Protocol Title: A Phase 3 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)

Protocol Number:	URO-901-3006
Version Number:	1.0 (Original)
Product:	Vibegron (URO-901, RVT-901, MK-4618, KRP-114V)
Development Phase:	3
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EudraCT Number:	2018-003136-72
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Approval Date:	22 May 2019
Sponsor Signatory:	[redacted], MD, PhD Chief Medical Officer

NCT Number: NCT04103450

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SPONSOR SIGNATURE PAGE

Study Title: A Phase 3 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)

Protocol Number: URO-901-3006

This protocol has been approved by a representative of Urovant Sciences, GmbH. The following signature documents this approval.

[redacted], MD, PhD
Chief Medical Officer

[redacted]
Date (DD/MMM/YYYY)

INVESTIGATOR STATEMENT

Study URO-901-3006: A Phase 3 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH) (Version 1.0)

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date (DD/MMM/YYYY)	Site Number

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)

Protocol Number: URO-901-3006

Brief Title: Extension Study of Vibegron in Men with OAB Symptoms With BPH

Study Rationale: Beta-3 adrenergic receptor (β_3-AR) agonists have shown efficacy (with improved safety relative to anticholinergics) in treating persistent OAB symptoms in men on BPH therapies. This subset of the broader OAB population setting has unique safety needs (eg, possibility of urinary retention) that have not been fully evaluated in previous clinical programs of OAB treatments. Study URO-901-3006 is designed to evaluate long-term safety and efficacy of vibegron (75 mg once daily [QD] administered for 28 weeks) in men with symptoms of OAB while receiving pharmacological therapy for BPH who have received 24 weeks of study drug in double-blind, placebo-controlled, Phase 3 Study URO-901-3005.

Objectives: The primary study objective is to assess the long-term safety of vibegron when dosed for up to 52 weeks in men with OAB symptoms on pharmacological therapy for BPH who previously completed treatment in Study URO-901-3005. The primary clinical hypothesis is that vibegron + BPH pharmacological therapy for BPH treatment is safe for long-term use in men with OAB symptoms and BPH.

The secondary study objective is to assess the long-term efficacy of vibegron when dosed for up to 52 weeks in men with OAB symptoms on pharmacological therapy for BPH who previously completed treatment in Study URO-901-3005.

Endpoints:

Note: With respect to study endpoints, “per day” refers to a “Diary Day”, which is defined as the time between when the subject gets up for the day each morning and the time the subject gets up for the day the next morning as recorded in the subject bladder diary (approximately a 24-hour period).

Safety assessments will include treatment emergent AEs, clinical laboratory tests, physical examinations, vital signs, PVR volume, and Total IPSS.

Efficacy endpoints include the following:

- Change from baseline (CFB) at Week 52 in the average number of micturition episodes per day
- CFB at Week 52 in the average number of urgency episodes (urgency: need to urinate immediately) per day
- CFB at Week 52 in the average the number of nocturia episodes per night
- CFB at Week 52 in the average number of urge urinary incontinence episodes per day in subjects with incontinence at baseline in Study URO-901-3005
- CFB at Week 52 in the average of International Prostate Symptom Score (IPSS) 1-week recall) Storage score (1-week recall)
- CFB at Week 52 in the average volume voided per micturition

See Section 3 (Objective and Endpoints) for the other/exploratory endpoints, including quality-of-life endpoints.

Statistical Methods:

Safety analyses will be based on all subjects who receive vibegron (through Week 52 of this extension study). Only one treatment group (vibegron) will be reported for safety data. Baseline will be the baseline for Study URO-901-3005. Descriptive statistics will be used to summarize safety endpoints.

The efficacy analyses will be for descriptive purposes only and will be conducted using the FAS-Extension population, which is a subset of the Study URO-901-3005 treated population which have completed the 24-week treatment period in Study URO-901-3005 and enrolled into this extension study.

The efficacy endpoints of change from baseline in average number of micturitions, average number of urgency episodes, average number of nocturia episodes, average number of urge urinary incontinence (UUI) episodes, average of IPSS storage score, and average volume voided per micturition will be analyzed separately using a mixed model for repeated measure (MMRM) with restricted maximum likelihood estimation. The analysis model for each efficacy endpoint will include terms or visit, baseline, baseline stratification factors (those found to be significant in Study URO-901-3005). An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make statistical inference. The adjusted means for vibegron and visit will be estimated along with the 95% CI. Only the week-52 subjects (those on active treatment in Study URO-901-3005 and in Study URO-901-3006) will be included in the model.

Descriptive statistics will be used to summarize all efficacy endpoints. Summaries of efficacy endpoint will be presented by two treatment groups: vibegron for 52 weeks and vibegron for 28 weeks as determined by the randomized treatment in Study URO-901-3005.

Overall Study Design: This is an international Phase 3, open-label 28-week extension study to evaluate the safety and efficacy of vibegron 75 mg in men with symptoms of OAB on stable doses of pharmacological therapy for BPH. This study is an extension for subjects who have completed the Phase 3, double-blind, randomized, 24-week Study URO-901-3005.

Approximately 300 men with symptoms of OAB on stable doses of pharmacological therapy for BPH who completed 24 weeks in Study URO-901-3005 and continue to qualify for this study may be permitted to enroll in this extension study, from approximately 60 study sites.

During this extension study, subjects who had been randomized in Study URO-901-3005 to receive vibegron 75 mg will continue their same treatment once daily for an additional 28 weeks, and subjects who had been randomized in Study URO-901-3005 to the placebo group will receive study treatment of vibegron 75 mg once daily for 28 weeks during the extension. Thus, through participation in both the URO-901-3005 and URO-901-3006 (extension) studies, subjects originally randomized to vibegron will receive 52 weeks total of vibegron treatment, and subjects originally randomized to placebo will receive 28 weeks total of vibegron treatment.

Study visits will be named to reflect continuation from Study URO-901-3005, with the first study visit of this extension study occurring at Week 24. Following enrollment in this extension study, subjects will return to the clinic for visits at Week 28, Week 36, and Week 52 (all relative to Day 1 of Study URO-901-3005). A telephone contact will occur at Week 44 to review AEs/serious AEs (SAEs) and concomitant medications.

This study consists of a 28-week open-label Treatment Period. Unscheduled Visit(s) may be arranged as needed.

Number of Subjects: Up to 300 subjects who complete Study URO-901-3005 may be offered the opportunity to roll over into this study.

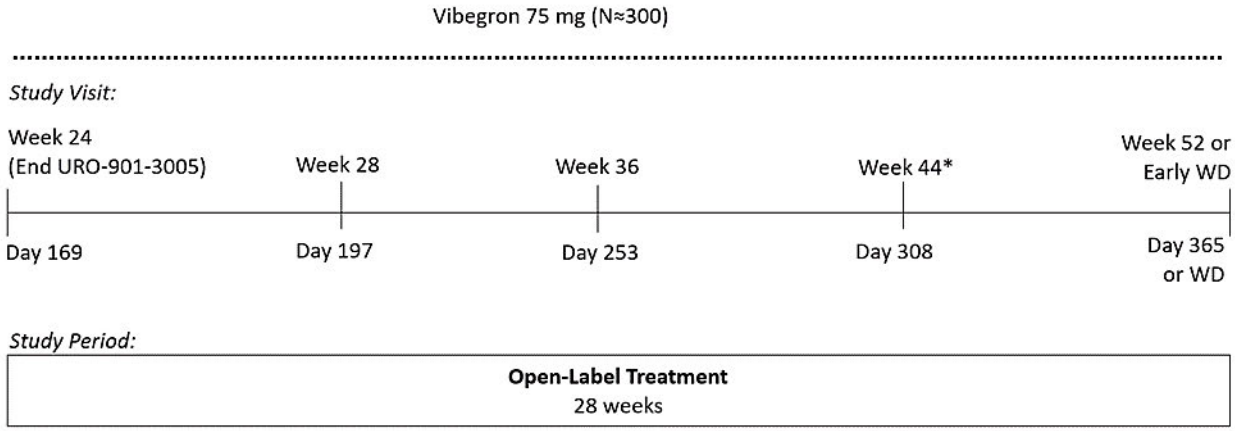
Number of Sites: Approximately 60 sites in North America and Europe.

Study Drug Groups and Study Duration: 75 mg vibegron, QD, administered orally. Study drug will be administered in an open-label (not blinded) manner for 28 weeks on Study URO-901-3006. Note: upon entering this extension study, all subjects will have already received 2 weeks of treatment with placebo plus an additional 24 weeks of blinded treatment with either vibegron or placebo in Study URO-901-3005. No dosage adjustments will be allowed.

Subjects will continue on the same alpha-blockers (eg, tamsulosin, doxazosin, and alfuzosin) with or without 5α-reductase inhibitors (5-ARIs) use (eg, finasteride, dutasteride, and alfatradiol) in Study URO-901-3006 as administered in Study URO-901-3005.

Data Safety Monitoring Board (DSMB): A DSMB will be retained to assess, on an ongoing basis, all safety aspects of this study. This will be an external independent DSMB that monitors the safety for both Study URO-901-3005 and Study URO-901-3006. The detailed activities including meeting plans will be described and documented in the DSMB Charter. A separate statistical analysis plan will be prepared for the DSMB.

1.2. Schema



*Week 44 consists of a telephone contact to review AEs/SAEs and concomitant medications; no clinic visit is required at that timepoint.

1.3. Schedule of Assessments

	Open-Label Treatment				
	Visit 11	**Visit 12**	**Visit 13**	**Telephone Call**	**Visit 14 or Early WD**
Day/Week	**Week 24 (Day 169)** [a]	**Week 28 (Day 197)**	**Week 36 (Day 253)**	**Week 44 (Day 308)**	**Week 52 or Early WD (Day 365)**
Visit Window	**±4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**
Informed Consent	X				
Subject Entry into IWRS	X				
Inclusion and Exclusion Criteria Review[a]	X				
AE/SAE Review	†	X	X	X	X
Concomitant Medication Review	†	X	X	X	X
IPSS[b]	†		X		X
[redacted]					
PGI[b]	†				X
[redacted]					
Vital Signs[c]	†	X	X		X
Brief Physical Examination	†				X
PVR volume	†	X	X		X
Laboratory Assessments[d]	†		X		X
Review and Data Enter Completed Bladder Diary[e]	†	X	X		X
Dispense Bladder Diary	X	X	X		
Dispense Open-label Study Drug	X	X	X		

AE = adverse event; [redacted] IPSS = International Prostate Symptom Score; IWRS = interactive web response system; OAB = overactive bladder; [redacted] PGI = Patient Global Impression; PRO = patient-reported outcomes; PVR = Post-void residual; SAE = serious adverse event; WD = withdrawal

† For noted procedures, the Week 24 (Visit 11) assessments for Study URO-901-3005 serve as initial on-study visit for Study URO-901-3006; these procedures will not be duplicated.

a Recheck clinical status before enrollment and first dose of open-label study drug. Initiation of Study URO-901-3006 should occur within 7 days of Study URO-901-3005 Week 24/End-of-Study visit.

b PRO questionnaires should be completed prior to other procedures, including vital signs, blood draws, and study drug dosing.

c Vital signs (including blood pressure [in triplicate], pulse, body temperature, respiration rate, and weight) should be taken prior to blood draws and study drug dosing.

d Refer to Section 10.2 for a list of laboratory assessments performed.

e Subject completes the Bladder Diary PRIOR to each visit.

