Protocol Title: A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety and Tolerability of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)

Protocol Number:	**URO-901-3005**
Version Number:	**4.0** (supersedes Version 3.0)
Amendment Number:	**3**
Product:	Vibegron (URO-901, RVT-901, MK-4618, KRP-114V)
Development Phase:	3
Sponsor:	Urovant Sciences, GmbH Grosspeter Tower Grosspeteranlage 29 Suites 2006-2010 4052 Basel, Switzerland Sponsor Contact: [redacted], PhD, MS Senior Director, Clinical Development [redacted] Telephone: [redacted] Email: [redacted]
IND Number:	106410
EudraCT Number:	2018-003135-30
Emergency Contact Telephone Number:	Refer to separate Study Contacts Page
Contact for Serious Adverse Events (SAEs):	Email: PHV_Urovant@iqvia.com Phone: +1- 866-599-1341 Phone: +1-984-219-4638 (International) Fax: +1-866-599-1342 Fax: +1-984-219-5032 (International)
Approval Date:	**25 February 2022**
Sponsor Signatory:	[redacted], MD, PhD Chief Medical Officer

NCT Number: NCT03902080

This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

SPONSOR SIGNATURE PAGE

Study Title: A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety and Tolerability of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)

Study Number: URO-901-3005 (Amendment 3)

This protocol, including Amendment 3, has been approved by a representative of Urovant Sciences GmbH. The following signature documents this approval.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 25-Feb-2022 | 11:24 PST
70DF4B4DAD644AAF9DC76C1237B20D3B

25-Feb-2022 | 11:24 PST

[redacted], MD, PhD
Chief Medical Officer

Date

INVESTIGATOR STATEMENT

Study URO-901-3005: A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety and Tolerability of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)

Revised Protocol (Amendment 3)

- 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

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Version**	**Date**
Original protocol	1.0	29 January 2019
Amendment 1	2.0	30 July 2020
Amendment 2	3.0	16 December 2020
Amendment 3	4.0	24 February 2022

The current protocol amendment is summarized below. The previous amendments are summarized in Appendix 9.

Protocol Amendment 3, 24 February 2022

This protocol was amended to include the following notable changes:

- Cover Page was updated with new Sponsor Contact information
- Section 1.1 Synopsis, Overall Study Design, and Section 4.1 Overall Design
    - Updated to include a potential decision point to transition to enrollment of only subjects willing to participate in the urodynamics sub-study
- Section 1.4 Schedule of Assessments – Part 2
    - Updated footnote c to remove statement regarding other procedures to be consistent with remainder of protocol
    - Updated footnote f to indicate that a historical urodynamics assessment will be acceptable
- Table 1 Bladder Diary Completion Schedule
    - Run-in Diary Completion Timepoint to 'Begin 3-day diary' and 'Acceptable completion window' have been updated to allow completion on any 3 consecutive days at any time within the Screening period prior to the Run-in Visit
- Section 5.2 Exclusion Criteria
    - Renumbered to be consistent with Note to File issued subsequent to Protocol Amendment 2
    - Exclusion Criterion 7 was reworded to clarify that irregular use of long-acting ED medications is excluded while irregular use short-acting ED medications is allowed

  - Exclusion Criterion 11 was corrected to reflect the change made in Protocol Amendment 2 removing Qmax measurement at Visit 3 (Baseline)
  - Exclusion Criterion 19 has been modified to exclude uncontrolled sleep apnea and self-reported sleep apnea that has been neither confirmed nor diagnosed by a physician
  - Exclusion Criterion 25 has been clarified to indicate that all subjects taking any anti-hypertensives must be taking stable doses for at least 3 months prior to the Screening Visit
  - Exclusion Criterion 36 has been modified to exclude all subjects who have been exposed to vibegron (through a clinical trial or commercial use)
- Section 8.2.1 Bladder Diaries
  - Updated to allow completion on any 3 consecutive days at any time within the Screening period prior to the Run-in Visit
- Section 8.3.7 Urodynamics Assessments
  - Added that use of a historical urodynamics trace obtained at the site within 6 months prior to Screening may be used in lieu of an assessment obtained between screening and randomization (Baseline/Visit 3) as long as the same equipment and procedure are used at the Week 12 (Visit 8) assessment
  - Clarified that the urodynamics assessment may be performed on a different day than the Week 12 (Visit 8) visit as long as it is performed within the ±4-day visit window
- Section 8.4.6 Adverse Events of Special Interest
  - Formatting was changed for ease of understanding
  - New language was added to differentiate between AESI terms for hypertension and worsening of hypertension
- Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, Events Meeting the AE Definition
  - Words added to clarify that events that meet the definition include abnormal laboratory test results or safety assessments that worsen from baseline **or are** considered clinically significant
- Section 10.7.1 Screening, Visit 1 (Day -49 to Day -14)

  - Clarified that Screening Visit assessments may be performed in a single day or over multiple days within the screening period

- Section 10.7.3 Baseline, Visit 3 (Day 1)
  - Updated window to obtain baseline urodynamics assessment

Table of Contents

Sponsor Signature Page **2**

Investigator Statement **3**

Protocol Amendment Summary of Changes Table **4**

Table of Contents **7**

List of Tables **10**

1. Protocol Summary **11**
1.1. Synopsis 11
1.2. Schema for Parts 1 and 2 14
1.3. Schedule of Assessments - Part 1 15
1.4. Schedule of Assessments - Part 2 17

2. Introduction **21**
2.1. Study Rationale 21
2.2. Background 21
2.3. Overactive Bladder in Men with Benign Prostatic Hyperplasia 21
2.3.1. Vibegron 22
2.4. Benefit/Risk Assessment 23
2.4.1. Potential Benefits 23
2.4.2. Potential Risks 23

3. Objectives and Endpoints **25**

4. Study Design **27**
4.1. Overall Design 27
4.2. Scientific Rationale for Study Design 28
4.2.1. Clinical Hypotheses 28
4.3. Justification for Dose 28
4.4. End of Study Definition 28

5. Study Population **29**
5.1. Inclusion Criteria 29
5.2. Exclusion Criteria 30
5.3. Lifestyle Considerations 32
5.4. Screen Failures 33

6. Study Drug **34**
6.1. Study Drugs Administered 34
6.1.1. Run-in Medications and Administration 34
6.1.2. Treatment Period Medications and Administration 35
6.2. Preparation/Handling/Storage/Accountability 35
6.3. Measures to Minimize Bias: Randomization and Blinding 35
6.4. Study Drug Compliance 36
6.5. Concomitant Therapy 36
6.5.1. Prohibited Drugs and Washout Before the Study 36
6.5.2. Permitted Drugs 36
6.6. Dose Modification 37

6.7. Drug After the End of the Study 37

7. Discontinuation of Study Drug and Subject Discontinuation or Withdrawal 38
7.1. Discontinuation of Study Drug 38
7.2. Subject Discontinuation/Withdrawal from the Study 38
7.3. Lost to Follow-Up 39
7.4. Early Study Termination 39

8. Study Assessments and Procedures 40
8.1. Baseline Procedures 40
8.1.1. Informed Consent 40
8.1.2. Assignment of Subject Number 40
8.1.3. Screening 40
8.1.4. Medical History 41
8.1.5. Demographics 41
8.1.6. Prior and Concomitant Medications 41
8.1.7. Inclusion and Exclusion Post Placebo Run-In 41
8.2. Efficacy Assessments 42
8.2.1. Bladder Diaries 42
8.2.2. Patient-Reported Outcomes 43
8.3. Safety Assessments 44
8.3.1. Vital Signs 44
8.3.2. Orthostatic Blood Pressure (Part 1 Only) 45
8.3.3. Physical Examinations 45
8.3.4. Electrocardiograms 46
8.3.5. Post-Void Residual Volume 46
8.3.6. Clinical Safety Laboratory Assessments 46
8.3.7. Urodynamics Assessments 47
8.3.8. Prostate Volume Measurement 48
8.4. Adverse Events and Serious Adverse Events 48
8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 48
8.4.2. Method of Detecting Adverse Events and Serious Adverse Events 49
8.4.3. Follow-up of Adverse Events and Serious Adverse Events 49
8.4.4. Regulatory Reporting Requirements for Serious Adverse Events 49
8.4.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events 50
8.4.6. Adverse Events of Special Interest 50
8.4.7. Pregnancy Management and Reporting to the Sponsor 53
8.4.8. Medication Errors 54
8.5. Treatment of Overdose 54
8.6. Safety Measures due to COVID-19 Pandemic 55

9. Statistical Considerations 56
9.1. Statistical Hypotheses 56
9.2. Sample Size Determination 56

9.3. Populations for Analyses 58
9.4. Statistical Analyses 59
9.4.1. Demographic and Other Baseline Characteristics 59
9.4.2. Efficacy Analyses 60
9.4.3. Safety Analyses 61
9.4.4. Other Analyses 63
9.5. Interim Analyses 63
9.6. Data Safety Monitoring Board 63

10. Supporting Documentation and Operational Considerations 64
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 64
10.1.1. Regulatory and Ethical Considerations 64
10.1.2. Financial Disclosure 64
10.1.3. Informed Consent Process 65
10.1.4. Data Protection 65
10.1.5. Committees Structure 65
10.1.6. Posting Clinical Study Data 65
10.1.7. Data Quality Assurance 66
10.1.8. Source Documents 67
10.1.9. Study and Site Closure 68
10.1.10. Publication Policy 68
10.1.11. Compliance with Protocol 68
10.2. Appendix 2: Clinical Laboratory Tests 69
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 70
10.4. Appendix 4: Abbreviations 75
10.5. Appendix 5: Study Tabular Summary 78
10.6. Appendix 6: Prohibited Medications and Non-Drug Therapies 80
10.7. Appendix 7: Study Schedule Supplement 81
10.7.1. Screening, Visit 1 (Day -49 to Day -14) 81
10.7.2. Run-in, Visit 2 (Day -14 ± 4 days) 82
10.7.3. Baseline, Visit 3 (Day 1) 82
10.7.4. REMOTE Double-blind Treatment Period, Visit 4 (Week 1 + 4 days) 83
10.7.5. Double-blind Treatment Period, Visit 5 (Week 2 ± 4 days) 83
10.7.6. Double-blind Treatment Period, Visit 6 (Week 4 ± 4 days) 84
10.7.7. Double-blind Treatment Period, Visit 7 (Week 8 ± 4 days) and Visit 10 (Week 20 ± 4 days) 84
10.7.8. Double-blind Treatment Period, Visit 8 (Week 12 ± 4 days) 85
10.7.9. REMOTE Double-blind Treatment Period, Visit 9 (Week 16 ± 4 days) 85
10.7.10. Double-blind Treatment Period, Visit 11 (Week 24 ± 4 days) or Early Withdrawal) 85

10.7.11. Safety Follow-up (for subjects who do not enter the extension Study URO-901-3006; 5 days after last dose of study drug [± 2 days]) 86
10.8. Appendix 8: Patient-Reported Outcomes Questionnaires, Descriptions, and Instructions 86
10.8.1. International Prostate Symptom Score (IPSS) 86
[redacted]
10.8.4. Patient Global Impression Scale 95
10.8.5. International Index of Erectile Function 98
10.9. Appendix 9: Summary of Previous Protocol Amendments 104
10.9.1. Protocol Amendment 1, 30 July 2020 104
10.9.2. Protocol Amendment 2, 16 December 2020 107
11. References 113

List of Tables

Table 1 Bladder Diary Completion Schedule 20
Table 2 Summary of Study Drugs 34
Table 3. Data and Sources Supporting Study Sample Size Calculations 57
Table 4 Clinical Laboratory Tests 69

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety and Tolerability of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)

Protocol Number: URO-901-3005

Brief Title: Vibegron in Men with BPH with OAB

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-901-3005 is designed to evaluate the safety, tolerability, and efficacy of vibegron (75 mg once daily [QD] administered for 24 weeks) or placebo in men with symptoms of OAB while receiving pharmacological therapy for BPH.

Objectives and Endpoints: The primary study objective is to assess the efficacy, safety, and tolerability of vibegron versus placebo in men with OAB symptoms on pharmacological therapy for BPH. The primary clinical efficacy hypothesis is that vibegron + BPH pharmacological therapy is more effective than placebo + BPH pharmacological therapy in reducing both a) the mean daily micturition episodes and b) mean daily urgency episodes, based on a 3-day diary. The safety hypothesis is that the vibegron + BPH pharmacological therapy is safe and tolerable in men with OAB symptoms and BPH.

Primary and secondary study endpoints are as follows: (Note “per day” refers to a continuous 24-hour period.)

Co-Primary Efficacy Endpoints

- Change from baseline (CFB) at Week 12 in the average number of micturition episodes per day
- CFB at Week 12 in the average number of urgency episodes (urgency: need to urinate immediately) per day

Secondary Efficacy Endpoints

- CFB at Week 12 in the average number of nocturia episodes per night
- CFB at Week 12 in the average number of urge urinary incontinence episodes per day for subjects with urinary incontinence at baseline

- CFB at Week 12 in the International Prostate Symptom Score (IPSS) Storage score (1-week recall)

- CFB at Week 12 in the average volume voided per micturition

Overall Study Design: This study is an international Phase 3, randomized, double-blind, placebo-controlled, 2-part, parallel-group, multicenter study to evaluate the safety, tolerability, and efficacy of vibegron 75 mg in men with symptoms of OAB on stable doses of pharmacological therapy for BPH. At Baseline, subjects who meet all eligibility criteria are randomized 1:1 to receive either vibegron 75 mg, or placebo in a double-blind fashion. Randomization will be stratified based on baseline average number of micturition episodes per day (≤ 12 or > 12), alpha blocker use with or without 5α-reductase inhibitors (5-ARIs) use (yes or no), and urinary incontinence (yes or no).

The study consists of two parts: Part 1 (approximately 80 subjects) and Part 2 (approximately 1008 subjects). Part 2 will proceed following review of 4-week safety data from Part 1 (including orthostatic blood pressure results) by an independent Data Safety Monitoring Board (DSMB). The 2 study parts are of the same overall design as outlined below but with the following exceptions:

- Part 1 includes additional orthostatic blood pressure and heart rate measurements at Screening, Run-in, Baseline, Week 2, and Week 4 to assess for potential orthostatic changes (pre-dose through 6 hours post dose, except pre-dose for Screening and Run-In).

- Part 2 will include a urodynamics sub-study (approximately 60 subjects), which is described in detail in Section 8.3.7.

    - The rate of enrollment into both the main study and the urodynamics sub-study will be closely monitored. In the case of a discrepancy between the estimated date of completion of enrollment in the urodynamics sub-study and the main study, a decision may be made to continue enrolling only those subjects who are willing to participate in the urodynamics sub-study.

Both study parts will consist of a Screening Period (approximately 1 to 4 weeks), a single-blind Run-in Period (approximately 2 weeks) in which placebo is added to BPH pharmacological therapy, and a randomized double-blind Treatment Period (24 weeks). Subjects who complete the Week 24 Visit may be offered the opportunity to enroll in a 28-week extension study, URO-901-3006, which will be conducted under a separate study protocol. Subjects who do not enroll into the extension study will have a Safety Follow-up assessment (via telephone call) approximately 5 days (± up to 2 days) after the subject's last dose of study treatment (or approximately 5 days [± up to 2 days] after withdrawal for subjects who discontinue the study early). Additionally, Unscheduled Visit(s) may be arranged as needed.

The study visit schedule is as follows:

Visit #	Study Timepoint
Visit 1	Screening
Visit 2	Run-in
Visit 3	Baseline
Visit 4	Week 1 (telephone/video call for Part 2 post Amendment 2)
Visit 5	Week 2
Visit 6	Week 4
Visit 7	Week 8
Visit 8	Week 12 (Primary efficacy timepoint)
Visit 9	Week 16 (telephone/video call for Part 2 post Amendment 2)
Visit 10	Week 20
Visit 11	Week 24 (End of the Treatment)
Safety Follow-up	5 (± 2) days after End of the Treatment (for subjects who do not enter the extension study) or after withdrawal (for subjects who discontinue early)

Number of Subjects: It is estimated that approximately 1088 subjects (80 Part 1, 1008 Part 2) will be randomized to achieve approximately 924 evaluable subjects (assuming a 15% drop-out rate). The sample size justification is provided in Section 9.2.

