[redacted]

# Statistical Analysis Plan for Interventional Studies

**Sponsor Name:** Urovant

**Protocol Number:** RVT-901-3004

**Protocol Title:** 52 week extension of an International Phase 3, Randomized, Double-Blind, Active (Tolterodine)-Controlled Multicenter Extension Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder

**Protocol Version and Date:**

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**Authors:** [redacted]

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| 2.0 | 09-Aug-2019 | [redacted] | Clarification of imputation rules for partial dates, change to section 9.2 (drug compliance) and feedback from Urovant on v1.3. |

I confirm that I have reviewed this document and agree with the content.

## Approvals

[redacted] **Approval**

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| [redacted] | [redacted] Signature | 09-Aug-2019 Date (DD-Mmm-YYYY) |

**Urovant Approval**

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[redacted] on behalf of [redacted], [redacted], Programming and Data Management

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## Table of Contents

[redacted]

# 1. Glossary of Abbreviations

| Abbreviation | Description |
|---|---|
| AE | Adverse Event |
| AIC | Akaike's Information Criteria |
| AR | Autoregressive |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass index |
| BP | Blood Pressure |
| BPH | Benign Prostatic Hyperplasia |
| BPM | Beats Per Minute |
| CI | Confidence Interval |
| CFB | Change From Baseline |
| CS | Compound Symmetry |
| ECDF | Empirical Cumulative Distribution Function |
| eCRF | Electronic Case Report Form |
| CV | Coefficient of Variation |
| DBL | Database Lock |
| DBP | Diastolic Blood Pressure |
| DRM | Data Review Meeting |
| ECG | Electrocardiogram |
| EQ-5D | EuroQual 5 Dimension Questionnaire |
| Ext | Extension |
| FAS-Ext | Full Analysis Set Extension |
| FAS-Ext-I | Full Analysis Set Extension for Incontinence |
| GPP | Good Pharmacoepidemiology Practice |
| HRQL | Health-Related Quality of Life |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IP | Investigational Product |
| IxRS | Interactive Voice/Web Response System |
| LOCF | Last Observation Carried Forward |
| LF | Long Form |
| Max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple Imputation |
| Min | Minimum |
| MMRM | Mixed Model for Repeated Measures |
| MNAR | Missing Not At Random |
| N/A | Not Applicable |
| NA | Not Applicable |
| NVU | Night Time Voids Associated with Urgency |
| OAB | Overactive Bladder |
| OAB Dry | OAB in the absence of Incontinence |
| OAB Type | Investigator-Defined Baseline OAB Categorization |
| OAB Wet | OAB with Incontinence |

| Abbreviation | Description |
|---|---|
| OAB-q | Overactive Bladder Questionnaire |
| PGI | Patient Global Impression |
| PRO | Patient Reported Outcomes |
| PPS-Ext | Per-Protocol Set Extension |
| PPS-Ext-I | Per-Protocol Set Extension for Incontinence |
| PT | Preferred Term |
| PVR | Post-Void Residual (Volume) |
| QC | Quality Control |
| QTc | Corrected QT Interval |
| REML | Restricted (or residual) Maximum Likelihood |
| RVT-901 | Vibegron (Urovant code number) |
| SAE | Serious Adverse Event |
| SAF | Safety Set |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SE | Standard Error |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SUI | Stress Urinary Incontinence |
| TEAE | Treatment Emergent Adverse Event |
| TLF | Table, Listing and Figure |
| Urovant | Urovant Sciences GmbH |
| US | United States |
| UUI | urge urinary incontinence |
| WHO | World Health Organization |
| WPAI-US | Work Productivity and Activity Impairment Questionnaire-Urinary Symptoms |

# 2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

## 2.1. Responsibilities

[redacted] will perform the statistical analyses and are responsible for the production and quality control (QC) of all tables, figures and listings.

## 2.2. Timings of Analyses

All safety and efficacy analyses will occur after all patients complete all study visits or terminate early from the study. No interim analyses will be performed and no Data Safety Monitoring Board has been set-up for this study. This SAP details these analyses and has been finalized prior to unblinding of the study.

# 3. Study Objectives

## 3.1. Primary Objective

To evaluate the safety and tolerability of vibegron (RVT-901) for up to 52 weeks in patients with symptoms of overactive bladder (OAB) who previously completed treatment in study RVT-901-3003.

## 3.2. Secondary Objective(s)

- To evaluate the overall efficacy of vibegron in patients with symptoms of OAB.

[redacted]

## 3.3. Brief Description

This is an international Phase 3, double-blind, active (tolterodine)-controlled, parallel-group, multicenter, 40-week extension study to evaluate the safety, tolerability, and efficacy of vibegron 75 mg in men and women with symptoms of overactive bladder syndrome (OAB). This study is an extension for patients who have completed the Phase 3, double-blind, randomized, 12-week study RVT-901-3003.