2. Introduction

2.1. Study Rationale

Men with overactive bladder (OAB) symptoms associated with benign prostatic hypertrophy (BPH) represent an OAB subpopulation that has not been extensively studied. Often in these patients, OAB symptoms remain inadequately addressed despite treatment for their BPH (ie, alpha-blocker with or without 5-ARI). For reasons described below, this population warrants specific clinical studies to adequately evaluate and address their unique medical needs. Study URO-901-3006 is an extension study to Phase 3 Study URO-901-3005 designed to evaluate safety, tolerability, and efficacy of vibegron (75 mg once daily [QD]) for up to 52 weeks in men with OAB symptoms on pharmacological therapy for BPH.

2.2. Background

2.3. Overactive Bladder in Men with Benign Prostatic Hyperplasia

OAB is highly prevalent and affects approximately 16% of the population in the United States and Europe. Prevalence increases with age, affecting approximately one third of people 75 years and older [Stewart, 2003; Milsom, 2001]. Despite similar prevalence between the sexes and growing clinical trial evidence that men benefit from pharmacotherapy, men are less likely to use treatment for OAB [Goldman, 2016].

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. Urgency incontinence is distinguished from stress urinary incontinence, which is the involuntary loss of urine on effort or physical exertion (eg, sporting activities), or upon sneezing or coughing. When both components are present, the classification is mixed urinary incontinence, with either urgency or stress specified as the predominant component.

Although the overall prevalence of OAB in men and women is similar, there are major differences in predominating symptoms. Men are more likely to experience urgency, frequency, and nocturia accompanied by lower urinary tract symptoms (LUTS) associated with voiding dysfunction, whereas women are twice as likely to experience incontinence [Tubaro, 2017]. Since most men with OAB symptoms do not have urinary incontinence, the micturition frequency and the urgency become the predominant symptoms that characterize the disease for

the men with OAB on pharmacological therapy for BPH [Helfand, 2012]. Among men, urinary incontinence significantly increases after the age of 65 years.

Historically in men with BPH, LUTS have been presumed to result from bladder outlet obstruction secondary to prostate enlargement. However, men may have OAB symptoms in the absence of, or in conjunction with, voiding symptoms associated with BPH or urodynamic evidence of bladder outlet obstruction [Nakagawa, 2008; Hyman, 2001]. BPH can be associated with debilitating LUTS, categorized by storage symptoms (eg, urinary frequency, urgency, and nocturia) and voiding dysfunction (eg, decreased and intermittent force of stream and the sensation of incomplete bladder emptying).

2.3.1. Vibegron

Initial pharmacologic therapy for OAB symptoms in men with BPH traditionally has been directed at minimizing the obstruction and has included α1-adrenergic receptor antagonists to relax the muscles of the prostate and bladder neck or 5-ARIs to reduce prostate growth [American Urological Association, 2010]. While patients may see some improvement in OAB symptoms with these BPH therapies (eg, improvement in urinary flow), symptom control for OAB symptoms is incomplete, for many, and urinary urgency, incontinence, frequency, or nocturia persists [Abrams, 2002]. To address persistent OAB symptoms in men with BPH, combinations of BPH therapies with OAB medications, such as anticholinergics, have shown promise [Chapple, 2009; Oelke, 2013]. However, the clinical use of anticholinergics is limited by mechanism-based side effects including dry mouth and constipation [MacDiarmid, 2008] and the potential for CNS adverse effects [Gray, 2015; Risacher, 2016]. Further, contraindications/precautions exist due to the possibility of urinary retention and bladder outflow obstruction [Detrol prescribing information, 2016].

ß3-adrenoceptor (β_3-AR) agonists for OAB (eg, mirabegron) have demonstrated efficacy in treating persistent OAB symptoms in men on BPH therapies [Ichihara, 2014] with a more favorable safety profile relative to the anticholinergics. In fact, experts have recommended that these agents be specifically studied in this patient population [Maman, 2014; Chapple, 2009; Van Kerrebroeck, 2001; Chapple, 2017].

Vibegron is a potent and highly selective β_3-AR agonist demonstrating > 9000-fold selectivity for activation of β_3-AR over β_2-AR and β_1-AR in cell based in vitro assays. β-adrenergic receptors are prototypic G-protein coupled receptors expressed on the surface of cells, and mediate intracellular signaling via coupling to G_s and increasing levels of intracellular cyclic adenosine monophosphate (cAMP). β_3-ARs are widely distributed in humans and are the most prevalent β-AR subtype expressed on human detrusor smooth muscle [Takeda, 2000]. In isolated human bladder smooth muscle, activation of β_3-AR using subtype-selective agonists results in smooth muscle relaxation suggesting a role for β_3-AR agonists during the filling phase of the micturition cycle [Yamaguchi, 2002; Biers, 2006]. In rodent models of bladder overactivity, β_3-AR agonists relax bladder smooth muscle and suppress detrusor smooth muscle instability and hyperreflexia [Takeda, 2000; Woods, 2001; Takeda, 2002; Kaidoh, 2002]. In rhesus monkeys,

dose dependent increases in bladder capacity and decreases in micturition pressure were observed with vibegron. Bladder capacity was further increased by vibegron in combination with tolterodine or darifenacin [Di Salvo, 2017]. These results have supported a large and comprehensive clinical development program for vibegron in the general OAB population, including both male and female subjects.

More than 2300 subjects (including 1840 with OAB and 460 healthy volunteers) have received vibegron in Phase 1, 2, and 3 clinical studies. Assessment of safety laboratory parameters and mean vital sign values over time, including heart rate and blood pressure, showed no clinically meaningful differences for any active treatment group relative to placebo or anti-muscarinic comparators. A large, multicenter Phase 3 study of vibegron for the treatment of OAB in women and men is ongoing. Discontinuation rates due to adverse events (AEs) were low (< 5%) in all clinical studies conducted to date with vibegron. In a completed Phase 3 study in Japan in more than 1200 subjects with symptoms of OAB, there were no notable mean changes in post voided residuals observed [Yoshida, 2018]. A more detailed description of vibegron, including pharmacology, efficacy, and safety data in overactive bladder, is provided in the Investigator's Brochure.

2.4. Benefit/Risk Assessment

2.4.1. Potential Benefits

Vibegron's mechanism of action has the potential to demonstrate significant therapeutic benefit in the treatment of OAB symptoms in men with BPH on pharmacological therapy for their BPH symptoms.

2.4.2. Potential Risks

The initial clinical program for vibegron in the treatment of OAB includes subjects of both sexes. It is estimated that the ongoing Phase 3 program in OAB (RVT-901-3003 and RVT-901-3004) will include approximately 15% males, which will contribute to safety data comprising more than 200 men in addition to those enrolled in the URO-901-3005 and URO-901-3006 studies.

Based on aggregate preclinical, clinical pharmacology, and Phase 2 and 3 studies, AEs of special interest (AESIs) predefined for specific evaluations in vibegron clinical studies are as follows:

- Potential major cardiovascular events
- Hypertension
- AEs suggestive of orthostatic hypotension as confirmed by orthostatic vital signs
- AEs suggestive of cystitis or urinary tract infection
- Elevated aspartate transaminase (AST) or alanine transaminase (ALT) laboratory value requiring that the study drug be temporarily withheld or permanently discontinued
- Neoplasm

In addition, the risk for increases in post void residual urine volume and urinary volume will be closely monitored for post-void retention during the study. Study URO-901-3005 enrollment criteria will exclude men with PVR volume ≥ 100 mL at screening and at baseline and those with maximum urinary flow (Qmax) less than 5 mL/second. Post-void residual urine volume will be assessed throughout the study, and subjects with a single PVR volume of ≥ 300 mL or an AE of urinary retention will be withdrawn.

Prespecified definitions of urinary retention and other AESIs are provided in the Adverse Event of Special Interest section (Section 8.4.6). More detailed information about the known and expected benefits and risks from the study and reasonably expected AEs of vibegron may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Assessments in Study URO-901-3006 are referenced to the initial Baseline (Visit 3) from Study URO-901-3005. Therefore, CFB study endpoints for Study URO-901-3006 are relative to Study URO-901-3005 baseline. At the Week 52 visit, CFB comprises 52 weeks of vibegron exposure for subjects randomized to vibegron in Study URO-901-3005 and 28 weeks of vibegron exposure for subjects randomized to placebo.

With respect to study endpoints, "per day" refers to a "Diary Day", which is defined as the time between when the subject gets up for the day each morning and the time the subject gets up for the day the next morning as recorded in the subject bladder diary (approximately a 24-hour period)

Objective	Endpoints
The primary study objective is to demonstrate the long-term safety of vibegron 75 mg in men with BPH with symptoms of OAB. The secondary study objective is to demonstrate the long-term efficacy of vibegron 75 mg in men with BPH with symptoms of OAB.	**Safety** • Including AEs, clinical laboratory, vital sign assessments, PVR volume, and Total IPSS **Efficacy** • CFB at Week 52 in the average number of micturition episodes per day • CFB at Week 52 in the average number of urgency episodes (urgency: need to urinate immediately) per day • CFB at Week 52 in the average number of nocturia episodes per night • CFB at Week 52 in the average number of urge urinary incontinence episodes per day in subjects with incontinence at Study URO-901-3005 baseline • CFB at Week 52 in the average of IPSS Storage score (1-week recall) • CFB at Week 52 in the average volume voided per micturition **Other/Exploratory – Efficacy** [redacted]

	Other/Exploratory – Quality of Life [redacted]

Notes: "change from baseline" (CFB) refers to the change from the baseline in the parent study, URO-901-3005; "per day" refers to a continuous 24-hour period as defined above; week timepoints (eg, Week 52) refer to the weeks since the baseline assessment in the parent study, URO-901-3005.

