CLINICAL STUDY PROTOCOL

Study Title:	An International Phase 3, Randomized, Double-Blind, Placebo- and Active (Tolterodine)-Controlled Multicenter Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder
Protocol Number:	RVT-901-3003
Compound Name and/or Number:	Vibegron
Indication	Treatment of Overactive Bladder
Sponsor:	Urovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Development Phase:	3
Regulatory Identifier(s):	IND# 106,410 EudraCT# 2017-003293-14
Current Version and Effective Date:	Version 3.0; 15 NOV 2018
Previous Version(s) and Effective Date(s):	Version 2.1; 12 FEB 2018 Version 2.0; 30 JAN 2018 Version 1.2; 01 NOV 2017 Version 1.1; 05 OCT 2017 Version 1.0; 29 SEP 2017
Study Director:	[redacted], [redacted] [redacted], Clinical Development

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NCT Number: NCT03492281
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SUMMARY OF CHANGES

Version	Location	Description of Change
3.0	Global	Minor typographical/formatting errors were corrected.
3.0	1; 3; 9.3.1	The key secondary efficacy endpoints were reordered. The following one key secondary efficacy endpoint was added: • Percent of OAB Wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12 The following four key secondary efficacy endpoints were removed (moved to and combined under exploratory endpoints): [redacted]
3.0	1; 3; 9.3.1	The following additional secondary endpoint was removed: [redacted]
3.0	1; 3; 9.3.1	Exploratory endpoints were reordered and analysis timepoints were updated for some endpoints. The following endpoints were added: [redacted]

Version	Location	Description of Change
		[redacted] The following exploratory endpoints were removed: [redacted]
3.0	1.1	Removed the phrase "and adverse events deemed related to Study Procedures" from footnote #15 (all adverse events are recorded).
3.0	7.8; 8.3.1	For consistency with the adverse collection window, removed language indicating that adverse events from time of informed consent to first dose of study treatment should be recorded as medical history.
3.0	9.2.2	For consistency with the updated key secondary endpoints, one objective/hypothesis was added, four key secondary objectives/hypotheses were deleted, and the objectives/hypotheses were reordered and renumbered accordingly.
2.1	Global	Minor typographical/formatting errors were corrected.
2.0	Cover page	Add Basel address; changed study director contact.
2.0	Global	Minor typographical/grammatical errors were corrected.
2.0	Global	Tables were renumbered sequentially without a chapter number included as part of the table number in the main body, and an appendix letter was added as part of the table numbering within the appendices.
2.0	Medical Contact / Sponsor Information Page	Change [redacted] email to [redacted]; change [redacted] to [redacted], to reflect new company names.
2.0	Table of Contents	Updated all page numbers; edited Section 5.4 and 5.4.1 from "Discontinuation" to "Interruption", deleted "Withdrawal from the Study".
2.0	1; 3; 9.3.1	[redacted]

Version	Location	Description of Change
2.0	1; 3; 9.2.2; 9.3.1; 9.5.1	Change of 5% in response efficacy endpoint (70 to 75%; Percent of OAB Wet patients with a 75% reduction from baseline in UUI episodes per 24 hours at Week 12).
2.0	1; 2.1	Addition of (RVT-901) after Vibegron to align with Certificate of Analysis for product.
2.0	1; 3; 9.5.1	[redacted]
2.0	1.1	Updated Schedule of Activities and visit events to reflect protocol text; updated and realigned footnotes accordingly.
2.0	1.1; 8.3.1	Update language around timing of data collection for AE and SAE.
2.0	1; 5.1.1; 7.10	Change days of screening compliance from 6 to 5.
2.0	5.4; 5.4.1	Replaced “discontinued” with “interrupted”; reversed order of sentences.
2.0	6.6	Removed study medication rechallenge in patients with a grade 3 or higher drug-related AE reported.
2.0	7.3	Moved Visit Reminders to 7.12.
2.0	7.10; 7.10.1	Updates to Patient Voiding Diary instructions, training, and description.
2.0	7.11; 7.11.1; 7.11.2	Updates to Urine Volume Collection instructions, training, and description.
2.0	7.12	Update to instructions on Reminders for Diary Collection.
2.0	7.13; 7.13.1; 7.13.2	Updates to Electronic Diary instructions and training.
2.0	7.26.1	Deletion of data collection of food/meal intake prior to PK sampling.
2.0	8.6	Updated MACCE language to match CAC Charter.
2.0	8.7	Addition of timeframe around pregnancy and infant outcome.
1.2	Global	Minor typographical/grammatical errors were corrected.
1.2	Sponsor Signature Page	Minor wording update to sentence: This protocol has been approved by a representative of Urovant Sciences GmbH.
1.2	1; 5.1.1	Inclusion criterion updated: #4 updated for OAB Wet criteria from “Screening diary” to “previous visit diary”; #5 updated to reflect wording in Section 5.2.1.

Version	Location	Description of Change
1.2	1; 5.1.2	The text "or ≥ 26 bacteria [moderate] per high-powered field in a spun specimen and/" was removed from Exclusion criterion #8.
1.2	1; 5.1.2	Exclusion added for narrow angle glaucoma.
1.2	1.1	Footnotes were updated to include: a note that paper diaries may be used; clarification that pelvic exams may be part of the physical exam; clarification that urinalysis will be performed if there is a positive dipstick result; FSH removed from chemistry.
1.2	1.1; 7.5	The timing for collection of paper diaries (if used) was added.
1.2	1.1; 7.5.2; 7.5.3	References to the Week 2 timepoint as a visit were reworded to clarify that a study visit does not occur at Week 2.
1.2	6.1	"Tablet" or "capsule" descriptors were added to Table 3 (formerly numbered as Table 6-1).
1.2	6.2	Wording was added to indicate the study treatment should be swallowed whole; Wording was added to require a witnessed dose at the clinic at Run-In and Baseline Visits; PK sub-study language was changed to collect pre-dose; dispense study medication was language was combined.
1.2	7.5.4	PK sub-study language was changed to hold dose on morning of study visit to collect pre-dose PK.
1.2	7.18.1	PK sub-study language was changed to collect pre-dose PK.
1.2	7.12.1	The Follicle Stimulating Hormone test was removed from the list of laboratory tests performed.
1.2	7.16	Clarified that tablet/capsule count will be recorded in the interactive voice or web response system rather than case report form.
1.2	8.6	Added adverse events suggestive of cystitis or urinary tract infection and moved liver test values to end of list.
1.1	5.2.1	Changes were made to description of contraception requirements and methods for female patients.
1.1	7.5	Plan to use a paper diary as backup was added.

SPONSOR SIGNATURE PAGE

Study Title: An International Phase 3, Randomized, Double-Blind, Placebo- and Active (Tolterodine)-Controlled Multicenter Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder

Protocol Number: RVT-901-3003

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

[redacted] Digitally signed by [redacted]
Date: 2018.11.20
15:26:04 -05'00'

[redacted] Clinical Development

MEDICAL CONTACT/SPONSOR INFORMATION PAGE

Sponsor Medical Contact/Serious Adverse Event Contact Information:

Role	Name	Day Time	After-Hours
Primary Medical Monitor	[redacted]	Office: [redacted] Mobile: [redacted] Fax: [redacted] E-mail: [redacted]	Office: [redacted] Mobile: [redacted] Fax: [redacted] E-mail: [redacted]
Secondary Medical Monitor	[redacted]	Office: [redacted] Mobile: [redacted] Fax: [redacted] E-mail: [redacted]	Office: [redacted] Mobile: [redacted] Fax: [redacted] E-mail: [redacted]
Contact for Serious Adverse Events (SAEs)		Email: [redacted] Phone: [redacted] Fax: [redacted]	

Study Sponsor:

This study is sponsored by Urovant Sciences GmbH.

INVESTIGATOR STATEMENT

- 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	Site

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1. SYNOPSIS

Study Title	An International Phase 3, Randomized, Double-Blind, Placebo- and Active (Tolterodine)-Controlled Multicenter Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder
Protocol Number	RVT-901-3003
Study Center Location(s)	International
Number of Study Centers Planned	~330
Study Phase	3
Target Population	Adult men and women with either: • Overactive bladder (OAB) Wet; or • OAB Dry
Number of Patients Planned	~1400
Study Objectives	
Primary Efficacy Objective	• To evaluate the efficacy of vibegron (RVT-901) compared to placebo in patients with symptoms of overactive bladder (OAB), specifically the frequency of micturitions and frequency of urge urinary incontinence episodes
Secondary Efficacy Objective	• To evaluate the overall efficacy of vibegron compared to placebo in patients with symptoms of OAB
Safety Objectives	• To evaluate the safety and tolerability of treatment with vibegron
Pharmacokinetic / Pharmacodynamic Objectives	• To evaluate the pharmacokinetic profile of vibegron in patients with symptoms of OAB • To assess relationships between exposure and efficacy/safety in patients with symptoms of OAB receiving vibegron
Exploratory Objectives	[redacted]

Study Design	This is an international, Phase 3, randomized, double-blind, placebo-controlled with active control (tolterodine), parallel-group, multicenter study to evaluate the safety, tolerability, and efficacy of vibegron 75 mg in men and women with symptoms of overactive bladder (OAB). Approximately 1,400 men and women with overactive bladder will be enrolled at approximately 330 study sites. At Baseline, patients who meet all eligibility criteria are randomized 5:5:4 to receive either vibegron 75 mg, placebo, or tolterodine ER 4 mg in a double-blind fashion. Between the Baseline and Week 12 Visits, patients will attend Visits at Weeks 4 and 8. This study consists of a Screening Period (1 to 5 weeks), a single-blind Run-in Period (2 weeks), a randomized double-blind Treatment Period (12 weeks), and a Safety Follow-up Period (4 weeks). Patients who complete the Week 12 Visit may be offered the opportunity to enroll in a 40-week double-blind extension study RVT-901-3004 (which will be conducted under a separate protocol), until enrollment in that study is complete. Patients who do not enroll into the optional extension study will have a Follow-up Visit approximately 28 days after the patient's last dose of Study Treatment (i.e., at Week 16 for patients who complete the Week 12 Visit, or approximately 4 weeks after withdrawal for patients who discontinue the study early). Additionally, Unscheduled Visit(s) may be arranged for patients with study-related safety concerns as needed.
Study Treatments	All treatments are dosed orally, once daily (QD). Patients are randomized to one of the following blinded treatments: • Vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule (N = 500) • Placebo tablet to match vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule (N = 500) • Tolterodine ER 4 mg capsule + placebo tablet to match vibegron 75 mg tablet (N = 400)
Duration of Treatment	12 weeks
Eligibility Criteria	
Inclusion Criteria	1. Willing and able to provide written informed consent. 2. Males or females ≥ 18 years of age. Note: Up to 15% of patients can be male. 3. Has a history of OAB (as diagnosed by a physician) for at least 3 months prior to the Screening Visit. Note: OAB is defined as urgency, with or without urge urinary incontinence (UUI), usually associated with frequency and nocturia. Urodynamic evaluation is not required.

	4. Meets either the OAB Wet or OAB Dry criteria described below, based on the Patient Voiding Diary returned both at the Run-in Visit and Baseline Visit (all Complete Diary Days must be used in determining eligibility). A minimum of 5 Complete Diary Days [not necessarily consecutive] are required for the diary returned at the Run-in Visit, and 4 Complete Diary Days are required for the diary returned at the Baseline Visit. Averages should not be rounded up to the whole number: • OAB Wet criteria: – An average of ≥ 8.0 micturitions per Diary Day; and – An average of ≥ 1.0 UUI episodes per Diary Day; and – If stress urinary incontinence is present, the total number of UUI episodes must be greater than the total number of stress urinary incontinence episodes from the previous visit diary. • OAB Dry criteria: – An average of ≥ 8.0 micturitions per Diary Day; and, – An average of ≥ 3.0 urgency episodes per Diary Day; and – An average of < 1.0 UUI episodes per Diary Day; and – If stress urinary incontinence is present, the total number of UUI episodes must be greater than the total number of stress urinary incontinence episodes from the previous visit diary. Note: Up to 25% of patients that meet OAB Dry criteria may be enrolled. 5. For females of reproductive potential: Agrees to remain abstinent or use (or have their male partner use) an acceptable method of birth control (as defined in Section 5.2.1) each time the patient has intercourse from the Screening Visit until completion of the Follow-up Visit. 6. For females of reproductive potential: Agrees not to donate ova (eggs) until at least 1 month after the last dose of Study Treatment. 7. Has demonstrated ≥ 80% compliance with self-administration of Study Treatment during the Run-in Period. 8. Is ambulatory and in good general physical and mental health as determined by the Investigator. 9. In the opinion of the Investigator, is able and willing to comply with the requirements of the protocol, including completing electronic versions of questionnaires, the Patient Voiding Diary, and the Urine Volume Diary (will require ability to collect, measure, and record voided volume by herself/himself using a graduated urine collection and measurement container [provided by the Sponsor, if needed]).

Exclusion Criteria Urology Medical History	1. Patient has a history of 24-hour urine volume greater than 3,000 mL in the past 6 months, or a Urine Volume Diary day measurement greater than 3,000 mL during the Run-in Period. 2. 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, urolithiasis, interstitial cystitis, prostate cancer, gastrointestinal (GI) cancer, tuberculosis, stone disease, urothelial tumor, prostatitis, and clinically relevant benign prostatic hypertrophy (BPH) or bladder outlet obstruction, as judged by the Investigator. Note: Male patients with mild to moderate BPH without evidence of bladder obstruction as determined by the Investigator may be included as long as they have been taking a medication for the treatment of BPH for at a least 1-year prior to Screening, with no change in dose of herbal medications, alpha antagonist medications or other symptomatic treatments or medications within 3 months prior to Screening, and no change in dose of 5 alpha reductase inhibitors within 6 months of Screening. 3. Has a history of surgery to correct stress urinary incontinence, pelvic organ prolapse, or procedural treatments for BPH within 6 months of Screening. 4. Has current history or evidence of Stage 2 or greater pelvic organ prolapse (prolapse extends beyond the hymenal ring). 5. Patient is currently using a pessary for the treatment of pelvic organ prolapse. 6. Has a known history of elevated post-void residual volume defined as greater than 150 mL. 7. Has undergone bladder training or electrostimulation within 28 days prior to Screening or plans to initiate either during the study. 8. Has an active or recurrent (> 3 episodes per year) urinary tract infection by clinical symptoms or laboratory criteria (≥ 5 white blood cells [WBC] and/or a positive urine culture, defined as ≥ 10^5 colony forming units [CFU]/mL in 1 specimen). Patients diagnosed with a urinary tract infection (UTI) at the Screening Visit may be treated and re-screened once the infection has resolved. 9. Has a requirement for an indwelling catheter or intermittent catheterization. 10. Has received an intradetrusor injection of botulinum toxin within 9 months prior to Screening.

Other Medical History	11. Has uncontrolled hyperglycemia (defined as fasting blood glucose > 150 mg/dL or 8.33 mmol/L and/or non-fasting blood glucose > 200 mg/dL or 11.1 mmol/L) or, if in the opinion of the Investigator, is uncontrolled. 12. Has evidence of diabetes insipidus. 13. Is pregnant, breast-feeding, or is planning to conceive within the projected duration of the study. 14. Has a concurrent malignancy or history of any malignancy within 5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. 15. 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. 16. Patients who have systolic blood pressures ≥ 160 mmHg but < 180 mmHg are excluded, unless deemed by the Investigator and/or Medical Monitor as safe to proceed in this study and able to complete the study per protocol; these patients must be on stable hypertension medication for at least 90 days. 17. All patients 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. 18. Has narrow angle glaucoma (primary open angle glaucoma is not excluded). 19. Has a history of cerebral vascular accident, transient ischemic attack, unstable angina, myocardial infarction, coronary artery interventions (e.g., coronary artery bypass grafting or percutaneous coronary interventions [e.g., angioplasty, stent insertion]), or neurovascular interventions (e.g., carotid artery stenting) within 6 months prior to the Screening Visit. Patients with these conditions should be on stable medical therapy for at least 3 months prior to the Screening Visit. 20. Has a known history of liver disease. 21. Has a history of injury, surgery, or neurodegenerative diseases (e.g., multiple sclerosis, Parkinson's) that could affect the lower urinary tract or its nerve supply.