Approximately 500 men and women with overactive bladder who completed 12 weeks in study RVT-901-3003 will be permitted to enroll in this extension study, at approximately 110 study sites.

During this extension study, all patients who had been randomized in RVT-901-3003 to receive either vibegron 75 mg or tolterodine ER 4 mg will continue their same treatment once daily in a blinded fashion for an additional 40 weeks; patients who had been randomized in RVT-901-3003 to the placebo group will be randomized 1:1 to receive blinded study treatment of vibegron 75 mg or tolterodine ER 4 mg once daily for 40 weeks during the extension. Thus, through participation in both the RVT-901-3003 study and RVT-901-3004 (extension) study, patients originally randomized to vibegron or tolterodine will receive 52 weeks total of vibegron or tolterodine treatment, and patients originally randomized to placebo will receive 40 weeks total of vibegron or tolterodine treatment.

## 3.4. Patient Selection

To be eligible for participation in this study, a patient must have completed participation in study RVT-901-3003, and continue to meet all the RVT-901-3004 study Inclusion Criteria, and none of the Exclusion Criteria.

### 3.4.1. Inclusion Criteria

1. Has completed participation in study RVT-901-3003.
2. Willing and able to provide written informed consent.
3. For females of reproductive potential: Agrees to remain abstinent or use (or have their male partner use) an acceptable method of birth control each time the patient has intercourse until the Follow-up Visit.
4. For females of reproductive potential: Agrees not to donate ova (eggs) until at least 1 month after the last dose of Study Treatment.
5. Has demonstrated ≥ 80% compliance with self-administration of Study Treatment in study RVT-901-3003.
6. Has completed a minimum of 4 Complete Diary Days for study RVT-901-3003 Week 12.
7. Is ambulatory and in good general physical and mental health as determined by the Investigator.

8. 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 Voiding Diary, and Voided 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]).

3.4.2. Exclusion Criteria

1. Was unable to complete participation in study RVT-901-3003 for any reason.
2. Has a change in history or current evidence of any clinically significant 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. Includes any serious or unstable, clinically relevant change in gastrointestinal, renal, hepatic, cardiovascular, lymphatic, or psychiatric, or other medical disorder during the RVT-901-3003 study
3. Has coronary or neurovascular interventions planned during the duration of the study.
4. Has uncontrolled hyperglycemia (defined as fasting blood glucose >150 mg/dL or 8.33 mmol/L and/or non-fasting blood glucose >200 mg/dL or 11.1 mmol/L) based on most recent available lab results in study RVT-901-3003 or, if in the opinion of the Investigator, is uncontrolled.
5. Has uncontrolled hypertension (systolic blood pressure of ≥ 180 mm Hg and/or diastolic blood pressure of ≥ 100 mm Hg) or has a resting heart rate (by pulse) > 100 beats per minute.
    a. Patients who have systolic blood pressures ≥ 160 mm Hg or < 180 mm Hg 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.
    b. 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, acute heart failure.
6. Has clinically significant ECG abnormality which, in the opinion of the Investigator, exposes the patient to risk by participating in the study
7. 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) based on most recent available lab results in study RVT-901-3003.
8. Has an estimated glomerular filtration rate (eGFR) < 30mL/min/1.73 $m^2$ based on most recent available lab results in study RVT-901-3003.
9. Use of any prohibited medications as detailed in the protocol.
10. Plans to initiate or change the dosing of any medications listed the protocol during the study that in the opinion of the investigator is assessed to be clinically significant.
11. 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.
12. Is currently participating or has participated in a study with an investigational compound or device within 28 days of signing informed consent, not including participation in study RVT-901-3003.

13. Has a history of significant drug or alcohol abuse/dependence within a year of informed consent, as assessed by the investigator.
14. Has a varying sleep schedule anticipated during times when the voiding diaries are to be completed.

### 3.5. Determination of Sample Size

Five hundred (500) patients rolling over from study RVT-901-3003, in addition to other long-term safety data with vibegron, is sufficient to characterize the long-term safety profile of vibegron 75 mg once daily and satisfies the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance for 1-year exposure. There is no formal sample size calculation.

### 3.6. Treatment Assignment & Blinding

Randomization will occur centrally using an IxRS. Enrollment in this extension study will be capped at approximately 500 patients. There are two treatment arms in the RVT-901-3004 study:

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

Patients will be assigned to double-blind Study Treatment as follows:

- All patients randomized to vibegron 75 mg in study RVT-901-3003 will be assigned to take vibegron 75 mg during the 40-week extension study.
- All patients randomized to placebo in study RVT-901-3003 will be randomized 1:1 and assigned to take vibegron 75 mg or tolterodine ER 4 mg during the 40-week extension study.
- All patients randomized to tolterodine ER 4 mg in study RVT-901-3003 will be assigned to take tolterodine ER 4 mg during the 40-week extension assignments.