Abbreviations: AE = adverse events; BPH = benign prostatic hypertrophy; CFB = change from baseline; [redacted] IPSS = International Prostate Symptom Score; OAB = overactive bladder; [redacted] PGI = Patient Global Impression; QoL = quality of life

4. Study Design

4.1. Overall Design

This study is a Phase 3, open-label, 28-week extension study to evaluate the safety and efficacy of vibegron 75 mg in men with symptoms of overactive bladder (OAB) on stable doses of pharmacological therapy for BPH. This study is an extension for subjects who have completed the Phase 3, double-blind, randomized, 24-week Study URO-901-3005.

Subjects who complete Study URO-901-3005 may be given the opportunity to enroll in this extension study. It is anticipated that approximately 300 men who completed Study URO-9013005 and continue to qualify for this study may be permitted to enroll in this extension study.

During this extension study, subjects who had been randomized to receive vibegron 75 mg in Study URO-901-3005 will continue their same treatment once daily for an additional 28 weeks; subjects who had been randomized to receive placebo in Study URO-901-3005 will receive study treatment of vibegron 75 mg once daily for 28 weeks during this extension study. Thus, through participation in both the URO-901-3005 and URO-901-3006 (extension) studies, subjects originally randomized to vibegron will receive 52 weeks total of vibegron treatment, and subjects originally randomized to placebo will receive 28 weeks total of vibegron treatment.

Study visits will be named to reflect continuation from the URO-901-3005 study, with the first study visit of this extension study occurring at Week 24 (Visit 11). Following enrollment in this extension study, subjects will return to the clinic for visits at Week 28, Week 36, and Week 52 (all relative to Day 1 of URO-901-3005). A telephone contact will occur at Week 44 to review AEs/SAEs and concomitant medications.

This study consists of a 28-week open-label Treatment Period. Unscheduled Visit(s) may be arranged as needed.

4.1.1. Clinical Hypotheses

The primary clinical hypothesis is that is that the vibegron + pharmacological therapy for BPH treatment is safe in men with OAB symptoms and BPH.

4.2. Scientific Rationale for Study Design

The clinical use of anticholinergics is limited by adverse effects and, notably, contraindications and precautions unique to men with OAB symptoms receiving treatment for BPH due to the possibility of urinary retention and bladder outflow obstruction. ß3-adrenoceptor agonists have shown efficacy (with improved safety relative to anticholinergics) in treating persistent OAB symptoms in men on BPH therapies [Ichihara, 2014]; however, no therapeutic agents are labeled specifically for this population, and clinical study data have been limited. In addition, this population has a distinct symptom profile and relevant efficacy needs (eg, nocturia) that warrant further study.

4.3. Justification for Dose

This study will use a vibegron dose of 75 mg QD, which is the same dose used for the pivotal Phase 3 study of OAB in men and women (RVT-901-3003) and the associated long-term Phase 3 extension study (RVT-901-3004) as well as in the parent OAB/BPH study, URO-901-3005.

4.4. End of Study Definition

The end of the study is defined as the date that the last subject has completed the study (ie, through the Week 52 Visit), discontinued from the study, or is lost to follow-up.

5. Study Population

The study is being conducted in men with OAB symptoms while receiving pharmacological therapy for BPH who have completed vibegron Study URO-901-3005. 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.

Eligibility for Study URO-901-3006, including blood pressure thresholds, should be confirmed at the Week 24 visit (Visit 11) of Study URO-901-3005. For laboratory assessments, the most recent results available from Study URO-901-3005, including those from Week 24, may be used to confirm eligibility. The subject should be enrolled into Study URO-901-3006 within 7 days of completing the Week 24 visit from Study URO-901-3005.

5.1. Inclusion Criteria

Subjects will be eligible for inclusion in this study only if all of the following criteria apply:

1. Has completed participation of the 24-week double-blind treatment period in Study URO-901-3005 and demonstrated compliance with the study procedures and study medication schedule in the opinion of the investigator.
2. Is capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
3. Has ability to continue to receive a stable dose of BPH treatment with either a) alpha blocker monotherapy or b) alpha blocker + 5-ARI.
4. In the opinion of the investigator, is able and willing to comply with the requirements of the protocol, including completing study questionnaires and the Bladder Diary.

5.2. Exclusion Criteria

Subjects will not be eligible for inclusion in this study if any of the following criteria apply:

1. Experienced any SAE in Study URO-901-3005 that was reported as “possibly or probably related” to study treatment by the investigator.
2. Is a night-shift worker or plans to become a night-shift worker during the study.
3. Is using any prohibited medications as detailed in Section 10.6 (Appendix 7).
4. Is taking or using any medications to treat erectile dysfunction (ED) but is not using them on a regular schedule. If taking less than 2 times per week, ED medications with a short half-life such as sildenafil and vardenafil are allowed.
5. Has any planned procedures to treat ED (eg, implantation of a penile device) during the treatment period or has any planned prostate procedure.
6. Has a planned procedure to implant a sacral neurostimulation (SNS) or use of any posterior tibial nerve stimulation (PTNS) device.
7. Has coronary or neurovascular interventions planned during the duration of the study.

8. Has uncontrolled hyperglycemia (defined as fasting blood glucose > 150 mg/dL or 8.33 mmol/L and/or non-fasting blood glucose > 200 mg/dL or 11.1 mmol/L) based on most recent available lab results in Study URO-901-3005 or uncontrolled in the opinion of the investigator.
9. Has uncontrolled hypertension (systolic blood pressure of ≥ 180 mmHg and/or diastolic blood pressure of ≥ 100 mmHg) or has a resting heart rate (by pulse) > 100 beats per minute.
10. Has systolic blood pressures ≥ 160 mmHg but < 180 mmHg, unless deemed by the investigator as safe to proceed in this study and able to complete the study per protocol.
11. Subject has current evidence of any clinically significant condition, therapy, lab 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 study procedures, 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

Not applicable for this study.

6. Study Drug

Subjects will retain the same subject identification number as was assigned in Study URO-901-3005.

6.1. Study Drugs Administered

Table 1 Summary of Study Drugs

Study Drug Name	Vibegron
Dosage Formulation	tablet
Identity of Formulation	75 mg
Route of Administration	oral
Dosing Instructions	once daily
Packaging and Labeling	Study drug will be provided in HDPE bottles with child-resistant caps. Each bottle will contain 32 tablets and will be labeled as required per country requirement.
Manufacturer	Patheon, Cincinnati, Ohio, US
Number and Timing of Drugs	Treatment Period: 1 tablet daily

The study drug will be supplied in bottles each containing 32 tablets (4-week treatment and 4-day extra supply) and labeled with the protocol number, lot number, expiration date, study drug name (vibegron 75 mg tablets) and number of tablets, directions for use, storage information, warning language (*Keep Out of Reach of Children. For Clinical Trial Use Only. To be used by qualified investigators only. Caution: New Drug—Limited by United States Law to Investigational Use.*), and the US Sponsor name and address. Immediately before dispensing the study drug, the investigator (or appropriately trained designee) will write the subject number, visit no. and the dispense date on the detachable panel of the label, which also includes the protocol number, bottle number and lot number.

Subjects will take 1 tablet of study drug (vibegron) once daily for up to 28 weeks.

6.2. Preparation/Handling/Storage/Accountability

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

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 to and returned by the subjects, 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.

6.3. Study Drug Compliance

Study drug compliance will be closely monitored by counting the number of tablets dispensed and returned. Before dispensing new study drug at applicable visits, study site personnel will make every effort to collect all unused study drug and empty bottles.

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.

6.4. 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.

6.4.1. Prohibited Drugs

Section 10.6 provides a listing of specific restrictions for concomitant therapy use during the study. If there is a clinical indication for any therapy that is specifically prohibited during the study, discontinuation from Study Treatment may be required. The investigator should discuss any questions regarding this with the Sponsor's representing 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 on Study Treatment 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.

6.4.2. Permitted Drugs

With the exception of the agents described in Section 10.6, 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 or receives during the study must be recorded in the eCRF.

6.5. Dose Modification

No dose modification of study drug is permitted. Study drug should be withheld for liver test abnormalities as described in Section 8.4.6.2.

6.6. Drug After the End of the Study

Study drug (vibegron) will not be provided after the Week 52 visit.

7. Discontinuation of Study Drug and Subject Discontinuation or Withdrawal

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

7.1. Discontinuation of Study Drug

Subjects who discontinue study drug will complete the Week 52/Early Withdrawal assessments specified in the Schedule of Assessments (Section 1.3).

Reasons for discontinuation from the study drug include the following:

- Any AE of urinary retention
- Any occurrence of PVR volume ≥ 300 mL

Discontinuation of study drug for abnormal liver function should be considered by the investigator when a subject meets all of the conditions outlined in Section 8.4.6.2 for Hy's law or if the investigator believes that it is in best interest of the subject (reason for discontinuation will be AE).

7.2. Subject Discontinuation/Withdrawal from the Study

- A subject who discontinues study drug will also be withdrawn from the study.
- A subject may choose to withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the investigator 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, he may request destruction of any blood or urine samples taken and not tested, and the investigator must document this in the site study records.
- Subjects who withdraw from the study will not be replaced.

The Week 52/Early Withdrawal assessments will be completed when a subject withdraws or is withdrawn from the study, if possible (see Schedule of Assessments in Section 1.3).

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
- Death
- Other

7.3. 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.

7.4. 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). A detailed listing of study assessments by visit is provided in Section 10.7. Site personnel should note the following:

- Protocol waivers or exemptions are not allowed. 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 discontinue study drug.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.
- Note that patient-reported outcome (PRO) assessments will be completed prior to vital signs, and vital signs will be taken prior to blood draws.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for the purposes of confirming eligibility (in addition to the most recent available assessments from Study URO-901-3005).

8.1. Study Entry Procedures

As this is an extension study that includes subjects from the ongoing parent study, URO-9013005, assessments performed at the end of the parent study will not be repeated on study entry into Study URO-901-3006. Specifically, vital sign, physical examination, laboratory, bladder diary, PVR urine, and PRO assessments performed at the Week 24 Visit of Study URO-901-3005 will be considered the initial study assessments at entry into extension Study URO-901-3006.

In addition, medical history and demographic information from entry into Study URO-901-3005 will be used as relevant to provide information for Study URO-901-3006.

8.1.1. Informed Consent

Documented consent (for Study URO-901-3006) must be obtained from each potential subject prior to the first dose of open-label study drug (vibegron) on Study URO-901-3006 according to the process described in Section 10.1.3.

8.1.2. Assignment of Subject Number

All subjects who enroll in Study URO-901-3006 will retain the same study number that they were assigned in Study URO-901-3005.