Laboratory/Procedure History	22. Has hematuria, including microscopic hematuria (> 5 red blood cells [RBCs]/hpf). Patients with known, fully evaluated, benign hematuria may participate. Documentation must be obtained indicating an unremarkable upper urinary tract (kidneys and ureters) imaging study (e.g., computerized tomography [CT] scan with and without contrast, renal ultrasound, magnetic resonance imaging [MRI] with and without contrast, intravenous pyelogram, etc.) and cystoscopy. Patients whose hematuria has not been previously evaluated may not be enrolled. 23. Has clinically significant electrocardiogram (ECG) abnormality that, in the opinion of the Investigator, exposes the patient to risk by participating in the study. 24. 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). 25. Has clinically significant laboratory abnormality (from the Screening Visit results) that remains unresolved after repeat testing (Refer to Algorithm for Laboratory Testing Appendix B) or that could confound the results of the study or indicate that it is not in the best interest of the patient to participate. 26. Has an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2.
Medication History	27. Use of any prohibited medications as detailed in Section 7.9.3 (suitable washout periods from these medications are also described therein). 28. Had changed the dose of any medications listed in Section 7.9.5 within 4 weeks prior to the Baseline Visit, or plans to initiate or change the dosing of any of these medications during the study. 29. Has an allergy, intolerance, or a history of a significant clinical or laboratory adverse experience associated with any of the active or inactive components of the vibegron formulation or tolterodine formulation.
Other	30. Is currently participating or has participated in a study with an investigational compound or device within 28 days prior to signing informed consent. 31. Is currently participating in or has participated in a study with vibegron. 32. Has a history of significant drug or alcohol abuse/dependence within a year prior to informed consent, as assessed by the investigator. 33. Has a varying sleep schedule anticipated during times when the voiding diaries are to be completed.

	34. Has coronary or neurovascular interventions planned during the duration of the study. 35. Has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that might, in the opinion of the Investigator, confound the results of the study, interfere with the patient's ability to comply with study procedures, or make participation in the study not in the patient's best interest.
Endpoints	
Co-Primary Efficacy Endpoints	• Change from baseline (CFB) at Week 12 in average number of micturitions per 24 hours in all OAB patients • CFB at Week 12 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients
Key Secondary Efficacy Endpoints	• CFB at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients • Percent of OAB Wet patients with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12 • Percent of OAB Wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12 • Percent of all OAB patients with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Week 12 • CFB at Week 12 in average number of total incontinence episodes over 24 hours in OAB Wet patients • CFB at Week 12 in Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB patients • CFB at Week 12 in average volume voided per micturition in all OAB patients
Additional Secondary Efficacy Endpoints	• CFB at Week 12 in Health-related Quality of Life (HRQL) Total Score from the OAB-q LF (1-week recall) in all OAB patients • CFB at Week 12 in Symptom Bother Score from the OAB-q-LF (1-week recall) in all OAB patients • Percent of all OAB patients with average number of micturitions < 8 per 24 hours at Week 12 • Percent of OAB Wet patients with at least a 50% reduction from baseline in total incontinence episodes per 24 hours at Week 12 • CFB at Week 12 in overall bladder symptoms based on Patient Global Impression of Severity (PGI-Severity) in all OAB patients • CFB at Week 12 in overall control over bladder symptoms based on Patient Global Impression of Control (PGI-Control) in all OAB patients

Safety Assessments	• Incidence of adverse events • Clinical laboratory assessments • Vital signs and physical examinations
Pharmacokinetic / Pharmacodynamic Endpoints	• AUC and C_{24} estimated from population PK modeling
Exploratory Endpoints	[redacted]

	[redacted]
Statistical Methods	
Efficacy Analyses	For the analysis of the co-primary endpoints (change from baseline in average number of daily micturitions at Week 12 and change from baseline in average number of daily UUI episodes at Week 12), a mixed model for repeated measure (MMRM) with restricted maximum likelihood estimation will be used. The analysis model for each efficacy endpoint will include terms for treatment, visit, OAB Type (Wet vs Dry), Sex (Female vs Male), Region (US vs Rest of World), baseline score, and interaction of visit by treatment. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make statistical inference. Other change from baseline endpoints will be analyzed using the same MMRM model. Response efficacy endpoints (proportion of patients with at least 75% reduction or 100% reduction in the average number of daily UUI episodes at Week 12 and proportion of patients with at least 50% reduction in the average number of daily urgency episodes at Week 12) 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 OAB Type (Wet vs Dry) and Sex (Female vs Male), with weights proposed by Greenland and Robins. *Multiplicity Adjustment*

	The key secondary endpoints will be tested using a hierarchical testing strategy using two-sided tests with $\alpha = 0.05$. No adjustment for multiplicity is needed.
Safety Analyses	Safety assessments (e.g., adverse events, clinical laboratory assessments, vital signs) will be summarized using descriptive statistics. No formal statistical comparisons will be performed.
Power and Sample Size	Approximately 1,400 patients will be randomized in a 5:5:4 ratio to receive one of the following Study Treatments: • Vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule (N = 500) • Placebo tablet to match vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule (N = 500) • Tolterodine ER 4 mg capsule + placebo tablet to match vibegron 75 mg tablet (N = 400) Approximately 500 patients will be assigned to the vibegron and placebo treatment groups, and approximately 400 patients will be assigned to the tolterodine treatment group. Assuming a total of 10% patients will discontinue prior to Week 12 (for any reason), there will be approximately 450 evaluable patients in the vibegron and placebo treatment groups at the end of Week 12. Assuming 75% of the population will have OAB Wet, there will be approximately 337 evaluable patients in the vibegron and placebo treatment groups for the incontinence endpoints. The study has: • Approximately 98% power to detect a true underlying between-group treatment difference of 0.6 in change from baseline in micturitions at a two-sided 0.05 level assuming a variability estimate of 2.20 based on vibegron Study 008 data. • Approximately 98% power to detect a true underlying between-group treatment difference of 0.51 in change from baseline in UUI episodes at a two-sided 0.05 level assuming a variability estimate of 1.68 based on vibegron Study 008 data. Assuming that these endpoints are uncorrelated, then this study has 96% power to reject both co-primary hypotheses.

1.1. Schedule of Activities

Table 1: RVT-901-3003 Schedule of Activities

Study Period:	Screening/ Washout	Run-in	Treatment					Safety Follow-up/ Unscheduled	
Visit Number:	Visit #1	Visit #2	Visit #3	Diary Only	Visit #4	Visit #5	Visit #6	UNS #	Visit #7
Visit Name:	Screening[1]	Run-in	Baseline	Week 2	Week 4	Week 8	Week 12 or Early WD	Unsch-eduled[25]	Follow-up[26]
Study Day:	-49 to -15	-14	1	15	29	57	85 or Early WD		113 or Early WD + 28
Permitted Visit Window:		± 3 Days			± 3 Days	± 3 Days	± 3 Days		± 3 Days
Informed Consent	X								
Inclusion/Exclusion Criteria Eligibility Review	X	X	X						
Medical and Medication History	X	X	X						
Electronic Diary (eDiary)[2]:									
eDiary Device:									
Device Setup/Function Check[3]	X	X	X		X	X	X	X	
Device Training/Re-Training[4]	X	X	X		X	X		X	
Dispense/Collect eDiary Device	X						X		
Patient Voiding Diary:									
Patient Voiding Diary Training/Re-Training[5]	X	X	X		X	X		X	
Patient Completes Patient Voiding Diary[6]	X	X		X	X	X	X		
Urine Volume Diary:									
Urine Volume Diary Training/Re-Training[5]	X	X	X		X	X		X	
Dispense Urine Collection/Measurement Supplies	X								
Patient Completes Urine Volume Diary[7]	X	X		X	X	X	X		
Diary and Visit Reminders									
Phone Calls / Optional SMS reminders[8]	X	X		X	X	X	X		

Study Period:	Screening/ Washout	Run-in	Treatment					Safety Follow-up/ Unscheduled	
Visit Number:	Visit #1	Visit #2	Visit #3	Diary Only	Visit #4	Visit #5	Visit #6	UNS #	Visit #7
Visit Name:	Screening[1]	Run-in	Baseline	Week 2	Week 4	Week 8	Week 12 or Early WD	Unsch-eduled[25]	Follow-up[26]
Study Day:	-49 to -15	-14	1	15	29	57	85 or Early WD		113 or Early WD + 28
Permitted Visit Window:		± 3 Days			± 3 Days	± 3 Days	± 3 Days		± 3 Days
Patient Reported Outcomes[9]:									
Global Impression Items (PGI-Severity, PGI-Control, PGI-Frequency, PGI-Leakage, and PGI-Change)			X		X	X	X		
Overactive Bladder Questionnaire (OAB-q LF)			X				X		
Work Productivity and Activity Impairment Questionnaire-Urinary Symptoms (WPAI-US)			X				X		
EQ-5D			X				X		
Post-Void Residual (PVR) Volume[10]		X					X		
Physical Exam[11]	X	X						X	X
ECG[12]	X							X	
Vital Signs[13]	X	X	X		X	X	X	X	X
Adverse Events[14]	←==========→								
Serious Adverse Events[15]	←==========→								
Concomitant Medication Review[16]	←==========→								
Clinical Laboratory Assessments:									
Chemistry	X		X		X		X	X	X
Hematology	X		X		X		X	X	X
Urinalysis Dipstick[17,18]	X		X		X		X	X	X
Urine Pregnancy β-hCG (women)[19]	X	X	X		X	X	X	X	X
IxRS Randomization to Study Treatment			X						
Dispense Study Treatment[20]		X	X		X	X		X	

Study Period:	Screening/ Washout	Run-in	Treatment					Safety Follow-up/ Unscheduled	
Visit Number:	Visit #1	Visit #2	Visit #3	Diary Only	Visit #4	Visit #5	Visit #6	UNS #	Visit #7
Visit Name:	Screening[1]	Run-in	Baseline	Week 2	Week 4	Week 8	Week 12 or Early WD	Unsch-eduled[25]	Follow-up[26]
Study Day:	-49 to -15	-14	1	15	29	57	85 or Early WD		113 or Early WD + 28
Permitted Visit Window:		± 3 Days			± 3 Days	± 3 Days	± 3 Days		± 3 Days
Study Treatment Return/Accountability Review[21]			X		X	X	X		
Administer Witnessed Dose of Study Treatment[22]		X	X						
Pharmacokinetic Sampling (PK Subset Only):									
PK Sample Collection[23]					X	X	X		
Collect Date/Time of Prior Dose[24]					X	X	X		

Abbreviations: IxRS, interactive voice or web response system, PK, pharmacokinetic; WD, withdrawal; β-hCG, β-human chorionic gonadotropin

Table Footnotes:

Screening

1. The time between the Screening and Run-in Visits may be up to 5 weeks, to allow for washout of prior OAB medications (if needed) and completion of the Patient Voiding Diary and Urine Volume Diary.

Electronic Diary (eDiary)

2. The Electronic Diary (eDiary) for this study includes both the Patient Voiding Diary and the Urine Volume Diary, and will be implemented via an eDiary device (provisioned smartphone). A paper diary will be provided to all patients to be used as a back-up when necessary. If a back-up paper diary is used, it should be collected at each study visit.

eDiary Device

3. At Screening, site personnel will setup the eDiary Device, confirm proper functioning, and dispense the eDiary Device to the patient. At each subsequent visit during the Treatment Period, site personnel will confirm that the eDiary Device is functioning properly.
4. Specific training on device operation will be provided to the patient at Screening, with re-training provided at each subsequent visit.

Patient Voiding Diary and Urine Volume Diary

5. Specific training on completion of the Patient Voiding Diary and Urine Volume Diary will be provided to the patient at Screening, with re-training provided at each subsequent visit.
6. The Patient Voiding Diary should be completed by the patient on all of the 7 Diary Days **prior to** the Run-in Visit (days -21 to -15), Baseline Visit (days -7 to -1), Week 2 Visit (days 8 to 14), Week 4 Visit (days 22 to 28), Week 8 Visit (days 50 to 56), and Week 12 Visit (days 78 to 84). Patient will receive SMS text alerts and/or phone call reminders to complete the Diary.
7. The Urine Volume collection and Urine Volume Diary completion should be performed by the patient on one (1) of the 7 Diary Days prior to the Run-in, Baseline, and Weeks 2, 4, 8, and 12 Visits.

Diary and Visit Reminders

8. Patient will receive phone call reminders from the site to complete the Diary on approximately the first day and third day of each diary collection period (or next business day). Patient may consent to additional SMS Text reminders (where available).

Patient Reported Outcomes

9. Vital signs, followed by PRO Questionnaires will be the first procedure performed at visits that include PRO administration. Questionnaires will be administered at the site in the order listed in the Schedule of Activities.

Post Void Residual Volume

10. All efforts will be made to ensure the same device and operator are used for all PVR volume measurements for individual patients.

Physical/ECG/Vitals

11. A Complete Physical Exam will be performed at the Screening Visit and will include a digital rectal exam for all males. Focused physical examinations will be performed at the Run-in and Follow-up Visits, which will include a pelvic exam for women only as needed to confirm prolapse.
12. A single 12-lead ECG will be obtained at Screening.
13. Vital Signs includes Blood Pressure (average of three measurements taken 1-2 minutes apart after sitting for 5 minutes), Heart Rate, Temperature, Respiration Rate and Weight. Height will be measured only at Screening.

Adverse Events

14. Adverse events will be collected from the time a patient provides informed consent to participate in the study until the Follow-up Visit is completed.
15. Serious adverse events will be collected from the time a patient provides informed consent to participate in the study until the Follow-up Visit is completed.

Prior and Concomitant Medications

16. Concomitant medications will be reviewed and recorded at each study visit from the Screening through the Week 12 and at any Unscheduled Visits. Medications taken within 1 year of the Screening Visit for the treatment of OAB will also be recorded.

Labs

17. At Week 8, the Urine Dipstick will only be performed if clinically indicated (e.g., symptoms of urinary retention or urinary tract infection).
18. Urinalysis will be performed only if the urine dipstick tests positive for the presence of leukocytes, nitrites, or blood cells, and will be performed by the central lab.
19. Urine beta-human chorionic gonadotropin (β-hCG) will be tested for women of childbearing potential only.

Dosing/Drug

20. Dosing will occur every day from the Witnessed Dose on the day of the Run-in Visit through the day before the Week 12 Visit.
21. Study Treatment bottles should be returned by the patient at each visit. Clinic staff will perform accountability and review any discrepancies with the patient during the visit.
22. All patients will take their dose of Study Treatment on the day of the Run-in and Baseline Visits at the site as a witnessed dose. The date and time of Study Treatment dosing will be recorded

Pharmacokinetics Subset Only

23. PK samples for Population PK Analysis will be collected from a subset of patients (approximately 30% of enrolled patients) at selected sites. Pre-dose blood samples will be collected at Week 4, Week 8, and Week 12. PK samples should be collected during the clinic visit after all other study assessments have been completed.
24. The date and time of the last dose of Study Treatment prior to PK sampling will be recorded.

Follow-up/Unscheduled

25. Unscheduled Visits and the specific procedures performed at these visits will be determined by the Investigator, as clinically indicated. The procedures indicated in the Schedule of Activities will be performed at these visits, as clinically indicated, based on the purpose of the visit (e.g., follow-up for an adverse event or abnormal laboratory test, study treatment dispensation). The reason for the visit will be captured in the source documents.
26. For Patients who do not enroll into the optional extension study (RVT-901-3004) or patients who Withdraw from the study for any reason, a Follow-up Visit should be performed approximately 28 days after the last dose of Study Treatment on Study Day 113 or approximately 28 days after a patient's Withdrawal from the study. When a patient withdraws from the study prior to study completion, all applicable activities scheduled for the Week 12 Visit should be performed at the time of withdrawal.

2. INTRODUCTION

2.1. Indication

Vibegron (RVT-901) is currently in development to reduce urge urinary incontinence, urgency, and urinary frequency in patients with overactive bladder (OAB).

2.2. Background

OAB affects approximately 16% of the population in the US and EU. Prevalence increases with age, affecting approximately 1/3 of people 75 years and older [Stewart, 2003; Milsom, 2001]. The International Continence Society (ICS) defines OAB as urgency, with or without urge incontinence, usually associated with frequency and nocturia [Abrams, 2002]. Urgency is defined as a sudden compelling desire to void which is difficult to defer. Urge urinary incontinence (UUI) 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. UUI is distinguished from stress urinary incontinence, which is the involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing. When both components are present, the classification is mixed urinary incontinence and the Investigator will make a determination of either urgency or stress specified as the predominant component.

Currently, the predominant class of drugs used to treat OAB is antimuscarinics. The clinical use of antimuscarinics is limited by modest efficacy and poor tolerability due to mechanism-based side effects including dry mouth, constipation, and the potential for CNS adverse effects (e.g., cognitive impairment). High discontinuation rates have been observed for both tolterodine and oxybutynin, two commonly prescribed antimuscarinics, in both clinical trials and marketed settings [D'Souza, 2008; Lawrence, 2000]. In a study evaluating the discontinuation rate of new prescriptions for tolterodine ER or oxybutynin, the mean time to discontinuation was 45 to 60 days, and over 55% of patients never refilled their original prescription [Lawrence, 2000]. At six months, less than 1/3 of patients were still refilling their prescriptions. The lack of efficacy or inability to tolerate antimuscarinics leaves patients with few alternative treatment options. As such, there is a clear unmet medical need for better treatment options for patients with OAB. In addition, recent evidence from observational studies suggests that higher cumulative anticholinergic use is associated with an increased risk of dementia [Gray, 2015; Gray, 2016].

