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	

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

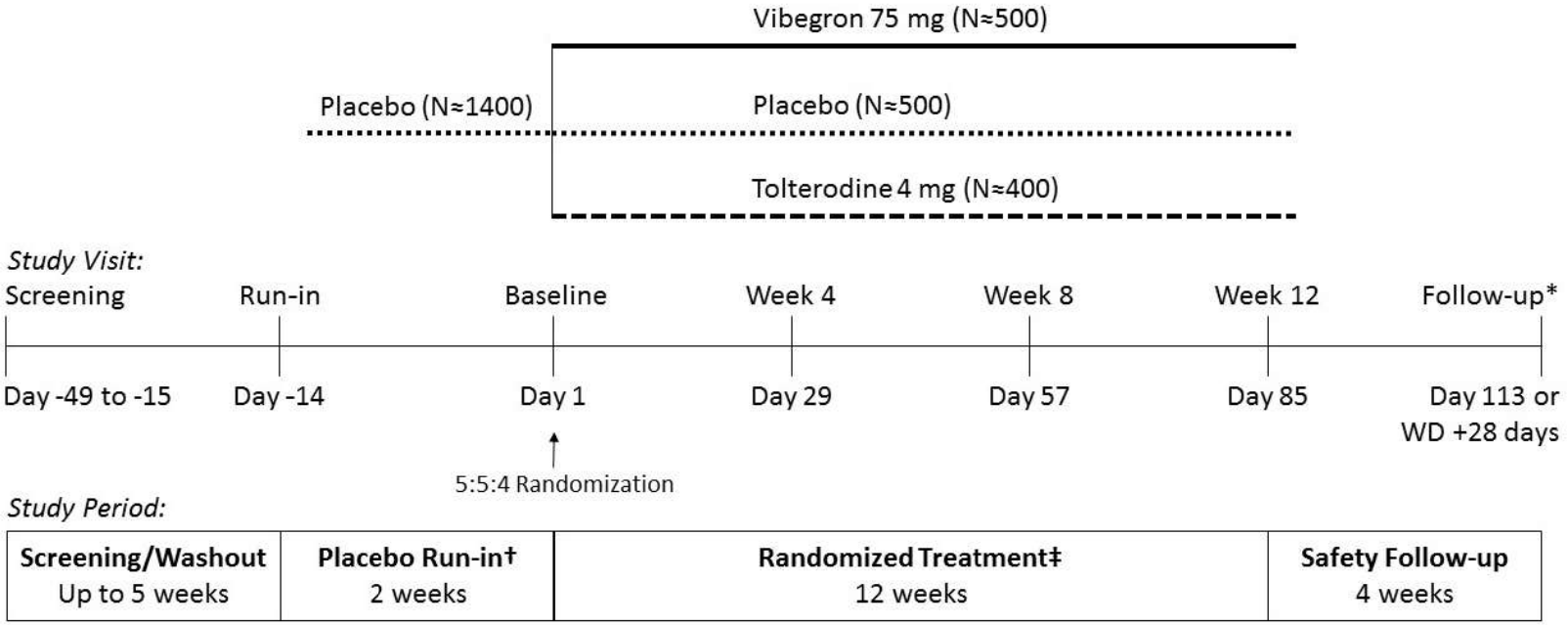
Elevated liver enzymes or bilirubin sufficient to require withholding study medication must be reported **within 24 hours of the study site personnel's knowledge of the event** using AECI specific eCRFs/forms/worksheets provided for the study.

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

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.

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]	

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

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.

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.

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.

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

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.

- 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:

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.

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)

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

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.

	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]).

Objectives	Efficacy Endpoints
	[redacted]

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).

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.

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

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.

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.

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

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

9.9. Interim Analyses

There is no planned interim analysis for efficacy.

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