, PVR volume, physical examination, ECGs, and concomitant medications and procedures.

9.4.3. Other Endpoints

Blood and urine *hSlo* cDNA concentrations.

9.5. Statistical Analyses

9.5.1. Statistical Methods for Efficacy Analysis

Descriptive statistics will be used to evaluate the efficacy endpoints. For continuous efficacy endpoints, estimates of least squares means, standard error, and 95% confidence intervals (CI) will be presented for each treatment group and the difference between each dose group relative to placebo. Nominal p-values from comparisons from each dose group relative to placebo may be provided for descriptive purposes.

Baseline will be defined as the diary assessments collected prior to randomization for all diary related efficacy endpoints and results of the questionnaires collected at the Day 1 Visit (Visit 3) for all health outcome endpoints.

For the analysis of continuous change from baseline endpoints (eg, change from baseline in average daily number of UUI episodes, change from baseline in average daily number of micturitions, change from baseline in average daily number of UI episodes, change from baseline in average daily number of urgency episodes, change from baseline in average volume voided per micturition, change from baseline in average I-QOL total summary score, change from baseline in OAB-q score, and change from baseline in PGI-C score), a mixed-effect model for repeated measures (MMRM) with restricted maximum likelihood estimation will be used. Analysis will be stratified by the randomization factors assuming there are greater than 5 subjects per stratum. This model corrects for dropout and accounts for the fact that measurements taken on the same subject over time tend to be correlated, by using all available information on subjects within the same covariate set to derive an estimate of the treatment effect for a drop-out free population.

The analysis model for each efficacy endpoint will include terms for treatment, visit, visit by treatment interaction term, and baseline score as covariates. If warranted, non-parametric methods will be used. For interim analyses, analysis of covariance (ANCOVA) may be performed instead of MMRM due to limited sample size. If there is a sufficient sample size, randomization factors will be considered for use in the model. Data for all visits will also be presented.

The proportion of subjects who has ≥ 50% reduction from baseline in UUI episodes at Week 12 will be calculated for each treatment group. In addition, responder analyses will also be calculated for subjects who achieve ≥ 75% and 100% decrease in episodes of UUI at Week 12 relative to baseline. The Cochran-Mantel-Haenszel (CMH) method will be utilized to compare the proportion of responders between the active and placebo groups by adjusting for the stratification factors. Data for all visits will also be presented. Further details of handling of missing data will be described in the SAP.

For the urodynamic variables evaluated, only the independent central reviewer's interpretation will be analyzed.

9.5.2. Safety Analyses

Safety analysis will be conducted using the safety population and summarized by treatment group. The treatment-emergent period will be defined as the period from initial exposure of the study drug through 48 weeks after treatment administration or the date of the initiation of another investigational agent or surgical intervention, whichever occurs first. Safety will be assessed through summaries of adverse events and clinical laboratory evaluations.

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA; version 21.0 or higher). All reported AEs (whether treatment emergent or not) will be included in by-patient AE listings. The severity of all adverse events will be evaluated by the investigator. The incidence of the adverse events will be presented by system organ class and preferred term, relationship to study treatment, and severity. Treatment emergent AESIs and treatment related AESIs will also be summarized by system organ class (SOC) and preferred term (PT). A list of all AESIs can be found in Section 8.5.6.

Laboratory data will consist of chemistry, hematology, and urinalysis data. Only data collected by the laboratory will be included in the analysis.

Descriptive statistics of observed values and change from baseline for vital signs and post void residual volume will be listed and summarized.

Supplemental safety analyses will be performed to separate subjects that did or did not receive additional OAB treatment at or after Week 24. Tables that are to be repeated with the alternative safety population will be described further in the SAP.

9.6. Multiplicity

All efficacy endpoints will be considered descriptive and no multiplicity adjustments will be performed for these endpoints.

9.7. Subgroup Analyses

Subgroup analyses of endpoints may be conducted. Additional details of any planned subgroup analyses will be provided in the SAP.

9.8. Planned Analyses

9.8.1. Interim Analyses

Two or more interim analyses may be conducted; when ≥ 50% of subjects in Cohort 1, and/or when ≥ 50% of subjects in Cohort 2 have completed at least 12 weeks of follow-up post-randomization (or prematurely exited the study prior to Week 12). Any interim analysis performed is for future planning purposes.

The planned interim analysis will be conducted to evaluate the objectives of the protocol at Week 12. These analyses will be performed after the completion of the following steps:

- All subjects in Cohorts 1 and 2 have completed Week 12 (or prematurely exited the study prior to Week 12)
- All required database cleaning activities have been completed and final database release and freeze has been declared by data management
- All criteria for unblinding the randomization code have been met.

For any interim analysis, the subject and the investigator or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will remain blinded to the treatment assignments. Limited personnel from the Sponsor will be unblinded (double-blind, sponsor-open design). Sponsor personnel who are directly involved with site interactions and communications (eg, study data manager and site monitors) will remain blinded to subject level treatment assignment.

9.8.2. Final Analyses

The planned final end-of-study analysis will be performed once the final clinical database lock (after all subjects complete the study or exit the study prematurely) has been achieved and treatment codes have been unblinded to the statistics and programming team. The clinical study report will be based on final analysis results.