Beta-3 adrenergic receptor (β_3-AR) agonists demonstrated efficacy in alleviating symptoms of OAB [Chapple, 2009; Chapple, 2010; Chapple, 2012]. To date, one β_3-AR agonist, mirabegron (Astellas Pharma Global Development, Inc.), has received marketing approval in Japan and the United States for the treatment of OAB. Reductions in micturition frequency, urinary incontinence and urgency episodes, and increases in mean volume voided per micturition were observed with mirabegron [Chapple, 2009; Chapple, 2010; Chapple, 2012]. Cross-study comparisons of the clinical profiles of β_3-AR agonists with the antimuscarinic, DETROL® LA (tolterodine tartrate extended release, hereafter referred to as tolterodine ER), suggest that β_3-AR agonists possess similar efficacy for the treatment of OAB with an improved tolerability profile [Chapple, 2009; Van Kerrebroeck, 2001]. A recent publication demonstrated that patients prescribed mirabegron remained on treatment longer and showed greater adherence than those

prescribed traditional antimuscarinics, and mirabegron was associated with a favorable safety and tolerability profile [Chapple, 2017].

Vibegron is a potent, highly selective, orally available β_3-AR agonist demonstrating > 9,000 fold selectivity for activation of β3-AR over β2-AR and β1-AR in cell based in vitro assays. Beta-adrenergic receptors (β-AR) are prototypic G-protein coupled receptors expressed on the surface of cells and mediate intracellular signaling via coupling to G proteins 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 of β_3-AR agonists during the filling phase of the micturition cycle [Yamaguchi, 2002; Biers, 2006]. In rodent models of bladder overactivity, β_3-AR agonists relax bladder smooth muscle and suppress non-neurogenic and neurogenic detrusor over activity [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.

2.3. Non-clinical Safety Summary

Nonclinical safety evaluation of vibegron included a comprehensive package of safety pharmacology, repeat-dose oral toxicity up to the chronic duration, genetic toxicology, carcinogenicity, reproductive developmental, and special safety studies to support the continued evaluation of long-term oral administration of vibegron in humans.

Cardiovascular safety pharmacology findings consisted of increased heart rates, decreased QT interval, and increased corrected QT (QTc) interval (≥ 2.5 mg/kg); the QRS interval and diastolic blood pressure were increased in monkeys at 135 mg/kg. At 2.5 mg/kg in monkeys, the maximum concentration (C_{max}) level was less than the estimated human exposure at 75 mg. All safety pharmacology changes were transient, and QT changes in the nonclinical model did not translate to humans. A clinical thorough QT (tQT) study did not identify clinically meaningful effects on QTc interval or blood pressure when evaluated up to the supratherapeutic dose of 400 mg.

Additional findings included neurobehavioral effects of reduced mobility with abnormal posture and gait in rats at ≥ 20 mg/kg (34-fold of C_{max} at the 75 mg); and increased respiration rates and body temperature in monkeys at ≥ 2.5 mg/kg.

In chronic toxicity studies, findings were limited to a transient clinical sign of salivation, a decreased body weight gain in rats, and a higher incidence of abdominal distension in monkeys. In monkeys, histopathology changes consisted of a slight cellular infiltration in the liver, which correlated with hepatic enzyme elevation in the 3-month study. Systemic exposures at no-observed-adverse-effect levels (NOAELs) in rats were 3- and 32-fold higher in males and females, respectively, compared to the gender-specific human exposures. In monkeys, the NOAEL was 21-fold higher than human exposure.

Vibegron was not phototoxic, genotoxic, or carcinogenic. The carcinogenicity NOAELs were at least 27- and 23-fold higher in mice and rats, respectively, compared to the human exposure. Fertility and embryo-fetal developmental findings consisted of reduced fertility in female rats

and an increased incidence of delayed skeletal ossification in fetuses of rabbits at a maternally toxic dose. The reproductive developmental NOAELs were greater than 349-fold of the human exposure. The nonclinical safety data supports the Phase 3 clinical studies of the proposed dose of 75 mg/day.

2.4. Summary of Relevant Clinical Experience with Vibegron

As of 03 February 2017, approximately 2,300 patients and healthy volunteers (including approximately 1,840 patients with OAB and 460 healthy volunteers) have received at least one dose of vibegron in 19 completed studies. Vibegron has been evaluated in 16 Phase 1 studies, one large international Phase 2 dose-ranging study in patients with OAB (Study 008), and two completed Phase 3 studies in Japanese patients with OAB (Study 301 and 302). A summary of available clinical data is included below. Refer to the vibegron Clinical Investigator's Brochure for additional information.

2.4.1. Efficacy

The efficacy of vibegron in the treatment of OAB has been assessed in one international Phase 2 (008) and 2 Phase 3 studies (301 and 302). A brief summary of these studies is included below.

Study 008 was an international, randomized, placebo- and active-controlled Phase 2 dose-ranging study conducted in 1,395 patients with OAB. Patients were equally randomized in a double-blind fashion to 8 weeks of treatment in the following study arms: vibegron 3 mg, 15 mg, 50 mg, or 100 mg once daily, tolterodine ER 4 mg once daily, or placebo once daily. An optional extension study for eligible patients continued vibegron (50 and 100 mg) and tolterodine treatment for a total duration of 52 weeks. Treatment of patients with OAB with vibegron resulted in a dose-dependent reduction in the average daily number of micturitions, total urinary incontinence episodes, UUI episodes, and urgency episodes. At doses of 50 and 100 mg of vibegron, statistically and clinically relevant lowering of important OAB endpoints was observed (Table 2).

Kyorin Pharmaceutical Company (Kyorin) has conducted a development program in Japan, consisting of two large Phase 3 clinical trials (Studies 301 and 302). Overall, 908 patients were treated with vibegron in the Kyorin Phase 3 program.

Study KRP114V-T301 (Study 301) was a double-blind, randomized, placebo controlled, multi-center, Phase 3 study designed to evaluate the safety and efficacy of vibegron in Japanese males and females with OAB. Upon completion of the placebo Run-in period, 1,232 patients were randomized to receive blinded study treatment for 12 weeks including: vibegron 50 mg (N=370), vibegron 100 mg (N=369), placebo (N=369), or imidafenacin 0.2 mg (comparator; N=117). Study 301 results demonstrate that once daily vibegron produced statistically significant reductions in efficacy parameters including: micturitions, UUI episodes, total incontinence episodes, and urgency episodes (Table 2).

Study KRP114V-T302 (Study 302) was an open-label, uncontrolled, multi-center, Phase 3 study designed to evaluate the long-term (52-week) safety and efficacy of vibegron in Japanese males and females with OAB. Upon completion of a 1-week observation period, 169 patients initiated vibegron 50 mg once daily. After eight weeks, the dose could be increased to 100 mg once daily as clinically indicated. Patients continued vibegron at a dose of 50 mg or 100 mg through

Week 52. Once daily vibegron reduced episodes of micturitions, UUI episodes, total incontinence episodes, and urgency episodes over a 52-week treatment period.

Table 2: Summary of Phase 2b Study 008 and Preliminary Phase 3 Study 301 Efficacy Results

	Merck (Study 008) Week 8		Kyorin (Study 301) Week 12	
	50 mg	**100 mg**	**50 mg**	**100 mg**
Micturitions (Merck N~140, Kyorin N~370)	-0.64 (-1.11, -0.18) p = 0.007	-0.91 (-1.37, -0.44) p < 0.001	-0.86 (-1.12, -0.60) p < 0.0001	-0.81 (-1.07, -0.55) p < 0.0001
Urge Urinary Incontinence Episodes (Merck N~115, Kyorin N~260)	-0.72 (-1.11, -0.33) p < 0.001	-0.71 (-1.10, -0.32) p < 0.001	-0.27 (-0.44, -0.10) p = 0.0015	-0.39 (-0.55, -0.22) p < 0.0001
Total Incontinence Episodes (Merck N~115, Kyorin N~260)	-0.60 (-1.02, -0.18) p = 0.005	-0.58 (-1.01, -0.16) p = 0.007	-0.30 (-0.49, -0.12) p = 0.0015	-0.43 (-0.61, -0.24) p < 0.0001
Urgency Episodes (Merck N~140, Kyorin N~370)	-0.76 (-1.43, -0.10) p = 0.024	-1.24 (-1.90, -0.58) p < 0.001	-0.51 (-0.76, -0.25) p = 0.0001	-0.67 (-0.93, -0.42) p < 0.0001
Volume Voided (mL) (Merck N~140, Kyorin N~370)	29.05 (14.36, 43.74) p < 0.001	23.36 (8.66, 38.06) p = 0.002	25.76 (20.02, 31.46) p < 0.0001	22.16 (16.44, 27.89) p < 0.0001

Note: Results presented as least squares mean placebo adjusted change from baseline (95% confidence interval [CI]), p-value. Sample sizes vary slightly by treatment arm and endpoint.

2.4.2. Safety and Tolerability

The safety of vibegron has been evaluated in 19 clinical studies. Over 450 subjects have received vibegron in Phase 1 clinical trials and over 1,900 patients have received vibegron in Phase 2 and 3 trials for overactive bladder. In addition to this overview, please refer to the Clinical Investigator's brochure for an in-depth review of the safety profile.

In 16 Phase 1 clinical studies, vibegron was well-tolerated following single dose administration of doses up to 600 mg and following multiple dose administration of doses up to 400 mg for 14 days and 150 mg for 28 days. In healthy volunteers, at doses ≥ 100 mg, vibegron was associated with increases in heart rate and blood pressure and occasional orthostatic symptoms. There were no serious adverse events in the Phase 1 program and most adverse events (AEs) were mild or moderate in intensity and transient. There were no clinically meaningful changes in laboratory safety or ECG parameters with vibegron alone or when co-administered with tolterodine. A clinical tQT/QTc study did not identify clinically meaningful effects on QTc interval or blood pressure.

There have been two large placebo-controlled studies with vibegron, as well as two 52-week long-term safety studies. The first placebo controlled trial, conducted by Merck, was a 2-part Phase 2 clinical study (Study 008); this also included an open-label 1-year extension in which 1,395 patients were enrolled, of whom 976 received treatment with vibegron. This study was designed to assess the safety, tolerability, and efficacy of vibegron, and to provide proof-of-concept for concomitant dosing with tolterodine ER 4 mg. Part 1 evaluated once-daily doses of vibegron ranging from 3 to 100 mg, tolterodine ER 4 mg, or placebo for 8 weeks and concomitant dosing of vibegron 50 mg with tolterodine ER 4 mg for 4 weeks. Part 2 evaluated once daily doses of vibegron 100 mg, tolterodine ER 4 mg, vibegron 100 mg with tolterodine ER 4 mg, or placebo once daily for 4 weeks. The most common adverse events for vibegron were dry mouth, headache, urinary tract infection, and nasopharyngitis, all of which were reported at < 5.5%. These AE rates were similar to the placebo and tolterodine ER 4 mg treatment groups. Assessment of safety laboratory parameters and mean vital sign values over time, including heart rate and blood pressure, showed no meaningful differences for any active treatment group relative to placebo.

Vibegron was generally well-tolerated during 52 weeks of treatment in the extension phase of Study 008 when administered alone or when co-administered with tolterodine, with no meaningful differences in the overall incidence or severity of adverse events observed among the treatment groups compared to placebo or in the combination treatment groups compared to either monotherapy.

Results from the Kyorin Study 301 demonstrated that both the 50 and 100 mg vibegron dose levels were well-tolerated in these 12-week studies. The incidence of AEs in vibegron treatment groups was similar to the placebo group, and the data showed a similar safety profile as observed in Study 008. Nasopharyngitis was the most commonly reported adverse event (7.3% in the placebo group; 8.6 and 9.5% of patients in the 50 and 100 mg vibegron dose groups, respectively). Dry mouth occurred in 0.5% of patients in the placebo group, and in 1.4% and 0.5% of patients in the 50 and 100 mg vibegron dose groups, respectively. Cystitis was reported in 0.8% of patients in the placebo group, and in 2.4% and 2.2% of patients in the 50 and 100 mg vibegron dose groups, respectively.

In a 52-week long term administration open-label study (Study 302), where patients had the option to increase their treatment dose from 50 to 100 mg, there were no trends toward increased frequency of AEs in 51 of the 169 vibegron-treated patients who elected to increase their dose.

In summary, data from Phase 1 through 3 clinical trials suggest that vibegron is generally safe and well- tolerated, when administered alone or when co-administered with the following drugs: antimuscarinics (imidafenacin or tolterodine); metoprolol (a representative beta-blocker); or amlodipine (a representative vasodilator). 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. Discontinuation rates due to adverse events were low (less than 5%) in all clinical studies.

These data support the ongoing evaluation of vibegron monotherapy in clinical safety and efficacy studies for the treatment of patients with symptoms of overactive bladder.

2.4.3. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Results of Phase 1 absorption distribution metabolism and excretion study 011, which evaluated a single-dose of ^{14}C-vibegron 100 mg in 6 subjects suggested that, found that the majority of vibegron was eliminated as parent indicating minimal metabolism. Approximately 30% and 50% of the absorbed dose was eliminated through renal and hepatic routes, respectively. Based on preclinical and preliminary clinical data, vibegron is metabolically stable and while CYP3A4 is likely the predominant cytochrome P450 (CYP) responsible for in vitro metabolism, metabolism appears to only play a minor role (< 10%) in the elimination of vibegron.

Pharmacokinetic (PK) data in young, middle-aged and elderly males and females with vibegron suggest good absorption with non-linear pharmacokinetics. Vibegron time to reach maximum concentration (t_{max}) values are generally similar across age groups and across genders, ranging from 1 to 3 hours. Preliminary data suggest that the area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24hr}) and C_{max} increase in a greater than dose-proportional manner as a result of an increase in bioavailability with increasing dose, possibly due to saturable P-glycoprotein (P-gp)-mediated efflux in the gut. Vibegron plasma concentrations are higher in females compared to males, in Japanese compared to non-Japanese and in elderly compared to middle aged and young. Exposures are similar in middle-aged males when compared to young males. The harmonic mean apparent terminal half-life ($t_{½}$) values following multiple-dose administration range from 59 to 94 hours, with accumulation half-lives of 25 hours and 38 hours in young and elderly subjects, respectively. Steady state trough concentrations appeared to have been approached by Day 7 across age groups. The steady state area under the concentration-time curve (AUC) geometric mean accumulation ratios were ~2 in young males and ~2.8 in the elderly (males and females). Food and ethnicity do not meaningfully alter the pharmacokinetic profile of vibegron.

2.5. Study Rationale

The use of vibegron in a large Phase 2b study (Study 008) in patients with OAB has demonstrated encouraging safety, tolerability, and efficacy results. Furthermore, Phase 3 data in Japan (Studies 301 and 302) have demonstrated that vibegron is a safe, well tolerated, and effective therapy for OAB patients. Given there are still OAB patients that do not reach their treatment goals with currently approved therapies, there remains an unmet need for new OAB therapies with a favorable safety, tolerability, and efficacy profile. This study is designed to evaluate the safety, tolerability, and efficacy of vibegron 75 mg administered once daily in patients with OAB.

2.6. Dose Rationale

Clinical and non-clinical data support selection of a Phase 3 dose of vibegron 75 mg administered once daily in patients with OAB. This pivotal Phase 3 study is designed to establish the safety, tolerability, and efficacy profile of vibegron 75 mg administered once daily in patients with OAB.

Several lines of evidence support evaluating a once daily 75 mg vibegron dose: 1) Study 008, a large Phase 2b dose ranging study, and two Phase 3 studies (Study 301 and Study 302) demonstrated that doses up to 100 mg for 52 weeks are safe and well tolerated in patients with

OAB; 2) Study 008 demonstrated dose-dependent efficacy across multiple clinical endpoints in OAB patients with the maximal effect generally estimated between 50 and 100 mg; 75 mg of vibegron is expected to capture approximately 90% of the efficacy of 100 mg; 3) slight increases in mean maximum heart rate and infrequent increases in systolic or diastolic blood pressure in patients with OAB were difficult to detect relative to placebo and were not readily distinguishable between 50 and 100 mg of vibegron; these effects appear similar to, or less than, marketed agents tolterodine ER 4 mg and mirabegron 50 mg; and 4) vibegron exhibits greater than dose-proportional increases in exposures with mean C_{max} increasing ~4-fold when dose increases from 50 to 100 mg. A simulated dose of 75 mg decreases C_{max} by approximately 40% and reduces extremes of exposure compared to 100 mg. Lowering C_{max} should maximize the benefit-risk profile for patients with OAB by minimizing the potential for heart rate or blood pressure increases.