Number of Sites: Approximately 135 sites in North America and Europe.

Study Drug Groups and Study Duration:

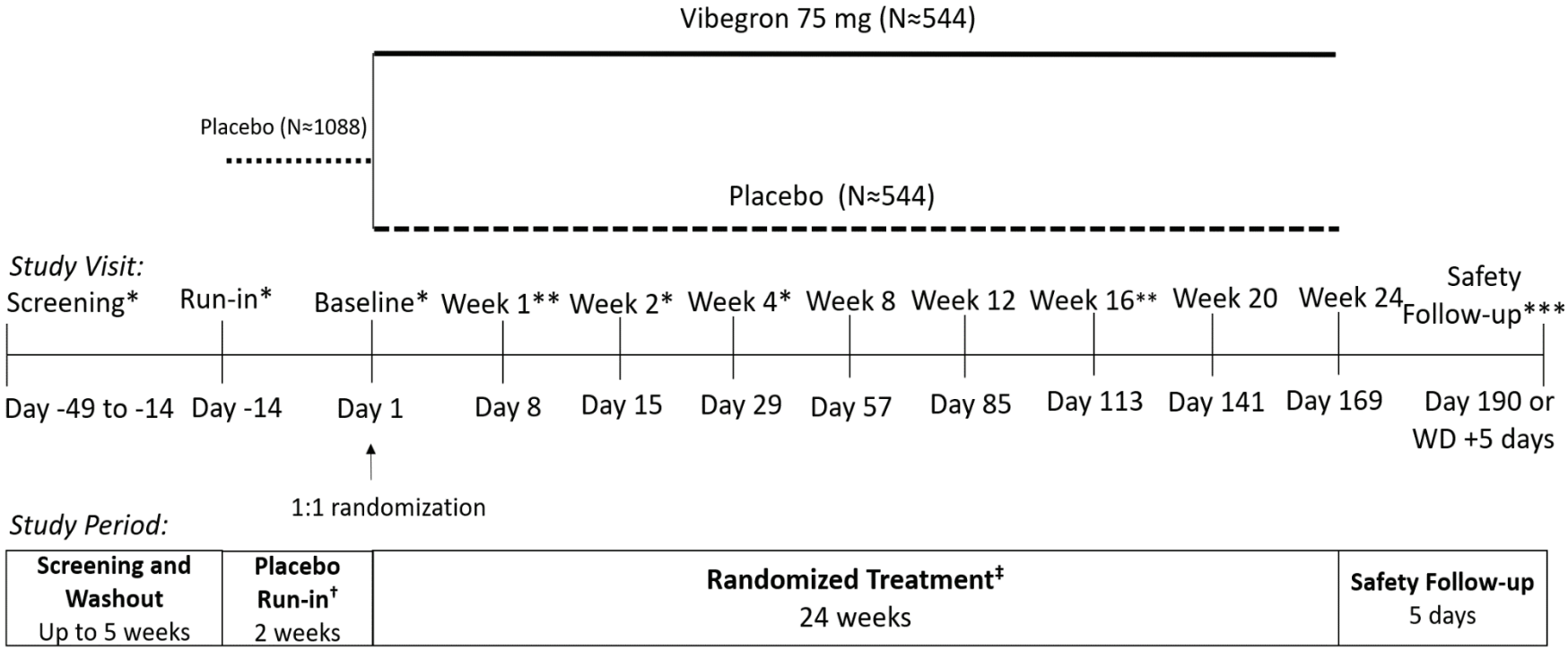
Single-blind Run-in: 1 matched placebo oral tablet daily for 2 weeks

Double-blind Treatment: 1 vibegron (75 mg) or matched placebo oral tablet daily for 24 weeks. No dosage adjustments will be allowed.

Prior to the study, subjects will have been on alpha-blockers (eg, alfuzosin, doxazosin, silodosin, tamsulosin, terazosin) with or without 5-ARI (eg, alfatradiol, dutasteride, finasteride); they will continue these agents after adding study drug (vibegron or placebo).

Data Safety Monitoring Board: A DSMB will be retained to assess, on an ongoing basis, all safety aspects of this study, including review of initial (4-week) safety/orthostatic blood pressure results from Part 1 prior to proceeding into Part 2. This committee will be an external independent DSMB that monitors the safety for both Study URO-901-3005 and the extension 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 for Parts 1 and 2



*: Screening, Run-in, Baseline, Week 2, and Week 4 include extended blood pressure and heart rate assessments for Part 1 participants only; safety data from Part 1 will be evaluated prior to initiating Part 2.

**: In Part 2, visits at Week 1 and Week 16 will be conducted by telephone/video call.

***: The Safety Follow-up occurs 5 days after the last dose for subjects who completed the Week 24 visit but do not enroll in the optional 28-week extension study or 5 days after withdrawal (WD) for subjects who withdraw early from the study.

†Single-blind Run-in (subjects will not know they are receiving placebo)

‡Double-blind

1.3. Schedule of Assessments - Part 1

	Screening	Run-in		Double-blind Treatment							Safety Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visits 9 & 10	Visit 11 or Early WD	Telephone Call[b]
Day/Week	Day -49 to -14[a]	Day -14	Baseline Day 1	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 8 (Day 57)	Week 12 (Day 85)	Week 16 (Day 113) & Week 20 (Day 141)	Week 24 (Day 169) or Early WD	5 days after last dose or Early WD
Visit Window		± 4 days		+4 days	± 4 days	± 4 days	± 4 days	± 4 days	± 4 days	± 4 days	± 2 days
Informed consent	X										
Subject entry into IWRS and subject registry	X										
Inclusion and Exclusion Criteria Review	X	X	X								
Demographics	X										
Medical History (includes drugs, alcohol, and tobacco usage)	X										
Prior OAB and BPH medication review	X										
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X
IPSS[c]	X		X			X	X	X	X	X	
[redacted]											
PGI[c]			X			X		X		X	
[redacted]			[redacted]					[redacted]		[redacted]	
Vital Signs[d] and Orthostatic Blood Pressure	X[e]	X[e]	X[e]	X	X[e]	X[e]	X	X	X	X	
Brief Physical Examination	X		X					X		X	
12-lead ECG	X										

	Screening	Run-in		Double-blind Treatment						Safety Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visits 9 & 10	Visit 11 or Early WD	Telephone Call[b]
Day/Week	**Day -49 to -14[a]**	**Day -14**	**Baseline Day 1**	**Week 1 (Day 8)**	**Week 2 (Day 15)**	**Week 4 (Day 29)**	**Week 8 (Day 57)**	**Week 12 (Day 85)**	**Week 16 (Day 113) & Week 20 (Day 141)**	**Week 24 (Day 169) or Early WD**	**5 days after last dose or Early WD**
PVR Volume	X	X	X	X	X	X	X	X	X	X	
Prostate Volume[f] Measurement (via ultrasound)	X									X	
Uroflowmetry	X		X							X	
Laboratory Assessments[g]	X		X			X		X		X	
Review and Data Enter Completed Bladder Diary[g]		X	X		X	X	X	X	X	X	
Dispense Bladder Diary[h]	X	X		X	X	X	X	X	X		
Dispense Run-in Study Drug		X									
Dispense Double-blind Study Drug			X			X	X	X	X		
Administer Witnessed Dose of Study Drug		X	X		X	X					

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

a All Screening procedures and the 3-day Bladder Diary must be completed prior to the Run-In (Visit 2).

b The Safety Follow-up is not applicable for subjects who enter the extension study (URO-901-3006).

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

d 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; height is measured at Screening only.

e For visits with orthostatic blood pressure, blood pressure (in triplicate) and heart rate (by pulse) taken in both sitting and standing positions, measurements will be taken pre-dose, 1 hour post dose, 2 hours post dose, 4 hours post dose, and 6 hours post dose. Post dose assessments of blood pressure and pulse may be ± 15 minutes of the scheduled timepoints. Refer to Section 8.3.2 for additional details and requirements.

f A historical prostate volume by ultrasound, performed within 12 months prior to the first day of Screening, is acceptable, if the criteria detailed in Section 8.3.8 are satisfied.

g Blood draws should be performed after all PRO and vital sign assessments, with the exception of visits for which orthostatic blood pressure assessments are performed. During those visits, the blood draws may be performed after the 4-hour post dose blood pressure assessment, provided they are completed at least 45 minutes prior to the 6-hour post dose blood pressure assessment. Refer to Section 10.2 for a list of laboratory assessments performed.

h Subject completes the Bladder Diary PRIOR TO each visit.

1.4. Schedule of Assessments - Part 2

	Screening	Run-in		Double-blind Treatment								Safety Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4 Telephone/ Video Call	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 Telephone/ Video Call	Visit 10	Visit 11 or Early WD	Telephone/ Video Call[b]
Day/Week	**Day -49 to -14[a]**	**Day -14**	**Baseline Day 1**	**Week 1 (Day 8)**	**Week 2 (Day 15)**	**Week 4 (Day 29)**	**Week 8 (Day 57)**	**Week 12 (Day 85)**	**Week 16 (Day 113)**	**Week 20 (Day 141)**	**Week 24 (Day 169) or Early WD**	**5 days after last dose or Early WD**
Visit Window		**± 4 days**		**+4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 2 days**
COVID Mitigation Window*				**None**	**+ 10 days**	**+ 3 weeks**	**+ 3 weeks**	**+6 weeks**	**None**	**+ 3 weeks**	**+ 3 weeks**	**None**
Informed consent	X											
Subject entry into IWRS and subject registry	X											
Inclusion and Exclusion Criteria Review	X	X	X									
Demographics	X											
Medical History (includes drugs, alcohol, and tobacco usage)	X											
Prior OAB and BPH medication review	X											
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X
IPSS[c]	X		X			X	X	X		X	X	
[redacted]												
PGI[c]			X			X		X			X	
[redacted]												
Vital Signs[d]	X	X	X		X	X	X	X		X	X	
Brief Physical Examination	X		X					X			X	

	Screening	Run-in		Double-blind Treatment								Safety Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4 Telephone/ Video Call	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 Telephone/ Video Call	Visit 10	Visit 11 or Early WD	Telephone/ Video Call[b]
Day/Week	**Day -49 to -14[a]**	**Day -14**	**Baseline Day 1**	**Week 1 (Day 8)**	**Week 2 (Day 15)**	**Week 4 (Day 29)**	**Week 8 (Day 57)**	**Week 12 (Day 85)**	**Week 16 (Day 113)**	**Week 20 (Day 141)**	**Week 24 (Day 169) or Early WD**	**5 days after last dose or Early WD**
Visit Window		**± 4 days**		**+4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 2 days**
COVID Mitigation Window*				**None**	**+ 10 days**	**+ 3 weeks**	**+ 3 weeks**	**+6 weeks**	**None**	**+ 3 weeks**	**+ 3 weeks**	**None**
12-lead ECG	X											
PVR Volume	X	X	X		X	X	X	X		X	X	
Prostate Volume[e] Measurement (via ultrasound)	X[e]											
Uroflowmetry	X										X	
Urodynamics[f]	X							X				
Laboratory Assessments[g]	X		X			X		X			X	
Dispense Bladder Diary[h]	X	X	X		X	X	X	X		X		
Dispense Run-in Study Drug		X										
Dispense Double-blind Study Drug[i]			X			X	X	X		X		
Administer Witnessed Dose of Study Drug		X	X									

AE = adverse event; BPH = benign prostatic hypertrophy; ECG = electrocardiogram; [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

NOTE: Certain study assessments and procedures also may be performed remotely to minimize contact, as outlined in Section 8.6.

* To account for additional time that may be necessary to ensure safety through COVID-19 preventive measures, a COVID Mitigation Window, with extended windows for visit timings, has been implemented. However, if safe and feasible, study visits should adhere to the schedule outlined Visit Window when.

a With the exception of prostate volume measurement (which can be completed any time prior to randomization), all Screening procedures and the initial 3-day Bladder Diary must be completed prior to Run-In (Visit 2).

b The Safety Follow-up is not applicable for subjects who enter the extension study (URO-901-3006).

[redacted]

d Vital signs (including blood pressure [triplicate], pulse, body temperature, respiration rate, and weight) should be taken prior to blood draws and study drug dosing; height is measured at Screening only.

e A historical prostate volume measurement by ultrasound, performed within 12 months prior to the first day of Screening, is acceptable if the criteria detailed in Section 8.3.8 are satisfied. For subjects with no acceptable historical measurement, a prostate volume measurement by ultrasound must be completed prior to randomization (Baseline/Visit 3).

f Urodynamics procedure only applies to the Urodynamics sub-study of 60 subjects. Subjects will provide an additional urodynamics sub-study consent at Screening. A historical urodynamics assessment, performed at the site within 6 months prior to screening, will be acceptable. For subjects with no acceptable historical trace, a urodynamics assessment must be completed prior to randomization (Baseline/Visit 3). The Week 12 urodynamics assessment may be conducted on a different day than the Week 12 visit if it is done within the ±4 day visit window. All assessments (historical/ Baseline and Week 12) must be performed using the same urodynamics equipment and procedure (fill rate, catheter size, fluid, etc).

g Blood draws should be performed after all PRO and vital sign assessments. Refer to Section 10.2 for a list of laboratory assessments performed.

h Refer to Table 1 for details on when subjects should complete the Bladder Diary for each study timepoint. Note that the Bladder Diary may be dispensed or returned remotely (ie, delivered by mail, courier, or curbside pickup) and may be dispensed at an earlier timepoint. If dispensing in-person, ensure an adequate supply of diaries is provided (eg, diaries to be completed by the subject prior to Week 2 are dispensed at Baseline, and diaries to be completed by the subject prior to Week 16 and Week 20 are dispensed at Week 12).

i For visits that occur after Baseline, double-blind study drug may be dispensed to the subject by means other than by in-person contact (eg, via curbside pickup, trackable courier, or another method approved by the Sponsor/CRO).

Table 1 Bladder Diary Completion Schedule

Diary Completion Timepoint	Run-In	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24 (Day 169)
Begin 3-day Diary	**At least 3 Days prior to Run-In Visit**	**3 to 7 Days prior to Baseline Visit**	**Day 8 to 12**	**Day 22 to 26**	**Day 50 to 54**	**Day 78 to 82**	**Day 106 to 110**	**Day 134 to 138**	**Day 162 to 166**
Acceptable completion window	**After Initial Screening Visit and prior to Run-In Visit**	**7 Days prior to Baseline Visit**	**Days 8 to 14**	**Days 22 to 28**	**Days 50 to 56**	**Days 78 to 84**	**Days 106 to 112**	**Days 134 to 140**	**Days 162 to 168**

NOTES:

- Subjects will complete the diary for 3 days (72 hours) in a row in the 7 days prior to each Diary Completion timepoint, during which they will be asked to record information in their diary every time they urinate in the toilet or whenever they have urinary urgency or urinary incontinence (accidental loss of urine).
- On one of the 3 Diary Completion days, subjects will measure how much urine they produce for 24 consecutive hours and enter the volume in the diary. Subjects may choose which of the 3 Diary Completion days they will measure urine.
- The study staff will call subjects before each 3-day diary period to remind them to complete the diary.
- Subjects will be given Bladder Diaries and a container to measure the urine for each applicable timepoint.
- Diaries may be dispensed and/or returned remotely (eg, by mail, courier, or curbside pickup). If dispensing in-person ensure an adequate supply of diaries is provided (eg, diaries to be completed by the subject prior to Week 2 are dispensed at Baseline, and diaries to be completed by the subject prior to Week 16 and Week 20 are dispensed at Week 12).

2. Introduction

2.1. Study Rationale

Vibegron is currently in Phase 3 clinical development for the treatment of overactive bladder (OAB) in women and men. This study is intended to evaluate use of vibegron for the treatment of persistent OAB symptoms in the subpopulation of men with benign prostatic hypertrophy (BPH) on pharmacological therapy.