The patient and the Investigator involved in the treatment or clinical evaluation of the patients are unaware of the treatment group assignments. Specific Sponsor personnel and delegate(s) will be partially unblinded once RVT-901-3003 reaches database lock. However, Sponsor personnel and delegates involved in patient-level decisions will remain blinded. Therefore, the blinding strategy for the RVT-901-3004 study will be double-blind, Sponsor open (partially unblinded).

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

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

### 3.7. Administration of Study Medication

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

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.

### 3.8. Study Procedures and Flowchart

This study consists of a randomized double-blind Treatment Period (40 weeks), and a Safety Follow-Up Period (4 weeks). All patients will have a Follow-Up Visit approximately 28 days after the patients' last dose of study treatment (i.e., at week 56 for patients who complete the Week 52 Visit, or approximately 4 weeks after withdrawal for patients who discontinue the study early). This study is an extension for patients who have complete the Phase 3, double-blind, randomized, 12-week study RVT-901-3003. Patients who received active treatment in RVT-901-3003 will therefore be randomized to receive 52-weeks of active treatment in total and patients who were randomized to placebo in RVT-901-3003 will be randomized to 40-weeks of active treatment. Study visits will be named to reflect continuation from the RVT-901-3003 study, with the first study visit of the extension study occurring at week 12. Following enrollment in this extension study, patients will return to the clinic for visits at Week 16, Week 24, Week 36, Week 44 and Week 52 (all relative to Day 1 of RVT-901-3003). The schedule of activities is given in Table 3.8.1 and Table 3.8.2.

[redacted]

**Table 3.8.1: Schedule of Activities in RVT-901-3003**

| Study Period: | Screening/ Washout | Run-in | Treatment | | | | |
|---|---|---|---|---|---|---|---|
| Visit Number: | Visit #1 | Visit #2 | Visit #3 | Diary Only | Visit #4 | Visit #5 | Visit #6 |
| Visit Name: | Screening[1] | Run-in | Baseline | Week 2 | Week 4 | Week 8 | Week 12 or Early WD |
| Study Day: | -49 to -15 | -14 | 1 | 15 | 29 | 57 | 85 or Early WD |
| Permitted Visit Window: | | ± 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 |
| Device Training/Re-Training[4] | 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 | |
| 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 | |
| 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 | | | | |
|---|---|---|---|---|---|---|---|
| Visit Number: | Visit #1 | Visit #2 | Visit #3 | Diary Only | Visit #4 | Visit #5 | Visit #6 |
| Visit Name: | Screening[1] | Run-in | Baseline | Week 2 | Week 4 | Week 8 | Week 12 or Early WD |
| Study Day: | -49 to -15 | -14 | 1 | 15 | 29 | 57 | 85 or Early WD |
| Permitted Visit Window: | | ± 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 | | | | | |
| ECG[12] | X | | | | | | |
| Vital Signs[13] | 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 |
| Hematology | X | | X | | X | | X |
| Urinalysis Dipstick[17][8] | X | | X | | X | | X |
| Urine Pregnancy β-hCG (women)[19] | X | X | X | | X | X | X |
| IxRS Randomization to Study Treatment | | | X | | | | |
| Dispense Study Treatment[20] | | X | X | | X | X | |

| Study Period: | Screening/ Washout | Run-in | Treatment | | | | |
|---|---|---|---|---|---|---|---|
| Visit Number: | Visit #1 | Visit #2 | Visit #3 | Diary Only | Visit #4 | Visit #5 | Visit #6 |
| Visit Name: | Screening[1] | Run-in | Baseline | Week 2 | Week 4 | Week 8 | Week 12 or Early WD |
| Study Day: | -49 to -15 | -14 | 1 | 15 | 29 | 57 | 85 or Early WD |
| Permitted Visit Window: | | ± 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.