2.7. Information on Other Study-Related Therapies

Placebo

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence recommends that OAB trials include a placebo arm to account for the recognized large placebo responses commonly observed in these studies [EMA, 2002]. To accurately demonstrate and measure the true efficacy of vibegron, a placebo arm will be included in this study. Furthermore, a single-blind Run-in Period will be used to assess the early placebo response and to ensure that patients have adequate experience with the Patient Voiding Diary prior to starting the blinded Treatment Period of the study.

Tolterodine ER

Tolterodine ER is an antimuscarinic approved for the treatment of overactive bladder and will be administered at the recommended labeled dose of 4 mg once daily (QD) orally. In this study, tolterodine ER 4 mg will be used as an active control.

3. OBJECTIVES AND ENDPOINTS

Objectives	Efficacy Endpoints
Primary Efficacy	
To evaluate the efficacy of vibegron compared to placebo in patients with symptoms of OAB, specifically the frequency of micturitions and frequency of urge urinary incontinence episodes	Co-primary Efficacy Endpoints: • Change from baseline (CFB) at Week 12 in average number of micturitions per 24 hours in all OAB patients • CFB at Week 12 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients
Secondary Efficacy	
To evaluate the overall efficacy of vibegron compared to placebo in patients with symptoms of OAB	Key Secondary Efficacy Endpoints: • CFB at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients • Percent of OAB Wet patients with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12 • Percent of OAB Wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12 • Percent of all OAB patients with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Week 12 • CFB at Week 12 in average number of total incontinence episodes over 24 hours in OAB Wet patients • CFB at Week 12 in Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB patients • CFB at Week 12 in average volume voided per micturition in all OAB patients

Objectives	Efficacy Endpoints
	Additional Secondary Endpoints: • CFB at Week 12 in Health-related Quality of Life (HRQL) Total Score from the OAB-q LF (1-week recall) in all OAB patients • CFB at Week 12 in Symptom Bother Score from the OAB-q-LF (1-week recall) in all OAB patients • Percent of all OAB patients with average number of micturitions < 8 per 24 hours at Week 12 • Percent of OAB Wet patients with at least a 50% reduction from baseline in total incontinence episodes per 24 hours at Week 12 • CFB at Week 12 in overall bladder symptoms based on Patient Global Impression of Severity (PGI-Severity) in all OAB patients • CFB at Week 12 in overall control over bladder symptoms based on Patient Global Impression of Control (PGI-Control) in all OAB patients
Safety	
To evaluate the safety and tolerability of treatment with vibegron	• Incidence of adverse events • Clinical laboratory assessments • Vital signs and physical examinations
Pharmacokinetic/Pharmacodynamic	
To evaluate the pharmacokinetic profile of vibegron in patients with symptoms of OAB To assess relationships between exposure and efficacy/safety in patients with symptoms of OAB receiving vibegron	• AUC and C_{24} estimated from population PK modeling
Exploratory	
[redacted]	

Objectives	Efficacy Endpoints
	[redacted]

Objectives	Efficacy Endpoints
	[redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an international, Phase 3, randomized, double-blind, placebo-controlled with active control (tolterodine), parallel-group, multicenter study in men and women with overactive bladder, to be conducted in conformance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice. Enrollment of patients will include individuals with OAB Wet (those with UUI, the involuntary loss of urine accompanied by urgency) and OAB Dry (those without UUI).

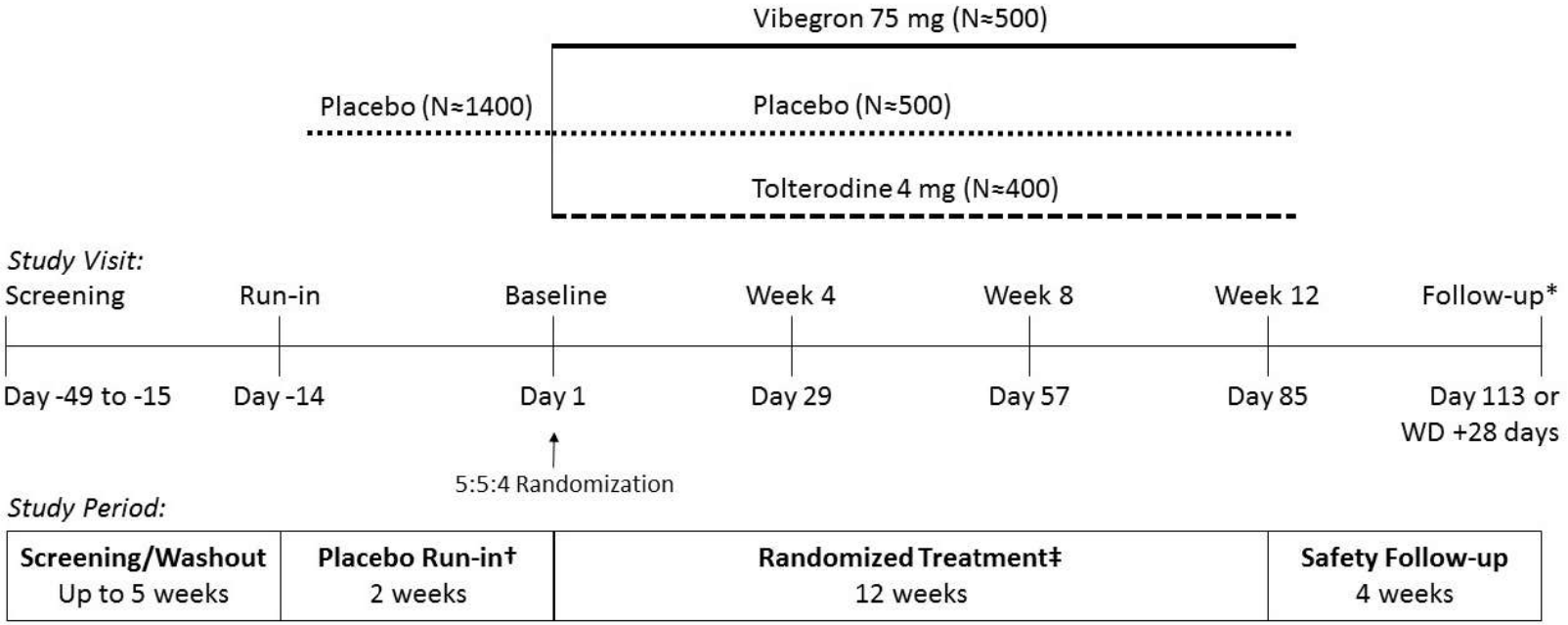
The study consists of a Screening Period (1 to 5 weeks), a single-blind Run-in Period (2 weeks), a randomized double-blind Treatment Period (12 weeks), and a Follow-up Period (4 weeks). Patients who complete the Week 12 Visit may be offered the opportunity to enroll in a 40-week double-blind extension study (RVT-901-3004), which will be conducted under a separate protocol, until enrollment in that study is complete. Patients who do not enroll into the optional extension study will have a Follow-up Visit approximately 28 days after the patient's last dose of Study Treatment (i.e., at Week 16 for patients who complete the Week 12 Visit, or approximately 4 weeks after withdrawal for patients who withdraw early from study participation). Additionally, Unscheduled Visit(s) may be arranged at any time during the study for patients with study-related safety concerns, as needed.

The study will assess the safety, tolerability, and efficacy of 75 mg vibegron versus placebo. Tolterodine ER 4 mg is the active control. Patients will be randomized 5:5:4 in a double-blind fashion to one of three treatment arms: vibegron 75 mg, placebo, or tolterodine ER 4 mg, all administered once daily for 12 weeks during the Treatment Period. Between the Baseline and Week 12 Visits, patients will have study assessments at Week 4 and Week 8. A schematic of the study design is shown as Figure 1.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Schedule of Activities (Table 1). Details of study procedures are provided in Section 7.

A schematic of the study design is shown as Figure 1.

Figure 1: RVT-901-3003 Study Schematic



*The Follow-up visit occurs at Day 113 for subjects who completed the Week 12 visit but do not enroll in the optional 40-week extension study (RVT-901-3004) or at 28 days after withdrawal (WD) for subjects who withdraw early from the study.
†Single-blind (subjects will not know they are receiving placebo)
‡Double-blind

4.2. Treatment Arms and Duration

Refer to Section 6 for full details of Study Treatments. Patients will be randomized 5:5:4 to one of the following blinded treatments during this study:

- Vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule; both oral and administered once daily
- Placebo tablet to match vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule; both oral and administered once daily
- Tolterodine ER 4 mg capsule + placebo tablet to match vibegron 75 mg tablet; both oral and administered once daily

Dosing will begin at the Baseline Visit (Day 1), and once daily dosing of the Study Treatment will continue through Study Day 84, the day before the Week 12 Visit.

Patients who complete the Week 12 Visit may be offered the opportunity to enroll in a 40-week double-blind extension study RVT-901-3004 (which will be conducted under a separate protocol), until enrollment in that study is complete.

4.3. Number of Participants

Approximately 1,400 patients will be enrolled at approximately 330 study sites.

4.4. Definition of Study Completion by a Patient

A patient is considered to have completed the study if she/he completes the Week 12 Visit.

4.5. End of Study Definition

End of study is defined as the date when the last patient has either completed the study (see Section 4.4 for definition of completion), has discontinued from the study, or is lost to follow-up (i.e., the patient is unable to be contacted by the Investigator).

5. STUDY POPULATION

5.1. Eligibility Criteria

To be eligible for participation in this study, a patient must meet all the Inclusion Criteria, and none of the Exclusion Criteria.

5.1.1. Inclusion Criteria

1. Willing and able to provide written informed consent.
2. Males or females ≥ 18 years of age. Note: Up to 15% of patients can be male.
3. Has a history of OAB (as diagnosed by a physician) for at least 3 months prior to the Screening Visit. Note: OAB is defined as urgency, with or without urge urinary incontinence (UUI), usually associated with frequency and nocturia. Urodynamic evaluation is not required.
4. Meets either the OAB Wet or OAB Dry criteria described below, based on the Patient Voiding Diary returned both at the Run-in Visit and Baseline Visit (all Complete Diary Days must be used in determining eligibility). A minimum of 5 Complete Diary Days [not necessarily consecutive] are required for the diary returned at the Run-in Visit, and 4 Complete Diary Days are required for the diary returned at the Baseline Visit. Averages should not be rounded up to the whole number:
   - OAB Wet criteria:
     - An average of ≥ 8.0 micturitions per Diary Day; and
     - An average of ≥ 1.0 UUI episodes per Diary Day; and
     - If stress urinary incontinence is present, the total number of UUI episodes must be greater than the total number of stress urinary incontinence episodes from the previous visit diary.
   - OAB Dry criteria:
     - An average of ≥ 8.0 micturitions per Diary Day; and,
     - An average of ≥ 3.0 urgency episodes per Diary Day; and
     - An average of < 1.0 UUI episodes per Diary Day; and
     - If stress urinary incontinence is present, the total number of UUI episodes must be greater than the total number of stress urinary incontinence episodes from the previous visit diary.

   Note: Up to 25% of patients that meet OAB Dry criteria may be enrolled.
5. For females of reproductive potential: Agrees to remain abstinent or use (or have their male partner use) an acceptable method of birth control (as defined in Section 5.2.1) each time the patient has intercourse from the Screening Visit until completion of the Follow-up Visit.
6. For females of reproductive potential: Agrees not to donate ova (eggs) until at least 1 month after the last dose of Study Treatment.
7. Has demonstrated ≥ 80% compliance with self-administration of Study Treatment during the Run-in Period.

8. Is ambulatory and in good general physical and mental health as determined by the Investigator.
9. In the opinion of the Investigator, is able and willing to comply with the requirements of the protocol, including completing electronic versions of questionnaires, the Patient Voiding Diary, and the Urine Volume Diary (will require ability to collect, measure, and record voided volume by herself/himself using a graduated urine collection and measurement container [provided by the Sponsor, if needed]).

5.1.2. Exclusion Criteria

Urology Medical History

1. Patient has a history of 24-hour urine volume greater than 3,000 mL in the past 6 months, or a Urine Volume Diary day measurement greater than 3,000 mL during the Run-in Period.
2. 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, urolithiasis, interstitial cystitis, prostate cancer, gastrointestinal (GI) cancer, tuberculosis, stone disease, urothelial tumor, prostatitis, and clinically relevant benign prostatic hypertrophy (BPH) or bladder outlet obstruction, as judged by the Investigator. Note: Male patients with mild to moderate BPH without evidence of bladder obstruction as determined by the Investigator may be included as long as they have been taking a medication for the treatment of BPH for at a least 1-year prior to Screening, with no change in dose of herbal medications, alpha antagonist medications or other symptomatic treatments or medications within 3 months prior to Screening, and no change in dose of 5 alpha reductase inhibitors within 6 months of Screening.
3. Has a history of surgery to correct stress urinary incontinence, pelvic organ prolapse, or procedural treatments for BPH within 6 months of Screening.
4. Has current history or evidence of Stage 2 or greater pelvic organ prolapse (prolapse extends beyond the hymenal ring).
5. Patient is currently using a pessary for the treatment of pelvic organ prolapse.
6. Has a known history of elevated post-void residual volume defined as greater than 150 mL.
7. Has undergone bladder training or electrostimulation within 28 days prior to Screening or plans to initiate either during the study.
8. Has an active or recurrent (> 3 episodes per year) urinary tract infection by clinical symptoms or laboratory criteria (≥ 5 white blood cells [WBC] or a positive urine culture, defined as $\geq 10^5$ colony forming units [CFU]/mL in 1 specimen). Patients diagnosed with a urinary tract infection (UTI) at the Screening Visit may be treated and re-screened once the infection has resolved.
9. Has a requirement for an indwelling catheter or intermittent catheterization.
10. Has received an intradetrusor injection of botulinum toxin within 9 months prior to Screening.

Other Medical History

11. Has uncontrolled hyperglycemia (defined as fasting blood glucose > 150 mg/dL or 8.33 mmol/L and/or non-fasting blood glucose > 200 mg/dL or 11.1 mmol/L) or, if in the opinion of the Investigator, is uncontrolled.
12. Has evidence of diabetes insipidus.
13. Is pregnant, breast-feeding, or is planning to conceive within the projected duration of the study.
14. Has a concurrent malignancy or history of any malignancy within 5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
15. 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.
16. Patients who have systolic blood pressures ≥ 160 mmHg but < 180 mmHg are excluded, unless deemed by the Investigator and/or Medical Monitor as safe to proceed in this study and able to complete the study per protocol; these patients must be on stable hypertension medication for at least 90 days.
17. All patients 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.
18. Has narrow angle glaucoma (primary open angle glaucoma is not excluded).
19. Has a history of cerebral vascular accident, transient ischemic attack, unstable angina, myocardial infarction, coronary artery interventions (e.g., coronary artery bypass grafting or percutaneous coronary interventions [e.g., angioplasty, stent insertion]), or neurovascular interventions (e.g., carotid artery stenting) within 6 months prior to the Screening Visit. Patients with these conditions should be on stable medical therapy for at least 3 months prior to the Screening Visit.
20. Has a known history of liver disease.
21. Has a history of injury, surgery, or neurodegenerative diseases (e.g., multiple sclerosis, Parkinson's) that could affect the lower urinary tract or its nerve supply.

Laboratory/Procedure History

22. Has hematuria, including microscopic hematuria (> 5 red blood cells [RBCs]/hpf). Patients with known, fully evaluated, benign hematuria may participate. Documentation must be obtained indicating an unremarkable upper urinary tract (kidneys and ureters) imaging study (e.g., computerized tomography [CT] scan with and without contrast, renal ultrasound, magnetic resonance imaging [MRI] with and without contrast, intravenous pyelogram, etc.) and cystoscopy. Patients whose hematuria has not been previously evaluated may not be enrolled.
23. Has clinically significant electrocardiogram (ECG) abnormality that, in the opinion of the Investigator, exposes the patient to risk by participating in the study.

24. 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).
25. Has clinically significant laboratory abnormality (from the Screening Visit results) that remains unresolved after repeat testing (Refer to Algorithm for Laboratory Testing Appendix B) or that could confound the results of the study or indicate that it is not in the best interest of the patient to participate.
26. Has an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.

Medication History

27. Use of any prohibited medications as detailed in Section 7.9.3 (suitable washout periods from these medications are also described therein).
28. Had changed the dose of any medications listed in Section 7.9.5 within 4 weeks prior to the Baseline Visit, or plans to initiate or change the dosing of any of these medications during the study.
29. Has an allergy, intolerance, or a history of a significant clinical or laboratory adverse experience associated with any of the active or inactive components of the vibegron formulation or tolterodine formulation.

Other

30. Is currently participating or has participated in a study with an investigational compound or device within 28 days prior to signing informed consent.
31. Is currently participating in or has participated in a study with vibegron.
32. Has a history of significant drug or alcohol abuse/dependence within a year prior to informed consent, as assessed by the investigator.
33. Has a varying sleep schedule anticipated during times when the voiding diaries are to be completed.
34. Has coronary or neurovascular interventions planned during the duration of the study.
35. Has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that might, in the opinion of the Investigator, confound the results of the study, interfere with the patient's ability to comply with study procedures, or make participation in the study not in the patient's best interest.