9.8.3. Data and Safety Monitoring Board

A DSMB will be retained to assess, on an ongoing basis, all safety aspects of this study including unblinded review of safety data after all subjects reach Week 6 (or prematurely exited the study prior to Week 6) in Cohort 1 (URO-902 24 mg). Randomization into Cohort 2 will begin only after the DSMB has recommended it is safe to proceed. This committee will be an external independent DSMB that monitors safety. The detailed activities including meeting plans will be

described and documented in the DSMB Charter. A separate statistical analysis plan may be prepared for the DSMB.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/International Organization for Standardization Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, subject-oriented materials) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the Sponsor or designee with sufficient, accurate financial information as requested to allow the Sponsor or designee to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier. Any subject records or datasets that are transferred to the Sponsor or designee will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. If a subject is rescreened and assigned a new subject number, both subject numbers for that individual will be linked.
- The subject must be informed that her personal study-related data will be used by the Sponsor or designee in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor or designee, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Not applicable.

10.1.6. Posting Clinical Study Data

Clinical study information will be posted on external registries and websites (eg, US National Institutes of Health's website www.ClinicalTrials.gov and European Clinical Trial Register) as per applicable regulatory requirements.

10.1.7. Data Quality Assurance

- All subject data relating to the study will be recorded on the eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor is responsible for the data management of this study including quality checking of the data. Management of clinical data will be performed in accordance with applicable Sponsor-approved standards and data cleaning procedures to ensure the integrity of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.7.1. Study Site

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The investigator must notify the Sponsor before destroying any clinical study records.

The study site and the record retainer should take measures in such a way that these records are not lost or abandoned during the designated period of preservation and that they are presented upon request.

10.1.7.2. Institutional Review Board, Independent Ethics Committee, and Research Ethics Board (IRB/IEC/REB)

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and any other relevant materials, including accompanying material to be provided to the subject (eg, advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB/REB/IEC. Initial approval from the IRB/REB/IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the following:

- Protocol number
- Protocol version
- Protocol date
- Documents reviewed
- Date on which the committee met and granted the approval

Any amendments to the protocol will require IRB/REB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following (and must retain applicable notices and records as above under Study Site):

- Providing written summaries of the status of the study to the IRB/REB/IEC's annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/REB/IEC
- Notifying the IRB/REB/IEC of serious adverse events or other significant safety findings as required by procedures established by the IRB/REB/IEC
- Notifying the IRB/REB/IEC when the study has been completed or when his/her individual study site has been closed

10.1.8. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must be available during the site monitor's visit.
- The required source documents are:
    - Subject identification (name, date of birth, sex)
    - Documentation that the subject meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria)
    - Participation in the study (including study number)
    - Study discussed and date of informed consent
    - Dates of all visits

- Documentation that protocol-defined procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug (drug dispensing and return should be documented as well)
- Record of all AEs and other safety parameters (start and end date, and causality and intensity as assigned by the investigator)
- Concomitant medication (including start and end date)
- Date of study completion and reason for early discontinuation, if applicable.

10.1.9. Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC/REB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

As stated above in Section 10.1.7, the investigator is responsible for notifying the IRB/IEC/REB upon closure of the site or completion of the study.

10.1.10. Publication Policy

- The Sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Sponsor or designee personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the Sponsor.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

10.1.11. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the Sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review subject and study drug accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification, and the investigator will document the deviation in the subject records and/or any applicable eCRF(s). Significant protocol deviations will be reported to the IRB/IEC/REB according to the IRB/IEC/REB's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The clinical laboratory tests to be performed are detailed in Table 2. Subjects do not need to fast prior to laboratory testing. Refer to the Laboratory Manual for information on where testing should be performed (site, local laboratory, central laboratory).

A urine dipstick will be performed at the study site at scheduled visits as noted in the Schedule of Assessments (Section 1.3) and when a subject presents with symptoms of a UTI at Unscheduled Visits. If the urine dipstick is positive for leukocytes, nitrites, or blood cells, then a urinalysis and culture/sensitivity testing will be performed on the sample. The urinalysis should be performed at the central laboratory and the culture and sensitivity should be performed at the site's designated local laboratory.

Table 2: Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis and Urine Culture/Sensitivity[a]	Other
Hematocrit	Albumin	Blood	FSH[b]
Hemoglobin	Alkaline phosphatase	Glucose	Urine cytology[d]
Platelet count	ALT	Protein	
WBC (total and differential)	AST	Specific gravity	
RBC	Bicarbonate	Ketones	
	Calcium	Occult blood	
	Chloride	Leukocyte esterase	
	Creatinine[c]	Nitrite	
	Glucose (non-fasting)	Bilirubin	
	Potassium	Urobilinogen	
	Sodium	Microscopic exam if positive for protein (RBCs, WBCs, epithelial cells, bacteria, yeast)	
	Blood urea nitrogen	pH	
		Color	
		Appearance	
		Culture/sensitivity: Culture, quantitation, isolation, identification, and susceptibility	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RBC = red blood cell count; WBC = white blood cell count

[a] A sample for urinalysis and urine culture/sensitivity will be sent to the laboratory only if the urine dipstick performed at the site is positive for the presence of leukocytes, nitrites, or blood cells.

[b] Follicle stimulating hormone testing may be performed at screening to confirm postmenopausal status

[c] estimated glomerular filtration rate will be calculated and reported by the laboratory.