## Table 3.8.2: Schedule of Activities in RVT-901-3004

| Study Period: | | Double-Blind Treatment | | | | | Safety Follow-Up/ Unscheduled | |
|---|---|---|---|---|---|---|---|---|
| Visit Number: | Visit #6 | Visit #7 | Visit #8 | Visit #9 | Visit #10 | Visit #11 | UNS # | Visit #12 |
| Visit Name: | Week 12 | Week 16 | Week 24 | Week 36 | Week 44 | Week 52 or Early WD | Unsch-eduled[23] | Follow -Up[24] |
| Study Day: | 85 | 113 | 169 | 253 | 308 | 365 | | 393 or WD +28 |
| Permitted Visit Window: | ± 3 Days | ± 3 Days | ± 3 Days | ± 3 Days | ± 3 Days | ± 3 Days | | ± 3 Days |
| Informed Consent | X[1] | | | | | | | |
| Inclusion/Exclusion Criteria Eligibility Review | X[1] | | | | | | | |
| Electronic Diary (eDiary)[2]: | | | | | | | | |
| eDiary Device | | | | | | | | |
| Device Function Check[4] | X[3] | X | X | X | X | X | X | |
| Device Re-Training[5] | X[1] | X | X | X | X | | X | |
| Collect eDiary Device | | | | | | X | | |
| Patient Voiding Diary: | | | | | | | | |
| Voiding Diary Re-Training[6] | X[1] | X | X | | X | X | X | |
| Patient Completes Voiding Diary[7] | X* | X | X | | X | X | | |
| Urine Volume Diary: | | | | | | | | |
| Voided Volume Diary Re-Training[6] | X[1] | X | X | | X | X | X | |
| Patient Completes Voided Volume Diary[8] | X* | X | X | | X | X | | |
| Diary and Visit Reminders | | | | | | | | |
| Phone Calls/ Optional SMS reminders[9] | X* | X | X | | X | X | | |
| Patient Reported Outcomes (PROs)[10]: | | | | | | | | |
| Global Impression Items (PGI-Severity, PGI-Control, PGI-Frequency, PGI-Leakage, and PGI-Change) | X* | | X | | | X | | |
| Overactive Bladder Questionnaire (OAB-q LF) | X* | | X | | | X | | |

| Study Period: | | Double-Blind Treatment | | | | | Safety Follow-Up/ Unscheduled | |
|---|---|---|---|---|---|---|---|---|
| Visit Number: | Visit #6 | Visit #7 | Visit #8 | Visit #9 | Visit #10 | Visit #11 | UNS # | Visit #12 |
| Visit Name: | Week 12 | Week 16 | Week 24 | Week 36 | Week 44 | Week 52 or Early WD | Unsch-eduled[23] | Follow -Up[24] |
| Study Day: | 85 | 113 | 169 | 253 | 308 | 365 | | 393 or WD +28 |
| Permitted Visit Window: | ± 3 Days | ± 3 Days | ± 3 Days | ± 3 Days | ± 3 Days | ± 3 Days | | ± 3 Days |
| Work Productivity and Activity Impairment Questionnaire-Urinary Symptoms (WPAI-US) | X* | | X | | | X | | |
| EQ-5D | X* | | X | | | X | | |
| Post-Void Residual (PVR) Volume[11] | X* | | X | | | X | | |
| Physical Exam[12] | X[1] | | | | | | X | X |
| ECG[13] | X[1] | | | | | | X | |
| Vital Signs[14] | X* | X | X | X | X | X | X | X |
| Adverse Event Review[15] | ←==========→ | | | | | | | |
| Serious Adverse Events[16] | ←==========→ | | | | | | | |
| Concomitant Medication Review[17] | ←==========→ | | | | | | | |
| Clinical Laboratory Assessments: | | | | | | | | |
| Chemistry | X* | X | X | | | X | X | X |
| Hematology | X* | X | X | | | X | X | X |
| Urine Dipstick[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[1] | | | | | | | |
| Dispense Study Treatment[20] | X[1] | X | X | X | X | | X | |
| Study Treatment Return/Accountability Review[21] | X* | X | X | X | X | X | | |
| Administer Witnessed Dose of Study Treatment[22] | X[1] | | | | | | | |

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

[redacted]

**Table Footnotes:**

**Week 12**

1. Patients continuing from the RVT-901-3003 study at Week 12 require additional study procedures for the RVT-901-3004 extension study.

   * Activities collected at Week 12 Visit in RVT-901-3003.

**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 the next visit.
3. The site will update the Subject Status Screen on the eDiary to move the patient to the RVT-901-3004 extension study.

**eDiary Device**

4. At each visit during the Treatment Period, site personnel will confirm that the eDiary Device is functioning properly.
5. Specific re-training on device operation will be provided to the patient at each visit.

**Patient Voiding Diary and Urine Volume Diary**

6. Specific re-training on completion of the Voiding Diary and Voided Volume Diary will be provided to the patient at each visit.
7. The Voiding Diary should be completed by the patient on all of the 7 Diary Days prior to the Week 16, 24, 44, and 52 Visits. Patient will receive an alert and/or phone call reminder to complete the diary.
8. The Voided Volume collection and Voided Volume Diary completion should be performed by the patient on one (1) of the 7 Diary Days prior to the Weeks 16, 24, 44, and 52 Visits.

**Diary and Visit Reminders**

9. 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 (PROs)**

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

**Post Void Residual Volume**

11. All efforts will be made to ensure the same device and operator are used for all PVR volume measurements for individual patients (in study RVT-901-3003 and RVT-901-3004).