5.2. On-Study Restrictions

5.2.1. Contraception

5.2.1.1. Female Patients

In this study, female patients must agree to use (or have their male partner use) a highly effective contraception, unless any of the following apply:

- has reached natural menopause, defined as at least 12 months of spontaneous amenorrhea without an alternative medical cause;
- is permanently sterile, following hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

The highly effective methods of contraception include the following:

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, which may be oral intravaginal or transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion (including ligation and blockage methods such as Essure™ at least 6 months prior to the initial Screening Visit [patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram])
- sexual partner(s) who was vasectomized at least 6 months prior to the Screening Visit
- sexual abstinence from heterosexual intercourse, as a preferred lifestyle; periodic abstinence is not acceptable

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign a consent form they understand the requirements for avoidance of pregnancy during the course of the study.

These methods of contraception are only effective when used consistently, correctly, and in accordance with the product label. The Investigator is responsible for ensuring that patients understand how to properly use these methods of contraception.

5.2.2. **Meals and Dietary Restrictions**

Patients may consume a normal, regular diet and take their Study Treatment daily without regard to food or other medications.

Patients do not need to fast prior to laboratory draws.

5.3. Screen Failure

After obtaining informed consent, study site personnel will access the interactive voice or web response system (IxRS) to assign a unique patient number to a potential study participant.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent, study site personnel should document the screen failure in the patients' source documents. The documentation should include demographics and medical history, the reason for screen failure, the eligibility criteria reviewed, procedures performed, etc.

For patients excluded during Screening and Run-in, the screen failure should be reported promptly to IxRS.

5.4. Interruption of Study Treatment

5.4.1. Temporary Interruption

The medical monitor should be contacted for Study Treatment interruption of >7 days in duration. Study treatment may be temporarily interrupted for up to 21 consecutive days if required for adverse event management, as described in Section 6.6.

5.4.2. Rechallenge

See Section 6.6.

5.5. Withdrawal from the Study

Patients may withdraw consent at any time for any reason or be withdrawn from the study at the discretion of the Investigator should any untoward effect occur. Every effort should be made to establish and document the possible reasons for withdrawal. A patient may be withdrawn by the Investigator or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. The patient may be discontinued from further study participation after discussion between the Investigator and the Sponsor clinical monitor (or designee) if the patient requires therapy with any excluded medication. Medications that may cause a patient to be discontinued have been described in Section 7.9.3.

A patient must be discontinued from the study for any of the following reasons:

- The patient or legal representative (such as a legal guardian) withdraws consent.
- Study treatment administration is interrupted for more than 21 consecutive days.
- The patient has a medical condition or personal circumstance which, in the opinion of the Investigator and/or Sponsor, places the patient at unnecessary risk through continued participation in the study or does not allow the patient to adhere to the requirements of the protocol.
- The patient has a confirmed positive serum pregnancy test.
- The patient is unable to complete the study procedures successfully, including completion of the Patient Voiding Diary.
- When a patient withdraws from the study prior to study completion, all applicable activities scheduled for the Week 12 Visit should be performed at the time of withdrawal. Any adverse events that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.
- Once a patient is withdrawn, he/she shall not be allowed to enroll again.

5.6. Lost to Follow Up

Should a patient fail to attend a required study visit, the site should attempt to contact the patient and re-schedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient so that they can

appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up". Including at least three documented attempts to contact the patient (i.e., phone, email, or certified letter). Efforts to establish the possible reason for discontinuation should be documented.

5.7. Early Study Termination

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 (GCP) and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6. STUDY TREATMENT

6.1. Study Treatments Description

Study treatment is defined as vibegron, tolterodine, or matching placebo for vibegron or tolterodine. All Study Treatments will be provided by the Sponsor.

Each Study Treatment is described in Table 3.

Table 3 RVT-901-3003 Study Treatments

Study Treatment	Dose	Frequency; Route of Administration; Description	Use
Vibegron	75 mg	Once daily; oral; tablet	Experimental
Tolterodine ER	4 mg	Once daily; oral; capsule	Active control
Placebo to match vibegron 75 mg	NA	Once daily; oral; tablet	Placebo control and Blinding
Placebo to match tolterodine ER 4 mg	NA	Once daily; oral; capsule	Placebo control and Blinding

6.2. Administration of Study Treatments

Throughout the study, all Study Treatments will be taken by mouth once daily in the morning with 8 ounces of water and should be swallowed whole. Study treatment may be taken without regard to meals.

During the Run-in Period, all patients will take placebo (1 tablet and 1 capsule) once daily for 2 weeks prior to the Baseline Visit. The Investigator will be aware that the Study Treatment during this period is placebo, however, the patient will NOT be told that the treatment administered during this period is placebo or that the patient needs to qualify to enter the randomized Treatment Period.

Study treatments will be taken either at the site or at home as follows:

- All patients will take their dose of Study Treatment on the day of the Run-in and Baseline Visits at the site as a witnessed dose.
- Patients in the population PK subset will hold their dose of Study Treatment on the day of the Week 4 and Week 8 Visits.
- All other doses of Study Treatment will be taken by the patient at home.

If a patient forgets to take Study Treatment in the morning, the missed dose should be taken as soon as possible on the same calendar day. However, if a dose is missed for an entire calendar

day, the missed dose should NOT be taken on the following calendar day. This will be recorded as a missed dose.

6.3. Study Treatment Assignment

Randomization will occur centrally using an interactive voice or web response system (IxRS) using central, stratified randomization. There are three treatment arms to which patients will be randomized in a 5:5:4 ratio:

- Vibegron 75 mg + placebo to match tolterodine ER 4 mg
- Placebo to match vibegron 75 mg + placebo to match tolterodine ER 4 mg
- Tolterodine ER 4 mg + placebo to match vibegron 75 mg

Randomization will be stratified based on baseline category of OAB Wet or OAB Dry and Sex (Female vs Male).

Enrollment will be capped based on OAB Dry criteria and sex as follows:

- Up to 25% of the patients enrolled may meet OAB Dry criteria.
- Up to 15% of the patients enrolled may be male.

  Note: The proportion of OAB Dry patients and male patients during Screening will be monitored in IxRS. The final proportion of OAB Dry and male patients will depend on both number of OAB Dry or male patients in the Screening queue at the time the stratum is closing and on total study enrollment.

6.4. Blinding

A single-blind (Run-in only) and double-blind/masking technique will be used: vibegron and its matching placebo and tolterodine ER and its matching placebo will be packaged identically so that treatment blind/masking is maintained. The patient, the Investigator, and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the patients are unaware of the treatment group assignments.

At the end of the study (including the 28-day Follow-up Period), 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 patients complete the study.

6.4.1. Unblinding

All efforts should be made to contact the Medical Monitor immediately if the need for emergent unblinding of treatment assignment is desired. In consultation with the Medical Monitor, IxRS should be used for emergency unblinding treatment assignment in the event that this is required for patient safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor notified as soon as possible. Only the Principal Investigator or delegate and the respective patient's code should be unblinded. Site

personnel and Sponsor personnel directly associated with the conduct of the study should not be unblinded.

6.5. Dose Modification

No dose modifications are allowed.

6.6. Treatment Discontinuation and Rechallenge

Refer to Section 8.6.1 and Section 8.6.2, respectively, for information regarding temporary withholding or permanent discontinuation of Study Treatment in association with liver test abnormalities.

Patients who experience a grade 3 or greater toxicity that is considered related to Study Treatment should have their treatment discontinued permanently.

Patients who experience an adverse event grade 3 or 4 adverse event that is not related to Study Treatment may have their Study Treatment interrupted for a period of up to 21 consecutive days if the Investigator believes it is in the best interest of the patient. (Refer to Table 6 for Criteria for Determining the Grade/Severity of Adverse Event Terms). Prior to restarting study drug, the adverse event must have improved to grade 0, 1, or 2.

If the adverse event that is not related to Study Treatment remains grade 3 or grade 4 after treatment interruption or the Investigator believes it is in the best interest of the patient, Study Treatment should be discontinued permanently.

6.7. Packaging and Labeling

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. During the Run-in Period, patients will receive a single-blind supply of Study Treatment bottles to support a 2-week Run-in Period and overage. Once randomized into the study, patients will receive a double-blind supply of Study Treatment bottles at each study visit during the Treatment Period.

6.8. 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 patients, 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.

6.9. Study Treatment Compliance

If a patient is persistently noncompliant with the Study Treatment, it may be appropriate to withdraw the patient from the study. Interruptions from the protocol specified treatment plan for compliance (≤ 75% or > 125%) require consultation between the Investigator and the Sponsor and written documentation of the collaborative decision on patient management.

6.10. Study Treatment Overdose

Refer to Section 8.3.3 for Overdose Management. An overdose is defined as a known deliberate or accidental administration of Study Treatment, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of vibegron or placebo > 2 tablets and any dose of tolterodine or placebo > 2 capsules within a 24-hour window (i.e., > 2 tablets and/or > 2 capsules of blinded Study Treatment within a 24-hour window) is an overdose. There is no known antidote for an overdose.

6.11. Treatment after the End of the Study

Other than patients who participate in the RVT-901-3004 extension study, patients will not receive any additional treatment with the Study Treatment from the Sponsor after completion of the study because the indication being studied is not life-threatening or seriously debilitating and/or other treatment options are available. The Investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition.

7. STUDY ASSESSMENTS AND PROCEDURES

The Schedule of Activities (Table 1) summarizes the study assessments/procedures to be performed at each visit. Individual assessments and procedures are described below.

It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Investigator and/or the Sponsor for reasons related to patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature, and thus local regulations may require that additional informed consent be obtained from the patient. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1. Order of Assessments

Vital signs, followed by PRO questionnaires, will be the first procedures performed at visits that include PRO administration. Blood draws should be performed after PRO administration. A urine pregnancy test (with a negative result) must be done prior to randomization.

7.2. Scheduling Visits

To the extent possible, all visits should occur at the same time across the study between the hours of 8 am and 12 pm. At the end of each visit, the next visit should be scheduled/confirmed. Every effort should be made to adhere to the visit scheduling window as described in the Schedule of Activities (Table 1) to ensure the patient has an adequate amount of Study Treatment to comply with protocol dosing instructions. Patients will be reminded to complete the Patient Voiding Diary and Urine Volume Diary within the 7 days prior to their next visit.

7.3. Unscheduled Visits

Unscheduled Visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the Investigator. The date and reason for the Unscheduled Visit should be recorded in the source documentation. The specific procedures performed at these visits will be determined by the Investigator, as clinically indicated. The recommended minimum procedures are indicated in the Schedule of Activities (Table 1).

7.4. Assignment of Patient Number

All consented patients will be issued a unique patient number that will be used to identify the patient for all procedures that occur. Each patient will be assigned only one unique patient number. Unique patient numbers must not be re-used for different patients. Any patient who is re-screened will obtain a new original unique patient number assigned at the repeated Screening Visit.

7.5. Screening/Washout

- Patients requiring washout of medications (see Section 7.9.3), can begin washout immediately following the Screening Visit. After the 28-day washout period, site staff should contact patients to begin completion of the 7-day eDiary (Patient Voiding

Diary and Urine Volume Diary). Patients not requiring washout can begin the 7-day eDiary the day after the Screening Visit.

- After laboratory results from the Screening Visit are reviewed and found to be clinically acceptable, patients will be eligible to continue to the Run-in Visit. An algorithm for assessing out-of-range laboratory results is in Appendix B.
- Patients that fail Screening may be re-screened only one time when the reason for exclusion has resolved, such as a resolved urinary tract infection. If a patient is rescreened, a unique patient number must be used. Patients cannot be re-screened after receiving placebo-run in Study Treatment. During the Screening or Run-in Periods, or after re-screening, if it is determined that a patient does not qualify for the study, he/she will be excluded. Patients excluded during Screening should be reported as a screen failure promptly to IxRS.

7.6. Informed Consent

Documented consent must be obtained from each potential patient prior to participating in study procedures. Consent must be documented by the patient's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the patient before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form, and any written information provided to the patient must receive institutional review board (IRB)/research ethics board (REB)/institutional ethics committee (IEC) approval/favorable opinion in advance of use. The patient should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the patient's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/REB/IEC requirements, applicable laws and regulations and Sponsor requirements.

7.7. Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee at the Screening, Run-in, and Baseline Visits to ensure that the patient qualifies for the study.

All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

Patients found ineligible during review of inclusion/exclusion will not proceed through the remaining Screening process.

Inclusion/Exclusion criteria for the eDiary completion parameters will be applied to both the Screening eDiary (7-day eDiary period prior to the Run-in Visit), and the Run-in eDiary (7-day eDiary period prior to the Baseline Visit).

Results from the Screening Visit will be used as a basis to confirm eligibility for glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and eGFR. Urine pregnancy test and average blood pressure measure will be confirmed at Screening Visit and Baseline Visit (prior to randomization). Concomitant medications will be reviewed at Baseline to ensure required stability.

7.8. Medical History

A medical history will be obtained by the Investigator or qualified designee. Medical history from the 5 years prior to the Screening Visit will be collected, including all chronic and ongoing conditions, regardless of year diagnosed. Medical history will include a review of any concurrent malignancy or history of any malignancy to confirm eligibility criteria.

Pelvic floor physiotherapy history will be collected.

7.9. Prior and Concomitant Medications

7.9.1. Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the patient within 28 days prior to beginning completion of the Screening eDiary.

All medications for the treatment of OAB taken within 1 year of the Screening Visit will also be recorded. Specific details on a patient's use of prior antimuscarinic therapy including the reason for discontinuation will be collected.

Medication history will be assessed for male patients with history of mild to moderate BPH to ensure a stable treatment regimen that meets eligibility criteria.

7.9.2. Concomitant Medications

Concomitant medications will be reviewed and recorded at each study visit from Screening through Week 12 and at any Unscheduled Visits. Patients will be informed at the study start regarding permissible medications during the study. The Investigator or qualified designee will record all medications, if any, taken by the patient during the study. This will include initiation of new medications, or changes to existing/ongoing medications.

Upon entry into the study, patients will be instructed to report the possible need for any prescription or nonprescription medications immediately (and before use) to the Investigator.

7.9.3. Prohibited Medications and Non-Drug Therapies

Table 4 provides a listing of specific restrictions for concomitant therapy use during the study, with any necessary washout periods described. This table provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications.

Use of other concomitant therapies that are listed in Section 7.9.5 are also prohibited if the patient's dose has changed in the 4 weeks prior to the Baseline Visit or if the patient plans to initiate or change any of these therapies during the study.

If there is a clinical indication for any therapy that is specifically prohibited during the study, discontinuation from Study Treatment may be required. The Investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on Study Treatment requires the mutual agreement of the Investigator, the Sponsor, and the patient.

Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 4: Listing of Prohibited Medications

Class	Examples	Washout Period/Comments
Anticholinergics	darifenacin, fesoterodine, hyoscyamine, oxybutynin, propantheline, solifenacin, tolterodine, and trospium	Patient must discontinue use at least 28 days prior to beginning completion of the Screening Patient Voiding Diary and remain off this therapy during the study
Smooth muscle relaxants	flavoxate, dicyclomine, propiverine	Patient must discontinue use at least 28 days prior to beginning completion of the Screening Patient Voiding Diary and remain off this therapy during the study
Beta-2 adrenergic agonists used for the treatment of stress urinary incontinence	clenbuterol	Patient must discontinue use at least 28 days prior to beginning completion of the Screening Patient Voiding Diary and remain off this therapy during the study
Systemic beta-2 adrenergic agonist	terbutaline	No washout period; patient must remain off this therapy during the study
Synthetic antidiuretic hormones	desmopressin	Patient must discontinue use at least 28 days prior to beginning completion of the Screening Patient Voiding Diary and remain off this therapy during the study
Beta-3 adrenergic agonists	mirabegron	Patient must discontinue use at least 28 days prior to beginning completion of the Screening Patient Voiding Diary and remain off this therapy during the study
Medications with a narrow therapeutic index	Warfarin, digoxin, lithium, phenytoin, theophylline	Patient must not have taken this therapy within 28 days prior to the Screening Visit and remain off this therapy during the study

Class	Examples	Washout Period/Comments
Intradetrusor botulinum toxins	intradetrusor injection of botulinum toxin	Patient must not have received an injection within 9 months prior to the Screening Visit and must not receive this therapy during the study

7.9.4. Permitted Medications and Non-Drug Therapies

Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

7.9.5. Requirements for Use of Stable Therapies

Patients who are receiving any of the therapies from the list below must have been on a stable dose for ≥ 28 days prior to Baseline to be eligible to enroll in the study. Additionally, patients who plan to initiate or change any of the following therapies during the study are not eligible to enroll in the study:

- Tricyclic antidepressants or combinations, including, but not limited to, amitriptyline, imipramine, and doxepin.
- Alpha-1-antagonists, unless used for BPH treatment, in which case, stable dosing for 3 months is required.
- Serotonin and/or norepinephrine reuptake inhibitors, including, but not limited to, fluoxetine, paroxetine, and duloxetine.
- Alpha-adrenergic agonists, including nonspecific sympathomimetic amines, such as, but not limited to, ephedrine, pseudoephedrine, and phenylephrine.
- Diuretic therapy, including, but not limited to, furosemide and hydrochlorothiazide.
- Inhaled anticholinergic, including, but not limited to, tiotropium bromide and ipratropium bromide.
- Regular use of phosphodiesterase type 5 (PDE 5) inhibitors, including, but not limited to, tadalafil, sildenafil, and vardenafil.