Men with OAB symptoms associated with BPH represent an OAB subpopulation that has not been extensively studied. Oftentimes in these patients, OAB symptoms remain inadequately addressed despite treatment for their BPH (ie, alpha-blocker with or without 5α-reductase inhibitors [5-ARIs]). For reasons described below, this population warrants specific clinical studies to adequately evaluate and address their unique medical needs. Study URO-901-3005 is designed to be a large (planned N = 1088 subjects), Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety, tolerability, and efficacy of vibegron (75 mg once daily [QD] administered for 24 weeks) in men with symptoms of OAB (ie, ≥ 8 and ≤ 20 micturition episodes per day and urgency episodes of ≥ 3 per day) 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 a 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, 2008]. 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 over activity, 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 included subjects of both sexes. The Phase 3 program in OAB (RVT-901-3003 and RVT-901-3004) included approximately 15% males, contributing safety data comprising 217 men in addition to those enrolled in Study URO-901-3005. 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.

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

- Potential major cardiovascular events
- Hypertension
- AEs suggestive of orthostatic hypotension
- 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. The study's 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).

3. Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy • To assess the efficacy of vibegron compared with placebo in men with OAB symptoms on pharmacological therapy for BPH as defined by micturition and urgency episodes **Secondary Efficacy** • To assess the efficacy of vibegron compared with placebo in men with OAB symptoms on pharmacological therapy for BPH as defined by other key measures **Safety** • To assess the safety and tolerability of vibegron compared with placebo in men with OAB symptoms on pharmacological therapy for BPH **Other Efficacy** [redacted]	**Primary Efficacy** • CFB at Week 12 in the average number of micturition episodes per day • CFB at Week 12 in the average number of urgency episodes (urgency: need to urinate immediately) per day **Secondary Efficacy** • CFB at Week 12 in the average number of nocturia episodes per night • CFB at Week 12 in the average number of urge urinary incontinence episodes per day for subjects with urinary incontinence at baseline • CFB at Week 12 in the IPSS Storage score (1-week recall) • CFB at Week 12 in the average volume voided per micturition **Safety** • AEs, concurrent medications, clinical laboratory, vital sign assessments, PVR volume, uroflow measures, IPSS, urodynamics (sub-study only) **Other/Exploratory - Efficacy** • CFB at Week 2, Week 4, Week 8, Week 16, Week 20 and Week 24 in the average number of micturition episodes per day • CFB at Week 2, Week 4, Week 8, Week 16, Week 20, and Week 24 in the average number of urgency episodes per day • CFB at Week 2, Week 4, Week 8, Week 16, Week 20 and Week 24 in the average number of nocturia episodes per night • CFB at Week 4, Week 8, Week 20, and Week 24 in the IPSS Storage score (1-week recall) • CFB at Week 4, Week 8, Week 12, Week 20, and Week 24 in the IPSS Quality of Life score (1-week recall) • CFB at Week 4, Week 8, Week 12, Week 20, and Week 24 in the IPSS Voiding score (1-week recall) • CFB at Week 2, Week 4, Week 8, Week 16, Week 20, and Week 24 in the average number of urge urinary incontinence episodes per day for subjects with urinary incontinence at baseline • CFB at Week 2, Week 4, Week 8, Week 16, Week 20, and Week 24 in the average volume voided per micturition • CFB at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 in the average number of total incontinence episodes per day for subjects with urinary incontinence at baseline

- Percent of all subjects with a 50% reduction from baseline in average urgency episodes (urgency: need to urinate immediately) per day at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24
- Percent of subjects with urinary incontinence at baseline with a 75% reduction from baseline in average urge urinary incontinence episodes per day at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24

Other/Exploratory - Quality-of-Life

- CFB at Week 12 in Symptom Bother Score as assessed by [redacted], 1-week recall)
- CFB at Week 12 in HRQL total score as assessed by [redacted] (HRQL includes subscales: coping, concern, sleep and social interaction. The total score will be calculated by adding the 4 subscales scores.)
- CFB at Week 12 and Week 24 in HRQL subscale Coping score as assessed by [redacted]
- CFB at Week 12 and Week 24 in HRQL subscale Concern score as assessed by [redacted]
- CFB at Week 12 and Week 24 in HRQL subscale Sleep score as assessed by [redacted]
- CFB at Week 12 and Week 24 in HRQL subscale Social Interaction score as assessed by [redacted]
- CFB at Week 12 and Week 24 in [redacted] as assessed by measure of health stat nnaire developed by the EuroQolGroup
- CFB at Week 4, Week 12, and Week 24 in overall bladder symptoms based on [redacted]
- CFB at Week 4, Week 12, and Week 24 in overall control over bladder symptoms based on [redacted]
- CFB at Week 4, Week 12, and Week 24 in overall symptom frequency based on [redacted]
- CFB at Week 4, Week 12, and Week 24 in overall urgency-related leakage over bladder symptoms based on [redacted] in subjects with urinary incontinence at baseline
- Overall change of bladder symptoms based on [redacted] at Week 4, Week 12, and Week 24
- CFB at Week 12 and Week 24 in the [redacted]

Note: "per day" refers to a continuous 24-hour period.
Abbreviations: AE = adverse events; BPH = benign prostatic hypertrophy; CFB = change from baseline; HRQL = health-related quality of life; [redacted] IPSS = International Prostate Symptom Score; OAB = overactive bladder; [redacted] PGI = Patient Global Impression; QoL = quality of life; PVR = post-void residual

4. Study Design

4.1. Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, 2-part, parallel-group, multicenter study to evaluate the safety, tolerability, and efficacy of vibegron 75 mg in men with symptoms of OAB on stable doses of pharmacological therapy for BPH. At Baseline, subjects who meet all eligibility criteria are randomized 1:1 to receive either vibegron 75 mg, or placebo in a double-blind fashion. Randomization will be stratified based on baseline average number of micturition episodes per day (≤ 12 vs > 12), alpha blocker use with or without 5-ARI (yes or no), and urinary incontinence (yes or no).

The study consists of two parts: Part 1 (approximately 80 subjects) and Part 2 (approximately 1008 subjects). Part 2 will proceed following review of 4-week safety data (including orthostatic blood pressure results) of all 80 subjects from Part 1 by an independent DSMB. The independent DSMB will review the safety data throughout the entire study. The 2 study parts are of the same overall design as outlined below but with the following exceptions:

- Part 1 includes additional orthostatic blood pressure and heart rate measurements at Screening, Run-in, Baseline, Week 2, and Week 4 to assess for potential orthostatic changes (pre-dose through 6 hours post dose, except pre-dose for Screening and Run-In).
- Part 2 will include a urodynamics sub-study (approximately 60 subjects), which is described in detail in Section 8.3.7.
    - The rate of enrollment into both the main study and the urodynamics sub-study will be closely monitored. In the case of a discrepancy between the estimated date of completion of enrollment in the urodynamics sub-study and the main study, a decision may be made to continue enrolling only those subjects who are willing to participate in the urodynamics sub-study.

Both study parts will consist of a Screening Period (approximately 1 to 4 weeks), a single-blind therapy plus placebo Run-in Period (approximately 2 weeks), and a randomized double-blind Treatment Period (24 weeks).

Study visit schedules: Visit 1 (Screening), Visit 2 (Run-in), Visit 3 (Baseline), Visit 4 (Week 1), Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), and Visit 11 (Week 24) (End of the Treatment). For subjects enrolled in Part 2 after implementation of Protocol Amendment #2, Visit 4 (Week 1) and Visit 9 (Week 16) will be conducted remotely (via telephone or video call).

Subjects who complete the Week 24 Visit may be offered the opportunity to enroll in a 28-week extension study URO-901-3006, which will be conducted under a separate study protocol. Subjects who do not enroll into the extension study will have a Safety Follow-up telephone call

approximately 5 days (± up to 2 days) after the subject's last dose of study treatment (ie, or approximately 5 days [± up to 2 days] after withdrawal for subjects who discontinue the study early). Additionally, Unscheduled Visit(s) may be arranged as needed.

Approximately 1088 subjects (544 per treatment group: 80 total in Part 1 and 1008 total in Part 2) will be randomized at up to approximately 135 sites in North America (United States and Canada) and Europe to have 924 subjects complete the study (assuming a 15% dropout rate). The sample size justification is provided in Section 9.2.

4.2. Scientific Rationale for Study Design

A single-blind, placebo Run-in Period will be used to assess placebo response and to ensure that subjects have adequate experience with dosing compliance and completing the Bladder Diaries. The double-blind Treatment Period will include a placebo arm to accurately demonstrate and measure the efficacy of vibegron. 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.

4.2.1. Clinical Hypotheses

The primary efficacy hypothesis is that vibegron + BPH pharmacological therapy is more effective than placebo + BPH pharmacological therapy in reducing both the mean daily micturition episodes and the mean daily urgency episodes, based on results from a 3-day diary. The safety hypothesis is that the vibegron + BPH pharmacological therapy is safe and tolerable in men with BPH with OAB.

4.3. Justification for Dose

This study will use a vibegron dose of 75 mg administered orally QD, which is the same dose used throughout the Phase 3 vibegron clinical program for the general OAB indication in both men and women. A placebo control was considered appropriate and justified because no active agents have been fully evaluated or approved specifically in this patient population.

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, completes Week 24 Visit for subjects who enroll into Study URO-901-3006 or Safety Follow-up for subjects who do not enroll into Study URO-901-3006), discontinued from the study, or are lost to follow-up.

5. Study Population

The study is being conducted in men with OAB symptoms while receiving pharmacological therapy for BPH. 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; however, subjects may be rescreened once to meet inclusion criteria.

5.1. Inclusion Criteria

At the **Visit 1 (Screening)** visit (and other timepoints as noted), a subject will be eligible for inclusion in this study only if all of the following criteria apply, unless otherwise noted:

1. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
2. Male subjects of 45 years of age and above.
3. Body weight ≥ 50 kg (inclusive).
4. Subject should have been on and agree to continue to stay on a stable dose of BPH treatment with either a) alpha blocker monotherapy or b) alpha blocker + 5 ARI. Subjects on alpha blockers should have started their therapy at least 3 months prior to screening and be on a stable dose at the start of screening. Subjects on a 5-ARI should have started therapy at least 6 months prior to screening and be on a stable dose at screening.
5. Has a history of overactive bladder symptoms (frequency of ≥ 8 micturition episodes per day and urgency episodes of ≥ 3 per day with or without incontinence) while taking pharmacological therapy for at least 2 months to treat LUTS due to BPH.
6. Subject has an IPSS total score of ≥ 8 at Screening and Visit 3 (Baseline).
7. Subject has a prostate-specific antigen (PSA) level < 4 ng/mL, or if ≥ 4 ng/mL but ≤ 10 ng/mL, prostate cancer has been ruled out to the satisfaction of the investigator.
8. Subjects agrees to not participate in another interventional drug or device clinical trial during the study.
9. 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.
10. At Visit 2 (Run-in) and Visit 3 (Baseline) visits, subject must have both additional qualifications based on the 3-day Bladder Diary period: a) having an average of ≥ 8 but ≤ 20 micturition episodes per day over the 3-day diary period, and (b) having an average of ≥ 3 urgency episodes per day over the 3-day diary period.
11. Subject must have a post void residual (PVR) volume value of < 100 mL at Screening, Visit 2 (Run-In) and Visit 3 (Baseline).

12. At Visit 2 (Run-in) and Visit 3 (Baseline) visits, having at least 2 average nocturia episodes per night based on 3-day Bladder Diary at baseline. Nocturia is defined as waking to pass urine during the main sleep period.

5.2. Exclusion Criteria

At the **Visit 1 (Screening)** visit (and other timepoints as noted), a subject will not be eligible for inclusion in this study if any of the following criteria apply, unless otherwise noted:

1. Subject has a history of 24-hour urine volume greater than 3,000 mL or over 3,000 mL based on 3-day Bladder Diary at Visit 2 (Run-In) or Visit 3 (Baseline) visits.
2. Subject is a night-shift worker or plans to become a night-shift worker during the study.
3. Has lower urinary tract pathology that could, in the opinion of the investigator, be responsible for urgency, frequency, or incontinence; including, but not limited to, bladder stones, interstitial cystitis, prostate cancer, persistent urethral stricture, urogenital tuberculosis, and urothelial tumor.
4. Has a history of prostate surgery, including minimally invasive transurethral or transrectal procedures, procedural treatments for BPH within 6 months of Screening or has a planned prostate surgery, including minimally invasive prostate procedures, during the study period. Has a previous or planned pelvic radiation, low anterior resections (LAR), or any abdominoperineal resections (APR) during the study period.
5. Subject had prostatitis in the past 6 months.
6. Has a history of urinary retention requiring an intervention (eg, catheterization) for any reason.
7. Irregular use of long-acting medications (eg, tadalafil) to treat erectile dysfunction (ED). Note: ED medications with a short half-life such as sildenafil and vardenafil may be used on an irregular basis.
8. Subject has any planned procedures to treat ED (eg, implantation of a penile device) during the treatment period, or has any planned prostate procedure.
9. Subject is using any herbal medications to treat overactive bladder, lower urinary tract symptoms/BPH symptoms, or erectile dysfunction in the past 28 days prior to Screening.
10. Subject started using diuretics within 28 days prior to Screening. Subjects already taking any diuretics on stable doses for at least 28 days prior to Screening are allowed to enroll to the study.
11. Has maximum urinary flow (Qmax) < 5.0 mL/second with a minimum voided volume of 125 mL at Screening.
12. Has a history of or current nocturnal polyuria at Visit 2 (Run-In) or Visit 3 (Baseline) visits, based on 3-day Bladder Diary. Nocturnal polyuria is defined as more than one third of the total urine output per 24 hours occurring at night time.
13. Has undergone bladder training or electrostimulation within 28 days prior to Screening or plans to initiate either during the study.

14. Has an active or recurrent (> 3 episodes per year) urinary tract infection by clinical symptoms or laboratory criteria (≥ 5 white blood cells [WBC]/hpf with presence of red blood cell [RBC] and/or a positive urine culture, defined as ≥ 10^5 colony forming units [CFU]/mL [ie, 100 × 10^3 CFU/mL] in a single specimen). Subjects diagnosed with a urinary tract infection (UTI) at the Screening Visit may be treated until the infection has resolved.
15. Has received an intravesical or intraprostatic treatment with any botulinum toxin, resiniferatoxin, or capsaicin within 6 months prior to Screening Visit.
16. Has an implanted sacral neurostimulation (SNS) or use of any posterior tibial nerve stimulation (PTNS) device.
17. Has uncontrolled hyperglycemia (defined as fasting blood glucose > 150 mg/dL or 8.33 mmol/L or non-fasting blood glucose > 200 mg/dL or 11.1 mmol/L) or, if in the opinion of the investigator, is uncontrolled.
18. Has a prior diagnosis of diabetes insipidus.
19. Has uncontrolled sleep apnea or has self-reported sleep apnea that has been neither confirmed nor diagnosed by a physician. (Note: Subjects with a prior diagnosis of sleep apnea who have been stable on treatment for ≥3 months prior to Screening or whose condition has resolved at least 3 months prior to Screening are not excluded based on this criterion.)
20. Has a concurrent malignancy or history of any malignancy within 5 years prior to screening, except for adequately treated basal cell or squamous cell skin cancer.
21. This exclusion criterion was removed with implementation of Amendment #1.
22. Has history of clinically relevant liver disease or severe hepatic impairment (Child-Pugh Class C).
23. Has clinically significant electrocardiogram (ECG) abnormality that, in the opinion of the investigator, exposes the subject to risk by participating in the study.
24. 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.
25. Subjects who have systolic blood pressures ≥ 160 mmHg but < 180 mmHg are excluded, unless deemed by the investigator as safe to proceed in this study and able to complete the study per protocol; All subjects taking anti-hypertensives must be on stable doses for at least 3 months prior to the Screening Visit.
26. All subjects with signs and symptoms of uncontrolled hypertension, regardless of blood pressure measurement, are excluded from the study. These include, but are not limited to neurological symptoms or findings, hematuria, proteinuria, retinopathy, unstable angina, and acute heart failure.
27. Has a history of cerebral vascular accident, transient ischemic attack, unstable angina, myocardial infarction, coronary artery interventions (eg, coronary artery bypass grafting or percutaneous coronary interventions [eg, angioplasty, stent insertion]), or neurovascular interventions (eg, carotid artery stenting) within 6 months prior to the Screening Visit.