The investigator will maintain a log to confirm eligibility or record reasons for ineligibility, as applicable. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will be reviewed by the investigator or qualified designee at Week 24 of Study URO-901-3005). If needed, the Week 24 laboratory results from Study URO-901-3005 may be used to confirm eligibility.

8.1.3. Concomitant Medications

Ongoing medications will be recorded beginning at the signing of the ICF and continuing until the last dose of study drug.

8.2. Efficacy Assessments

Efficacy assessments will be collected as outlined in the Schedule of Assessments (Section 1.3) in the form of 3-day Bladder Diary. Information collected in the diaries will be used for assessment of the efficacy endpoints related to the number of micturition, urgency, nocturia, and incontinence episodes per day as well as the volume voided per micturition. In addition, subjects will complete IPSS assessments and [redacted] Patient Global Impression (PGI), and [redacted] scores to assess quality of life parameters.

Subjects will complete questionnaires at the site at the start of each required study visit (before vital signs and blood draws). The PRO questionnaires are provided in Section 10.8. Additional information on the Bladder Diary and questionnaires is provided below.

8.2.1. Bladder Diaries

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

The Bladder Diary should be completed by the subject on 3 consecutive days within the 7 days prior to Visit 12 (Week 28), Visit 13 (Week 36) and Visit 14 (Week 52). 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). Urine volume may be collected during any one (1) of the 3 Diary Days prior to the visit.

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).

8.2.2. Patient-Reported Outcomes

Subjects will complete questionnaires at the site at the start of each required study visit (before vital signs and blood draws) to assess subject-perceived symptom relief, symptom bother, and health-related quality of life. These include the following questionnaires:

- The IPSS includes 8 questions (7 concerning urinary symptoms and 1 concerning quality of life), each with answers based on a 6-point scale indicating increasing severity. The urinary symptom responses are assigned points from 0 to 5. The Total IPSS Score can therefore range from 0 to 35 (asymptomatic to very symptomatic). The quality of life responses are assigned points from 0 to 6. A sample of the IPSS is provided in Section 10.8.1.

- [redacted] (1-week recall) is a multi-item questionnaire that was developed to assess symptom bother and the impact of [redacted] The instrument was developed and validated in both continent and incontinent OAB patients, including both men and women. A sample of the [redacted] scales is provided in Section 10.8.2.

- The EQ-5D health questionnaire is a standardized instrument for use as a measure of health outcome [Rabin 2014]. It is applicable to a wide range of health conditions and treatments; it provides a simple descriptive profile and a single index value for health status. A sample of the EQ-5D health questionnaire is provided in Section 10.8.3.

- Global Impression Items include [redacted] A sample of the PGI scale is provided in Section 10.8.4.

- [redacted]

The investigator should not provide any additional information to subjects prior to completing the questionnaires that might influence responses.

8.3. Safety Assessments

Planned timepoints for all safety assessments, including assessments for PVR, 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.

8.3.1. Vital Signs

Vital signs, including blood pressure, heart rate (by pulse), body temperature, and weight, will be assessed at the timepoints specified in the Schedule of Activities and Section 10.7 as follows:

- Blood pressure and pulse will be measured after the subject has been resting in a seated position for 5 minutes, after PRO assessments 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.
- Sitting systolic and diastolic blood pressures will be determined by averaging 3 replicate measurements obtained approximately 1 to 2 minutes apart. The average of the 3 measurements will be used for eligibility and safety assessments.
- 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.

8.3.2. 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 at Baseline or a subject has a complaint or AE will be examined.

8.3.3. 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 8.4.6 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). All efforts will be made to ensure the same device and operator are used for all PVR volume measurements for individual subjects.

8.3.4. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the Schedule of Assessments. 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 Week 24 of Study URO-901-3005, 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 or within 21 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the 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.

8.4. Adverse Events and Serious Adverse Events

The definitions of an AE or 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).

8.4.1. 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 informed consent form through the end of study. In addition, any AEs and SAEs reported within 21 days after the last dose of study drug (5 half-lives of vibegron [half-life approximately 80 hours]) will also be collected. AEs will be collected 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 AESIs) will be recorded and reported on the eCRF within **24 hours** of the study site personnel's knowledge of the event, as indicated in Section 8.4.4. 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.

8.4.2. 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.

8.4.3. 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 AEs will be followed until approximately 21 days after the last dose of study drug. 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 7.3). If a subject dies during participation in the study or within 21 days of the last dose of study drug, the investigator will provide the Sponsor or designee with a copy of any postmortem findings including 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.

8.4.4. 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, IRBs/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/REB, if appropriate according to local requirements.

8.4.5. 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. Any worsening of OAB or BPH symptoms or any events of bladder obstruction should be collected as AEs.

8.4.6. 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.

Adverse events of special interest 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 clean intermittent catherization (CIC) or temporary placement of a urinary catheter according to the following criteria:
    a) subject has a PVR of ≥ 300 mL (regardless of symptoms), OR

b) subject has a PVR ≥ 200 mL and < 300 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. As stated above in Section 7, subjects with a single PVR volume of ≥ 300 mL or an AE of urinary retention will be withdrawn from the study.

- Adverse events suggestive of cystitis or urinary tract infection (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
    - 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).
- Potential major cardiac and cerebrovascular events, including death (or any event with fatal outcome), myocardial infarction, cerebrovascular accident, hospitalization for unstable angina or chest pain, hospitalization for heart failure requiring hospitalization, and coronary revascularization/angioplasty/stent
- Hypertension, defined as follows:
  - For subjects with systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg at the Study URO-901-3005 baseline assessment, the average of 3 systolic blood pressures ≥ 140 mmHg or diastolic blood pressures ≥ 90 mmHg (or both) at any 2 consecutive visits after baseline
  - For subjects with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at Study URO-901-3005 baseline, an increase compared to baseline at 2 consecutive visits in the average of 3 systolic blood pressures by ≥ 20 mmHg or 3 diastolic blood pressures by ≥ 10 mmHg
  - Initiation or increase in dose of medication for treatment of hypertension in any subject
- Adverse events consistent with orthostatic hypotension as confirmed by orthostatic vital signs

- Elevated serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value requiring that study drug be temporarily withheld or permanently discontinued (see Section 8.4.6.1 and 8.4.6.2). To date, no concern regarding drug-induced liver toxicity has been identified; however, the Sponsor is monitoring laboratory data for a potential safety signal, consistent with Food and Drug Administration guidance [FDA Guidance, 2009].
- Neoplasms

Serious AESIs and elevated liver enzymes or bilirubin requiring withholding of study drug (see Section 8.4.6.1) must be reported within 24 hours of the study site personnel's knowledge of the event by marking the appropriate box on the AE eCRF and assigning the most appropriate category. Additional information should be provided as directed in the eCRF Completion Guidelines. AESIs that also meet the definition of an SAE must be reported as an SAE, as described in Section 8.4.4. Nonserious AESIs should be reported within 72 hours of the site personnel's knowledge, using the AE eCRF.

8.4.6.1. Criteria for Temporary Withholding of Study Treatment in Association with Liver Test Abnormalities

Elevated liver enzymes or bilirubin sufficient to require withholding study medication must be reported **within 24 hours of the study site personnel's knowledge of the event** using AESI specific eCRFs/forms/worksheets provided for the study.

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If **any** of the following liver test abnormalities develop, Study Treatment should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status), and the event reported as an SAE:

- ALT or AST > 8 x upper limit of normal (ULN)
- ALT or AST > 5 x ULN and persists for more than 2 weeks
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and Sponsor's designated Medical Monitor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

8.4.6.2. Criteria for Permanent Discontinuation of Study Treatment in Association with Liver Test Abnormalities

Study treatment should be discontinued permanently if **all** of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

- Total bilirubin increases to > 2 x ULN or INR > 1.5 **and**
- AST or ALT increases to ≥ 3 x ULN **and**
- Alkaline phosphatase value does not reach 2 x ULN **and**
- No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus)
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
  - Alcoholic hepatitis
  - Non-alcoholic steatohepatitis
  - Autoimmune hepatitis

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug should be withheld or permanently discontinued as appropriate for the safety of the subject, following consultation with the Sponsor's designated Medical Monitor.

8.4.7. Pregnancy Management and Reporting to the Sponsor

In the event that a partner of a male study subject becomes pregnant during the study, if the subject agrees, the subject's pregnant partner should be notified of the subject's study participation and be requested to sign a Release of Information form, permitting transfer of information regarding the pregnancy and outcome to the Sponsor. If the subject and the subject's partner agree, the investigator should notify the partner's primary care physician and provide details of the subject's participation in the study.

Partner pregnancies are to be reported to the Sponsor **within 24 hours of awareness** by the study site personnel, using the pregnancy reporting forms and information for safety event reporting in Section 10.3. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, neonatal data, etc. should be included in this information, as available.

If the subject and partner agree, the investigator will follow the medical status of the mother, the pregnancy, as well as the outcome of the infant at birth, and will report the outcome to the Sponsor.

8.4.8. 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 8.5 for treatment and reporting of overdose). For this study, any dose of vibegron of 3 or more tablets within a 24-hour window is an overdose. There is no known antidote for an overdose.

Underdose: No underdose is defined for this study.

8.5. Treatment of Overdose

In the event of an overdose (3 or more tablets of study drug within 24 hours), the investigator or treating physician should:

- Contact the Sponsor's designated Medical Monitor immediately
- Closely monitor the subject for any AEs, SAEs, and laboratory abnormalities
- Report all overdose events on the eCRF, whether or not the overdose is associated with an AE. If the overdose resulted in an AE or SAE, refer to Section 10.3 for reporting requirements.
- 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).

9.1. Hypotheses

9.1.1 Primary Objective and Hypothesis

The primary study objective is to demonstrate long-term safety of vibegron 75 mg in men with BPH with symptoms of OAB. There is no formal statistical primary endpoint hypothesis. Descriptive statistics will be used to evaluate safety endpoints, including the incidence of treatment-emergent AEs (SOC and PT) by originally randomized treatment group and for vibegron treatment overall, including events during all vibegron exposure from both Study URO-901-3005 and URO-301-3006.

9.1.2 Secondary Objectives and Hypotheses

There are no formal statistical hypotheses for this trial. The secondary study objective is to demonstrate long-term efficacy of vibegron 75 mg in men with BPH with symptoms of OAB.

9.2. Analysis Endpoints

The description of the endpoints and study time points at which each is measured are described in Section 3 and Section 1.3, respectively.