  Note: Occasional use of PDE 5 inhibitors (e.g., for the treatment of erectile dysfunction) is allowed throughout the study.

Male patients with mild to moderate BPH without evidence of bladder obstruction as determined by the Investigator may be included as long as they have been taking a medication for the treatment of BPH for at a least 1-year prior to Baseline, with no change in dose of herbal medications, alpha antagonist medications, or other symptomatic treatments or medications within 3 months prior to Baseline. To be eligible for the study, these BPH medication/s must be stable from Screening until Baseline Visit.

Patients with a history of hypertension must be on a stable blood pressure treatment regimen for 90 days prior to the Baseline Visit and must be deemed by the Investigator and/or Medical Monitor as safe to proceed in this study and able to complete the study per protocol.

Patients with a history of cerebral vascular accident, transient ischemic attack, unstable angina, myocardial infarction, coronary artery interventions (e.g., coronary artery bypass grafting or

percutaneous coronary interventions [e.g., angioplasty, stent insertion]), or neurovascular interventions (e.g., carotid artery stenting) should be on stable medical therapy for at least 3 months prior to the Screening Visit until the Baseline Visit and anticipated to be stable throughout the study.

7.9.6. Washout of Prior Medications

All consented patients meeting the Screening Visit entry criteria that are taking certain medications (as outlined in Section 7.9.3) will be required to begin wash-out of these medications following the Screening Visit for a minimum of 28 days prior to beginning completion of the Screening Patient Voiding Diary. These medications must not be used from the point of initiation of washout following the Screening Visit, through the Week 12 Visit.

7.10. Patient Voiding Diary

The Patient Voiding Diary is used by participants (via the eDiary or paper Diary) to record the frequency of daily OAB symptoms including all micturitions, urgency, incontinence, and main reason for incontinence by selecting the respective box for each symptom occurring during the course of a given day and night.

The Patient Voiding Diary should be completed by the patient on all of the 7 days prior to the Run-in Visit, Baseline Visit, Week 2 (diary only; no clinic visit), and the Weeks 4, 8, and 12 Visits.

Patients will complete the Patient Voiding Diary between the Screening Visit and Run-in Visit (over the 7 days prior to the Run-in Visit). After the Screening Visit, patients not requiring wash-out can begin the Patient Voiding Diary the morning after the Screening Visit (upon getting up for the day). Patients requiring wash-out of medications can begin completing the Patient Voiding Diary after the 28-day wash-out period.

Patients will also complete the Patient Voiding Diary between the Run-in Visit and the Baseline Visit (over the 7 days prior to the Baseline Visit, while the patient is taking Run-in Study Treatment).

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

A **"Complete Diary Day**" is defined as a Diary Day for which the patient indicates that they have recorded all urinations and any leakages that occurred during that Diary Day. Specifically, on the eDiary the patient will respond Yes to the corresponding item in the Begin Day Questionnaire to indicate that their data are complete for the preceding Diary Day. On the paper Patient Voiding Diary the patient will check Yes in response to the question "Did you record each time you urinated or leaked during this diary day?"

If a subject completes more than the required 7 days of entry in the Diary, only "Complete" Diary Days within 10 days prior to the current visit are used to calculate eligibility.

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

- 5 Complete Diary Days (not necessarily consecutive) during the Screening Period (over the 7 days prior to the Run-in Visit), and
- 4 Complete Diary Days (not necessarily consecutive) 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.

To meet eligibility, patients must meet either the OAB Wet or OAB Dry criteria at the Run-in Visit and then the Baseline Visit, based on their Patient Voiding Diary data. Patients will be randomized to the appropriate stratum based on which criteria are met at the Baseline Visit. When both components are present, the classification is specified as the predominant component.

7.10.1. Patient Voiding Diary Training/Re-Training

All Visits

The site staff should inquire whether patients had any difficulties with the diary and address any questions patients may have.

Instructions for proper completion of the Patient Voiding Diary should be re-reviewed, and, if available, patients may view an instructional video to reinforce their understanding of Patient Voiding Diary instructions.

Patients 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 (e.g., upon getting up for the day).

Run-in and Baseline Visits

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

7.11. Urine Volume Diary

Urine volume data are collected separately by patients using the Urine Volume component of the eDiary, or the paper Urine Volume Chart. The Urine Volume Chart is a tool routinely used in clinical practice and clinical investigation to assess voiding functions over a 24-hour period and is regarded as a useful instrument in the investigation of patients with voiding symptoms. Urine volume may be collected during any one (1) of the 7 Diary Days prior to the visit, 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.

Patients will be asked to complete the Urine Volume Diary to record their urine volume passed during that day. The Urine Volume collection and Urine Volume Diary completion should be performed by the patient on a day that they choose for one (1) complete day of the 7 days prior to

the Run-in Visit, Baseline Visit, and Week 2 (Diary only; no cinic visit), and the Weeks 4, 8, and 12 Visits. The definition of a Diary Day and data entry instructions will be the same as for the Patient Voiding Diary (i.e., the data should be recorded in real time, morning to morning).

7.11.1. Urine Volume Collection Training/Re-Training

At the Screening Visit, all patients will receive detailed instructions on urine volume collection and measurement and/or be provided and review instructions with site staff. The site staff should demonstrate how to measure a volume of water in a sample collection supplies before asking patients to demonstrate their ability to measure a volume of water as practice. At each subsequent visit the site staff should confirm the patient's understanding and ability to measure a volume of water as practice.

Patients should be instructed that on the days the paper Urine Volume Chart Diary is completed:

- Every micturition recorded on the Patient Voiding Diary must have a corresponding entry recorded on the Urine Volume Chart (this is automatically done on the eDiary).
- Every entry recorded on the Urine Volume Chart must have a corresponding micturition recorded on the Patient Voiding Diary (this is automatically done on the eDiary).

Site staff should reinstruct the patient on Urine Volume collection procedures as needed. Instructions for proper completion of the Urine Volume Chart should be re-reviewed, and, if available, patients may view an instructional video to reinforce their understanding of the Urine Volume Chart and collection instructions.

7.11.2. Dispense Urine Collection and Measurement Supplies

The urine collection and measurement container (if needed) are reusable and should be rinsed by patients and reused for the days that they will be collecting their urine volume throughout the study. Patients should be reminded to keep the urine collection container with them during the period of time when urine volume is being collected.

7.12. Reminders for Diary Collection

The site will phone the patient on approximately the first day and the third (or next business days) of the 7 Diary collection days. Patients will be reminded to enter data immediately following each micturition (in real time); they will also be asked to input data from any "missed" events and confirm that data from all micturitions occurring within the preceding 24 hours have been entered at a consistent time each morning (e.g., upon getting up for the day). Patients participating in the PK subset will be reminded to **withhold** Study Treatment on the morning of the study visit for PK sampling (patients in population PK subset only).

Patients may consent to receive additional reminders via SMS text to their personal mobile phone. In addition to visit reminders, these diary completion reminders will be sent the day before each diary collection period begins (to remind patients to start diary completion) and two days prior to the end of each diary collect window (to ensure urine volume collection has been completed prior to the visit).

7.13. Electronic Diary

The Electronic Diary (eDiary) for this study includes both the Patient Voiding Diary, and the Urine Volume Diary, and will be implemented via an eDiary device (provisioned smartphone). Paper diaries will be provided to all patients to be used when necessary. When a paper diary is used, it should be collected at each visit.

7.13.1. eDiary Device Set-Up and Training

Device Setup/Function Check

The eDiary device will be set-up by the site at the Screening Visit and dispensed to the Patient. At each subsequent visit, site personnel will check that the device is functioning correctly. Instructions on how to perform the set-up task will be provided by the Sponsor.

7.13.2. Device Training/Re-Training

Prior to study initiation, site staff will be trained on how to instruct patients on the use of the eDiary. Training materials for site staff, including general instructions and specific questions relating to completion of the eDiary, will be provided to each site and should be used as a guide on how to instruct patients.

At the Screening Visit, site staff will carefully explain the collection of the Patient Voiding Diary and Urine Volume Diary on the eDiary device to patients and will clearly demonstrate how to record the occurrence of urinating in the toilet (micturition), episodes of needing to urinate immediately (urgency), and episodes of accidental urine leakage (incontinence) along with the main reason for leakage. Site staff will answer any questions that patients may have and will instruct patients to call the site with any questions they may have about the eDiary after they have left the clinic. Patients will complete the eDiary for several example situations prior to taking the eDiary home.

At subsequent visits, patients will be reinstructed as needed. Instructions for proper completion of the eDiary should be re-reviewed, and, if available, patients may view an instructional video to reinforce their understanding.

7.14. Patient-Reported Outcomes

Patients will complete paper questionnaires at the site at the start of each required study visit to assess patient-perceived symptom relief, symptom bother, and health-related quality of life at the study visits. These include the following questionnaires:

- Global Impression Items include Patient Global Impression of Severity (PGI-Severity), Patient Global Impression of Control (PGI-Control), Patient Global Impression of Frequency (PGI-Frequency), Patient Global Impression of Leakage (PGI-Leakage), and Patient Global Impression of Change (PGI-Change).
- Overactive Bladder Questionnaire (OAB-q long form [OAB-q LF], 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.

- Work Productivity and Activity Impairment Questionnaire-Urinary Symptoms (WPAI-US), version 2.0, is a 6-item questionnaire that assesses health-related work productivity loss due to urinary symptoms with a 1-week recall period.
- The EQ-5D health questionnaire is a standardized instrument for use as a measure of health outcome [Rabin, 2014]. It is applicable to a wide range of health conditions and treatments; it provides a simple descriptive profile and a single index value for health status.

The Investigator should not provide any additional information to patients prior to completing the questionnaires which might influence responses.

7.15. Post-Void Residual Volume

The risk of acute urinary retention or morbidities related to an increase in Post-Void Residual (PVR) is a concern with antimuscarinic therapy that promotes smooth muscle relaxation by inhibiting acetylcholine-induced smooth muscle contraction. If, during contraction, the bladder cannot generate enough pressure to overcome the outlet resistance in the urethra, either because of poor detrusor contractility or profound obstruction (most commonly from BPH), acute urinary retention or incomplete emptying of the bladder may result.

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 patients with an increase in PVR for an adverse event.

PVR will be performed via ultrasound at the visits indicated in the Schedule of Activities (Table 1). All efforts will be made to ensure the same device and operator are used for all PVR volume measurements for individual patients.

7.16. Physical Examination

Complete physical examinations will include a digital rectal examination for men at the Screening Visit to confirm entry criteria.

Focused physical examinations will be performed at the Run-in and Follow-up Visit and will include examination of heart, lungs, abdomen, and pelvic exam (only as needed to confirm prolapse), as well as any other organ system in which a previous abnormality was noted at Baseline or relates to a patient complaint of an adverse event.

7.17. Electrocardiogram

A single twelve-lead ECG will be performed at the Screening Visit and may be performed, as clinically indicated, at an Unscheduled Visit.

ECG should be performed after 10 minutes of rest in a semi-recumbent position.

7.18. Vital Signs

Vital signs including blood pressure, heart rate, respiration rate, and temperature (oral or tympanic) will be obtained at all visits after patients have rested quietly in a sitting position for 5 minutes.

Three blood pressure measurements will be taken in a sitting position and performed on the same arm and by the same site staff, if possible, for each patient throughout the study. The following instructions should be followed:

- Sitting systolic and diastolic blood pressures will be determined by averaging 3 replicate measurements obtained 1 to 2 minutes apart. The average of the 3 replicate blood pressure measurements will be used for eligibility and safety assessments (not an individual value).

The same method for assessing temperature should be used at all visits for a particular patient.

Body weight will be measured with patients in street clothing with jacket/coat and shoes removed.

Standing height will be measured without shoes at Screening only.

7.19. Adverse Events

Spontaneously reported adverse events will be recorded at each visit. The Investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an adverse event or serious adverse event. See Section 8 for details on adverse event definitions and reporting.

7.20. Clinical Laboratory Assessments

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per patient can be found in Appendix C.

Please refer to the Schedule of Activities (Table 1) for specific laboratory tests performed at each study visit.

7.20.1. Chemistry, Hematology, and Urinalysis (Laboratory Safety Evaluations)

Laboratory tests for chemistry, hematology, and urinalysis are specified in Table 5. Patients do not need to fast prior to laboratory safety tests.

Analysis of hematology and chemistry will be performed by the central laboratory chosen by the Sponsor. A urine dipstick and urine pregnancy test (for women of childbearing potential) will be performed at the site (supplied by the central laboratory). A sample for urinalysis (including microscopy [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 patient reports symptoms that are suggestive of a uriary tract infection at any visit, a urine dipstick should be performed and a sample sent for urinalysis and culture, as needed.

If all laboratory values are within the normal reference range, the patient may continue to be evaluated for study entry. If one or more values fall outside the normal range, the Investigator may either exclude the patient from the study or investigate further to determine clinical

relevance. Please refer to Appendix B for an algorithm for assessing out-of-range laboratory values.

Table 5: Laboratory Tests

Hematology	Chemistry	Urinalysis[a]	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[b]
Hemoglobin	Alkaline phosphatase	Glucose	
Platelet count	Alanine aminotransferase (ALT)	Protein	
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	
RBC	Bicarbonate	Microscopic exam, (RBCs, WBCs, epithelial cells, and bacteria)	
	Calcium	pH	
	Chloride	Color	
	Creatinine[c]	Urine pregnancy test (β-hCG)	
	Glucose (fasting or non-fasting)		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin[d]		
	Blood Urea Nitrogen		
	Total Cholesterol		

a. A sample for urinalysis and urine culture will be sent to the central laboratory only if the urine dipstick performed at the site tests positive for the presence of leukocytes, nitrites, or blood cells.
b. Urine β-hCG will be tested for women of childbearing potential only. If urine β-hCG is positive, a serum β-hCG must be performed.
c. eGFR will be calculated and reported by the central lab.
d. If total bilirubin is elevated above the upper limit of normal.

7.20.2. Urine β-hCG

Women of childbearing potential only must have a urine β-hCG pregnancy test at each study visit indicated on the Schedule of Activities (Table 1). A urine pregnancy test (supplied by the central laboratory) will be performed at the site. A positive urine β-hCG test must be followed up with a serum β-hCG pregnancy test. A positive pregnancy test prior to randomization requires exclusion. A positive urine β-hCG test after randomization requires immediate interruption of Study Treatment until a serum β-hCG is performed and found to be negative. Patient must be discontinued from the study and followed if pregnancy is confirmed by a positive serum β-hCG.

7.21. Dispense Single-Blind Run-in Study Treatment

At the Run-in Visit, single-blind Study Treatment will be dispensed to patients, as described in Section 6.

7.22. IxRS Randomization to Study Treatment

A unique [redacted] patient number will be allocated to each subject during the Screening Visit using the IxRS. The identifier will consist of [redacted]. The patient number identifies the patient for all procedures occurring after screening. Once a patient number is assigned to a patient, it can never be re-assigned to another patient.

At the Baseline Visit, all eligible patients will be randomly allocated to double-blind Study Treatment using IxRS.

7.23. Dispense Double-Blind Study Treatment

At the Baseline, Week 4, and Week 8 Visits, double-blind Study Treatment will be dispensed to patients, as described in Section 6, and according to their randomized treatment assigned per IxRS.

7.24. Study Treatment Return/Accountability Review

Patients should bring all unused study drug to each study visit. A complete tablet/capsule count will be performed, and results will be recorded as the primary source of patient Study Treatment compliance. Tablet/capsule counts will also be recorded in the IxRS. All patients should be reinstructed regarding dosing compliance during study visits. The authorized study personnel conducting the re-education must document the process in the patient's source records.

7.25. Administer Witnessed Dose of Study Treatment

Study treatments will be taken as a witnessed dose as described in Section 6.2.

7.26. Pharmacokinetic (PK) Sampling (PK Subset Only)

7.26.1. Pharmacokinetic Sample Collection

PK sampling will be conducted in a sub-population of patients (approximately 30% of the total study population) at selected sites for assessment of the effect of demographic covariates by population PK analysis. The patient must consent to participate in PK sampling.