Subjects with these conditions should be on stable medical therapy for at least 3 months prior to the Screening Visit.

28. Has a history of injury, surgery, or neurodegenerative diseases (eg, multiple sclerosis, Parkinson's) that could affect the lower urinary tract or its nerve supply.
29. Has hematuria that was not evaluated, including microscopic hematuria (> 5 RBCs/hpf). Subjects with known, fully evaluated, benign hematuria may participate. Documentation must be obtained indicating an unremarkable upper urinary tract (kidneys and ureters) imaging study (eg, computerized tomography [CT] scan with and without contrast, renal ultrasound, magnetic resonance imaging [MRI], intravenous pyelogram, etc.) and cystoscopy. Subjects whose hematuria has not been previously evaluated may not be enrolled.
30. Has alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome).
31. Has an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.
32. Use of any prohibited medications as detailed in Section 6.5.1 (suitable washout periods from these medications are also described therein).
33. Had changed the dose of any medications listed in Section 6.5.2 within 28 days prior to the Screening Visit or plans to initiate or change the dosing of any of these medications during the study.
34. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the investigator, contraindicates their participation.
35. Is currently participating or has participated in a study with an investigational compound or device or procedure within 28 days prior to Screening Visit.
36. Prior exposure to vibegron (either through clinical trial or commercial use).
37. Has a history of significant drug or alcohol abuse/dependence within a year prior to screening, as assessed by the Investigator.
38. Has coronary or neurovascular interventions planned during the duration of the study.
39. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstances that might, in the opinion of the investigator, confound the results of the study, interfere with the subject's ability to comply with the study procedure, or make participation in the study not in the subject's best interest.
40. At Visit 3 (Baseline), subject was non-compliant during the 2-week placebo -controlled run-in period (taking < 80% or > 120% of the study medication).

5.3. Lifestyle Considerations

Not applicable for this study.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) that occurred within the Screening period. Individuals who do not meet the criteria for participation in this study (screen failures prior to initiation of run-in study medication) may be rescreened once upon consultation with, and approval by, the Sponsor or its designee. Subjects who initiate Run-in study drug dosing may not be rescreened. Rescreened subjects will be assigned a new subject number, and both subject numbers will be linked to the subject.

6. Study Drug

6.1. Study Drugs Administered

Table 2 provides a summary of the finished study drug products (vibegron and placebo).

Table 2 Summary of Study Drugs

Study Drug Name	Vibegron	Matched Placebo
Dosage Formulation	tablet	tablet
Identity of Formulation	75 mg	placebo
Route of Administration	oral	oral
Dosing Instructions	once daily	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.	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	Patheon, Cincinnati, Ohio, US
Number and Timing of Drugs	Treatment Period: 1 tablet daily	Run-in Period: 1 tablet daily Treatment Period: 1 tablet daily

HDPE = high density polyethylene

The study drug will be supplied in bottles each containing 32 tablets (4-week supply) and labeled with the protocol number, bottle number, lot number, expiration date, study drug name (vibegron 75 mg or placebo 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 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.

To minimize in-person contact during the COVID-19 pandemic, double-blind study drug may be dispensed and delivered directly to the subject by means other than by in-person contact (eg, via curbside pickup, trackable courier, or another method approved by the Sponsor/CRO).

6.1.1. Run-in Medications and Administration

During the single-blind Run-in Period, all subjects will take 1 tablet of study drug (ie, placebo) once daily for approximately 2 weeks. All subjects will take their first dose of study drug at the study site as a witnessed dose. The date and time of the study drug dosing will be recorded. The investigator will be aware that the study drug is placebo, but the subject will not know the

identity of the treatment or that entry into the double-blind Treatment Period is dependent on compliance with dosing in the Run-in Period. The matched placebo will be identical in appearance to the study drug administered during double-blind treatment.

6.1.2. Treatment Period Medications and Administration

During the double-blind Treatment Period, subjects will take 1 tablet of study drug (vibegron or matched placebo) once daily for up to 24 weeks. The appearance of the vibegron and placebo tablets will be identical. All subjects will be administered a witnessed dose of study drug at the study site at Visit 3 (Baseline). Subjects in Part 1 additionally will be administered a witnessed dose of study drug at Visit 5 (Week 2) and Visit 6 (Week 4). The date and time of the study drug dosing will be recorded.

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. Measures to Minimize Bias: Randomization and Blinding

Single-blind (Run-in only) and double-blind (Treatment Period) techniques will be used. Vibegron and its matching placebo will be packaged identically so that the treatment blind is maintained. The subject, investigator, and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will be unaware of the treatment group assignments during the double-blind Treatment Period. Subjects will be centrally assigned to randomized study drug using an interactive web response system (IWRS) and the randomization schedule generated by the sponsor or designee. Before screening is initiated at each site, login information and directions for the IWRS will be provided.

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

assignment is unblinded, the Sponsor or designee must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

At the end of the study, the official, final database will be frozen and unblinded after medical/scientific review has been performed, and data have been declared final and complete. The Sponsor will be granted access to the unblinded database in order to analyze the data. A clinical study report will be prepared after all subjects complete the study.

6.4. 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 should 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.

6.5. 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.

6.5.1. Prohibited Drugs and Washout Before the Study

Section 10.6 provides a listing of specific restrictions for concomitant therapy use during the study, with any necessary washout periods described and examples of prohibited drug categories. 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.

6.5.2. 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.

6.6. 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.

6.7. Drug After the End of the Study

Subjects who complete the study through the Week 24 Visit may be offered the opportunity to enroll in a 28-week extension study (URO-901-3006), in which open-label vibegron will be provided.

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 randomized 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 24/Early Withdrawal assessments specified in the Schedule of Assessments (Section 1.3 and Section 1.4).

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 the best interest of the subject (reason for discontinuation will be AE).

7.2. Subject Discontinuation/Withdrawal from the Study

- Subjects who discontinue study drug will also withdraw 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 (enrollment accounts for a predetermined dropout rate).

The Week 24/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 and Section 1.4).

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
- Screen failure
- Run-in Failure
- 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 and 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 and all dispensed study medication is returned. If the subject cannot be reached, the subject should 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 [Part 1] and Section 1.4 [Part 2]). 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; however, subjects who fail to meet eligibility criteria may be rescreened once, as appropriate. 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 if done on-site (in person), PRO assessments will be completed prior to vital signs, and vital signs will be taken prior to blood draws.
- Certain study assessments and procedures may be performed remotely (eg, by telephone or video call). Refer to Section 8.6 for additional details.

8.1. Baseline Procedures

8.1.1. Informed Consent

Documented consent must be obtained from each potential subject prior to participating in any study procedures according to the process described in Section 10.1.3.

8.1.2. Assignment of Subject Number

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

8.1.3. Screening

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will be reviewed by the investigator or qualified designee at Screening, the start of the Run-in Period, and the start of the double-blind Treatment Period.

Subjects who fail to meet entry criteria may be rescreened **once**. (See Section 8.1.2 regarding assignment of subject number.)

The Screening period may also be used for washout of prohibited medications (see Section 6.5.1).

8.1.4. Medical History

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

8.1.5. Demographics

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

8.1.6. Prior and Concomitant Medications

Prior OAB and BPH medications, as well as ongoing (concomitant) medications will be recorded beginning at the signing of the ICF and continuing until the Safety Follow-up call (5 days after the last dose of study drug).

8.1.7. Inclusion and Exclusion Post Placebo Run-In

All Inclusion and Exclusion criteria are to be rechecked for eligibility at the end of Placebo Run-In (prior to randomization). Specific inclusion criteria to be checked upon completion of the Placebo Run-In will include:

- Laboratory assessments (as defined in Section 5.1)
- 3-day Bladder Diary review to confirm:
    - average of ≥ 8 but ≤ 20 micturition episodes per day
    - average of ≥ 3 urgency episodes per day over the 3-day diary period
    - average of ≥ 2 nocturia episodes per night
- IPSS total score of ≥ 8
- PVR volume value of < 100 mL

Specific exclusion criteria to be checked upon completion of the Placebo Run-In will include:

- Laboratory assessments (as defined in Section 5.2)

- 24-hour urine volume > 3,000 mL based on 3-day Bladder Diary
- Qmax < 5.0 mL/second with a minimum voided volume of 125 mL
- Subject has taken < 80% or > 120% of the study medication during the Run-In period

8.2. Efficacy Assessments

Efficacy assessments will be collected as outlined in the Schedule of Assessments (Section 1.3 and Section 1.4) in the form of 3-day Bladder Diary (refer to Table 1). Information collected in the diaries will be used for assessment of the primary and secondary efficacy endpoints related to the number of micturition, urgency, nocturia, and incontinence episodes per day as well as one 24-hr volume voided of urine. In addition, subjects will complete IPSS assessments, and [redacted] PGI, and [redacted] scores to assess quality of life endpoints.

Subjects will complete questionnaires either at the start of each required study visit (before vital signs and blood draws) or just prior to the visit if completing the forms remotely to assess subject-perceived symptom relief and health-related quality of life. 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

The 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, 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. To minimize unnecessary on-site contact and ensure that the subject has a basic understanding and ability to comply with completion of the diary, an optional prescreening diary may be provided to potential study subjects prior to completion of screening procedures.

A schedule of completion timelines for the Bladder Diaries for each associated visit is provided in Table 1. The Bladder Diary should be completed by the subject on 3 consecutive days within the 7 days prior to each Bladder Diary Completion timepoint as outlined in in Table 1. Urine volume may be collected during any one (1) of the Bladder Diary Days, and it should be recorded for ~24 hours starting from the time the patient gets up for the day and continues until the time the patient gets up for the day on the next day.

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

To be eligible for the study, subjects must have a minimum of:

- 3 consecutive Diary Days during the Screening Period (prior to the Run-in Visit), and
- 3 consecutive Diary Days during the Run-in Period (over the 7 days prior to the Baseline Visit), and
- be capable in the investigator's opinion of maintaining compliance with the diary requirements, including the measurement and recording of urine volume, as required, at Baseline and throughout the course of the study.

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

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

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 International Prostate Symptom Score (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 overactive bladder on health-related quality of life. The instrument was developed and validated in both continent and incontinent OAB patients, including both men and women. A sample of the [redacted] scale is provided in Section 10.8.2.

- The [redacted] 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 [redacted] health questionnaire is provided in Section 10.8.3.

- Global Impression Items include Patient Global Impression of [redacted] (PGI [redacted] Patient Global Impression of [redacted] (PGI-[redacted], Patient Global Impression of [redacted] (PGI-[redacted], Patient Global Impression of [redacted] (PGI-[redacted] and Patient Global Impression of [redacted] (PGI-[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 volume and orthostatic blood pressure and heart rate, are provided in the Schedule of Assessments (Section 1.3 and Section 1.4). 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, respiration rate, weight, and height, will be assessed at the timepoints specified in the Schedule of Assessments (Section 1.3 and Section 1.4) and in 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. Note additional requirements on timing for blood pressure assessments for visits with orthostatic assessments in Part 1 (Section 8.3.2).

- 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.

- Standing height will be measured without shoes at Screening only.

8.3.2. Orthostatic Blood Pressure (Part 1 Only)

In addition to routine vital signs (including standard blood pressure assessments), subjects in Part 1 of the study (ie, the first 80 subjects enrolled) will undergo serial blood pressure and heart rate (by pulse) assessments at Screening, Run-In, Baseline, and Weeks 2 and 4. Blood pressure should be assessed as described in Section 8.3.1, with the following additional requirements:

- Triplicate measurements should be obtained for both sitting and standing blood pressure assessments at Hour 0 (pre-dose) and Hours 1, 2, 4, and 6 post dose. (For Screening Visit and Run-In assessments, use Hour 0 as the time from which subsequent assessments are collected.) A singular pulse rate also should be obtained in sitting and standing positions at the same hourly timepoint. Post-dose assessments of blood pressure and pulse may be ± 15 minutes of each scheduled timepoint.

- Sitting blood pressure and pulse will be measured after the subject has been resting in a sitting position for 5 minutes; standing blood pressure will be measured within 3 minutes of standing (after rising from the sitting position).

- Subjects will be permitted to eat or drink during the 6-hour testing window, however caffeinated beverages will not be allowed.

- Subjects are encouraged to eat breakfast and have the test done at least 1 hour after the meal.

- Subjects should remain relatively inactive and should remain within or close to the facility during the 6-hour test window.

- As stated above in Section 8.3.1, blood draws should be obtained either after all blood pressure assessments are completed or between the 4-hour and 6-hour post-dose blood pressure assessments, provided that blood draws are complete at least 45 minutes before the 6-hour timepoint.

8.3.3. 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.

8.3.4. Electrocardiograms

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

8.3.5. 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 (eg, bladder scanner) at the visits indicated in the Schedule of Assessments (Section 1.3 and Section 1.4). All efforts should be made to ensure the same device and operator are used for all PVR volume measurements for individual subjects.

8.3.6. 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 Screening (and at other eligibility assessment timepoints as specified in Section 5.1 and Section 5.2), 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 5 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 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.

8.3.7. Urodynamics Assessments

For the approximately 60 subjects participating in the urodynamics sub-study in Part 2, urodynamics will be taken at Baseline and Week 12 to measure the following parameters:

- Instilled volume at first involuntary detrusor contraction (IDC) (Vol@1st IDC) (mL), if an IDC occurs
- Corrected maximum detrusor pressure during the first involuntary detrusor contraction (P_{det}@1st IDC) (cmH_2O), if an IDC occurs
- Corrected maximum cystometric capacity (MCC) (mL)
- Corrected maximum detrusor pressure during the storage phase (P_{det}@$_{Max\ Storage}$) (cmH_2O)
- Peak flow rate during voiding (Q_{Max}) (mL/s)
- Corrected detrusor pressure at peak flow rate (P_{det}@Q_{Max}) (cmH_2O)
- Voided volume (VV) (mL)

The urodynamics sub-study will be conducted at selected sites which meet the qualifications set by the independent urodynamics central reader.

Randomization for the urodynamic sub-study will be stratified based on baseline average number of micturition episodes per day (≤ 12 or > 12), alpha blocker use with or without 5-ARI (yes or no), and urinary incontinence (yes or no).

A historical urodynamics trace obtained at the site within 6 months prior to screening, which has the above parameters clearly identified will be accepted in lieu of an assessment obtained after the start of screening but prior to randomization (Baseline/Visit 3). For subjects with no acceptable historical trace, a urodynamics assessment must be completed prior to randomization (Baseline/Visit 3).

The Week 12 (Visit 8) urodynamics assessment may be conducted on a different day than the Week 12 visit if done within the ±4-day visit window.

All assessments (historical/Baseline and Week 12) must be performed using the same urodynamics equipment and procedure (fill rate, catheter size, fluid, etc).

8.3.8. Prostate Volume Measurement

Prostate volume measurement will be collected via ultrasound prior to randomization (Baseline/Visit 3). Prostate volume measurement (by ultrasound) assessed within 12 months prior to Screening may be accepted in lieu of a measurement collected at any time prior to randomization (Baseline/Visit 3).

8.4. Adverse Events and Serious Adverse Events

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

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

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

8.4.1. 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 5 days after the last dose of study drug. AEs will be collected at the timepoints specified in the Schedule of Assessments (Section 1.3 and Section 1.4), 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 the Safety Follow-up telephone call (5 days [± up to 2 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 5 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, 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 and 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 **in addition to** one of 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 increased 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 (ie, 100×10^3 CFU/mL)
    AND
    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: An AESI of **Hypertension** (or **Worsening Hypertension**, if the subject has history of hypertension) should be recorded if any of the following three criteria are met (regardless of clinical significance):

  - For subjects with systolic blood pressure < 140 mmHg **AND** diastolic blood pressure < 90 mmHg at ***baseline*** (Visit 3):
    The average of 3 systolic blood pressures ≥ 140 mmHg ***or*** diastolic blood pressures ≥ 90 mmHg (or both) at **any 2 consecutive visits** after baseline (Visit 3)
  - For subjects with systolic blood pressure ≥ 140 mmHg **OR** diastolic blood pressure ≥ 90 mmHg at ***baseline*** (Visit 3):
    An increase, compared to baseline (Visit 3) 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

  Note 1: The onset date for an AESI hypertension is the first of the dates when the event meets any of the above criteria.