9.2.1. Efficacy and Health Outcome Endpoints

For purposes of this study, the number of micturitions will be defined as the number of times a subject has voided in the toilet as indicated on the Bladder Diary. Average daily micturitions are calculated using the daily entries in the Bladder Diary, which is completed prior to each study visit. Average daily number of micturitions will be calculated as the total number of micturitions that occur on a Diary Day divided by the number of Diary Days in the Bladder Diary. Baseline will be the same baseline determined from the URO-901-3005 trial.

An urgency episode is defined as the “Need to Urinate Immediately” as indicated on the Bladder Diary. Average daily urgency episodes at each study visit will be calculated in the same manner as described above for the micturitions.

A UUI episode is defined as having "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.

A nocturia episode is defined as waking to pass urine during the main sleep period as indicated on the Bladder diary.

Efficacy Endpoints:

- CFB at Week 52 in the average number of micturition episodes per day
- CFB at Week 52 in the average number of urgency episodes (urgency: need to urinate immediately) per day
- CFB at Week 52 in the average number of nocturia episodes per night
- CFB at Week 52 in the average number of UUI episodes per day in subjects with incontinence at Study URO-901-3005 baseline
- CFB at Week 52 in the average of IPSS Storage score (1-week recall)
- CFB at the Week 52 in the average volume voided per micturition

Other/Exploratory – Efficacy

Other/Exploratory – Quality of Life

9.2.2. Safety Endpoints

Safety will be assessed via clinical review of all relevant safety parameters including AEs, clinical laboratory, vital sign assessments, PVR volume, and Total IPSS.

9.3. Analysis Populations

9.3.1. Efficacy Analysis Populations

The Full Analysis Set Extension (FAS-Ext) population will serve as the population for the analysis of efficacy data in this study. Since the endpoints related to incontinence would only apply to subjects who meet the definition of incontinence at study entry, it is necessary to have a separate FAS definition with the additional criterion to define the analysis population for incontinence endpoints.

The following FAS populations are defined in this study:

- Full Analysis Set Extension (FAS-Ext): All OAB subjects who took at least one dose of vibegron in the extension study and have at least one evaluable change from baseline micturition measurement in this study.
- Full Analysis Set Extension for incontinence (FAS-Ext-I): All OAB subjects who took at least one dose of vibegron in the extension study, were included in the FAS-I population in the URO-901-3005 study, and have at least one evaluable change from baseline (ie, Study URO-901-3005 baseline) urge urinary incontinence measurement.

Per-Protocol Extension population (PP-Ext) and Per-Protocol extension population for incontinence (PP-Ext-I) exclude subjects due to important deviations from the protocol that may substantially affect the results of the efficacy endpoints. A supportive analysis using the Per Protocol populations will be performed for 6 efficacy endpoints as defined in Section 3 (ie, CFB in micturition, urgency, nocturia, and urinary incontinence episodes; IPSS Storage score; and

volume voided per micturition). The final determination of protocol violations, and thereby the composition of the Per-Protocol populations will be made prior to database lock and will be documented.

Using the Full Analysis Set and Per-Protocol populations, subjects will be included in one of two vibegron treatment groups based on the original randomization from the parent study (URO-901-3005): vibegron for 52 weeks or vibegron for 28 weeks. Efficacy endpoints will be descriptively summarized by treatment group.

9.3.2. Safety Analysis Populations

The Safety Analysis Set - Extension (SAF-Ext) population will be used to for the analysis of safety data in this study.

The SAF-Ext consists of all randomized subjects in Study URO-901-3005 who

a) have completed the 24-week treatment period in the Study URO-901-3005, and
b) enrolled into the extension Study URO-901-3006 and received at least one dose of vibegron in this study.

The SAF-Ext will be used for all the safety analyses. Safety endpoints will be descriptively summarized based on the treatment in study URO-901-3006. This means there will be one vibegron treatment group (combining 52 weeks of vibegron dosing for those continuing vibegron from Study URO-901-3005 and 28 weeks of vibegron dosing for those who received placebo in Study URO-901-3005).

No imputation will be performed for missing safety data. Baseline will be the same as the baseline defined in the parent study. Further inclusion of data from URO-901-3005 in the reporting of this study will be described in the SAP.

9.4. Statistical Analyses

9.4.1. Statistical Methods for Efficacy Analysis

Statistical analysis of efficacy endpoints will be for descriptive purposes only. Baseline will be defined as the baseline from the Study URO-901-3005. Further inclusion of data from URO-901-3005 in the reporting of this study will be described in the SAP.

For the analysis of continuous change from baseline endpoints (eg, change from baseline in average number of micturitions, change from baseline in the average number of urgency episodes, change from baseline in average number of nocturia episodes, change from baseline in daily urge urinary incontinence episodes, change from baseline in average IPSS Storage score, and change from baseline in average volume voided per micturitions), a mixed model for repeated measure (MMRM) with restricted maximum likelihood estimation will be used. 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 dropout-free population.

The analysis model for each efficacy endpoint will include terms for visit, baseline, stratification factors (only those that were statistically significant in URO-901-3005 will be included in the models), and baseline score. Only subjects on active treatment in both URO-901-3005 and URO-901-3006 will be included in the model. Adjusted means and 95% confidence intervals will be presented for each visit.

An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual maximum likelihood (REML) to make proper statistical inference. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance will be used to model the correlation among repeated measurements.

In general, continuous variables will be summarized by treatment to indicate the population sample size (N), number of subjects with available data (n), arithmetic mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by N, n, number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data.

9.4.2. Safety Analyses

Safety analysis will be conducted using the SAF-Ext population and summarized by the Vibegron treatment group. The treatment-emergent period will be defined as the period of time from the first dose date of vibegron in this study through 21 days after the last dose of treatment, or the date of initiation of another investigational agent or surgical intervention, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuation due to adverse events, and clinical laboratory evaluations.

AEs will be coded using the latest version of MedDRA (20.0 or higher). The severity of all adverse events will be evaluated by the Investigator. The incidence of adverse events will be presented by system organ class and preferred term, relationship to study treatment and severity.

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

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

9.5. Multiplicity

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

9.6. Subgroup Analyses

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

9.7. Sample Size Determination

Approximately 300 subjects rolling over from Study URO-901-3005, in addition to other long-term safety data with vibegron, is sufficient to characterize the long-term safety profile of vibegron 75 mg once daily men with symptoms of OAB on stable doses of pharmacological therapy for BPH. With the assumption of approximately 33% dropout, 100 subjects will be expected to complete the study for the duration of 1-year on vibegron.

9.8. Interim Analyses

There are no interim analyses planned for this study.

9.9. Data Safety Monitoring Board

One external independent DSMB will be formed for Studies URO-901-3005 and URO-901-3006. The detailed activities including meeting and analysis plan will be described and documented in the DSMB charter and the DSMB SAP, respectively.

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 ICH/ISO Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC/REB by the investigator and reviewed and approved by the IRB/IEC/REB before the study is initiated.
- Any amendments to the protocol will require IRB/IEC/REB 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/REB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC/REB
  - Notifying the IRB/IEC/REB of SAEs or other significant safety findings as required by IRB/IEC/REB 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/REB, 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 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 his 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, HIPAA requirements, where applicable, and the IRB/IEC/REB 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.

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.
- The subject must be informed that his 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 his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor or designee, by appropriate IRB/IEC/REB 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 case report forms (CRFs) 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 CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC/REB 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.

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.

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, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB/REB/IEC. 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 participants.

The investigator will be responsible for the following:

- 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 SAEs or other significant safety findings as required by procedures established by the IRB/REB/IEC

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-specific procedures were performed
  - Results of efficacy parameters, as required by the protocol
  - Start and end date (including dose regimen) of Study Treatment (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

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. The use of the data collected for the subject will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. 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 tests detailed in Table 10-1 will be performed by the central laboratory chosen by the Sponsor. Subjects do not need to fast prior to laboratory testing. A sample for urinalysis (including microscopy for RBCs, WBCs, epithelial cells, and bacteria) and urine culture will be sent to the central laboratory only if the urine dipstick tests positive for the presence of leukocytes, nitrites, or blood cells. If a subject reports symptoms suggestive of a urinary tract infection at any visit, a urine dipstick should be performed as needed, and a sample will be sent out for urinalysis and culture and sensitivity testing.

Table 10-1 Clinical Laboratory Tests

Hematology	**Chemistry**	**Urinalysis[a]**	**Other**
Hematocrit	Albumin	Blood	Coagulation INR/PT/APTT[d]
Hemoglobin	Alkaline phosphatase	Glucose	
Platelet count	ALT	Protein	
WBC (total and differential)	AST	Specific gravity	
RBC	Bicarbonate	Microscopic exam (RBCs, WBCs, epithelial cells and bacteria)	
	Calcium	pH	
	Chloride	Color	
	Creatine[b]		
	Glucose (fasting or non-fasting)		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin[c]		
	Blood urea nitrogen		
	Total cholesterol		

ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; eGRF = estimated glomerular filtration rate; INR = international normalized ratio; PSA = prostate-specific antigen; PT = prothrombin time; RBC = red blood cell count; WBC = white blood cell count

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

[b] eGFR will be calculated and reported by the central lab.

[c] If total bilirubin is elevated above the upper limit of normal.

[d] Only upon request from Principal Investigator (if ALT, AST and bilirubin are increased).