PK samples should be collected during the clinic visit after all other study assessments have been completed.

Pre-dose PK samples will be collected at three visits: Week 4, Week 8, and Week 12. The time of last dose of study medication (taken the day prior to the visit) should be recorded.

Details regarding the collection procedure, handling, storage, and shipment of these samples will be provided by the central laboratory.

Continuation into Extension Study

Patients who complete the Week 12 Visit may be offered the opportunity to enroll in a 40-week double-blind extension study (RVT-901-3004), which will be conducted under a separate protocol, until enrollment in that study is complete.

Participation in the extension study is separate from this study and is optional. Patients will provide separate informed consent to participate in the extension study.

7.27. Follow-up Visit

For patients who do not enroll in the optional extension study (RVT-901-3004), the Follow-up Visit should be performed 28 days after the patient's last dose of Study Treatment to collect information about any serious adverse events that occurred during this period. For a patient who discontinues Study Treatment early, the Follow-up Visit should occur 28 days after the last dose of Study Treatment. However, if the discontinuation visit occurs ≥ 28 days after the patient's last dose of Study Treatment, that visit will serve as the Follow-up Visit. Safety labs may be collected for the evaluation of adverse experiences during discontinuation at the discretion of the Investigator.

8. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), and clinical laboratory tests.

8.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event 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 a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- A new condition detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (e.g., for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately);
- An investigational abnormality (e.g., laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the Investigator based on at least one of the following criteria:
  - Induces clinical signs or symptoms;
  - Requires active intervention;
  - Requires interruption or discontinuation of Study Treatment.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication.
- Events that **do not** meet the definition of an adverse event include:
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition;
- Medical or surgical procedure (e.g., endoscopy, appendectomy) should be entered into the eCRF. If not planned prior to signing the informed consent, the condition that leads to the procedure is reported as an adverse or serious event, as appropriate.

Periodic procedures for routine maintenance of a medical device should not be considered associated with an adverse event (e.g., expected change of a stent);

- Situations where an untoward medical occurrence did not occur (e.g., planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent; 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.

Adverse events that occur during the study should be evaluated by the Investigator and assessed for causal relationship to Study Treatment and severity, as described in Section 8.4 and Section 8.5. Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous". Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of Study Treatment are permitted; however, Study Treatment can be held for a period of up to 21 days for evaluation and treatment of an adverse event. The Study Treatment may be restarted if deemed safe for the patient by the Investigator.

8.2. Definition of a Serious Adverse Event

If an event is not an adverse event per Section 8.1, then it cannot be a serious adverse event if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc.). A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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 hospitalization or prolongation of existing hospitalization
   NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. 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 adverse event should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity
   NOTE: 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 (e.g., sprained ankle) which may

interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether 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 patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment 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.

8.3. Adverse Event Reporting

The Investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an adverse event or serious adverse event.

The reporting of serious adverse events by the sponsor (Urovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the Investigator to report serious adverse events to their local IRB, REB, or IEC, as required by their local IRB/REB/IEC requirements.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

The patient's eDiary entries and responses to questionnaires used in the study will not be used as a primary means to collect adverse events however, they should be reviewed by the study site personnel and the study monitors. Should the Investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals and followed until the event resolves, becomes stable or chronic, or the patient is deemed lost to follow-up. At the conclusion of the study, the Investigator and medical monitor will assess unresolved adverse events and determine if additional/continued follow-up is warranted.

All adverse events, whether related to the Study Treatment or not, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded

on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the Investigator should record each sign and symptom as an individual adverse event.

Reporting for overdose and for pregnancy in the patient or patient's partner will be reported as described in Section 8.3.3 and Section 8.7, respectively.

8.3.1. Period for Reporting Adverse Events

Adverse events and serious adverse events will be collected from the time a patient provides informed consent to participate in the study until the Follow-up Visit is completed approximately 28 days after the last dose of Study Treatment or the date of initiation of another investigational agent, an alternate therapeutic drug for overactive bladder, or surgical intervention for overactive bladder, whichever occurs first. Serious adverse events reported to the Investigator after the safety reporting period should be reported to the sponsor if the Investigator assesses the event as related to the Study Treatment.

Reporting instructions for serious adverse events are provided in Section 8.3.2.

8.3.2. Reporting Serious Adverse Events

All serious adverse events 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 Treatment.

The event term, start date, severity, and initial causality assessment must be entered in the Adverse Event 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 review.

The initial serious adverse event report should include:

- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity); and
- Causal relationship to the Study Treatment.

A discharge summary should be provided for all hospitalizations. If the patient 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 Treatment, as well as the autopsy findings, if available.

Do not delay reporting a suspected serious adverse event to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report.

All patients who experience a serious adverse event will be evaluated at appropriate time intervals and followed until the event resolves, becomes stable or chronic, or the patient is deemed lost to follow-up. Serious adverse events reported to the Investigator after the safety

reporting period should be reported to the sponsor if the Investigator assesses the event as related to the Study Treatment.

8.3.3. Study Treatment Overdose Management

The medical monitor must be contacted in the event of any Study Treatment overdose.

An overdose is defined as a known deliberate or accidental administration of Study Treatment, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of vibegron or placebo > 2 tablets and any dose of tolterodine or placebo > 2 capsules within a 24-hour window (i.e., > 2 tablets and/or > 2 capsules of blinded Study Treatment within a 24-hour window) is an overdose. There is no known antidote for an overdose.

In the event of an overdose, the Investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- Report all overdose events within 24 hours of awareness by the study site, using a serious adverse event form according to Section 8.3.2, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for PK analysis within 2 days from the date of the last dose of Study Treatment if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the Investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

8.4. Assigning Causal Relationship to Study Treatment

The reasonable possibility of the relationship of an adverse event to Study Treatment is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to Study Treatment:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, or that follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).
- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or

in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether related to Study Treatment or not, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, the primary reason for withdrawal (i.e., due to an adverse event) must be recorded on the eCRF as such.

8.5. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The Investigator must determine the severity of each adverse event according to the criteria in Table 6.

Table 6 Criteria for Determining the Grade/Severity of Adverse Event Terms

Grade	Criteria
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

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

8.6. Adverse Events of Clinical Interest

Selected non-serious and serious adverse events will be reported as Adverse Events of Clinical Interest (AECI) and must be reported **within 24 hours of the study site personnel's knowledge of the event** as an AECI by marking the appropriate box on the AE eCRF form and assigning the most appropriate category. Additional information requested should be provided as directed in the eCRF Completion Guidelines (eCCGs).

AECIs that also meet the definition of a serious adverse event must be reported as a serious adverse event, as described in Section 8.3.2.

Adverse Events of Clinical Interest for this study include:

- Potential Major Adverse Cardiac and Cerebrovascular Events (MACCE), which will be adjudicated by an independent external expert clinical adjudication committee (CAC) into the following categories according to the definitions in the CAC Charter:
  - Death or any event with fatal outcome
  - Myocardial infarction / Heart Attack
  - Cerebrovascular Accident / Stroke
  - Hospitalization for Unstable Angina / Chest Pain
  - Hospitalization for Heart Failure
  - Coronary revascularization / Angioplasty / Stent
- Hypertension:

  An adverse event of hypertension should be reported and will be an AECI as follows:
  - For patients without hypertension (average SBP <140 mmHg, DBP <90 mmHg) at baseline, at two consecutive visits, the average of three systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg (or both); at 2 consecutive visits in patients who were not hypertensive at baseline; or,
  - For patients with hypertension at baseline, an increase compared to baseline at 2 consecutive visits in the average of three SBP by ≥20 mmHg OR DBP by ≥10 mmHg;
  - Initiation of, or increase in dose of, medication for treatment of hypertension in any patient.
- Adverse events consistent with orthostatic hypotension as confirmed by orthostatic vital signs.
- Adverse events suggestive of cystitis or urinary tract infection.
- Elevated AST or ALT lab value requiring that study drug be temporarily withheld or permanently discontinued (see Section 8.6.1 and Section 8.6.2).

Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. Study site guidance for assessment and follow up of these criteria can be found in the Study Reference Manual.

8.6.1. 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 AECI 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 the following liver test abnormalities develop, Study Treatment should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- 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 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.

8.6.2. 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 (i.e., potential severe drug-induced liver injury/Hy's law case):

1. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
2. AST or ALT increases to ≥ 3 x ULN; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. 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 (e.g., 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; or
   - 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 Treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

8.7. Pregnancy Management and Reporting to the Sponsor

If any patient or female partner of a patient becomes pregnant during the study, the site must discontinue the patient from Study Treatment immediately and have the patient return for an Early Withdrawal Visit (Week 12 Visit activities). The Investigator must inform the patient of their right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

In the case of a pregnant patient, if she agrees, the Investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment (blinded or unblinded, as applicable).

In the case of a male patient 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.

A pregnancy is to be reported to the sponsor **within 24 hours of awareness** by the study site personnel, using the pregnancy reporting forms and the contact information in Section 8.3.2. 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.

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.

8.8. Benefit/Risk Assessment

Patients may not expect to receive direct benefit from treatment during participation, as this study is designed to provide information about the safety and effectiveness of an investigational medicine compared to placebo. Some patients will receive tolterodine, an approved medication for treating overactive bladder with symptoms of urinary frequency, urgency, and leakage.

Additional details about vibegron may be found in the current vibegron Investigator's Brochure (IB) and Informed Consent documents.

9. STATISTICAL CONSIDERATIONS

This section contains a brief summary of the statistical analyses for this study; full details shall be provided in the Reporting and Statistical Analysis Plan.

9.1. Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the designee of the Sponsor.

The study will be conducted as a double-blind study. The randomized allocation schedule will be generated by an external vendor, and implemented by the vendor of the study IxRS.

At the end of the study (including the period of 28 days follow-up), the official, final database will be frozen and unblinded after medical/scientific review has been performed, and data have been declared final and complete. A Reporting and Statistical Analysis Plan will be approved prior to data being unblinded. A clinical study report will be prepared after all patients complete the study.

9.2. Hypotheses

9.2.1. Primary Objective and Hypotheses

The primary objective will be to demonstrate superiority of vibegron 75 mg over placebo in patients with OAB based on the co-primary endpoints of the average change in daily micturitions and the average change in daily UUI episodes from baseline to Week 12. The co-primary statistical hypotheses are listed below:

- **Co-Primary Hypothesis 1**: In patients with OAB, vibegron 75 mg will have a different average change from baseline (CFB) in the number of daily micturitions than placebo at Week 12.
- **Co-Primary Hypothesis 2**: In patients with OAB Wet, vibegron 75 mg will have a different average CFB in the number of daily UUI episodes than placebo at Week 12.

9.2.2. Key Secondary Objectives and Hypotheses

(1) **Objective**: To evaluate the efficacy of vibegron in reducing the average number of urgency episodes from baseline compared with placebo at Week 12 in all patients with OAB.

Hypothesis: In patients with OAB, vibegron 75 mg will have a different average change from baseline in the number of urgency episodes than placebo at Week 12.

(2) **Objective**: To evaluate the efficacy of vibegron in proportion of patients with at least 75% reduction from baseline in the average number of daily UUI episodes compared with placebo at Week 12 in patients with OAB Wet.

Hypothesis: In patients with OAB Wet, vibegron 75 mg will have a different proportion of patients attaining at least 75% reduction from baseline in the average number of daily UUI episodes than placebo at Week 12.

(3) **Objective**: To evaluate the efficacy of vibegron in proportion of patients with at least 100% reduction from baseline in the average number of daily UUI episodes compared with placebo at Week 12 in patients with OAB Wet.

Hypothesis: In patients with OAB Wet, vibegron 75 mg will have a different proportion of patients attaining at least 100% reduction from baseline in the average number of daily UUI episodes than placebo at Week 12.

(4) **Objective**: To evaluate the efficacy of vibegron in proportion of patients with at least 50% reduction from baseline in the average number of daily urgency episodes compared with placebo at Week 12 in patients with OAB.

Hypothesis: In patients with OAB, vibegron 75 mg will have a different proportion of patients attaining at least 50% reduction from baseline in the average number of daily urgency episodes than placebo at Week 12.

(5) **Objective**: To evaluate the efficacy of vibegron in reducing the average number of total incontinence episodes from baseline compared with placebo at Week 12 in all patients with OAB Wet.

Hypothesis: In patients with OAB Wet, vibegron 75 mg will have a different average change from baseline in the number of total incontinence episodes than placebo at Week 12.

(6) **Objective**: To evaluate the efficacy of vibegron in improving quality of life from baseline, the average change from baseline in the Coping Score from the OAB-q LF (1-week recall) will be compared with placebo at Week 12 in all patients with OAB.

Hypothesis: In patients with OAB, vibegron 75 mg will have a different average change from baseline in the Coping Score from the OAB-q LF (1-week recall) than placebo at Week 12.

(7) **Objective**: To evaluate the efficacy of vibegron in change in the average volume voided per micturition from baseline compared with placebo at Week 12 in all patients with OAB.

Hypothesis: In patients with OAB, vibegron 75 mg will have a different average change from baseline in the average volume voided per micturition than placebo at Week 12.

The assessments of superiority of vibegron 75 mg over placebo on the additional secondary endpoints will also be performed and details will be provided in the Reporting and Statistical Analysis Plan.

9.3. Analysis Endpoints

Efficacy, safety, and exploratory endpoints that will be evaluated for within- and/or between-treatment differences are listed below. The descriptions of the endpoints and time points at which they are measured are described in Section 3 and Table 1 (Schedule of Activities), respectively.

No formal comparisons of vibegron vs. tolterodine are planned; all between-treatment analyses between these two groups will be considered descriptive.

9.3.1. Efficacy Endpoints

In describing the efficacy variables of interest below, the descriptions are restricted to the primary time point of interest at Week 12 in the study. However, many variables are measured at additional time points, as indicated in the Schedule of Activities, and will be analyzed at other time points.

Co-Primary Efficacy Endpoints:

- Change from baseline (CFB) at Week 12 in average number of micturitions per 24 hours in all OAB patients
- CFB at Week 12 in average number of UUI episodes per 24 hours in OAB Wet patients

For the purpose of this study, the number of micturitions will be defined as the number of times a patient has voided in the toilet as indicated on the Patient Voiding Diary. Average daily micturitions are calculated using the daily entries in the Patient Voiding Diary, which is completed over the 7 days prior to each study visit. Average daily number of micturitions will be calculated as the total number of micturitions that occur on a Complete Diary Day divided by the number of Complete Diary Days in the Patient Voiding Diary. A complete diary day requires confirmation by the patient in the Patient Voiding Diary that all voids and leakages have been recorded for the diary day. Baseline is defined as the average number of micturitions occurring during the last evaluable diary prior to the Baseline Visit.

The number of UUI episodes will be defined as the number of times a patient has checked "urge" as the reason for accidental urine leakage. Average daily UUI episodes at each study visit will be calculated in the same manner as described above for the micturition endpoint. The UUI endpoint will be analyzed using only OAB Wet patients.

Key Secondary Efficacy Endpoints:

- CFB at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients
- Percent of OAB Wet patients with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12
- Percent of OAB Wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12
- Percent of all OAB patients with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Week 12

- CFB at Week 12 in average number of total incontinence episodes over 24 hours in OAB Wet patients
- CFB at Week 12 in Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB patients
- CFB at Week 12 in average volume voided per micturition in all OAB patients

Additional Secondary Efficacy Endpoints:

- CFB at Week 12 in HRQL Total Score from the OAB-q LF (1-week recall) in all OAB patients
- CFB at Week 12 in Symptom Bother Score from the OAB-q-LF (1-week recall) in all OAB patients
- Percent of all OAB patients with average number of micturitions < 8 per 24 hours at Week 12
- Percent of OAB Wet patients with at least a 50% reduction from baseline in total incontinence episodes per 24 hours at Week 12
- CFB at Week 12 in overall bladder symptoms based on PGI-Severity in all OAB patients
- CFB at Week 12 in overall control over bladder symptoms based on PGI-Control in all OAB patients

Exploratory Endpoints:

9.3.2. Safety Endpoints

Safety and tolerability will be assessed via clinical review of all relevant safety parameters including clinical adverse events, clinical laboratories, vital signs, and physical examinations that occurred during the respective study period.

9.4. Analysis Populations

9.4.1. Efficacy Analysis Populations

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

The following FAS populations are defined in the study:

- Full analysis set (FAS): all randomized OAB patients who took at least one dose of double-blind Study Treatment and have at least one evaluable change from baseline micturition measurement
- Full analysis set for incontinence (FAS-I): all randomized OAB Wet patients who took at least one dose of double-blind Study Treatment and have at least one evaluable change from baseline UUI measurement

The Per-Protocol population (PP) and Per-Protocol population for incontinence (PP-I) exclude patients due to important deviations from the protocol that may substantially affect the results of

the primary efficacy endpoints. A supportive analysis using the Per-Protocol populations will be performed for the co-primary and key secondary efficacy endpoints. The final determination on protocol violations, and thereby the composition of the Per-Protocol population, will be made prior to the unblinding of the database and will be documented in a separate memo.