  Note 2: An *AE of "increased blood pressure"* should be recorded if, in the investigator's opinion, an elevated blood pressure measurement is clinically significant but does not fulfill the above definition for hypertension.

- 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 Sections 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 drug 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 case of a male subject with a pregnant partner, if the patient agrees, the patient's pregnant partner should be notified and requested to sign a Release of Information form, permitting transfer of information regarding the pregnancy and outcome to the sponsor.

The investigator must inform the subject of his right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the subject. The study team will remain blinded to the subject's treatment assignment.

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 and treatment (blinded or unblinded, as applicable).

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 or placebo 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 more tablets of study drug within 24 hours), the investigator or treating physician should:

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

8.6. Safety Measures due to COVID-19 Pandemic

To minimize direct, in-person contact between site personnel and subjects, certain study procedures may be performed remotely by telephone contact or video call. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:

- Informed consent (where applicable, per approved IRB/IEC process)
- Medical history
- Demography
- Prior medications (including prior OAB and BPH medication review)
- Collection and dispensation of paper PRO questionnaires
- Collection and dispensation of Bladder Diaries
- Review of AEs/SAEs
- Concomitant medications
- Dispensation of study drug during Double-blind Treatment Phase for visits after Baseline (Visit 3)

If a subject cannot attend the Week 12 visit (Visit 8), the site should bring him/her in for an early withdrawal visit (Visit 11) when safe and feasible.

If a subject misses any other single on-site study visit as a result of the COVID-19 pandemic, then the site should collect the completed Bladder Diary (eg, by curbside pickup, mail, or courier) for review and data entry when feasible, and remotely review AEs/SAEs and concomitant medications. Study drug should be dispensed (eg, curbside pickup or shipped via trackable courier or other methods approved by the Sponsor/CRO), and the next visit's bladder diary should be provided. In such cases, the subject will not be considered lost to follow-up or early withdrawal, if he remains in contact with the site and is compliant with study drug administration, completing study procedures as appropriate, and attends subsequent visits.

9. Statistical Considerations

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

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

A subject is considered enrolled in the study at randomization.

9.1. Statistical Hypotheses

The primary clinical efficacy hypothesis is that vibegron + pharmacological therapy is more effective than placebo + pharmacological therapy in reducing both a) the mean daily micturition episodes and b) mean daily urgency episodes, based on a 3-day diary.

9.2. Sample Size Determination

Approximately 1088 subjects will be randomized in a 1:1 ratio to receive one of the following study treatments:

- Vibegron 75 mg tablet (N = 544)
- Matching placebo tablet (N = 544)

Approximately 544 subjects each will be assigned to the vibegron and placebo treatment groups. Assuming a total of 15% of subjects will discontinue prior to Week 12 (for any reason), there will be approximately 462 evaluable subjects in the vibegron and placebo treatment groups (924 subjects total) at the end of Week 12. The study has approximately 94.3% power to detect a between-group treatment difference of 0.46 in change from baseline in micturitions at a 2-sided 0.05 level assuming a variability estimate of 1.972 based on vibegron Study MRK-008 data and the FDA's statistical reviewer of mirabegron NDA data showing that the micturition treatment effect in men taking 50 mg of mirabegron is 70% of the overall 50 mg of mirabegron population. Additional details are provided at the end of this section.

For the second co-primary endpoint, 462 evaluable subjects per treatment group has approximately 90% power to detect a between-group treatment difference of 0.60 in change from baseline in urgency episodes at a 2-sided 0.05 level assuming a variability estimate of 2.811 based on vibegron Study MRK-008 data and the FDA's statistical reviewer of mirabegron NDA data. Additional details are provided at the end of this section.

The overall study power will be more than 84% with the co-primary endpoints based on the Bonferroni inequality (ie, for any events A and B, $P(A \cap B) \geq P(A) + P(B) - 1$).

Derivation of Estimated Treatment Effect in Men

Based on the published results of the Phase 2 trial of mirabegron and the FDA statistical reviewer of the OAB NDA, we estimated the following:

- The Phase 3 results will have at least 85% of the treatment difference of the Phase 2 results
- The treatment difference for men is at least 70% of the effect of the general OAB population

Table 3 summarizes this information and sources.

Table 3. Data and Sources Supporting Study Sample Size Calculations

Mirabegon Results			
	N		**PBO Adj CFB**
Study	**Overall**	**Men**	**Overall**
178-CL-046	473	133	-0.6
178-CL-047	425	116	-0.61
		Simple Average	-0.61

	Phase 2 Micturition PBO Adj CFB	**Phase 3 Micturition PBO Adj CFB**	**Phase 3 as a % of Phase 2**
Comparing Phase 3 to Phase 2	-0.64	-0.605	94.5%

Merck 008 Results and Ph 3 Projections			
Measure	**Vib 50mg**	**Vib 100mg**	**SD**
Micturition	-0.64	-0.91	1.972
Urgency Episodes	-0.76	-1.24	2.811

Midpoint between 50mg and 100mg	**Micturition**	**Urgency Episodes**
Ph 2 Projected Effect of 75mg	-0.78	-1.00
Ph 3 Projected Effect of 75mg	-0.66	-0.85
Ph 3 Projected Effect of 75mg in Men	-0.46	-0.60

Power in Baseline BPH Treatment Subgroups:

Although this study will not formally test the treatment effect in subgroups by baseline BPH treatments, it is sufficiently sized to estimate treatment differences within these subgroups. Assuming that approximately half of the subjects are on alpha blockers alone and half on alpha blockers plus 5-ARI, then approximately 544 subjects will be randomized to each subgroup with 462 evaluable (231 per arm). Using the above assumptions with a two-sided test with a type-I error of 0.10, each subgroup will have 97.1% power for micturitions and 94.5% power for urgency episodes. Assuming that the endpoints and subgroups are independent, then the power for each subgroup to be significant on both endpoints is 91.7%, and the power for both subgroups to be significant on both endpoints is 84.0%.

The impact of imbalances in 5-ARI plus alpha blockers versus alpha blockers alone will be monitored and controlled if needed.

9.3. Populations for Analyses

Analysis Populations

Screened Set

The Screened Set consists of all subjects who are screened for the study. This population is used primarily for subject accounting purposes and will generally not be used for summary or analysis.

Run-in Set

The Run-in set consists of all subjects who entered the run-in period of the study. Subjects will be considered run-in failures if they enter the run-in period but are not randomized to receive double-blind medication.

Randomized Set

The Randomized Set consists of all subjects who are randomized to receive study medication regardless of whether they take a dose.

Safety Analysis Set (SAF)

The Safety Analysis Set consists of all subjects who receive at least one dose of double-blind study medication. Subjects will be classified according to the treatment they actually received.

Full Analysis Set (FAS)

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

FAS consists of all randomized subjects who took at least one dose of double-blind study medication and have at least one evaluable change from baseline micturition measurement. Subjects will be analyzed according to their randomized treatment, irrespective of premature discontinuation, according to the Intent-to-Treat (ITT) principle.

Full Analysis Set for Incontinence(FAS-I)

FAS-I consists of all randomized subjects with incontinence at baseline who took at least one dose of double-blind study medication, have an evaluable baseline urgency urinary incontinence measurement, and have at least one evaluable change from baseline urgency urinary incontinence measurement.

Note that "subjects with incontinence at baseline" are defined as meeting the following criteria:

- An average of ≥ 8.0 micturitions per Diary Day
- An average of ≥ 1.0 urinary incontinence episodes per Diary Day

Per-Protocol Set (PPS) and Per-Protocol Set for Incontinence (PPS-I)

The PPS and PPS-I exclude patients from the FAS and FAS-I due to important protocol deviations that may substantially affect the results of the efficacy endpoints (ie, major protocol deviations associated with efficacy). The final determination on protocol deviations, and thereby the composition of the PPS and PPS-I, will be made prior to the unblinding of the database

A supportive analysis using the PPS and PPS-I will be performed for the co-primary efficacy and secondary endpoints. Subjects will be included in the treatment group to which they are randomized, regardless of which treatment actually received, for the analyses of efficacy data using the PPS and PPS-I.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Demographic and Other Baseline Characteristics

All demographic data such as age, race, and ethnicity and baseline characteristic data will be summarized by treatment group for the FAS. Subject disposition will be summarized using Screened Set.

Descriptions of medical history findings will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version. Medical history may be summarized in the descending order of overall frequency, by system organ class and preferred term.

Prior and concomitant medications will be coded using the latest version of World Health Organization (WHO) Drug Dictionary. The number and percentage of subjects receiving prior or concomitant medications will be summarized by treatment group.

Baseline prostate volume, Qmax, IPSS, and PVR will be summarized. Baseline disease characteristics related to primary and secondary variables will be summarized under primary and/or secondary efficacy analyses.

9.4.2. Efficacy Analyses

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

9.4.2.1. Analysis Endpoints

The primary and secondary efficacy endpoints are listed below and analyses will be defined in the following sections. All analyses for other efficacy/effectiveness and safety endpoints listed below will be defined in the SAP.

Co-Primary Efficacy Endpoints

- CFB at Week 12 in the average number of micturition episodes per day
- CFB at Week 12 in the average number of urgency episodes (urgency: need to urinate immediately) per day

Secondary Efficacy Endpoints

- CFB at Week 12 in the average number of nocturia episodes per night
- CFB at Week 12 in the average number of urge urinary incontinence episodes per day for subjects with urinary incontinence at baseline
- CFB at Week 12 in the IPSS Storage score (1-week recall)
- CFB at Week 12 in the average volume voided per micturition

9.4.2.2. Primary Analyses

For the analysis of the first co-primary endpoint (change from baseline in the average daily number of micturition episodes at Week 12), a mixed model for repeated measure (MMRM) with restricted maximum likelihood estimation will be used. The analysis model for the efficacy endpoint will include terms for treatment, visit, baseline micturition score, alpha blocker use (yes or no), baseline urinary incontinence (yes or no), region (US vs non-US), and interaction of visit by treatment. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment for denominator degrees of freedom will be used with restricted (or residual) maximum likelihood (REML) to make statistical inference.

For the analysis of the second co-primary endpoint (change from baseline in the average daily number of urgency episodes at Week 12), a similar MMRM model will be used. The analysis model for the efficacy endpoint will include terms for treatment, visit, baseline score, baseline average micturition episodes per day (≤ 12 vs > 12), alpha blocker use with or without 5-ARI (yes or no), baseline urinary incontinence (yes or no), region (US vs non-US), and interaction of visit by treatment.

Other change from baseline endpoints will be analyzed using the same MMRM model as urgency episodes.

9.4.2.3. Secondary Analyses

If the null hypothesis is rejected for both co-primary endpoints, then the secondary efficacy endpoints will be tested using a fixed-sequence testing procedure until a two-sided p-value ≥ 0.05 is observed. The fixed-sequence testing procedure controls the family-wise error rate at a 2-sided alpha level of 0.05. The order of the secondary efficacy endpoints is as specified in Section 9.4.2.1.

9.4.3. Safety Analyses

The safety analysis will be performed using the Safety Analysis Set and will be fully defined in the SAP. The safety parameters will include AEs and clinical laboratory and vital sign, parameters. For each safety parameter of the clinical laboratory and vital sign parameters, the last nonmissing safety assessment before the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

9.4.3.1. Adverse Events

An AE will be considered a treatment-emergent AE (TEAE) if:

- The AE began on or after the date of the first dose of study drug; or

- The AE was present before the date of the first dose of study drug, but increased in severity or became serious on or after the date of the first dose of study drug

An AE that occurs more than 5 days after the last dose of study drug will not be counted as a TEAE.

An AE will be considered a treatment-emergent SAE (TESAE) if it is a TEAE that additionally meets any SAE criteria.

AEs will be coded using the latest version of MedDRA. An overall summary table of AEs by treatment group will be presented with number and percentage of subjects. The incidence of all TEAEs by primary SOC and PT will be prepared for all TEAEs, TESAEs, treatment-related TEAEs/TESAEs, TEAEs leading to discontinuation from study treatment and all TEAEs by maximum intensity. All AEs will be listed. The number and percentage of subjects with AEs of special interest, as defined in Section 8.4.6, will be summarized by treatment group.

9.4.3.2. Clinical Laboratory Assessments

All continuous safety laboratory parameters will be summarized descriptively by absolute value at each visit by treatment group, together with the corresponding changes from baseline. Laboratory reference ranges will be used to identify abnormalities with low, normal, or high values.

9.4.3.3. Vital Signs

Descriptive statistics of observed values and change from baseline for vital signs will be presented for each treatment group by visit.

9.4.3.4. Urodynamics

Descriptive statistics of observed values at Baseline and Week 12, and the change from baseline at Week 12 for the following urodynamic parameters will be presented for each treatment group by visit:

- Instilled volume at first involuntary detrusor contraction (Vol@1st IDC) (mL)
- Corrected maximum detrusor pressure during the first involuntary detrusor contraction (P_{det}@1st IDC) (cmH_2O)
- Corrected maximum cystometric capacity (MCC) (mL)
- Corrected maximum detrusor pressure during the storage phase (P_{det}@$_{Max\ Storage}$) (cmH_2O)
- Peak flow rate during voiding (Q_{Max}) (mL/s)

- Corrected detrusor pressure at peak flow rate ($P_{det}@Q_{Max}$) (cmH_2O)
- Voided volume (VV) (mL)

This analysis will only apply to the sub-study in Part 2.

9.4.4. Other Analyses

Response efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel risk difference estimate. Missing Week 12 data will be analyzed using multiple imputation. For each imputed dataset, the estimated difference in the proportion of responders and 95% confidence interval for the difference will be calculated using the Cochran-Mantel-Haenszel risk difference estimate stratified by baseline average micturition episodes per day (≤ 12 vs > 12) and alpha blocker use with or without 5-ARI (yes or no) with weights proposed by Greenland and Robins.

9.4.4.1. Subgroup Analyses

Subgroup analyses of primary and secondary endpoints may be conducted. These may include analysis by alpha blocker use with or without 5-ARI (yes or no), baseline urinary incontinence (yes or no), and region (US vs non-US).

Sub-study may need to have a separate demographic and baseline characteristics analyses together with the urodynamic analysis to assess the effects of vibegron treatment on urodynamic parameters.

9.5. Interim Analyses

There are no interim analyses planned for this study.

9.6. Data Safety Monitoring Board

One external independent DSMB will be formed for the study URO-901-3005 and the extension study 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 by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or 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 or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier. Any subject records or datasets that are transferred to the Sponsor or designee will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. If a subject is rescreened and assigned a new subject number, both subject numbers for that individual will be linked.
- The subject must be informed that 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 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 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 subjects.

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 drug (drug dispensing and return should be documented as well)

- Record of all AEs and other safety parameters (start and end date, and causality and intensity as assigned by the investigator)
- Concomitant medication (including start and end date)
- Date of study completion and reason for early discontinuation, if applicable

10.1.9. Study and Site Closure

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

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

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

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

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 4 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 4 Clinical Laboratory Tests

Hematology	**Chemistry**	**Urinalysis[a]**	**Other**
Hematocrit	Albumin	Blood	PSA[d]
Hemoglobin	Alkaline phosphatase	Glucose	Coagulation INR/PT/APTT[e]
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	
	Creatinine[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] PSA performed by central laboratory at Screening.

[e] 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

Definition of an AE

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, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, or are 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. • Abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) identified during Screening.

Definition of an SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been admitted to the hospital or kept in the Emergency Room for ≥ 24 hours for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent activities of daily living but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such medically significant events include invasive or malignant cancers, intensive treatment with a drug in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the eCRF.
- All SAEs (including serious AESIs) must be **reported in the eCRF within 24 hours of the study site personnel's knowledge of the event**, regardless of the investigator assessment of the relationship of the event to study drug.
  - The event term, start date, severity, and initial causality assessment must be entered in the AE eCRF page and the event must be marked as "Serious". This will activate additional assessment fields including "action taken with study drug", "seriousness criteria", and "brief description" which should be completed as soon as information is available. Marking the event as "serious" will automatically send required notifications for Sponsor or designee review.