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 (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's study drug/device or program, which warrants 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 8.4.6 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, electrocardiograms, 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.
- 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 or BPH/bladder obstruction 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 drug of a pre-existing 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 drug 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/SADE, 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 (IB) 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
β3-AR	beta-3 adrenergic receptor
5-ARI	5α-reductase inhibitors
AE	adverse event
AESI	Adverse Events of Special Interest
ALT	alanine aminotransferase
APR	abdominoperineal resection
AR	adrenergic receptor
AST	aspartate aminotransferase
BPH	benign prostatic hypertrophy
cAMP	cyclic adenosine monophosphate
CFB	change from baseline
CFR	Code of Federal Regulations
CFU	colony-forming unit
CIC	clean intermittent catheterization
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CT	computerized tomography
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
ED	erectile dysfunction
eGFR	estimated glomerular filtration rate
[redacted]	[redacted]
FAS	full analysis set
FAS-I	full analysis set for incontinence
FDA	(United States) Food and Drug Administration
GCP	good clinical practice
[redacted]	[redacted]
ICH	International C on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	informed consent form
ICS	International Continence Society

Term	Description
IDC	involuntary detrusor contraction
IEC	independent ethics committee
[redacted]	[redacted]
INR	international normalized ratio
IPSS	International Prostate Symptom Score
IRB	institutional review board
IWRS	interactive web response system
LAR	low anterior resection
LF	long form
LUTS	lower urinary tract symptoms
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measure
MRI	magnetic resonance imaging
OAB	overactive bladder
[redacted]	[redacted]
PGI	Patient Global Impression
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	preferred term
PTNS	percutaneous tibial nerve stimulation
PVR	post-void residual
QD	once daily
Qmax	maximum urinary flow; peak flow rate during voiding
QTc	corrected QT
RBC	red blood cell
REB	research ethics board
REML	restricted (or residual) maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SNS	sacral neurostimulation
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction

Term	Description
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
Urovant	Urovant Sciences GmbH
US	United States
UTI	urinary tract infection
UUI	urge urinary incontinence
WBC	white blood cell
WHO-DDE	World Health Organization Drug Dictionary Enhanced

10.5. Appendix 6: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 3 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)
	Clinical Study Sponsor	Urovant Sciences, GmbH
	Trial Phase Classification	Phase 3
	Trial Indication	OAB Symptoms in Men with BPH
	Trial Indication Type	Treatment
	Trial Type	Long-term extension
	Trial Length	Up to 28 weeks
	Planned Country of Investigational Sites	North America and Europe
	Planned Number of Subjects	Approximately 300
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	OAB Symptoms with BPH
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	45
	Planned Maximum Age of Subjects	None
	Sex of Subjects	Male
	Stable Disease Minimum Duration	3 months

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	vibegron
	Drug Type	drug
	Pharmacological Class of Invest. Therapy	beta-3 adrenergic receptor agonist
	Dose per Administration	75
	Dose Units	mg
	Dosing Frequency	Twice daily
	Route of Administration	Oral
	Current Therapy or Treatment	Pharmacotherapy for BPH: alpha blocker monotherapy or alpha blocker + 5-ARI
	Added on to Existing Treatments	Subjects not receiving current treatments for OAB symptoms
	Control Type	Not applicable
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Long-term extension
	Drug Model	Single-arm, open-label
	Planned Number of Arms	1
	Trial is Randomized	No
	Randomization Quotient	NA
	Trial Blinding Schema	Open-label
	Stratification Factor	From Parent Study URO-901-3005: Baseline average micturition episodes per day (≤ 12 vs > 12), alpha blocker use with or without 5-ARI (yes or no), and urinary incontinence (yes or no)
	Adaptive Design	No

BPH = benign prostatic hypertrophy; OAB = overactive bladder

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

The following medications are prohibited, as outlined in Section 6.4.1.

Prohibited Medications Class	Examples	Comments
Anticholinergics	darifenacin, fesoterodine, hyoscyamine, oxybutynin, propantheline, solifenacin, tolterodine, and trospium	Subject must remain off this therapy during the study. If an anticholinergic/ antimuscarinic is used in an inhaler on a PRN/ as needed basis for the treatment of chronic obstructive pulmonary disease, it will be permitted.
Smooth muscle relaxants	flavoxate, dicyclomine, propiverine	Subject must remain off this therapy during the study
Beta-2 adrenergic agonists used for the treatment of stress urinary incontinence	clenbuterol	Subject must remain off this therapy during the study
Systemic beta-2 adrenergic agonist	terbutaline	No washout period; subject must remain off this therapy during the study
Antidiuretic hormones	desmopressin	Subject must remain off this therapy during the study
Beta-3 adrenergic agonists	mirabegron	Subject must remain off this therapy during the study
New start of BPH medications	Alpha-Blockers, eg, tamsulosin, doxazosin, and alfuzosin 5-ARI, eg, Finasteride, and dutasteride PDE5 inhibitors, eg, tadalafil	Subject must not start new use of these therapies during the study.
Intradetrusor or intraprostatic botulinum toxins	Intradetrusor injection of botulinum toxin or intraprostatic injections	Subject must not receive this therapy during the study
Any herbal medications to treat OAB symptoms, lower urinary tract symptoms of BPH or erectile dysfunction		Subject must not receive them during the study.
Diuretics		Subject must not start new diuretics during the study.
Percutaneous tibial nerve stimulation (PTNS)		Subject must not start new PTNS or related therapies during the study.

10.7. Appendix 12: Study Schedule Supplement

10.7.1. Study Entry, Visit 11 (Week 24 [Day 169 ± 4 days])

- Obtain Informed Consent
- Assess inclusion/exclusion criteria
- Enter subject in IWRS
- Dispense open-label study drug

Note: The below (*) assessments performed at Week 24 of Study URO-901-3005 will be used for the initial procedures for Study URO-901-3006; they do not need to be repeated.

* Review AEs/SAEs
* Review concomitant medications
* Administer IPSS, [redacted] PGI, [redacted]scales
* Record blood pressure (3 results taken 1-2 minutes apart after sitting for 5 minutes), pulse, respiration, temperature, and weight
* Perform brief physical examination
* Measure post-void residual volume
* Perform laboratory assessments
* Review and data enter completed Bladder Diary

10.7.2. Open-label Treatment Period, Visit 12 (Week 28 [Day 197 ± 4 days])

- Review AEs/SAEs
- Review concomitant medications
- Record blood pressure (3 results taken 1-2 minutes apart after sitting for 5 minutes), pulse, respiration, temperature, and weight
- Measure post-void residual volume
- Review and data enter completed Bladder Diary
- Dispense Bladder Diary
- Dispense open-label study drug

10.7.3. Open-label Treatment Period, Visit 13 (Week 36 [Day 253 ± 4 days])

- Review AEs/SAEs
- Review concomitant medications
- Administer IPSS and [redacted] assessments
- Record blood pressure (3 results taken 1-2 minutes apart after sitting for 5 minutes), pulse, respiration, temperature, and weight
- Measure post-void residual volume
- Perform laboratory assessments
- Review and data enter completed Bladder Diary
- Dispense Bladder Diary
- Dispense open-label study drug

10.7.4. Open-label Treatment Period, Telephone Contact (Week 44 [Day 308 ± 4 days])

- Review AEs/SAEs
- Review concomitant medications

10.7.5. Open-label Treatment Period, Visit 14 (Week 52 [Day 365 ± 4 days]) or Early Withdrawal

- Review AEs/SAEs
- Review concomitant medications
- Administer IPSS, [redacted], PGI, [redacted] scales
- Record blood pressure (3 results taken 1-2 minutes apart after sitting for 5 minutes), pulse, respiration, temperature, and weight
- Perform brief physical examination
- Measure post-void residual volume
- Perform laboratory assessments
- Review and data enter completed Bladder Diary

10.8. Appendix 14: 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.

10.8.1. International Prostate Symptom Score (IPSS)

The International Prostate Symptom Score (IPSS) is based on the answers to 7 questions concerning urinary symptoms and 1 question concerning quality of life. Each question concerning urinary symptoms allows the subject to choose 1 out of 6 answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 to 5. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic).

The questions refer to the following urinary symptoms:

Questions	Symptom
1	Incomplete emptying
2	Frequency
3	Intermittency
4	Urgency
5	Weak Stream
6	Straining
7	Nocturia

Question 8 refers to the subject's perceived quality of life.

The first 7 questions of the I-PSS are identical to the questions appearing on the American Urological Association (AUA) Symptom Index which currently categorizes symptoms as follows:

Mild (symptom score ≤ 7) Moderate (symptom score range 8 to 19) Severe (symptom score range 20 to 35)

The answers to the single question to assess the quality of life this question range from "delighted" to "terrible" or 0 to 6. Although this single question may or may not capture the global impact of BPH Symptoms or quality of life, it may serve as a valuable starting point for a doctor-patient conversation.

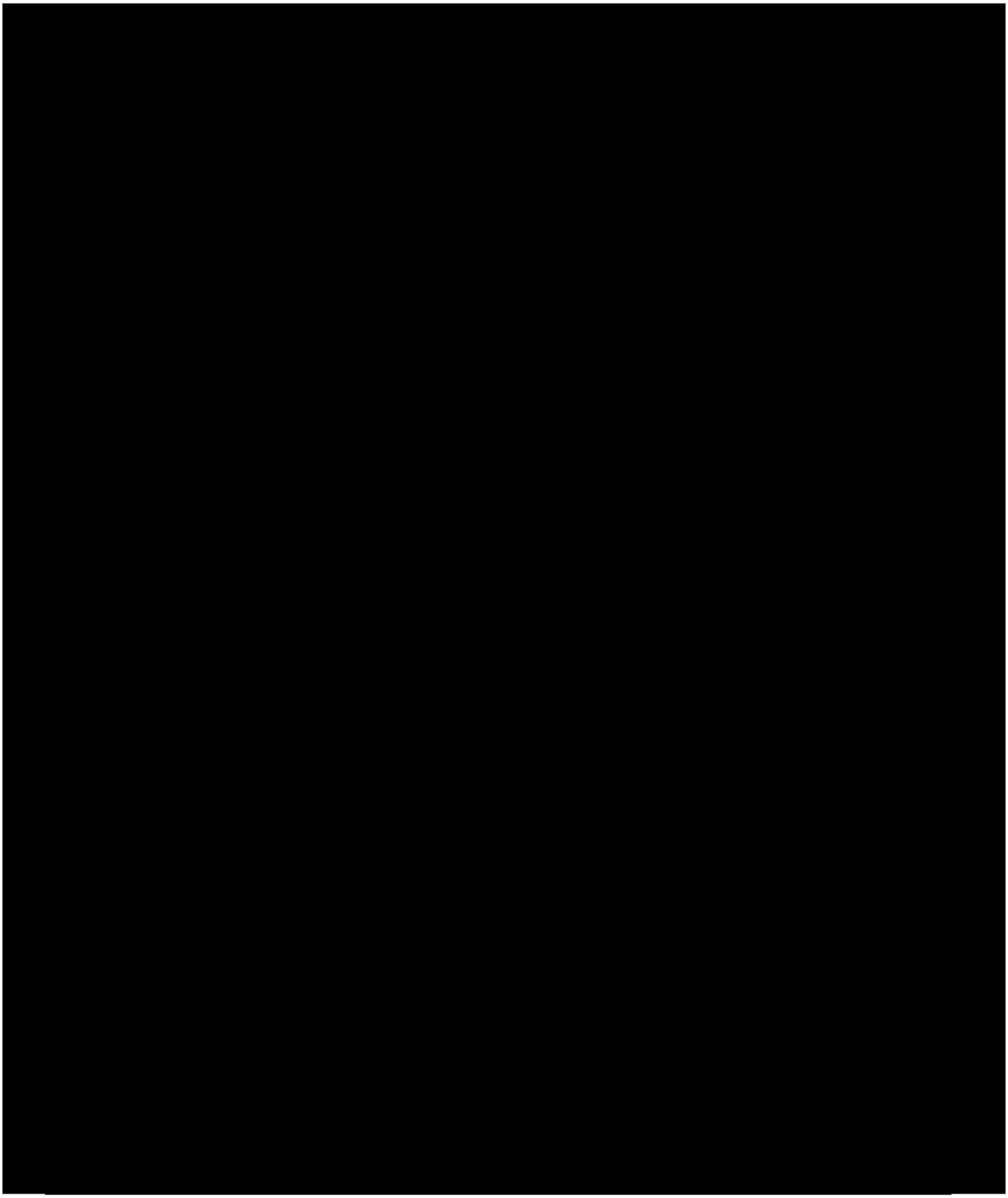
A sample of the IPSS is provided below:

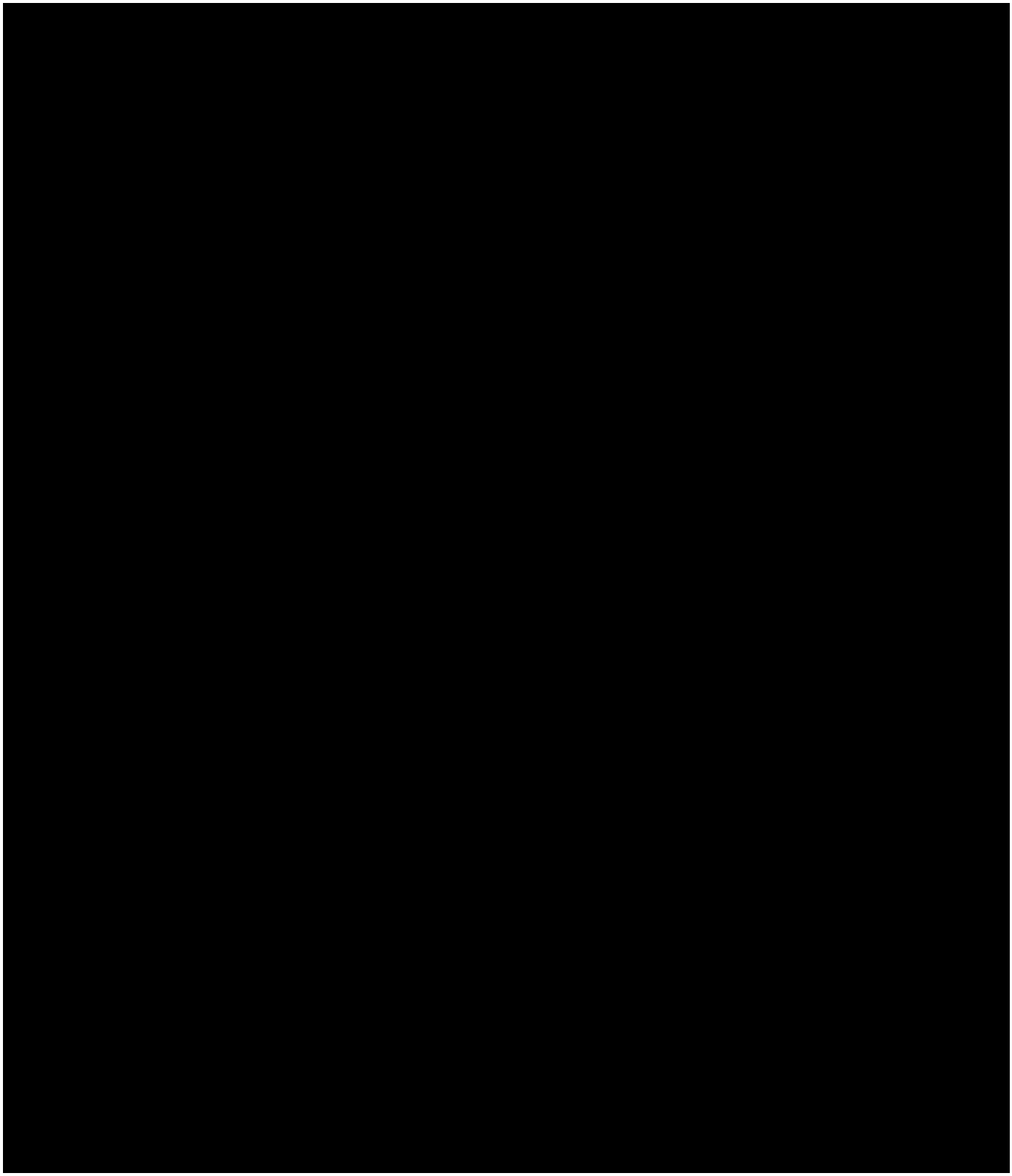
INTERNATIONAL-PROSTATE SYMPTOM SCORE (I-PSS)

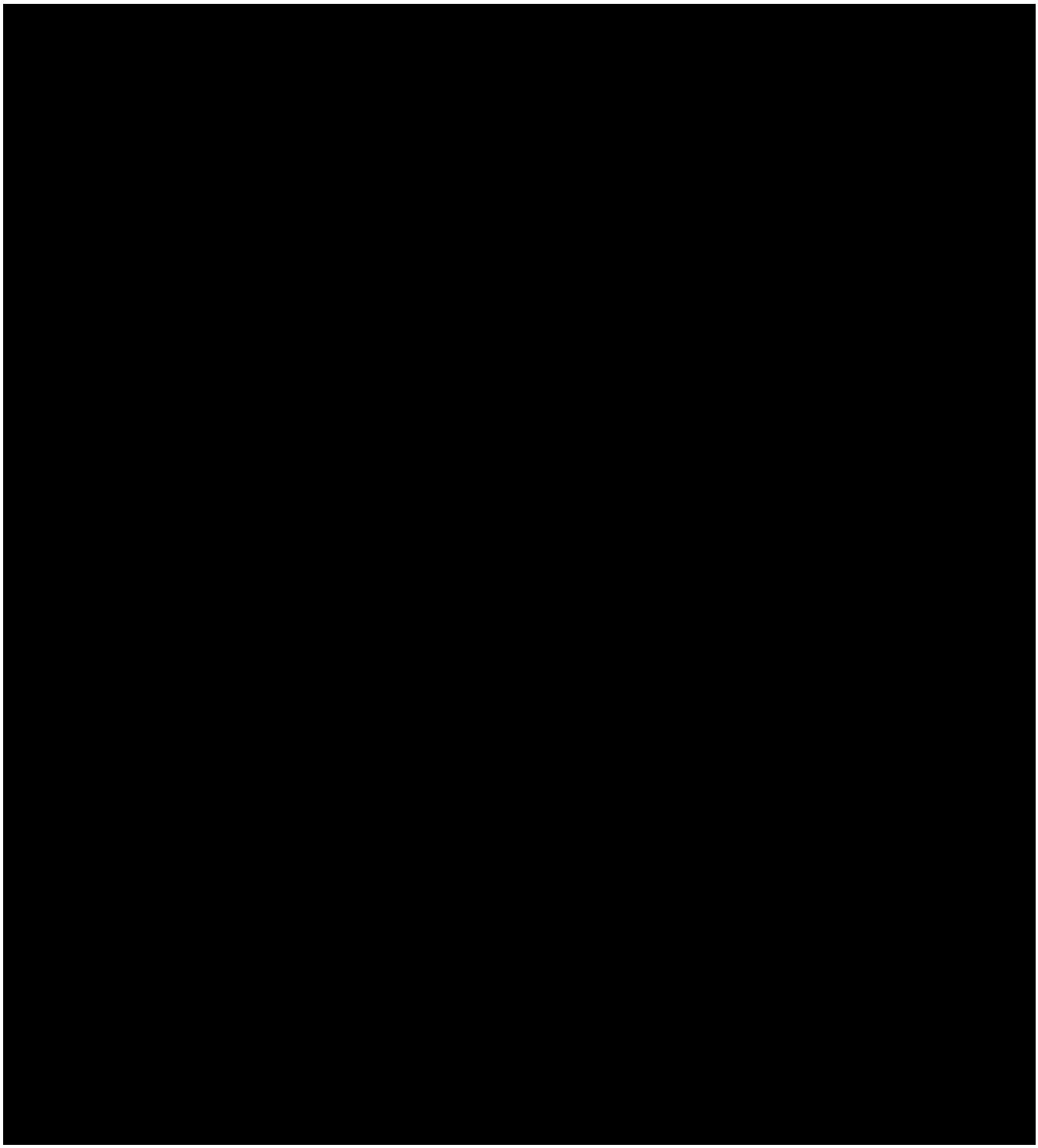
Question	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past week, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past week, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Over the past week, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past week, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past week, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past week, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 or more times
7. Over the past week, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

QUALITY OF LIFE DUE TO URINARY SYMPTOMS

Question	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
1. If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