[d] at Screening only

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition
An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

AE of Special Interest

An AESI is one of scientific and medical concern specific to the Sponsor's study drug/device or program, which may warrant ongoing monitoring and rapid communication by the investigator to the Sponsor or designee. Such an event might warrant further investigation in order to characterize and understand it. See Section 8.5.6 for AESIs defined for this study.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. For this study, report all overdose events within 24 hours of awareness by the study site, using the eCRF, whether or not the overdose is associated with an AE.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE. Any worsening of OAB symptoms should be collected as an AE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.
- The disease/disorder being studied or expected signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been admitted to the hospital or kept in the Emergency Room for ≥ 24 hours for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent activities of daily living but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medically significant events include invasive or malignant cancers, intensive treatment with a drug in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the eCRF.
- All SAEs (including serious AESIs) must be **reported in the eCRF within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug.
  - The event term, start date, severity, and initial causality assessment must be entered in the AE eCRF page and the event must be marked as "Serious". This will activate additional assessment fields including "action taken with study drug", "seriousness criteria", and "brief description" which should be completed as soon as information is available. Marking the event as "serious" will automatically send required notifications for Sponsor or designee review.
  - The initial SAE report should include:
    - The date of the report
    - A description of the SAE (event term, seriousness of the event, date of onset, intensity)
    - Causal relationship to the study drug
  - A discharge summary should be provided for all hospitalizations. If the subject died, the report should include the cause of death as the event term (with death as the outcome) and whether the event leading to death was related to study drug, as well as the autopsy findings, if available
- Nonserious AESIs should be reported on the eCRF within 72 hours of knowledge of the information.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of the AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

1/MILD	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
2/MODERATE	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/SEVERE OR MEDICALLY SIGNIFICANT	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/LIFE-THREATENING	Life threatening consequences; urgent intervention indicated
5/DEATH	Death related to adverse event

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE or SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE to the Sponsor or designee.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
All SAEs must be **reported in the eCRF within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug. Marking the event as "Serious" will activate additional assessment fields.

10.4. Appendix 4: Abbreviations

Term	Description
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
cDNA	complementary deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	confidence interval
CIC	clean intermittent catheterization
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
DNA	deoxyribonucleic acid
DO	detrusor overactivity
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
ED	erectile dysfunction
EW	early withdrawal
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
FSV	cystometric volume at 1st sensation to void
GCP	Good Clinical Practice
HRQL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure

Term	Description
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	International Continence Society
IDC	involuntary detrusor contraction
IEC	independent ethics committee
I-QOL	Incontinence-Specific Quality-of-Life Instrument
IRB	institutional review board
ITT-E	intent-to-treat exposed
IWRS	interactive web response system
K	potassium
MCC	maximum cystometric capacity
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
OAB	overactive bladder
OAB-q	Overactive Bladder Questionnaire
PBS	phosphate buffered saline
P_{det}@1stIDC	maximum detrusor pressure during the first involuntary detrusor contraction
$Pdet_{MaxStorage}$	maximum detrusor pressure during the storage phase
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic
PRO	patient-reported outcome
PT	preferred term
PUO	partial urethral outlet
PVR	post-void residual
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOA	Schedule of Assessments
SOC	system organ class
TEAE	treatment-emergent adverse event
UI	urinary incontinence

Term	Description
URO-902	formerly known as *h*Maxi-K or pVAX/*hSlo*. GMP manufactured double-stranded DNA plasmid (pVAX) containing a cDNA insert encoding the pore-forming α subunit of the human smooth muscle Maxi-K channel, *hSlo*
Urovant	Urovant Sciences GmbH
US	United States
UTI	urinary tract infection
UUI	urge urinary incontinence
Vol@1stIDC	volume at first involuntary detrusor contraction

10.5. Appendix 5: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	An Exploratory Phase 2a Study Evaluating the Efficacy and Safety of URO-902 in Subjects with Overactive Bladder and Urge Urinary Incontinence
	Clinical Study Sponsor	Urovant Sciences GmbH
	Trial Phase Classification	Phase 2a
	Trial Indication	Overactive Bladder (OAB) and Urge Urinary Incontinence (UUI)
	Trial Indication Type	Treatment
	Trial Type	Multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2-cohort, dose-escalation
	Trial Length	Up to 53 weeks
	Planned Country of Investigational Sites	North America
	Planned Number of Subjects	78
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	OAB with UUI
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	40
	Planned Maximum Age of Subjects	79
	Sex of Subjects	Female
	Stable Disease Minimum Duration	At least 6 months prior to screening

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	URO-902
	Drug Type	URO-902 consists of the gene for the α pore of the Maxi-K channel, *hSlo*, inserted into a plasmid vector, pVAX, called pVAX/*hSlo*
	Pharmacological Class of Invest. Therapy	Gene therapy
	Dose per Administration	24 or 48
	Dose Units	mg
	Dosing Frequency	Single administration
	Route of Administration	Intradetrusor injections via cystoscopy
	Current Therapy or Treatment	Current therapy or treatment for symptoms of OAB not allowed
	Added on to Existing Treatments	Not applicable
	Control Type	Placebo
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Randomized, double-blind, placebo-controlled, single-treatment
	Drug Model	2-cohort, sequential, dose-escalation
	Planned Number of Arms	Placebo and 2 dose groups of URO-902
	Trial is Randomized	Yes
	Randomization Quotient	2:1
	Trial Blinding Schema	Double-blind
	Stratification Factor	Cohort 1a: Baseline UUI episodes per day (ie, ≤ 3 vs. > 3 UUI episodes per day) and presence or absence of DO (as determined by the investigator) at randomization. Cohort 1b and Cohort 2: randomization will be stratified by baseline UUI episodes per day and previous use of onabotulinumtoxinA (naïve vs. prior use). OnabotulinumtoxinA use for urological indications must have occurred at least 12 months prior to the beginning of recording symptoms into the Screening Bladder Diary
	Adaptive Design	No

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

The current study will enroll eligible female subjects aged 40 to 79 years old at screening who are non-childbearing and satisfy at least one of the following:

- is postmenopausal with documentation of cessation of menses for ≥ 12 consecutive months at the start of screening, without an alternative medical cause.