**Physical/ECG/Vitals**

12. A Complete Physical Exam will be performed at the Follow-up Visit.
13. A single 12-lead ECG will be obtained at Week 12.
14. Vital Signs includes Blood Pressure (average of three measurements taken 1-2 minutes apart after sitting for 5 min), Heart Rate, Temperature, Respiration Rate, and Weight.

**Adverse Events**

15. Adverse Events will be collected from the time a patient takes the first dose of Study Treatment in the RVT-901-3004 study until the Follow-up Visit is completed.
16. Serious Adverse Events will be collected from the time a patient takes the first dose of Study treatment in the RVT-901-3004 study until the Follow-up Visit is completed.

**Concomitant Medications**

17. Concomitant medications from RVT-901-3003 will be reviewed and confirmed to be stable. Concomitant medications will be recorded at each study visit and at any Unscheduled Visits.

**Labs**

18. At Weeks 36 and 44, the Urine Dipstick will only be performed if clinically indicated (e.g., symptoms of urinary retention or urinary tract infection). 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 Week 12 Visit through the day before the Week 52 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 Week 12 Visit at the site as a witnessed dose. The date and time of Study Treatment dosing will be recorded.

**Follow-up/Unscheduled**

23. 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, dispense study treatment medication). The reason for the visit will be captured in the source documents.
24. For patients who complete the study or who Withdraw from the study early for any reason, a Follow-up Visit should be performed approximately 28 days after the last dose of Study Treatment (on Study Day 393 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 52 Visit should be performed at the time of withdrawal.

# 4. Endpoints

## 4.1. Safety Endpoints

Primary:

- Incidence of any treatment emergent adverse event by system organ class and preferred term

Additional Safety:

- Clinical Laboratory Assessments
- Vital Signs
- PVR
- Physical Examinations

## 4.2. Efficacy Endpoints

Efficacy is a secondary objective for this study and there are no primary efficacy endpoints. The secondary efficacy endpoints for this trial are as follows:

- Change from baseline (CFB) at Week 52 in average number of micturitions per 24 hours in all OAB patients
- CFB at Week 52 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients
- CFB at Week 52 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients
- CFB at Week 52 in average number of total urinary incontinence episodes over 24 hours in OAB Wet patients

## 4.3. Exploratory Endpoints

# 5. Analysis Sets

## 5.1. Screened Set Extension

The Screened Set Extension comprises all patients who signed the informed consent form (ICF) for RVT-901-3004 and have screening data entered into the database. This set includes screen failures and randomized patients. For clarity, screen failure patients are those patients who fail to meet inclusion criteria or meet exclusion criteria and discontinued the study/withdrew consent prior to randomization in RVT-901-3004.

[redacted]

## 5.2. Randomized Set Extension

The Randomized Set Extension will include all patients who were randomized. Unless specified otherwise, this set will be used for patient listings and for summaries of patient disposition.

[redacted]

## 5.3. Safety Analysis Set Extension

The Safety Analysis Set Extension (SAF-Ext) consists of all patients who received at least one dose of double-blind study treatment during RVT-901-3004. This means that there will be 2 treatment groups including vibegron (52 weeks and 40 weeks combined) and tolterodine (52 weeks and 40 weeks combined). The SAF-Ext will be used for all analyses of safety endpoints and for the presentation of patients in all patient listings. Patients will be included in the treatment group corresponding to the Study Treatment they actually received in RVT-901-3004 for the analysis of safety data using the SAF-Ext 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 in RVT-901-3004 is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a Baseline measurement is also required.

[redacted]

## 5.4. Full Analysis Set Extension

The Full Analysis Set Extension (FAS-Ext) will serve as the population for the analysis of efficacy data in this study. Patients will be included in the combination of treatment groups from RVT-901-3003 and RVT-901-3004 to which they are randomized, regardless of which treatment they actually received. This means there will be 4 treatment groups: 52-weeks vibegron, 52-weeks tolterodine, 40-weeks vibegron and 40-weeks tolterodine. Since the endpoints related to incontinence 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 analysis population for incontinence endpoints.

The following FAS populations are defined in the study:

- Full Analysis Set Extension (FAS-Ext): all randomized OAB patients who took at least one dose of double-blind Study Treatment in RVT-901-3004 and have at least one subsequent evaluable change from baseline micturition measurement in this study.
- Full Analysis Set Extension for Incontinence (FAS-Ext-I): all randomized OAB Wet patients who were included in the FAS-I population in the RVT-901-3003 study, who took at least one dose of double-blind Study Treatment in RVT-901-3004 and have at least one subsequent evaluable change from baseline (RVT-901-3004) urge urinary incontinence measurement. The FAS-I population in the RVT-901-3003 study was defined as 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 in the RVT-901-3003 study.
- The definition of OAB criteria are presented in Section 6.3 of this document.