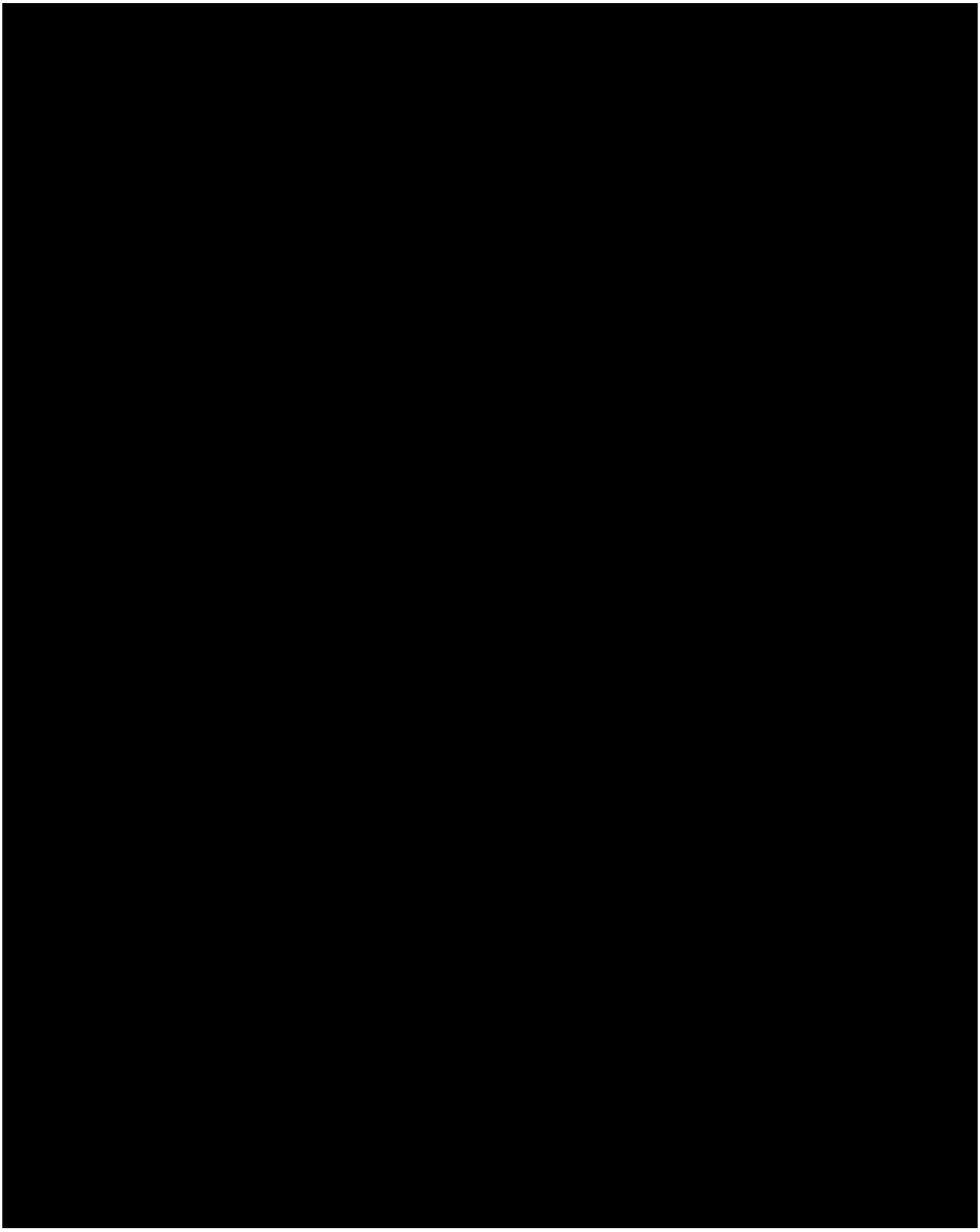


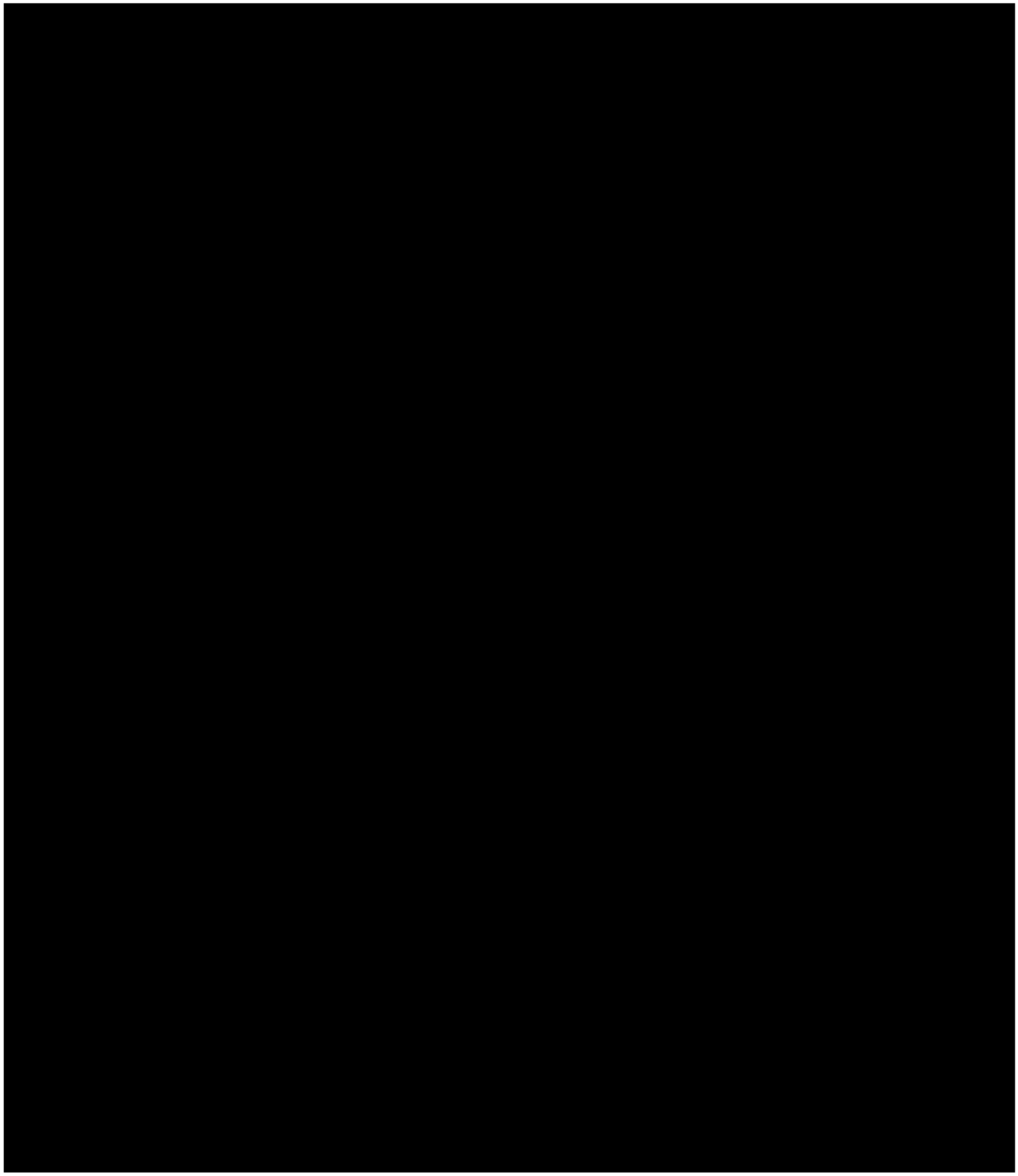




Health Questionnaire

English version for the USA





10.8.4. Patient Global Impression Scale

The Patient Global Impression (PGI) scale in this study is an OAB-specific quality of life questionnaire focused on 3 key aspects of the symptoms of the condition [redacted] Bother [PGI-B] and Improvement [PGI-I]). The tool was designed to assess the impact (and improvement) of urinary incontinence on activities of daily living, wellbeing, and function. The PGI scales are brief, general (ie, do not collect specific symptoms in contrast to other outcome measures for OAB), and easily completed.

A sample of the PGI scales is provided below:

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

[redacted]

These questions ask about the effect your erection problems have had on your sex life **over the past 4 weeks**. Please answer these questions as honestly and as clearly as possible. Please answer every question by checking the appropriate box [□]. If you are unsure about how to answer, please give the best answer you can.

In answering these questions, the following definitions apply:

* **Sexual intercourse**

Is defined as sexual penetration (entry) of the partner.

** **Sexual Activity**

Includes intercourse, caressing, foreplay and masturbation.

*** **Ejaculate**

Is defined as the ejection of semen from the penis (or the sensation of this).

**** **Sexual stimulation**

Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

1. **Over the past 4 weeks** how often were you able to get an erection during sexual activity**?
   Please check one box only.

   No sexual activity ..... □
   Almost always or always ..... □
   Most times (much more than half the time) ..... □
   Sometimes (about half the time) ..... □
   A few times (much less than half the time) ..... □
   Almost never or never ..... □

2. **Over the past 4 weeks** when you had erections with sexual stimulation****, how often were your erections hard enough for penetration?
   Please check one box only.

   No sexual stimulation ..... □
   Almost always or always ..... □
   Most times (much more than half the time) ..... □
   Sometimes (about half the time) ..... □
   A few times (much less than half the time) ..... □
   Almost never or never ..... □

The next 3 questions will ask about the erections you may have had during sexual intercourse*.

3. **Over the past 4 weeks** when you attempted sexual intercourse* how often were you able to penetrate (enter) your partner?
Please check one box only.

- Did not attempt intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

4. **Over the past 4 weeks** during sexual intercourse* **how often** were you able to maintain your erection after you had penetrated (entered) your partner?
Please check one box only.

- Did not attempt intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

5. **Over the past 4 weeks** during sexual intercourse* **how difficult** was it to maintain your erection to completion of intercourse?
Please check one box only.

- Did not attempt intercourse ☐
- Extremely difficult ☐
- Very difficult ☐
- Difficult ☐
- Slightly difficult ☐
- Not difficult ☐

6. **Over the past 4 weeks** how many times have you attempted sexual intercourse*?
Please check one box only.

No attempts	☐
1-2 attempts	☐
3-4 attempts	☐
5-6 attempts	☐
7-10 attempts	☐
11 + attempts	☐

7. **Over the past 4 weeks** when you attempted sexual intercourse* how often was it satisfactory for **you**?
Please check one box only.

Did not attempt intercourse	☐
Almost always or always	☐
Most times (much more than half the time)	☐
Sometimes (about half the time)	☐
A few times (much less than half the time)	☐
Almost never or never	☐

8. **Over the past 4 weeks** how much have you enjoyed sexual intercourse*?
Please check one box only.

No intercourse	☐
Very highly enjoyable	☐
Highly enjoyable	☐
Fairly enjoyable	☐
Not very enjoyable	☐
Not enjoyable	☐

9. **Over the past 4 weeks** when you had sexual stimulation**** or intercourse* how often did you ejaculate***?
Please check one box only.

- No sexual stimulation or intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

10. **Over the past 4 weeks** when you had sexual stimulation**** or intercourse* how often did you have the feeling of orgasm with or without ejaculation***?
Please check one box only.

- No sexual stimulation or intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

The next 2 questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (e.g. masturbation or intercourse*), thinking about sex, or feeling frustrated due to lack of sex.

11. **Over the past 4 weeks** how often have you felt **sexual desire**?
Please check one box only.

- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

12. **Over the past 4 weeks** how would you rate your level of **sexual desire**?
Please check one box only.

- Very high ☐
- High ☐
- Moderate ☐
- Low ☐
- Very low or none at all ☐

13. **Over the past 4 weeks** how satisfied have you been with your overall **sex life**?
Please check one box only.

- Very satisfied ☐
- Moderately satisfied ☐
- About equally satisfied and dissatisfied ☐
- Moderately dissatisfied ☐
- Very dissatisfied ☐

14. **Over the past 4 weeks** how satisfied have you been with your **sexual relationship** with your partner?
Please check one box only.

- Very satisfied ☐
- Moderately satisfied ☐
- About equally satisfied and dissatisfied ☐
- Moderately dissatisfied ☐
- Very dissatisfied ☐

15. **Over the past 4 weeks** how would you rate your **confidence** that you could get and keep an erection?
Please check one box only.

- Very high ☐
- High ☐
- Moderate ☐
- Low ☐
- Very low. ☐

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