- The initial SAE report should include:
  - The date of the report
  - A description of the SAE (event term, seriousness of the event, date of onset, intensity)
  - Causal relationship to the study drug
- A discharge summary should be provided for all hospitalizations. If the subject died, the report should include the cause of death as the event term (with death as the outcome) and whether the event leading to death was related to study drug, as well as the autopsy findings, if available

- Nonserious AESIs should be reported on the eCRF within 72 hours of knowledge of the information.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of the AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Reporting of SAEs

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

10.4. Appendix 4: Abbreviations

Term	Description
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
β3-AR	beta-3 adrenergic receptor
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
HRQL	health-related quality of life
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Term	Description
ICS	International Continence Society
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
MCC	maximum cystometric capacity
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measure
MRI	magnetic resonance imaging
OAB	overactive bladder
[redacted]	[redacted]
P_{det}@1st IDC	maximum detrusor pressure during the first involuntary detrusor contraction
P_{det}@$_{Max\ Storage}$	maximum detrusor pressure during the storage phase
P_{det}@Q_{Max}	Detrusor pressure at peak flow rate
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

Term	Description
SAF	Safety Analysis Set
SAP	statistical analysis plan
SNS	sacral neurostimulation
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
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
Vol@1st IDC	volume at first involuntary detrusor contraction
VV	voided volume
WBC	white blood cell
WHO-DDE	World Health Organization Drug Dictionary Enhanced

10.5. Appendix 5: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety and Tolerability 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	Randomized, controlled, double-blind
	Trial Length	Up to 25 weeks
	Planned Country of Investigational Sites	North America and Europe
	Planned Number of Subjects	1088 enrolled; 924 evaluable
	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	Once 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	Placebo
	Comparative Treatment Name	--
Trial design	Study Type	Randomized, controlled, double-blind
	Drug Model	Parallel
	Planned Number of Arms	2
	Trial is Randomized	Yes
	Randomization Quotient	1:1
	Trial Blinding Schema	Double blind
	Stratification Factor	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; FDA = Food and Drug Administration; OAB = overactive bladder

10.6. Appendix 6: Prohibited Medications and Non-Drug Therapies

The following medications are prohibited, as outlined in Section 6.5.1.

Prohibited Medications Class	Examples	Washout Period/Comments
Anticholinergics	darifenacin, fesoterodine, hyoscyamine, oxybutynin, propantheline, solifenacin, tolterodine, and trospium	Subject must discontinue use at least 28 days prior to beginning completion of the Screening Bladder Diary and 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 discontinue use at least 28 days prior to beginning completion of the Screening Bladder Diary and remain off this therapy during the study
Beta-2 adrenergic agonists used for the treatment of stress urinary incontinence	clenbuterol	Subject must discontinue use at least 28 days prior to beginning completion of the Screening Bladder Diary and 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 discontinue use at least 28 days prior to beginning completion of the Screening Bladder Diary and remain off this therapy during the study
Beta-3 adrenergic agonists	mirabegron	Subject must discontinue use at least 28 days prior to beginning completion of the Screening Bladder Diary and remain off this therapy during the study
New start of BPH medications	Alpha-Blockers, eg, alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin 5-ARI, eg, alfatradiol, dutasteride, and finasteride 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 have received an injection within 6 months prior to the Screening Visit and 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 have received the herbal medications within 28 days prior to the Screening Visit and 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 7: Study Schedule Supplement

Note that subject assessments and procedures that can be done either on-site or remotely (without in-person subject contact) are marked with an asterisk (*).

In addition, to account for additional time that may be necessary to ensure site and subject safety through COVID-19 preventive measures, extended windows for visit timings have been implemented for Part 2. Refer to the Schedule of Assessments – Part 2 (Section 1.4) for additional details. As feasible, study visits should adhere to the schedule outlined in the original protocol and shown in the sections below.

Note that Bladder Diaries may be dispensed or returned remotely (ie, delivered by mail or courier) and may be dispensed at an earlier timepoint. If dispensing in-person, ensure an adequate supply of diaries is provided (eg, diaries to be completed by the subject prior to Week 16 and Week 20 are dispensed at Week 12).

10.7.1. Screening, Visit 1 (Day -49 to Day -14)

Screening visit assessments must be performed prior to Run-in to determine subject eligibility with time for analysis and reporting of all results. Assessments may be performed in a single day or may be done over multiple days within the screening period.

- Obtain Informed Consent (*may be conducted remotely per approved IRB/IEC process, where applicable)
- Begin recording AEs/SAEs after signing ICF*
- Enter subject into IWRS and subject registry
- Assess inclusion/exclusion criteria*
- Collect demographic data*
- Collect medical and surgical history data including use of illicit drugs, alcohol, and tobacco*
- Collect prior and current OAB and BPH pharmacotherapies*
- Collect concomitant medications*
- Administer IPSS scale*
- Record blood pressure (3 results taken 1-2 minutes apart after sitting for 5 minutes), pulse, respiration, temperature, weight, and height (Part 2 subjects only)
- Record respiration, temperature, weight, and height, and record triplicate orthostatic blood pressure (sitting blood pressure taken 1-2 minutes apart after sitting for 5 minutes, standing blood pressure taken 1-2 minutes apart within 3 minutes of standing) and orthostatic heart rate (by pulse) measurements (Part 1 subjects only)

- Perform brief physical examination
- Perform 12-lead ECG
- Collect uroflowmetry (eg, Qmax)
- Collect prostate volume (in mL) via ultrasound (if no measurement is available in preceding 12 months); note that the prostate volume may be completed at any time prior to randomization
- Measure post-void residual volume
- Perform laboratory assessments
- Dispense Bladder Diary and instruct subject on its completion*

10.7.2. Run-in, Visit 2 (Day -14 ± 4 days)

- Assess inclusion/exclusion criteria
- Review concomitant medications*
- Review AEs/SAEs*
- Review and data enter completed Bladder Diary*
- Record blood pressure (3 results taken 1-2 minutes apart after sitting for 5 minutes), pulse, respiration, temperature, and weight (Part 2 subjects only)
- Record respiration, temperature, and weight at Hour 0, and record triplicate orthostatic blood pressure (sitting blood pressure taken 1-2 minutes apart after sitting for 5 minutes, standing blood pressure taken 1-2 minutes apart within 3 minutes of standing) and orthostatic heart rate (by pulse) measurements at Hour 0 (pre-dose) (Part 1 subjects only)
- Measure post-void residual volume
- Dispense study drug for single-blind Run-in Period
- Administer witnessed dose of study drug (Part 1 subjects only)
- Dispense Bladder Diary*
- If not collected previously (and not available within 12 months of Screening), collect prostate volume (in mL) via ultrasound any time prior to randomization

10.7.3. Baseline, Visit 3 (Day 1)

- Assess inclusion/exclusion criteria
- Review concomitant medications*
- Review AEs/SAEs*
- Review and data enter completed Bladder Diary*

- 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 (Part 2 subjects only)
- Record respiration, temperature, and weight at Hour 0, and record triplicate orthostatic blood pressure (sitting blood pressure taken 1-2 minutes apart after sitting for 5 minutes, standing blood pressure taken 1-2 minutes apart within 3 minutes of standing) and orthostatic heart rate (by pulse) measurements at Hour 0 (pre-dose) and 1, 2, 4, and 6 hours (± 15 minutes) post-dose (Part 1 subjects only)
- Perform brief physical examination
- If not performed previously (and not available within 6 months prior to Screening), perform urodynamics assessment any time prior to randomization (for sub-study in Part 2 only)
- Measure post-void residual volume
- Perform laboratory assessments
- Dispense double-blind study drug
- Administer witnessed dose of study drug
- Option to dispense paper PRO questionnaires and diaries
- Dispense Bladder Diaries* (for completion at Week 2)

10.7.4. REMOTE Double-blind Treatment Period, Visit 4 (Week 1 + 4 days)

- Review concomitant medications*
- Review AEs/SAEs*

10.7.5. Double-blind Treatment Period, Visit 5 (Week 2 ± 4 days)

- Review concomitant medications*
- Review AEs/SAEs*
- Review and data enter completed Bladder Diary*
- Record blood pressure (3 results taken 1-2 minutes apart after sitting for 5 minutes), pulse, respiration, temperature, and weight (Part 2 subjects only)
- Record respiration, temperature, and weight at Hour 0, and record triplicate orthostatic blood pressure (sitting blood pressure taken 1-2 minutes apart after sitting for 5 minutes, standing blood pressure taken 1-2 minutes apart within 3 minutes of standing) and orthostatic heart rate (by pulse) measurements at Hour 0 (pre-dose) and 1, 2, 4, and 6 hours (± 15 minutes) post-dose (Part 1 subjects only)
- Measure post-void residual volume

- Administer witnessed dose of study drug (Part 1 subjects only)
- Dispense Bladder Diary*

10.7.6. Double-blind Treatment Period, Visit 6 (Week 4 ± 4 days)

- Review concomitant medications*
- Review AEs/SAEs*
- Review and data enter completed Bladder Diary*
- Administer IPSS and PGI scales*
- Record blood pressure (3 results taken 1-2 minutes apart after sitting for 5 minutes), pulse, respiration, temperature, and weight (Part 2 subjects only)
- Record respiration, temperature, and weight at Hour 0, and record triplicate orthostatic blood pressure (sitting blood pressure taken 1-2 minutes apart after sitting for 5 minutes, standing blood pressure taken 1-2 minutes apart within 3 minutes of standing) and orthostatic heart rate (by pulse) measurements at Hour 0 (pre-dose) and 1, 2, 4, and 6 hours (± 15 minutes) post-dose (Part 1 subjects only)
- Measure post-void residual volume
- Perform laboratory assessments
- Dispense double-blind study drug*
- Administer witnessed dose of study drug (Part 1 subjects only)
- Dispense Bladder Diary*

10.7.7. Double-blind Treatment Period, Visit 7 (Week 8 ± 4 days) and Visit 10 (Week 20 ± 4 days)

- Review concomitant medications*
- Review AEs/SAEs*
- Review and data enter completed Bladder Diary*
- Administer IPSS scale*
- 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
- Dispense double-blind study drug*
- Dispense Bladder Diary*

10.7.8. Double-blind Treatment Period, Visit 8 (Week 12 ± 4 days)

- Review concomitant medications*
- Review AEs/SAEs*
- Review and data enter completed Bladder Diary*
- 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
- Urodynamics (for sub-study in Part 2 only)
- Perform laboratory assessments
- Dispense double-blind study drug*
- Dispense Bladder Diaries* (for Week 16 and Week 20)

10.7.9. REMOTE Double-blind Treatment Period, Visit 9 (Week 16 ± 4 days)

- Review concomitant medications*
- Review AEs/SAEs*
- Review and data enter completed Bladder Diary*
- Remind subject to mail/drop-off Week 16 diary or bring it to the Week 20 visit
- Dispense Bladder Diary (if not previously dispensed)*

10.7.10. Double-blind Treatment Period, Visit 11 (Week 24 ± 4 days) or Early Withdrawal)

- Review concomitant medications*
- Review AEs/SAEs*
- Review and data enter completed Bladder Diary*
- 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
- Collect prostate volume (in mL) via ultrasound
- Measure post-void residual volume
- Collect uroflowmetry (eg, Qmax)

- Perform laboratory assessments

10.7.11. Safety Follow-up (for subjects who do not enter the extension Study URO-901-3006; 5 days after last dose of study drug [± 2 days])

Telephone contact with the subject for the following follow-up:

- Review concomitant medications
- Review AEs/SAEs

10.8. Appendix 8: 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 responses 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 responses 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:

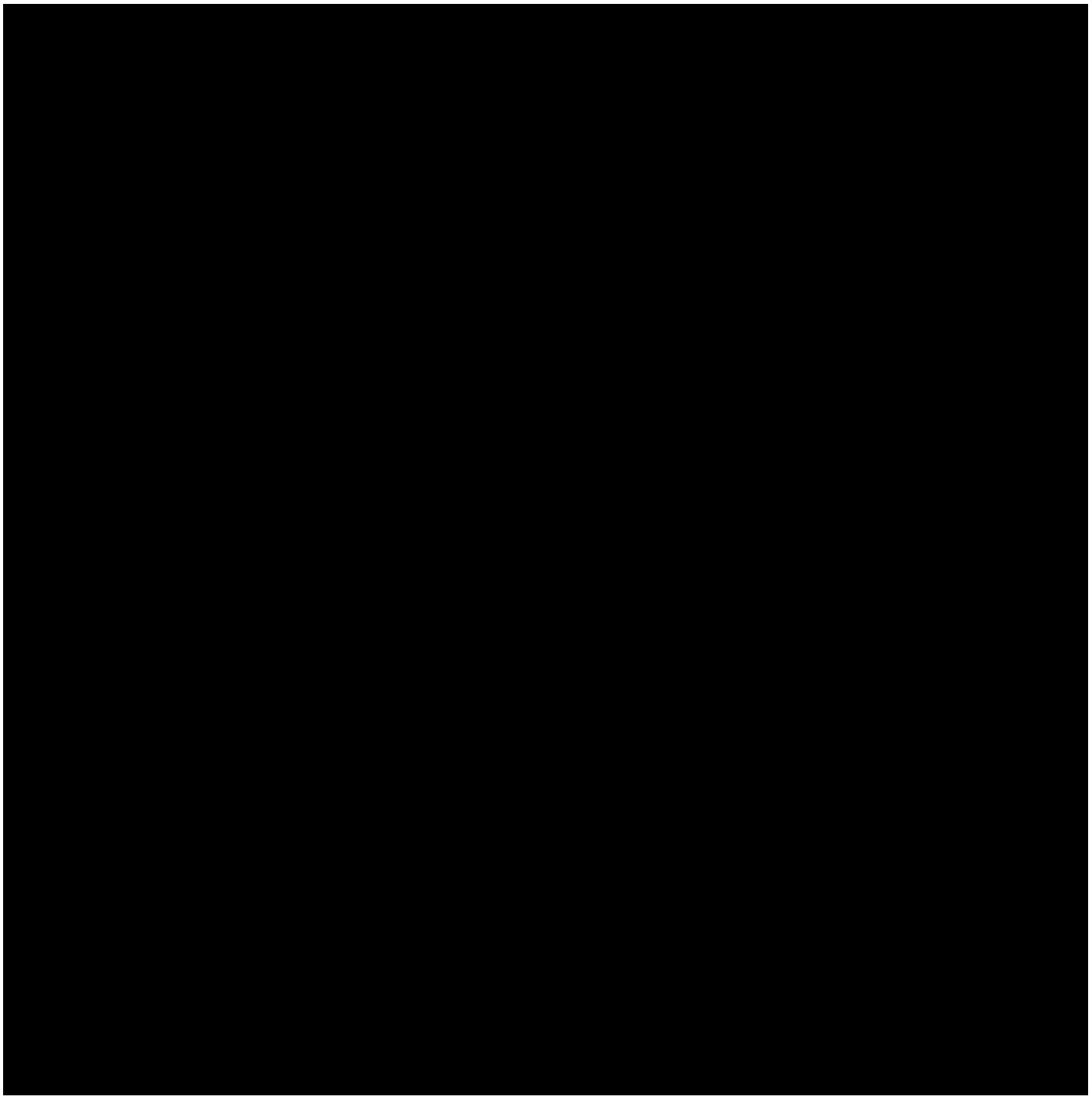
INTERNATIONAL-PROSTATE SYMPTOM SCORE (I-PSS)