  - If the investigator believes that additional confirmation of postmenopausal status is necessary, a follicle-stimulating hormone (FSH) level in the postmenopausal range (≥ 30 mU/mL at Screening) may be used to confirm a postmenopausal state; systemic HRT must be temporarily discontinued (duration determined by the investigator) prior to testing FSH levels. Women whose postmenopausal status is in doubt must be deemed ineligible for study participation.

- is permanently sterile, following bilateral tubal ligation (performed ≥ 6 months prior to the start of screening), hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

Pregnancy tests will not be conducted during this study.

10.7. Appendix 7: Prohibited Medications and Non-Drug Therapies

The following medications/procedures are prohibited prior to the study and during the study (until Week 24), as outlined in Section 6.9.1.

Prohibited Medications Class	Examples	Washout Period/Comments
Anticholinergics[a]	Darifenacin, fesoterodine, hyoscyamine, oxybutynin, propantheline, solifenacin, tolterodine, and trospium	Subject must discontinue use at least 14 days prior to beginning recording of symptoms into the Screening Bladder Diary and remain off this therapy during the study (until Week 24). Inhaled anticholinergics used on an as needed basis are permitted
Anticholinergic intravesical therapy	Oxybutynin, trospium	Subject must discontinue use at least 4 weeks prior to beginning recording of symptoms into the Screening Bladder Diary and remain off this therapy during the study (until Week 24)
Antidiuretic hormones	Desmopressin	Subject must discontinue use at least 1 day prior to beginning recording of symptoms into the Screening Bladder Diary and remain off this therapy during the study (until Week 24)
Beta-3 adrenergic agonists	Mirabegron	Subject must discontinue use at least 14 days prior to beginning recording of symptoms into the Screening Bladder Diary and remain off this therapy during the study (until Week 24)
Botulinum toxins	Intradetrusor injection or intravesical administration of botulinum toxin	Subject must discontinue onabotulinumtoxinA use at least 12 months prior to starting the Screening Bladder Diary and remain off this therapy or any other toxin used for urological indications during the study (until Week 24)
Intravesical pharmacologic agent	Capsaicin, resiniferatoxin	Subject must discontinue use within 12 months of randomization and remain off this therapy during the study (until Week 24)
Implanted electrostimulation/ neuromodulation device Use of other non-implantable electrostimulatory devices	InterStim™, NURO™	Current or planned use prohibited for the duration of the study (until Week 24)

a Refers to prescription medications used on a daily basis to treat chronic conditions.

10.8. Appendix 8: Study Schedule Supplement

Please see Section 1.3 for the Schedule of Assessments.

10.9. Appendix 9: Patient-reported Outcomes Questionnaires Descriptions and Instructions

Information on each of the scales and questionnaires for patient-reported outcomes are provided below. A sample for each assessment is also provided.

10.9.1. Incontinence-Specific Quality-of-Life Instrument (I-QOL)

The I-QOL is a validated, disease-specific quality of life questionnaire designed to measure the impact of urinary incontinence on patients' lives [Patrick 1999]. It contains 22 items and is designed for self-administration, requiring approximately 5 minutes to complete. The response options and values for each item are: "Extremely" (value = 1), "Quite a bit" (value = 2), "Moderately" (value = 3), "A little" (value = 4), and "Not at all" (value = 5). A total summary score is calculated based on the 22 items; additionally, three domain scores (Avoidance and Limiting Behavior, Psychosocial Impact, and Social Embarrassment) can be calculated based on responses to items corresponding to each respective domain. The total summary and domain scores range from 0 to 100, with higher scores indicating better quality of life.

Incontinence Quality of Life Instrument

PLEASE WRITE IN

PARTICIPANT ID:

TODAY'S DATE: ___ _____ ___

Day Month Year

PLEASE READ THIS CAREFULLY

ON THE FOLLOWING PAGES YOU WILL FIND SOME STATEMENTS THAT HAVE BEEN MADE BY PEOPLE WHO HAVE URINARY INCONTINENCE (LEAKING URINE WHEN YOU DON'T WANT TO).

PLEASE CHOOSE THE RESPONSE THAT APPLIES BEST TO YOU RIGHT NOW AND CIRCLE THE NUMBER OF YOUR ANSWER.

IF YOU ARE UNSURE ABOUT HOW TO ANSWER A QUESTION, PLEASE GIVE THE BEST ANSWER YOU CAN. **THERE ARE NO RIGHT OR WRONG ANSWERS.**

YOUR ANSWERS WILL BE KEPT STRICTLY CONFIDENTIAL.

IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT:

Your Feelings

(Please circle the number of your answer)

1. I worry about not being able to get to the toilet on time
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

2. I worry about coughing or sneezing because of my urinary problems or incontinence.
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

3. I have to be careful standing up after I've been sitting down because of my urinary problems or incontinence.
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

4. I worry about where toilets are in new places.
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

5. I feel depressed because of my urinary problems or incontinence.
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

(Please circle the number of your answer)

6. Because of my urinary problems or incontinence, I don't feel free to leave my home for long periods of time.
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

7. I feel frustrated because my urinary problems or incontinence prevents me from doing what I want.
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

8. I worry about others smelling urine on me.
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

9. My urinary problems or incontinence is always on my mind.
   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

10. It's important for me to make frequent trips to the toilet.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

(Please circle the number of your answer)

11. Because of my urinary problems or incontinence, it's important to plan every detail in advance.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

12. I worry about my urinary problems or incontinence getting worse as I grow older.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

13. I have a hard time getting a good night of sleep because of my urinary problems or incontinence.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

14. I worry about being embarrassed or humiliated because of my urinary problems or incontinence.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

15. My urinary problems or incontinence makes me feel like I'm not a healthy person.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

(Please circle the number of your answer)

16. My urinary problems or incontinence makes me feel helpless.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

17. I get less enjoyment out of life because of my urinary problems or incontinence.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

18. I worry about wetting myself.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

19. I feel like I have no control over my bladder.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

20. I have to watch what or how much I drink because of my urinary problems or incontinence.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

(Please circle the number of your answer)

21. My urinary problems or incontinence limit my choice of clothing.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

22. I worry about having sex because of my urinary problems or incontinence.
    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

10.9.2. Overactive Bladder Questionnaire (OAB-q)

The Overactive Bladder Questionnaire (OAB-q) was developed to assess symptom bother and the impact of overactive bladder (OAB) on health-related quality of life (HRQL) [Coyne 2002]. The instrument was developed and validated in both continent and incontinent OAB patients, including both men and women. It contains 33 items and is designed for self-administration, requiring approximately 5 to 10 minutes to complete. The response options and values for each item are: "Not at all/None of the time" (value = 1), "A little bit/A little of the time" (value = 2), "Somewhat/Some of the time" (value = 3), "Quite a bit/A good bit of the time" (value = 4), "A great deal/Most of the time" (value = 5), and "A very great deal/All of the time" (value = 6). The instrument yields a symptom severity score, a HRQL total score, and four HRQL subscores (coping, concern, sleep, and social). All scores range from 0 to 100, with a higher score indicating greater symptom severity for the symptom severity score and better HRQL for the total and subscale HRQL scores.

Overactive Bladder Questionnaire (OAB-q)

Date of (dd-MMM-yyyy) ___ - ___ - ___

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past week. Please place a ✓ or × in the box that best describes the extent to which you were bothered by each symptom during the past week. There are no right or wrong answers. Please be sure to answer every question.

During the past week, how bothered were you by. . .	Not at all	A little bit	Somewhat	Quite a bit	A great deal	A very great deal
1. Frequent urination during the daytime hours?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. An uncomfortable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. A sudden urge to urinate with little or no warning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Accidental loss of small amounts of urine?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Nighttime urination?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Waking up at night because you had to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
7. An uncontrollable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
8. Urine loss associated with a strong desire to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

The above questions asked about your feelings about individual bladder symptoms. For the following questions, please think about your overall bladder symptoms in the past week and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a ✓ or × in the box that best answers each question.

Overactive Bladder Questionnaire (OAB-q)

During the past week, how often have your bladder symptoms . . .	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
9. Made you carefully plan your commute?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Caused you to plan "escape routes" to restrooms in public places?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
12. Caused you distress?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
13. Frustrated you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
14. Made you feel like there is something wrong with you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
15. Interfered with your ability to get a good night's rest?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
16. Caused you to decrease your physical activities (exercising, sports, etc.)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
17. Prevented you from feeling rested upon waking in the morning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
18. Frustrated your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
19. Caused you anxiety or worry?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
20. Caused you to stay home more often than you would prefer?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
21. Caused you to adjust your travel plans so that you are always near a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
22. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Overactive Bladder Questionnaire (OAB-q)

During the past week, how often bladder symptoms . . .	None of the time	A little bit of the time	Some of the time	A good the time	Most of the time	All of the time have your
23. Made you frustrated or annoyed about the amount of time you spend in the restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
24. Awakened you during sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
25. Made you worry about odor or hygiene?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
26. Made you uncomfortable while traveling with others because of needing to stop for a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
27. Affected your relationships with family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
28. Caused you to decrease participating in social gatherings, such as parties or visits with family or friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
30. Interfered with getting the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
31. Caused you to have problems with your partner or spouse?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
32. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
33. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

10.9.3. Patient Global Impression of Change Scale (PGI-C)

The Patient Global Impression (PGI) scale in this study is an OAB-specific quality of life questionnaire. The tool was designed to assess the impact (and improvement) of urinary incontinence on activities of daily living, wellbeing, and function. The scale is brief, general (ie, does not collect specific symptoms in contrast to other outcome measures for OAB), and easily completed.