[redacted]

## 5.5. Per Protocol Set Extension

The Per-Protocol Set Extension (PPS-Ext) and Per-Protocol Set Extension for incontinence (PPS-Ext-I) exclude patients from the FAS-Ext due to important deviations from the protocol that may substantially affect the results of the efficacy endpoints (i.e., Major PDs for efficacy). A supportive analysis using the PPS-Ext and PPS-Ext-I will be performed for the 4 key secondary efficacy endpoints. The final determination on protocol deviations, and thereby the composition of the Per-Protocol Extension sets, will be made prior to the unblinding of the database and will be documented per the Protocol Deviation Plan during the BDRM.

Patients will be included in the combination of treatment groups from RVT-901-3003 and RVT-901-3004 to which they are randomized, regardless of which treatment they actually received.

## 5.6. Protocol Deviations

Protocol deviations are collected and agreed at the Protocol Deviation review meetings occurring prior to database lock (DBL); to evaluate protocol deviations considered to have a major impact on patient safety, efficacy or the validity of the study data. The protocol deviations are classified into 5 major categories and 1 minor category. The major categories are as follows:

- Major (Efficacy)
- Major (Efficacy Duplicate Patient)
- Major (Efficacy and Safety)
- Major (Safety)
- Major (Other)

Patients with major efficacy protocol deviations, which includes the 3 major categories above associated with efficacy, will be excluded from the PPS-Ext and PPS-Ext-I under the assumption that the deviation may have an impact on the efficacy analysis. Efficacy protocol deviation categories may include, but are not limited to the following:

- Inclusion/Exclusion Criteria Not Met
- Concomitant Medication (Prohibited Meds)
- Missed Study Visit
- Visit Out of Window

- Other (e.g. IP Compliance)
- Procedure Not Per Protocol

Other Major protocol deviation categories may include, but are not limited to the following:

- Informed Consent Issues
- IP Dispensation/Storage
- Lab Sample Issues (Missing/Not Analyzed etc.)
- AECI Not Reported

All major protocol deviations related to efficacy will be discussed during the BDRM, and decisions relating to exclusion for the PPS-Ext (-I) will be documented in the BDRM Report, finalized prior to unblinding.

# 6. General Aspects for Statistical Analysis

## 6.1. General Methods

All patients entered into the database will be included in patient data listings, listings will include all data relevant to the definition of baseline per endpoint and will include all data after active treatment has started in RVT-901-3003 and RVT-901-3004. Unscheduled assessments will be included in listings but will not be included in by-visit summaries of the data. Summary tables will be provided for all patients randomized in RVT-901-3004. Unless otherwise specified; all demographic and baseline data will be presented by the combination of treatments received in RVT-901-3003 and RVT-901-3004 (i.e. 52-weeks Vibegron 75mg, 52-weeks Tolterodine ER 4mg, 40-weeks Vibegron 75mg, 40-weeks Tolterodine ER 4mg) and treatment received in RVT-901-3004 (i.e. Vibegron 75mg and Tolterodine ER 4mg with 52 weeks and 40 weeks scheduled treatment combined). Unless otherwise specified; all efficacy data will be presented by the combination of treatments received in RVT-901-3003 and RVT-901-3004 (i.e. 52-weeks Vibegron 75mg, 52-weeks Tolterodine ER 4mg, 40-weeks Vibegron 75mg, 40-weeks Tolterodine ER 4mg). All safety data will be presented by treatment received in RVT-901-3004 (i.e. Vibegron 75mg and Tolterodine ER 4mg with 52 weeks and 40 weeks scheduled treatment combined). Unless otherwise specified baseline will refer to data from the end of the run-in phase of RVT-901-3003.

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

Quantitative (continuous) data - absolute values and changes from baseline, where appropriate - will be summarized with the population sample size (N), number of patients with available data (n), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum.

Qualitative (categorical) data will be summarized using the population sample size (N), number of patients with available data (n), frequency and percentages of patients. Unless stated otherwise, the calculation of percentages will be based on the total number of patients with non-missing data (n) in the set of interest.

The population for efficacy analysis will be the FAS-Ext for micturition endpoints and urgency episodes while the FAS-Ext-I will be used for the following incontinence endpoints: UUI and total incontinence episodes. Supportive efficacy analyses based on the PPS-Ext and PPS-Ext-I will be conducted for the 4 key secondary endpoints. The SAF-Ext will be used to conduct analyses of the safety endpoints.

The analyzed data will include data from RVT-901-3003 and RVT-901-3004 for the subset of patients randomized in RVT-901-3004 from study periods where patients were randomized to receive active treatment, i.e. patients randomized to receive placebo in RVT-901-3003 will have data from Week 2, Visit #4 (Week 4), Visit #5 (Week 8) and Visit #6 (Week 12) excluded. Patients randomized to receive either active vibegron or tolterodine during RVT-901-3003 (and extension) will have diary and safety data (AE, labs, vital signs) from RVT-901-3003 included in this analysis. Patients randomized to receive placebo during RVT-901-3003 will have only baseline data from RVT-901-3003 and diary and safety data from RVT-901-3004 included for analysis.