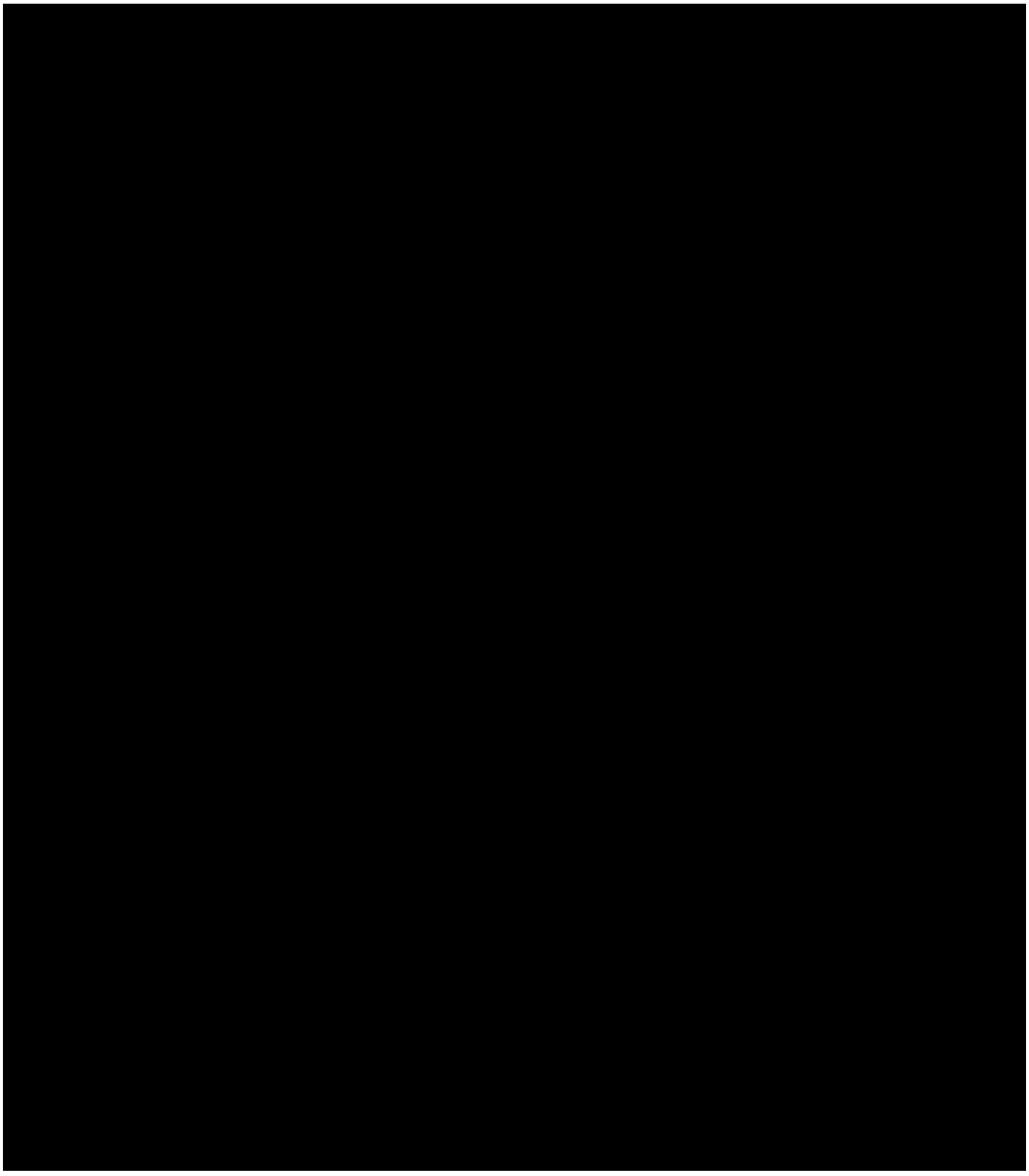
Question	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past week, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past week, how often have 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

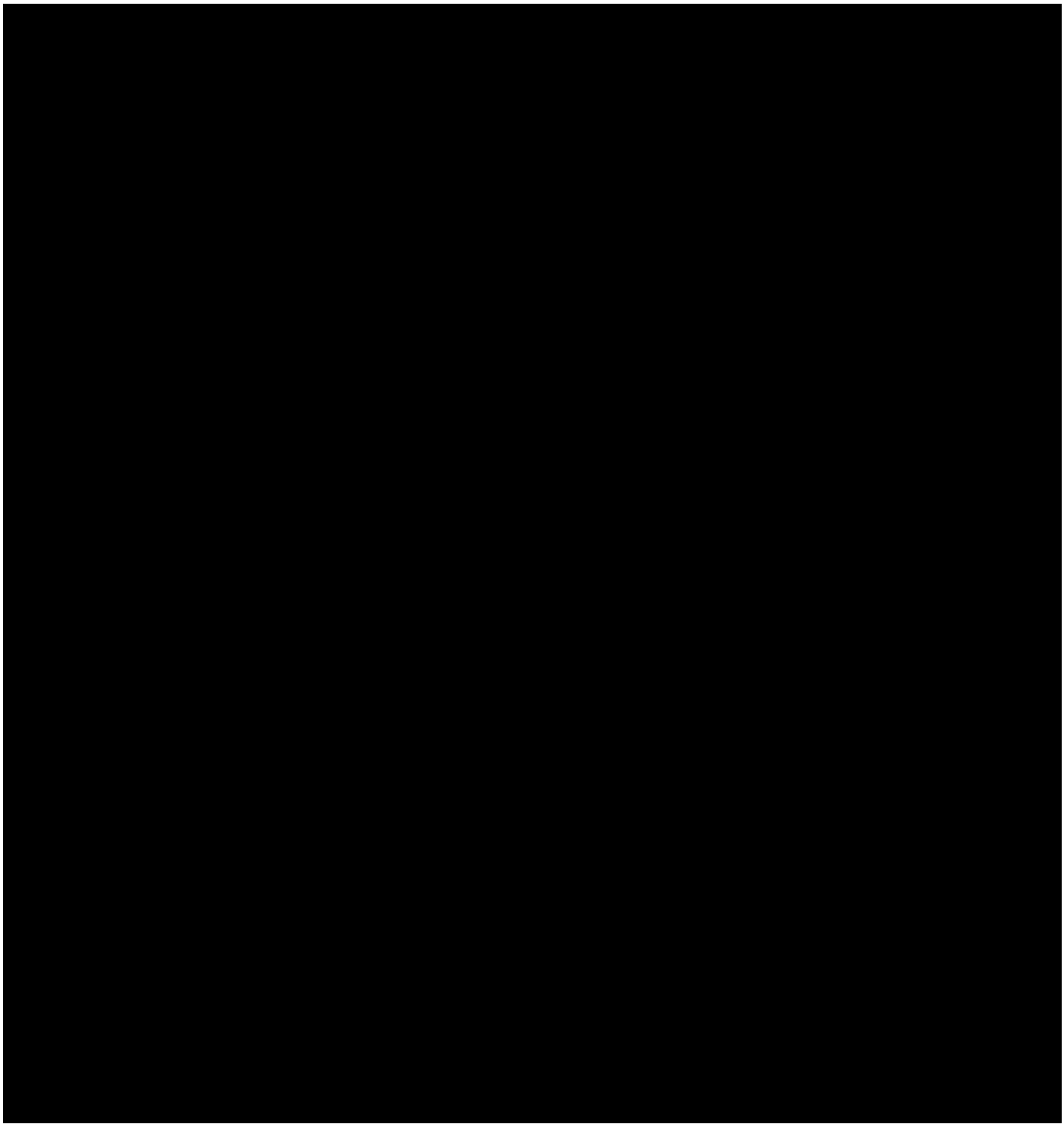
QUALITY OF LIFE DUE TO URINARY SYMPTOMS

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

[redacted]

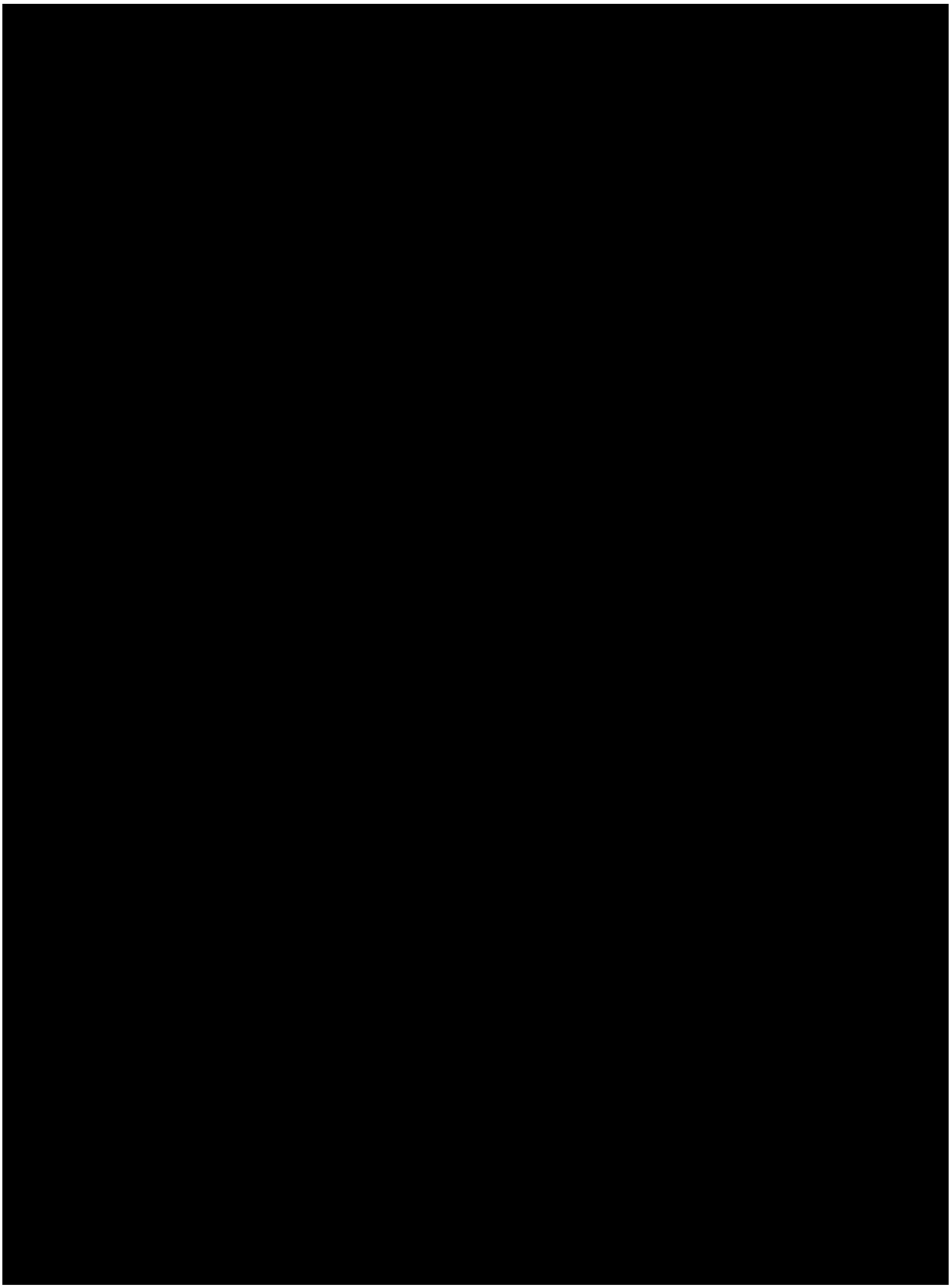






Health Questionnaire

English version for the USA



[redacted]

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] [PGI- [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.

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. ☐

10.9. Appendix 9: Summary of Previous Protocol Amendments

10.9.1. Protocol Amendment 1, 30 July 2020

The study protocol was previously amended on 30 July 2020 with the following notable changes:

- Cover Page
    - Corrected street address for Urovant GmbH Swiss offices
    - Updated street address for Urovant US offices
- Section 1.1 Synopsis, Overall Study Design
    - Changed the timing for Safety Follow Up telephone call from "21 days (+ up to 4 days) after the subject's last dose of study treatment (ie, at Week 27 for subjects who complete the Week 24 Visit, or approximately 3 weeks after withdrawal for subjects who discontinue the study early)" to "5 days (± up to 2 days) after the subject's last dose of study treatment (or approximately 5 days [± up to 2 days] after withdrawal for subjects who discontinue the study early)"
    - Updated table with study visit schedule accordingly
- Section 1.2, Schema for Parts 1 and 2
    - Changed timing for Safety Follow-Up telephone call from Day 190 (or 21 days following withdrawal) to Day 174 (or 5 days following withdrawal) for subjects who do not participate in the optional 28-week extension study
- Sections 1.3 and 1.4, Schedule of Assessments (Part 1 and Part 2, respectively)
    - Changed window for Screening (Visit 1) from "-49 to -21 days" to "-49 to -14 days"; added new footnote "a" and updated numbering for other footnotes to clarify that all Screening procedures and the 3-day Bladder Diary must be completed prior to the Run-In (Visit 2).
    - Updated timing for Safety Follow-Up telephone call (ie, to 5 days ± 2)
    - Clarified that a prostate volume measurement taken within 12 months prior to the first day of Screening may be accepted in lieu of a Screening (Visit 1) measurement

- Section 4.1 Overall Design
    - Changed the timing for Safety Follow Up telephone call from "21 days (+ up to 4 days) after the subject's last dose of study treatment (ie, at Week 27 for subjects who complete the Week 24 Visit, or approximately 3 weeks after withdrawal for subjects who discontinue the study early)" to "5 days (± up to 2 days) after the subject's last dose of study treatment (or approximately 5 days [± up to 2 days] after withdrawal for subjects who discontinue the study early)"
- Section 4.4 End of Study Definition
    - Removed "Week 27" descriptor used to define the Safety Follow-up timepoint
- Section 5.2 Exclusion Criteria
    - Changed Exclusion Criterion #7 from "Subject is taking or using any medications to treat erectile dysfunction (ED) and is not using them on a regular schedule. (ED medications with a short half-life such as sildenafil and vardenafil are allowed if used 2 times or less per week in the past 3 months and during the study.)" to "Irregular use of any medications to treat erectile dysfunction (ED). If ED medication is used on an irregular basis, ED medications with a short half-life such as sildenafil and vardenafil are allowed."
    - Changed timeframe in Exclusion Criterion #9 for exclusion of herbal supplements from "in the past 3 months" to "in the past 28 days prior to Screening"
    - Changed timeframe for Exclusion Criterion #10 for subject who started using diuretics from "within 3 months prior to Screening" to "within 28 days prior to Screening". Also, changed timeframe in Exclusion Criterion #10 for subjects who were already taking a diuretic to allow for continuation of stable doses of diuretics from "at least 3 months prior to Screening" to "at least 28 days prior to Screening".
    - Clarified that "prior" diagnosis of diabetes insipidus (Exclusion Criterion #18) or sleep apnea (Exclusion Criterion #19) were exclusionary (ie, not just diagnoses identified at the Screening visit).
    - Removed Exclusion Criterion #21: "Has known or suspected HIV or AIDS or unexplained alarm symptoms (eg, anemia, gastrointestinal bleeding, unintentional weight loss, suspected malignancy)." The item Exclusion Criterion #21 has been left

as blank intentionally to preserve the exclusion criteria numbering from the original protocol.

  - Removed Exclusion Criterion #33: Clarified duration for stable doses of prior medication from "4 weeks" to "28 days" for consistency in terminology with other criteria.
  - Additional minor clarifications were made to ensure consistency for duration of 1 month (4 weeks) for consistency (Exclusion Criterion #33)

- Section 5.4 Screen Failures
  - Removed redundant restriction that, if applicable, rescreening must occur "during the screening period"
- Section 6.1.1 Run-in Medication and Administration
  - Clarified that the duration of medication administration during Run-in Period is "approximately" 2 weeks to account for the allowable ± 4-day window
- Section 8.1.6, Prior and Concomitant Medications
  - Changed duration of monitoring of concomitant medications from 21 days to 5 days after the last dose of study drug
- Section 8.3.6, Clinical Safety Laboratory Assessments
  - Changed duration of monitoring for clinically significant laboratory abnormalities from 21 days to 5 days after the last dose of study drug
- Section 8.3.8, Prostate Volume Measurement
  - Added the following statement "Prostate volume measurement (by ultrasound) assessed within 12 months prior to the first day of Screening may be accepted in lieu of a Screening (Visit 1) measurement."
- Section 8.4.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information
  - Changed timeframe for collection of AEs and SAEs from through 21 days after the last dose of study drug to through 5 days after the last dose of study drug.
- Section 9.4.3.1, Adverse Events
  - Changed window for definition of treatment-emergent adverse events from "An AE that occurs more than 21 days after the last dose of study drug will not be counted as

a TEAE." to An AE that occurs more than 5 days after the last dose of study drug will not be counted as a TEAE."