Patients will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS and Per-Protocol populations.

9.4.2. Safety Analysis Populations

The Safety Set (SAF) will be used for the analysis of safety data in this study. The SAF consists of all patients who received at least one dose of Study Treatment. Patients will be included in the treatment group corresponding to the Study Treatment they actually received for the analysis of safety data using the SAF population. For most patients this will be the treatment group to which they are randomized.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of Study Treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a Baseline measurement is also required.

No imputation will be performed for missing safety data. Baseline will be defined as the last non-missing value before treatment.

9.4.3. Pharmacokinetic Population

The PK population will include all subjects in the Safety Set who undergo plasma PK sampling and have evaluable PK assay results.

9.5. Statistical Methods

Statistical testing and inference methods for safety and efficacy analyses are described below. Efficacy results that will be considered statistically significant after consideration of the strategy for controlling the Type I error are described in Section 9.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (two-sided) level.

9.5.1. Statistical Methods for Efficacy Analyses

9.5.1.1. Primary Efficacy Endpoints

For the analysis of the co-primary endpoints (change from baseline in average number of daily micturitions at Week 12 and change from baseline in average number of daily urge urinary incontinence episodes at Week 12), a mixed model for repeated measure (MMRM) with restricted maximum likelihood estimation will be used. This model corrects for dropout and accounts for the fact that measurements taken on the same patient over time tend to be correlated by using all available information on patients within the same covariate set to derive an estimate of the treatment effect for a dropout-free population. The analysis model for each efficacy endpoint will include terms for treatment, visit, OAB Type (Wet vs Dry), Sex (Female vs Male), Region (US vs Rest of World), baseline score, and interaction of visit by treatment.

Primary inferences will be drawn from treatment differences for the changes from baseline derived from the MMRM models at Week 12. As part of secondary objectives, the treatment differences for each post baseline visit will also be derived using the same MMRM model. The estimated treatment difference for at each visit will be displayed in the summary of statistical analysis together with the 95% confidence interval and the associated p-value.

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

9.5.1.2. Sensitivity Analyses

9.5.1.3. Secondary Efficacy Endpoints

The change from baseline efficacy endpoints will be analyzed using the same MMRM model described for co-primary endpoints.

Analysis of the efficacy endpoints of proportion of patients with at least 75% reduction or a 100% reduction in the average number of daily UUI episodes at Week 12 and proportion of patients with at least 50% reduction in the average number of daily urgency episodes at Week 12 will be analyzed using the Cochran-Mantel-Haenszel risk difference estimate. Missing Week 12 data will be analyzed using multiple imputation. 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 OAB Type (Wet vs Dry) and Sex (Female vs Male), with weights proposed by Greenland and Robins. Further details will be provided in the SAP.

9.5.1.4. Exploratory Efficacy Endpoints

[redacted]

9.5.2. Statistical Methods for Safety Analyses

Safety analyses will be conducted using the SAF and summarized by treatment group as treated. The treatment-emergent period will be defined as the period of time from the first dose date of the double blinded Study Treatment through 28 days after the last dose of Study Treatment, or the date of initiation of another investigational agent or surgical intervention or rollover to the extension study, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, and clinical laboratory evaluations.

The severity of all adverse events will be evaluated by the Investigator as described in Section 8.5. All adverse events will be coded to preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA) 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to Study Treatment, and severity.

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

Vital signs parameters, including temperature, will be listed and summarized by visit.

9.5.3. PK Analysis

Plasma concentrations will be listed and summarized by study visit and treatment group.

Pharmacokinetic parameters for RVT-901 for each subject may be estimated via nonlinear mixed effect modeling using a population PK model and described in a separate report.

9.6. Multiplicity

A stepwise gate-keeping procedure will be used to control the overall Type-I error rate at α=0.05 level (two-sided) over the co-primary and key secondary hypotheses. If both co-primary endpoints are achieved, then the key secondary endpoints will be tested sequentially in the predefined order given in Section 9.2. If statistical significance is achieved at all previous key secondary endpoints, the next sequential key secondary endpoint will be tested. Once a key secondary endpoint is found to be insignificant (i.e. p-value $\geq$ 0.05), the testing procedure will stop. For all subsequent key secondary endpoints, nominal p-values will be provided.

All other efficacy endpoints will be considered supportive and no multiplicity adjustments will be performed for these other efficacy endpoints. Nominal p-values will be computed for other efficacy endpoints as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the (two-sided) α=0.05 level of significance.

9.7. Sample Size Determination

Approximately 1,400 patients will be randomized in a 5:5:4 ratio to receive one of the following Study Treatments:

- Vibegron 75 mg + placebo to match tolterodine ER 4 mg;
- Placebo to match vibegron 75 mg + placebo to match tolterodine ER 4 mg; or
- Tolterodine ER 4 mg + placebo to match vibegron 75 mg

Approximately 500 patients will be assigned to the vibegron and placebo treatment groups, and approximately 400 patients will be assigned to the tolterodine treatment group. Assuming that a total of 10% patients will discontinue prior to Week 12 (for any reason), there will be approximately 450 evaluable patients in the vibegron and placebo treatment groups at the end of Week 12. Assuming 75% of the population will have OAB Wet, there will be approximately 337 evaluable patients in the vibegron and placebo treatment groups for the incontinence endpoints. The study has:

- Approximately 98% power to detect a true underlying between-group treatment difference of 0.6 in change from baseline in micturitions at a two-sided 0.05 level assuming a variability estimate of 2.20 based on vibegron Study 008 data.
- Approximately 98% power to detect a true underlying between-group treatment difference of 0.51 in change from baseline in urge urinary incontinence at a two-sided 0.05 level assuming a variability estimate of 1.68 based on vibegron Study 008 data.

Assuming that these endpoints are uncorrelated, then this study has 96% power to reject both co-primary hypotheses.

9.8. Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% confidence interval [CI]) for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- Region (US vs. Rest of World)
- Age category (< 40, ≥ 40 to < 55, ≥ 55 to < 65, ≥ 65 to 75, ≥ 75 years)
- Age category (< 65, ≥ 65 years)
- Race (white vs. other)
- Sex (female vs. male)
- Prior OAB therapy (naïve vs. non-naïve)
- OAB Type (OAB Wet vs. OAB Dry)

For each subgroup, the primary MMRM model will be fit including a subgroup by treatment interaction term and model results will be presented. The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

9.9. Interim Analyses

There is no planned interim analysis for efficacy.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Financial Disclosure

Financial disclosure requirements are outlined by the US Code of Federal Regulations Title 21, Part 54 (21 CFR 54), Financial Disclosure by Clinical Investigators. It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the Investigator's and Sub-Investigator's responsibility to comply with any such request.

This is a "covered clinical study", defined under 21 CFR 54 as "any study of a drug or device in humans submitted in a marketing application or reclassification petition patient to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single Investigator makes a significant contribution to the demonstration of safety." As such, all Investigators and Sub-Investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any Sub-Investigator. The Investigator and Sub-Investigator agree to notify the Sponsor of any change in reportable interests during the study and for 1 year following completion of the study.

10.2. Pre-Initiation Visit

Sponsor personnel or designee(s) may visit the study site as necessary prior to initiation of the study to review information about the Study Treatment, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

10.3. Data Management

Patient data will be entered into a Sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the Sponsor or designee.

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 (e.g., errors will be corrected and inconsistencies clarified).

Adverse events and concomitant medications terms will be coded using the most current versions of the MedDRA (i.e., 20.0 or higher) and the World Health Organization Drug Dictionary Enhanced (WHO-DDE), respectively.

The Investigator will retain original source documents and the Sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the Sponsor.

10.4. Monitoring

This study will be monitored by the Sponsor (or designee) in accordance with current GCP regulations. By signing this protocol, the Investigator grants permission to the Sponsor (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to verify the accuracy of data collected in the eCRF, the monitor will require direct access to original source documents (e.g., patient records, patient charts, and laboratory reports).

During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness, and accuracy of all eCRF entries, and to meet with the Investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.5. Auditing or Inspections

Representatives of regulatory authorities, health authorities, the Sponsor, or IRB/REB/IEC's may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the Sponsor's medical monitor immediately. By signing this protocol, the Investigator agrees to provide to appropriately qualified personnel from such groups, access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.6. Study Oversight Committees

10.6.1. Clinical Adjudication Committee

As noted in Section 8.6, MACCE event diagnosis will be adjudicated by an independent external expert committee.

10.6.2. Steering Committee

A Steering Committee may be formed, if deemed necessary. If formed, the committee will be comprised of both Sponsor and non-Sponsor scientific experts who will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignments and all unblinded data until the database is officially locked and unblinded.

10.7. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB/REB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The Investigator must not deviate from the protocol without first obtaining approval from the Sponsor and the IRB/REB/IEC, if required. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, then notify the Sponsor (or designee) and the IRB/REB/IEC immediately regarding the type of emergency and the course of action taken. The Investigator must notify the Sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB/REB/IEC, and all patients on treatment will again provide informed consent.

10.8. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRB/REB/IEC. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the study participants' interests.

10.9. Publications

After conclusion of the study and without prior written approval from the Sponsor, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of the Sponsor in an abstract, manuscript, or presentation form; or

The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Urovant Sciences GmbH confidential information (see Section 10.10.5).

The Investigator will submit to the Sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The Investigator will comply with Sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

10.10. Investigator-Specific Responsibilities

10.10.1. Compliance with Regulations and Ethical Standards

The Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States investigational new drug application, the Investigator will ensure that the basic principles of GCP, as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

The Investigator will also comply with financial disclosure requirements as described in Section 10.1.

10.10.2. Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.10.3. Institutional Review Board/Independent Ethics Committee Requirements

The protocol, protocol amendments, informed consent form, IB, and any other relevant materials, including accompanying material to be provided to the patient (e.g., 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; and
- Date on which the committee met and granted the approval.

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

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/REB/IEC's annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/REB/IEC;
- Notifying the IRB/REB/IEC of serious adverse events or other significant safety findings as required by procedures established by the IRB/REB/IEC.

10.10.4. **Informed Consent**

The Investigator (or designee) is responsible for obtaining written informed consent from each study participant prior to any study activities. To help the individual make an informed decision about participating, the Investigator (or designee) shall discuss with the potential participant the purpose of the research, procedures, risks, benefits, alternative options to participating, confidentiality, how to contact study personnel, and the patient's rights. Potential participants must be informed that their participation is voluntary and must be given ample time to ask the Investigator questions and obtain clarifications regarding the study prior to providing consent.

The Investigator must utilize an IRB/REB/IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

As described in Section 10.7, patients must be re-consented to participate in the study if a protocol amendment is made that substantially alters the study design or the potential risks or burden to patients.

10.10.5. **Confidentiality**

The Investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number (i.e., not names) and date of birth (as allowed) should be recorded on any form or biological sample submitted to the Sponsor, IRB/REB/IEC, or laboratory. The Investigator must keep a Screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The Investigator agrees that all information received from the Sponsor, including, but not limited to, the IB, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.10.6. **Study Files and Retention of Records**

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

Investigator's study file. The Investigator's study file will contain the IB, protocol/amendments, IRB/REB/IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.

Patient clinical source documents. The required source data should include the following for each patient:

- Patient identification (name, date of birth, sex);
- Documentation that the patient meets eligibility criteria, (e.g., history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
- Participation in the study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of Study Treatment (drug dispensing and return should be documented as well);
- Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the Investigator);
- Concomitant medication (including start and end date); and
- Date of study completion and reason for early discontinuation, if applicable.

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 (i.e., 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.

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/REB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.10.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the Investigator or Sub-Investigator (as appropriate) listed on Food and Drug Administration Form 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization Screening Period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.10.8. Investigational Product Accountability

The Investigator or Investigator's designee (e.g., pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused Study Treatment (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Number, and the initials of the person dispensing the Study Treatment.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the Sponsor requirements. Drug may be returned (by the monitor) or destroyed on-site, if appropriate per site standard operating procedures (SOPs). At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused Study Treatment supplies, including empty containers, according to these procedures. If the site cannot meet the Sponsor's requirements for disposal, arrangements will be made between the site and the Sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.11. Sponsor-Specific Responsibilities

10.11.1. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.11.2. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

11. REFERENCES

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APPENDICES

APPENDIX A. LIST OF ABBREVIATIONS

Term	Description
AE	adverse event
AECI	Adverse Events of Clinical Interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adrenergic receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-24	area under the concentration-time curve from time 0 to 24 hours
BP	blood pressure
BPH	benign prostatic hypertrophy
bpm	beats per minute
CAC	clinical adjudication committee
cAMP	cyclic adenosine monophosphate
CFB	change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum concentration
CT	computerized tomography
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 dimension
ER	extended release
EU	European Union
FAS	full analysis set

Term	Description
FAS-I	full analysis set for incontinence
FDA	(United States) Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
HRQL	health-related quality of life
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	institutional ethics committee
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IxRS	interactive voice or web response system
LF	long form
LFT	liver function tests
LOCF	last observation carried forward
MACCE	major adverse cardiovascular and cerebrovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measure
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect level
NVU	nighttime voids associated with urgency
OAB	overactive bladder
OAB-q	Overactive Bladder Questionnaire
OAB-q LF	Overactive Bladder Questionnaire Long Form
PD	pharmacodynamic(s)
PDE 5	phosphodiesterase type 5
PGI	Patient Global Impression
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PP	per-protocol population
PP-I	per-protocol population for incontinence
PRO	patient-reported outcome(s)

Term	Description
PVR	patient void residual
QD	once daily
QTc	corrected QT
RBC	red blood cell
REB	research ethics board
REML	restricted (or residual) maximum likelihood
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SOP	standard operating procedures
t1/2	half-life
TIA	transient ischemic attack
Tmax	time to reach maximum concentration
tQT	thorough QT
ULN	upper limit of normal
Urovant	Urovant Sciences GmbH
US	United States
UTI	urinary tract infection
UUI	urge urinary incontinence
WBC	white blood cell
WHO-DDE	World Health Organization Drug Dictionary Enhanced
WPAI-US	Work Productivity and Activity Impairment Questionnaire-Urinary Symptoms
β3-AR	beta-3 adrenergic receptor
β-AR	beta adrenergic receptor
β-hCG	beta-human chorionic gonadotropin

APPENDIX B. ALGORITHM FOR ASSESSING LABORATORY VALUES

For all laboratory values obtained at pre-study evaluation:

1. If all values are normal, the patient may enter the study.
2. If a value is outside the normal range, the following choices are available:
   - The patient may be excluded from the study;
   - The abnormal test may be repeated.
   - The result may be deemed "Not Clinically Significant" and the patient may be enrolled in the study.
3. If the Investigator decides to repeat an abnormal test and if it is within the normal range, the patient may enter the study.
4. If the Investigator decides to repeat an abnormal test and if the repeat test is still abnormal, the Investigator will evaluate the potential patient with a complete history and physical examination, looking especially for diseases that could result in an abnormality in the laboratory value in question. If such diseases can be excluded, and if the Investigator feels that the abnormal laboratory value is not clinically relevant, then the patient may enter the study. The Urovant clinical monitor will be included in the decision of whether or not to enroll the patient in the study.
5. If there is any clinical uncertainty regarding the significance of an abnormal value, the patient will be excluded from the study.

APPENDIX C. APPROXIMATE BLOOD/TISSUE VOLUMES DRAWN/COLLECTED BY SAMPLE TYPE

	Number of collections	Approximate amount per collection	Total Amount
Hematology	5	10 mL	50 mL
Serum/Plasma Chemistry	5	10 mL	50 mL
Pharmacokinetic (Subset of the total population)	3	4 mL	12 mL
Total			112 mL

APPENDIX D. GUIDELINES FOR ELEVATIONS IN HEPATIC ENZYMES

Study treatment should be withheld for any liver test abnormality listed in Section 8.6.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Table D-1, and per the investigations in Table D-2. If close monitoring is not possible, Study Treatment should be withheld, even if the results do not meet the criteria for withholding in Section 8.6.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Table D-1 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests[a]
If AST or ALT ≥ 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 x ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions

Table D-2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination: • Detailed history of symptoms (e.g., right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (e.g., travel, new sexual exposure, exposure to ill family members or coworkers, etc.) and/or industrial chemical agents; • Prior and concurrent use of alcohol, recreational drugs, and special diets; • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms; • Physical examination.
Recommended tests: • Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist. • Repeat liver tests as per Table D-1[a]; • Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests; • Complete blood count with differential to assess for eosinophilia; • Serum acetaminophen (paracetamol) concentration; • Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus; • Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.; • Serology for celiac disease; • Appropriate liver imaging; and • Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

Abbreviations: INR, international normalized ratio

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.