Global Impression Items

1. Over the past week, how would you rate your overactive bladder symptoms?

□ None

□ Mild

□ Moderate

□ Severe

2. Over the past week, how much control did you have over your overactive bladder symptoms?

□ Complete control

□ A lot of control

□ Some control

□ Only a little control

□ No control

3. Over the past week, how often did you have overactive bladder symptoms?

□ Never

□ Rarely

□ Sometimes

□ Often

□ Very often

4. Over the past week, how often did you have accidental urine leakage?

□ Never

□ Rarely

□ Sometimes

□ Often

□ Very often

5. Overall, compared to the start of the study, how would you rate your overactive bladder symptoms over the past week?

□ Much better

□ Moderately better

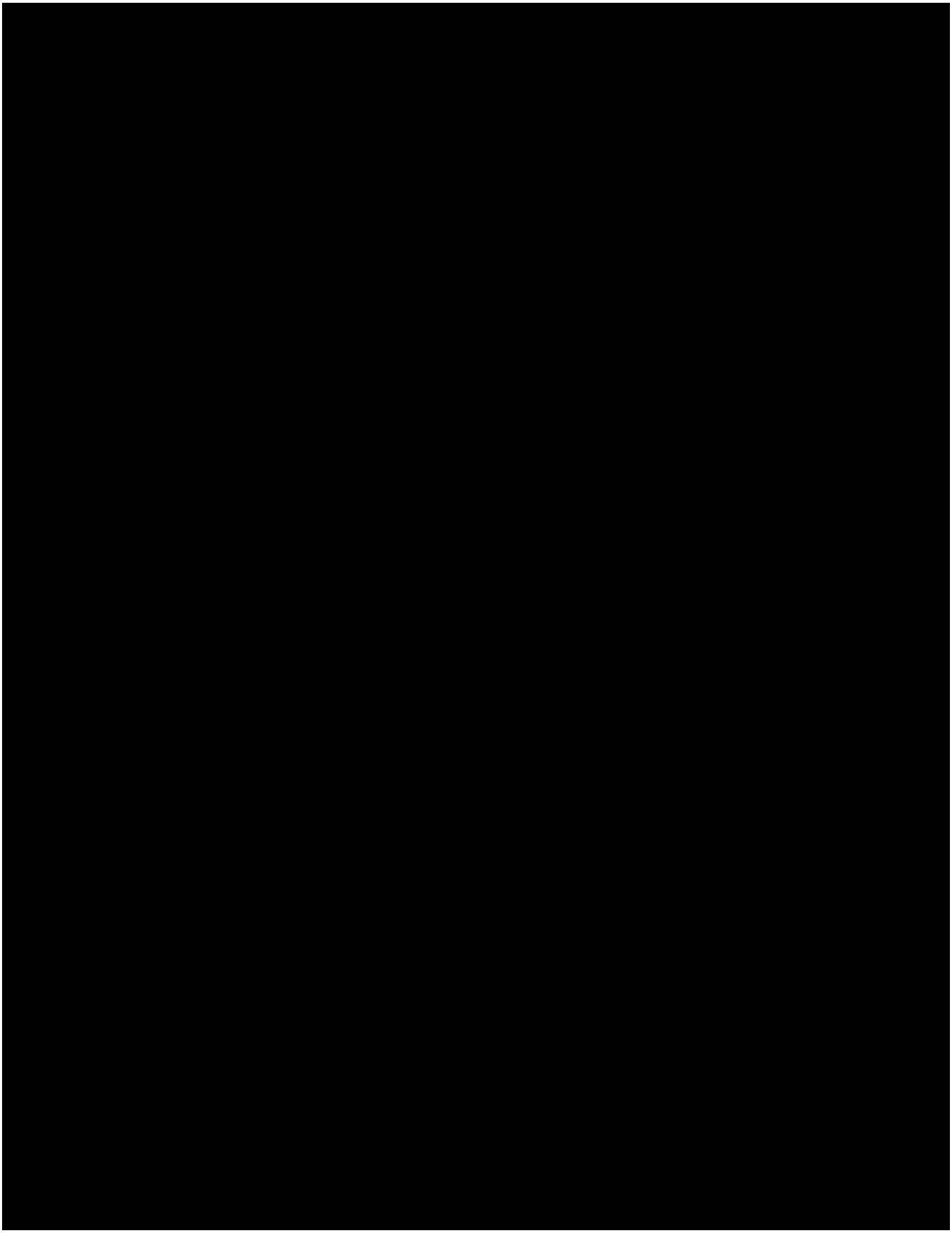
□ A little better

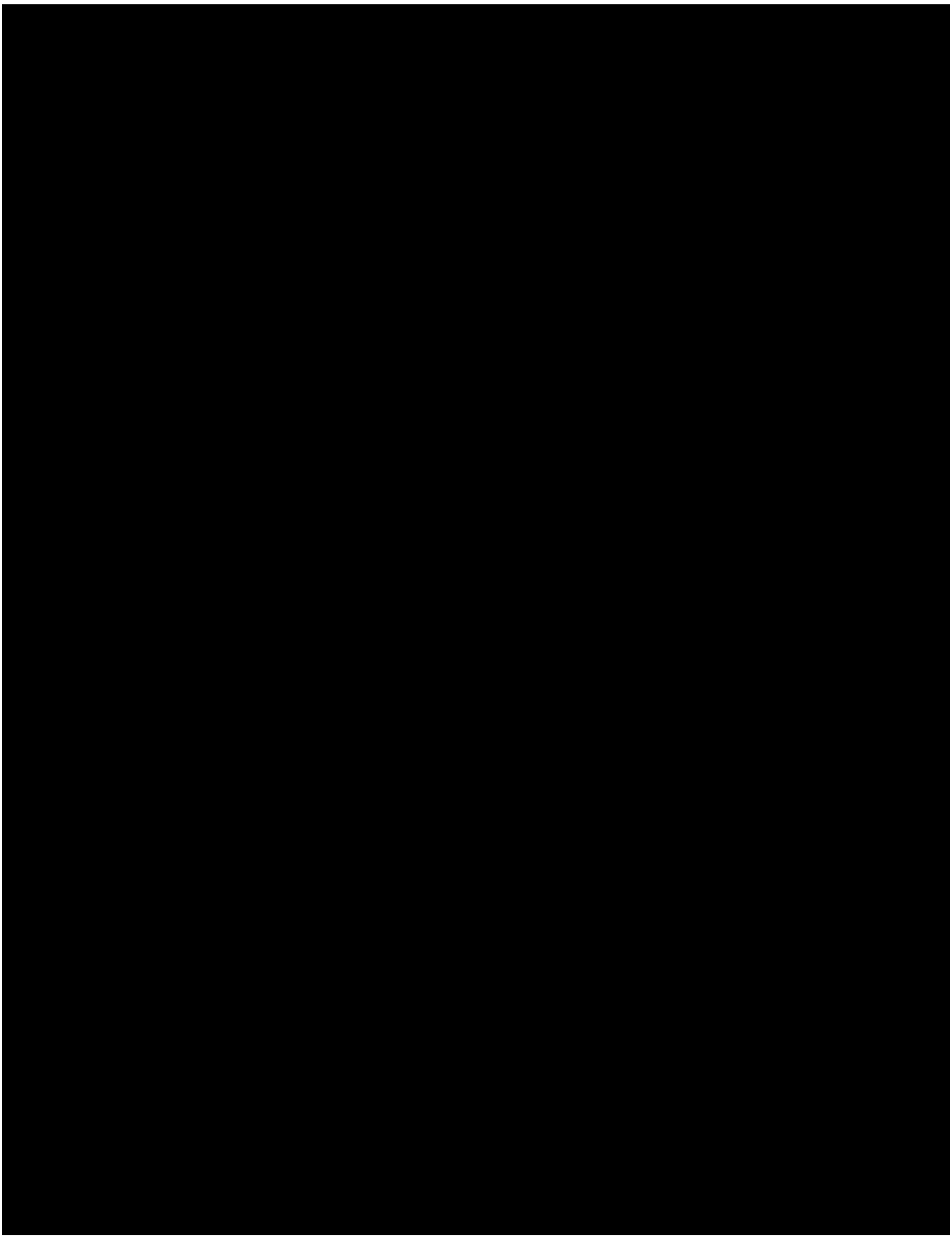
□ No change

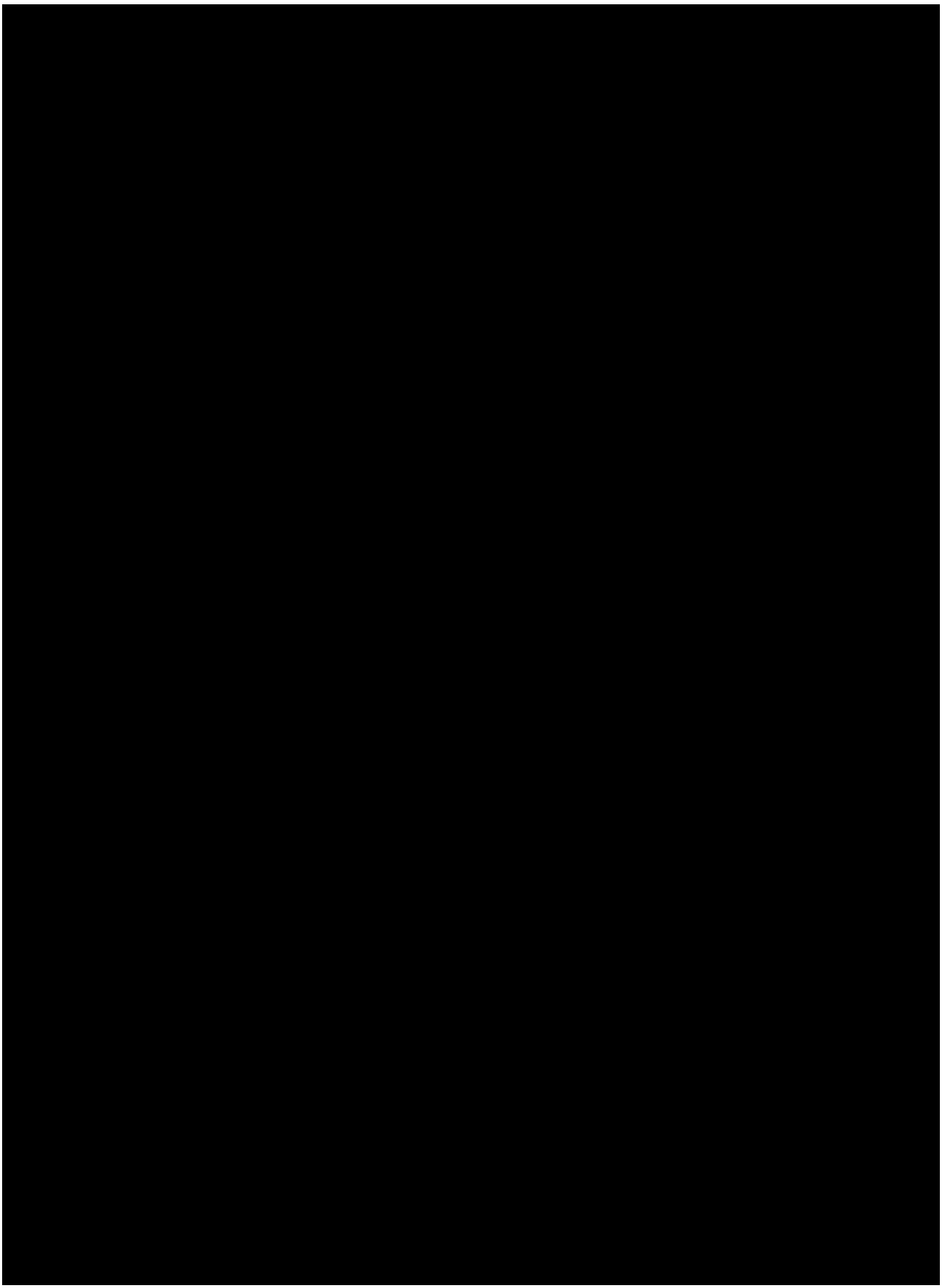
□ A little worse

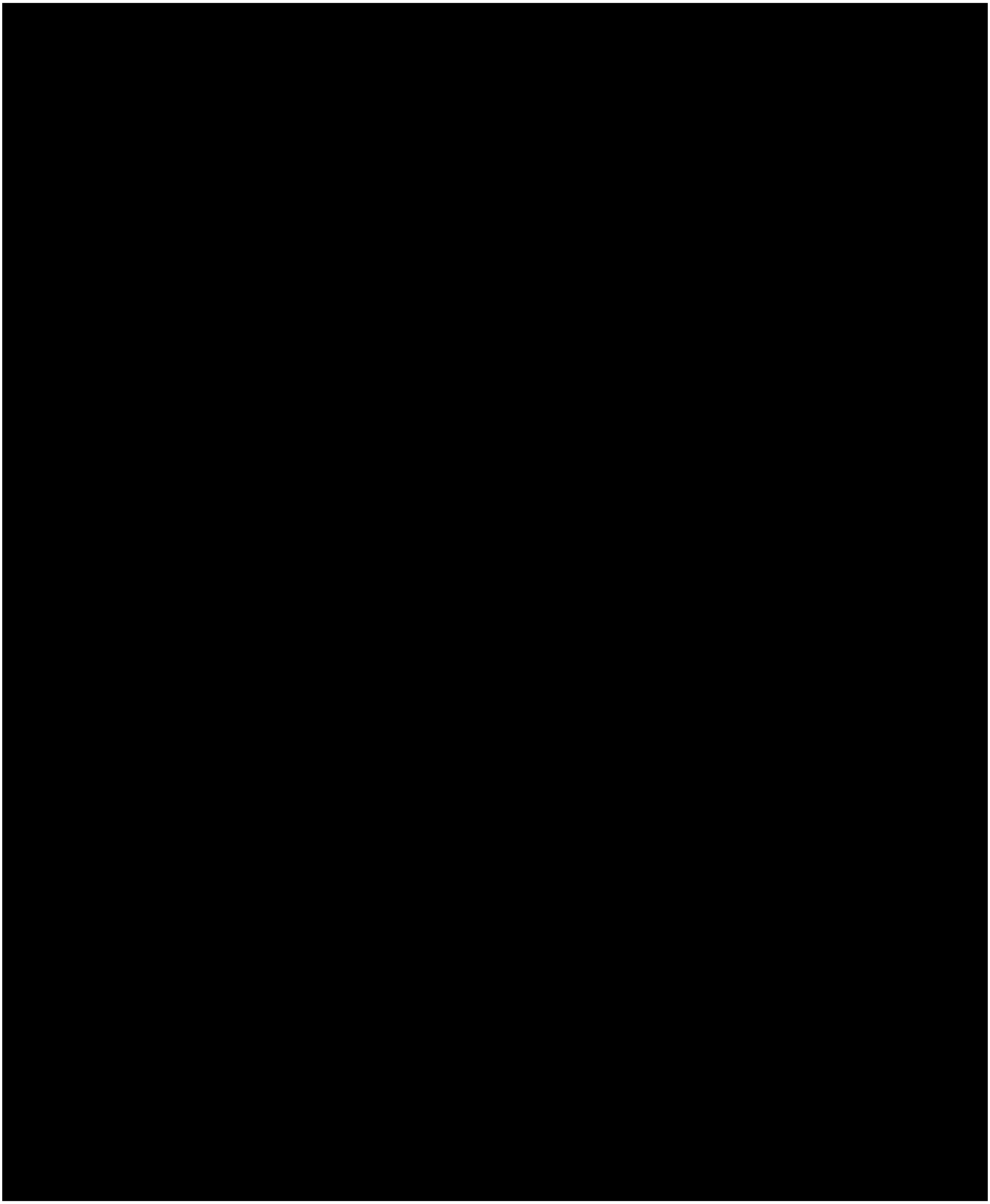
□ Moderately worse

□ Much worse









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