- Appendix 3, Definition of an AE
  - Added that abnormal laboratory results (hematology, clinical chemistry, or urinalysis) identified during Screening will *not* be considered as adverse events
- Appendix 5, Study Tabular Summary
  - Changed trial length from "Up to 27 weeks" to "Up to 25 weeks"
- Appendix 6, Prohibited Medications and Non-Drug Therapies
  - Reduced window of restriction for "any herbal medications to treat OAB symptoms, lower urinary tract symptoms of BPH or erectile dysfunction" from "in the past 3 months" to "within 28 days prior to the Screening Visit".
- Appendix 7, Section 10.7.1, Screening Visit
  - Changed window for Screening (Visit 1) from "(Day -49 to Day -21)" to "(Day -49 to Day -14)"
  - Added "(if no measurement is available in preceding 12 months)" to bullet: *Collect prostate volume (in mL) via ultrasound*
- Appendix 7, Section 10.7.10, Safety Follow-Up Visit
  - Changed timing from 3 weeks (±4 days) to 5 days (±2 days)

10.9.2. Protocol Amendment 2, 16 December 2020

The study protocol was previously amended on 16 December 2020 with the following notable changes:

- Cover Page was updated with new Sponsor Contact information
- Section 1.1 Synopsis, Secondary Efficacy Endpoints
  - Clarified that the International Prostate Symptom Score (IPSS) Storage (1-week recall) endpoint was not based on an average score
- Section 1.1 Synopsis, Overall Study Design and Section 1.2, Schema for Parts 1 and 2
  - Updated to reflect that visits at Week 1 (Visit 4) and Week 16 (Visit 9) in Part 2 will be conducted by telephone/video call to minimize in-person contact during the COVID-19 pandemic; this change will remain in effect after resolution of the COVID-19 pandemic

- Section 1.1 Synopsis, Study Drug Groups and Study Duration
    - Added additional examples of alpha blockers (terazosin and silodosin)
- Section 1.2 Schema for Parts 1 and 2
    - Updated to reflect the changes to study visits as described above (ie, Visit 4 and Visit 9 to be conducted by telephone or video call)
- Section 1.4, Schedule of Assessments - Part 2
    - Added an extended COVID-19 mitigation window in Part 2 to provide for additional timing for visits impacted by restrictions due to the COVID-19 pandemic
    - Updated to reflect that visits at Week 1 (Visit 4) and Week 16 (Visit 9) in Part 2 will be conducted via telephone or video call to minimize in-person contact during the COVID-19 pandemic; this change will remain in effect after resolution of the COVID-19 pandemic
    - Removed prostate volume measurement from Week 24 or Early Withdrawal (Visit 11) because the prostate volume is not expected to have a clinically relevant change between Baseline and Visit 11
    - Removed uroflowmetry from Baseline (Visit 3) because this assessment will have been done at Screening and does not need to be repeated
    - Clarified that if no historical prostate volume measurement is available within 12 months of Screening, a prostate volume measurement by ultrasound must be performed prior to randomization (ie, done at any time between Screening and Baseline)
    - Updated footnotes to reflect the above changes
    - Clarified the timing for collection of 3-day Bladder Diaries
- Section 2.4.2, Potential Risks
    - Updated background information to reflect study population in Phase 3 program in OAB (RVT-901-3003 and RVT-901-3004)
- Section 3, Objectives and Endpoints
    - Clarified that the IPSS Storage (1-week recall) endpoint is not based on an average score, because it is based on a single value reported at each relevant timepoint

  - Added CFB at Week 4, Week 8, Week 12, Week 20, and Week 24 in the IPSS Voiding score (1-week recall) as an "Other/exploratory endpoint"
  - Removed Week 16 timepoint from IPSS-associated endpoints
  - Clarified that endpoints for 50% and 75% reduction from baseline in urgency and urge urinary incontinence are based on average number of daily episodes
- Section 4.1, Objectives and Endpoints
  - Updated to reflect that visits at Week 1 (Visit 4) and Week 16 (Visit 9) in Part 2 will be conducted via telephone or video call to minimize in-person contact during the COVID-19 pandemic; this change will remain in effect after resolution of the COVID-19 pandemic
- Section 5.2, Exclusion Criteria
  - Clarified definition of positive urine culture results (ie, 10^5 CFU/mL, equivalent to 100×10^3 CFU/mL)
- Section 6.1, Study Drugs Administered
  - Clarified that for post-Baseline timepoints, double-blind study drug may be dispensed to the subject by means to minimize in-person contact (eg, trackable courier or curbside pickup)
- Section 7.3, Lost to Follow-Up
  - Clarified that if a subject misses a visit and does not return for a rescheduled visit and cannot be reached to reschedule, the site should make every effort to ensure that all dispensed study medication is returned in addition to attempting to regain contact with the subject so that they can appropriately be withdrawn from the study
- Section 8, Study Assessments and Procedures
  - Added a bulleted note that certain study assessments and procedures may be performed telephone/video call due to the COVID-19 pandemic.
- Section 8.2, Efficacy Assessments
  - Clarified that when subjects complete PRO assessment forms remotely, they should be completed just prior to the applicable visit
- Section 8, Study Assessments and Procedures

  - Added a bulleted note that certain study assessments and procedures may be performed telephone/video call due to the COVID-19 pandemic.
- Section 8.2.1, Bladder Diaries
  - Added that a prescreening Bladder Diary may be provided to potential study subjects in order to minimize on-site contact and assess subject's ability to comply with diary completion.
- Section 8.3.4, Electrocardiograms
  - Added that electrocardiograms (ECGs) may be read by appropriate site delegates who are medically qualified
- Section 8.3.5, Post-Void Residual Volume
  - Clarified that "ultrasound" also refers to a bladder scanner
- Section 8.3.7, Urodynamics Assessment
  - Clarified that the number of subjects expected to participate in the Urodynamics Substudy is approximately 60.
- Section 8.3.8, Prostate Volume Measurement
  - Clarified that if no historical prostate volume measurement is available within 12 months of Screening, a prostate volume measurement by ultrasound must be performed prior to randomization (ie, done at any time between Screening and Baseline)
- Section 8.4.6, Adverse Events of Special Interest
  - Clarified that adverse events (AEs) of urinary retention are those events in which the subject has a raised PVR that requires catherization *in addition to* one of the criteria specified in the bulleted list
  - Clarified definition of positive urine culture results (ie, 10^5 CFU/mL, equivalent to 100×10^3 CFU/mL)
  - Clarified that an AE of "increased blood pressure" should be recorded if, in the investigator's opinion, an elevated blood pressure measurement is clinically significant but does not fulfill the definition for hypertension
- Section 8.6, Safety Measures due to COVID-19 Pandemic

  - Added this section to clarify the types of subject assessments that may be done remotely (via telephone or video call) to minimize in-person contact
  - Clarified that if a subject misses the Week 12 visit (Visit 8) due to restrictions resulting from the COVID-19 pandemic an early withdrawal visit (Visit 11) should be conducted when safe and feasible. However, if a subject missed any other single on-site visit, then the site should collect the completed Bladder Diary (eg, by curbside pickup, mail, or courier) and remotely review AEs/SAEs and concomitant medications and dispense study drug (ie, subject will not be considered lost to follow-up).
- Section 9.2, Populations for Analyses
  - Made minor clarifications to the defined populations to align with the statistical analysis plan, including the addition of the Per-Protocol Set (PPS) and Per-Protocol Set for Incontinence (PPS-I)
  - Added the following statement to clarify sample size and statistical power estimates for Baseline BPH treatment subgroups: "The impact of imbalances in 5-ARI plus alpha blockers versus alpha blockers alone will be monitored and controlled if needed."
- Section 9.4.2.1, Analysis Endpoints
  - Clarified that the IPSS Storage (1-week recall) endpoint is not based on an average score, because it is based on a single value reported at each relevant timepoint
- Section 10.6 Appendix 6, Prohibited Medications and Non-Drug Therapies
  - Added additional examples of alpha blockers (terazosin and silodosin)
- Section 10.7, Appendix 7: Study Schedule Supplement
  - Added option to dispense paper PRO questionnaires and diaries
  - Clarified subject assessments and study procedures that may be done remotely for COVID-19 safety precautions; this change will remain in effect after resolution of the COVID-19 pandemic
  - Removed requirement for blood pressure measurement and post-void residual volume from list of study assessments for Visit 4 and Visit 9, as these visits will be conducted

by telephone or video call, and there are on-site assessments of these parameters before and after both visits.

- Clarified procedures to align with the Schedule of Assessments – Part 2
- Separated Visit 9 (Week 16) schedule into a new (standalone) subsection to reflect that this visit will be conducted remotely via telephone or video call

- Section 10.9, Appendix 9: Summary of Previous Protocol Amendments
  - Created a new appendix to provide a list of changes previously implemented by Protocol Amendment 1

In addition to the above-listed changes, minor edits were made for clarity throughout document (eg, added "approximately" to duration of study periods, added/updated cross-references, fixed punctuation or minor typographical errors).

11. References

Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: Report from the standardisation sub-committee of the international continence society. Neurourol Urodyn 2002;21:167–78.

American Urological Association. McVary K, Roehrborn C, Avins A, Barry M, Bruskewitz R, Donnell R, Foster H, Gonzalez C, Kaplan S, Penson D, Ulchaker J, Wei, J. Management of Benign Prostatic Hyperplasia; Published 2010; Reviewed and Validity Confirmed 2014. Accessed 16 August 2018: https://www.auanet.org/benign-prostatic-hyperplasia-(2010-reviewed-and-validity-confirmed-2014)

Biers, SM, Reynard, JM and Brading, AF. The effects of a new selective β3- adrenoceptor agonist (GW427353) on spontaneous activity and detrusor relaxation in human bladder. BJU International 2006; 98: 1310-4.

Chapple CR, et al. Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. Eur Urol. 2017; http://dx.doi.org/10.1016/j.eururo.2017.01.037.

Chapple CR, Yamaguchi O, Ridder ALJ, Carl S, Mattiasson A, Aramburu MAL, et al. Clinical proof of concept study (BLOSSOM) shows novel β3 adrenoceptor agonist YM178 is effective and well tolerated in the treatment of symptoms of overactive bladder. Poster presentation at the 2009 European Urologic Association Annual Meeting, Milan, Italy.

Di Salvo J, Nagabukuro H, Wickham LA, DeMartino JA, Fitzmaurice A, Gichuru L, Kulick A, Donnelly AJ, Jochnowitz N, Hurley AL, Pereira A, Sanfiz A, Veronin G, Villa K, Woods J, Zamlynny B, Zycband E, Salituro GM, Frenkl T, Weber AE, Edmondson SD, Struthers M. Pharmacological characterization of a novel beta 3 adrenergic agonist, vibegron: evaluation of antimuscarinic receptor selectivity for combination therapy for overactive bladder. J Pharm Exp Ther 2017; 360: 346-355.

FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf. Accessed: 29 July 2018.

Goldman HB, Anger JT, Esinduy CB, Zou KH, Russell D, Luo X, Ntanios F, Carlsson MO, Clemens JQ. Real-World Patterns of Care for the Overactive Bladder Syndrome in the United States. Urol 2016;87:64-9.

Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, Yu O, Crane PK, Larson EB. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med 2015 Mar;175(3):401-7.

Helfand BT, Evans RM, McVary KT. A Comparison of the Frequencies of Medical Therapies for Overactive Bladder in Men and Women: Analysis of More than 7.2 Million Aging Patients. Eur Assoc Urol 2012;57:586-591.

Hyman MJ, Groutz A, Blaivas JG. Detrusor instability in men: correlation of lower urinary tract symptoms with urodynamic findings. J Urol 2001;166: 550-552.

Ichihara K, Masumori N, Fukuta F, TsukamotoT, Iwasawa A, Tanaka Y. A Randomized Controlled Study of the Efficacy of Tamsulosin Monotherapy and its Combination with Mirabegron for Overactive Bladder Induced by Benign Prostatic Obstruction. J Urol. 2014;193(3).

Kaidoh K, Igawa Y, Takeda H, Yamazaki Y, Akahane S, Miyata H, Ajisawa Y, Nishizawa O, Andersson KE. Effects of selective [beta]2 and [beta]3- Adrenoceptor agonists on detrusor hyperreflexia in conscious cerebral infarcted rats. J Urol 2002;168:1247-52.

MacDiarmid SA, Peters KM, Chen A, Armstrong RB, Orman C, Aquilina JW, et al. Efficacy and safety of extended- release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double- blind, placebo- controlled study. Mayo Clinic Proceedings. 2008;83(9):1002- 10.

Maman K, Aballea S, Nazir J, Desroziers K, Neine ME, Siddiqui E, Odeyemi I, Hakimi Z. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. Eur Urol. 2014 Apr;65(4):755-65.

Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU International 2001;87:760-6.

Mybertiq Prescribing Information. Astellas. Revised: [08/2016]. Available at: https://www.myrbetriq.com/. Accessed: 02 April 2017.

Nakagawa H, Ikeda Y, Niu K, Kaiho Y, Ohmori-Matsuda K, Nakaya N, et al. Does nocturia increase fall-related fractures and mortality in a community-dwelling elderly population aged 70 years and over? Results of a 3-year prospective cohort study in Japan. Neurourol Urodyn. 2008;27:674–5.

Oelke M, Baard J, Wijkstra H, et al. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. Eur Urol. 2008;54: 419-426.

Rabin R, Gudex C, Selai C, Herdman M. From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value Health 2014 Jan;17(1):70-76, 01-01-2014.

Risacher SL, McDonald BC, Tallman EF, West JD, Farlow MR, Unverzagt FW, Gao S, Boustani M, Crane PK, Petersen RC, Jack CR Jr, Jagust WJ, Aisen PS, Weiner MW, Saykin AJ; Alzheimer's Disease Neuroimaging Initiative. Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults. JAMA Neurol. 2016 Jun 1;73(6):721-32.

Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20: 327-36.

Takeda H, Yamazaki Y, Akahane M, Igawa Y, Ajisawa Y, Nishizawa O. Role of the β 3-adrenoceptor in urine storage in the rat: comparison between the selective β 3-adrenoceptor agonist, CL316, 243, and various smooth muscle relaxants. J Pharm Exp Ther 2000;293: 939-45.

Takeda H, Yamazaki Y, Igawa Y, Kaidoh K, Akahane S, Miyata H, Nishizawa O, Akahane M, Andersson KE. Effects of β3-adrenoceptor stimulation on prostaglandin E2-induced bladder hyperactivity and on the cardiovascular system in conscious rats. Neurology and Urodynamics 2002;21: 558-65.

Tubaro, A, Batista JE, Nitti, VW, et al. Efficacy and safety of daily mirabegron 50 mg in male patients with overactive bladder: a critical analysis of five phase III studies. The Adv Urol, 2017, Vol, 9(6): 137-154.

Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, and Wein A. Tolterodine once daily: superior efficacy and tolerability in the treatment of the overactive bladder. Urol 2001;57: 414–21.

Woods M, Carson N, Norton N, Wesley S, Jeffery H, Argentieri TM. Efficacy of the [Beta]3-adrenergic receptor agonist CL-316243 on experimental bladder hyperreflexia and detrusor instability in the rat. J Urol 2001;166: 1142-7.

Yamaguchi O. β3-adrenoceptors in human detrusor muscle. Urology 2002;59 (Supplement 5A): 25-29.

Yoshida M, Takeda M, Gotoh M, Nagai S, Kurose T. Vibegron, a novel potent and selective B3-Adrenoreceptor Agonist, for the treatment of patients with overactive bladder: a randomized, double-blind, placebo-controlled Phase 3 study. Euro Urol. 2018;73:783-90.