Data from RVT-901-3003 and RVT-901-3004 will be mapped independently to SDTM. Then a subsequent combined set of SDTMs for the subset of patients in RVT-901-3004 will be created to include data from both studies.

## 6.2. Testing Strategy and Multiplicity

No statistical comparisons between Vibegron and Tolterodine will be made. All analyses will be descriptive in nature.

## 6.3. Key Definitions

The patient voiding diary asked patients to record what time they woke up for the day, what time they went to bed, and asked the patients to record every time they had a urination event. For each event, patients recorded the time, if they had a need to urinate immediately, if they urinated in the toilet, if they had accidental urine leakage, and if they had leakage what the reason was for the leakage (urge, stress, or other). The following are key definitions based on the diary data:

**Diary Parameters**

**Micturition**

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 Voiding Diary. Average daily micturitions are calculated using the daily entries in the Voiding Diary, which is completed prior to each study visit. Average daily number of micturitions will be calculated as the total number of micturitions that occur on all Complete Diary Days divided by the number of Complete Diary Days in the Voiding Diary. Unless a patient indicated “No” to the question of “Did you record each time you urinated or leaked during this Diary Day” the Diary Day is considered complete.

**Urgency Episodes**

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

**Urge Urinary Incontinence (UUI) Episodes**

A UUI episode is defined as having "urge" as the main reason for the leakage as indicated on the voiding diary, regardless of whether more than one reason for leakage in addition to “urge” is checked. Average daily urge urinary incontinence episodes at each study visit will be calculated in the same manner as described above for the micturition endpoint. The urge urinary incontinence endpoint will be analyzed using only OAB Wet patients.

**Total Incontinence**

Total incontinence is defined as having any reason for “Accidental Urine Leakage” and/or “Accidental Urine Leakage” checked, as indicated on the voiding diary. It is assumed that if the patient recorded a reason for leakage then the accidental urine leakage occurred.

**Nighttime Voids Associated with Urgency (NVU)**

An NVU is defined as the “Need to Urinate Immediately” occurring after going to bed, but prior to getting up the next day.

**Nighttime Voids**

A nighttime void is defined as “Urinated in Toilet” as indicated on the voiding diary, after going to bed but prior to getting up the next day.

**Nighttime UUI**

A nighttime UUI episode is defined as having "urge" as the main reason for the leakage as indicated on the voiding diary, regardless of whether more than one reason for leakage is checked, and occurring after going to bed, but prior to getting up the next day.

**OAB Categorization**

OAB Type will be based on the randomization strata.

**Diary Day**

A “Diary Day” is defined as the time between when the patient gets up for the day each morning and the time the patient gets up for the day the next morning as recorded in the patient voiding diary. The “Diary Day” is derived as the time period used in evaluating endpoints described as “per 24 hours” and is not necessarily an exact 24 hour period.

**Complete Diary Day**

A “Complete Diary Day” is defined as a Diary Day that includes input of micturition data by patients on the Voiding Diary. Unless a patient indicated “No” to the questions of “Did you record each time you urinated or leaked during this Diary Day” the Diary Day is considered complete.

For the Week 12/Early Termination and Week 52/withdrawal diary, only complete diary days within 14 days prior to the study visit will be included. For the Week 2 diary, complete diary days within 10 days prior to the target Week 2 day will be used. For diaries at all visits, if a patient has fewer than 4 complete diary days, that will be identified as a significant protocol deviation and that diary data will be excluded from all analysis.

**Definition of Baseline for Patient Voiding Diary Endpoints**

Baseline will be the data collected during the Run-in Period of the RVT-901-3003 study. If greater than 10 complete diary days are available in the Run-in diary, only the complete diary days within the 10 days prior to the Baseline visit will be used; if 4 or more and less than or equal to 10 complete diary days are available, all complete diary days in the Run-in diary will be used to calculate Baseline. If less than 4 complete diary days are available, the Baseline will be regarded as missing. For a patient to have an evaluable change from baseline, the patient must have both a baseline diary and a post-baseline diary from any post-week 12 timepoint in RVT-901-3004, after analysis window has been applied (i.e., Week 16, Week 24, Week 36, Week 44, or Week 52 or early WD).

**Definition of Baseline for Endpoints not Derived from the Patient Voiding Diary**

Baseline value for all secondary efficacy, exploratory and safety endpoints will be defined as the last non-missing assessment before starting double-blind treatment in the RVT-901-3003 study.

**Run-in Period**

The Run-in Period covers the duration between screening (Day -14) and the day before baseline (Day 1) in the RVT-901-3003 study. There is no day 0 included in the study.

**Treatment Period**

The Treatment Period covers the duration that a patient is in the study from Baseline (Day 1) and Week 52 and randomized to receive study treatment.

**Active Treatment Period**

For subjects who have been randomized to active treatment in RVT-901-3003, the Active Treatment Period covers the duration that a patient is in the study from Baseline (Day 1, RVT-901-3003) to Week 52 and randomized to receive either vibegron 75mg or tolterodine ER 4mg. For subjects who have been randomized to placebo in RVT-901-3003, the active treatment period in RVT-901-3004 will start with the first dose received in RVT-901-3004.

**Safety Follow-up Period**

There is a 4-week Safety Follow-up Period in this study which will occur approximately 28 days after the patient's last dose of study treatment (i.e. at week 56 for patients who complete the week 52 visit, or approximately 4 weeks after withdrawal for patients who discontinue the study early).

**Definition of Study Completion**

A patient will be defined as "completed" if she/he completes the Week 52 study visit.

**End of Study Definition**

End of study is defined as the date when the patient has completed one of the following: completed the Week 52 visit, permanently discontinued from the study, or lost to follow-up.

**Day of Study Event (post-randomization)**

Day of study event = Event Date – Date of Baseline in the RVT-901-3003 study (Day 1) + 1.

**Day of Study Event (pre-randomization)**

Day of study event = Event Date – Date of Baseline in the RVT-901-3003 study (Day 1).

**Change from Baseline**

Absolute CFB = Post-baseline value – Value at baseline

**Percent Change from Baseline**

Percent CFB = 100 * (Post-baseline value – Value at baseline) / Value at baseline

### 6.4. Missing Data

For all CFB analyses of the secondary efficacy endpoints no imputation of missing data will be performed as the Mixed Model for Repeated Measures (MMRM) accounts for this. Analyses of responder endpoints will be performed using multiple imputation (MI) for missing data and this is detailed in Appendix 1.

**Incomplete AE/concomitant medication start date:**

If only the start day is missing, then the start day will be imputed as the first day of the month that the event occurred with the following exceptions: (1) if the partial date is the same month and year as the date of first dose of active treatment in either RVT-901-3003 or RVT-901-3004, then the partial date will be imputed as the date of first dose of active treatment in either RVT-901-3003 or RVT-901-3004.

If the start date is missing both the day and month, then the day and month will be imputed as the first day of the year (i.e., 01-Jan) with the following exceptions: if the partial date is in the same year as the first dose dose of double-blind medication in RVT-901-3003, then the partial date will be imputed as the date of first dose of double-blind medication in RVT-901-3003. (2) if the start year is before the year of first dose of active treatment in either RVT-901-3003 or RVT-901-3004, then the start date will be set as the date of informed consent in either RVT-901-3003 or RVT-901-3004 respectively.

**Incomplete AE/concomitant medication or treatment end date:**

If only the end day is missing, then the end day will be imputed as the last day (28/29/30/31) of the month of occurance with the follow exceptions: (1) if the partial date is the same month and year as the date of end of study participation, then the partial date willl be imputed as the date of end of study participation. (2) If the subject died in the same month, then set the imputed date as the death date.

If the day and month are missing, then the end day will be imputed as the date of end of study participation. If the subject died in the same year, then set the imputed date as the death date.

**Missing Wake/Bed Time**

For a subject with a complete diary day, if the wake and/or bed time is missing for that day then the missing time will be imputed as the average of the other wake and/or bed times from that diary. E.g., for the Week 12 diary, if the subject has 4 complete diary days with 4 wake times, but only 3 bed times of 10:00pm, 10:10pm, and 10:20pm, then the missing bed time will be imputed as the average of the observed data which is 10:10pm.

**Other Data:**

For all other data, all available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified, there will be no substitution of missing data, i.e., missing data will not be replaced; missing data will be handled as 'missing' in the statistical evaluation.

### 6.5. Visit Windows

Visit windows will be assigned based on the analysis need and the type of data. There are two types of data to be assigned an analysis visit: diary data and non-diary data.

**Visit Windowing for Diary Data:**

For diary data (micturitions, UUI, urgency episodes, total incontinence etc.), where the assessment has been performed at a specific visit (for example confirmation of completion of diary) the assessment will be analyzed at the scheduled visit entered. For diary data whereby only a date/time is given, the record will be assigned based on the dates of the scheduled visits performed. For example, if Run-in visit occurs on 01SEP2018 and Baseline visit occurs on 14SEP2018, any diary data occurring after 01SEP2018 up to and including the day before Baseline visit (13SEP2018) will be windowed for the analysis as "Baseline". This applies for all analysis visits except for Week 2 and Week 4 as there is no Week 2 scheduled visit; in this instance, Week 2 and Week 4 will be assigned based on the assessment being windowed as Week 4 per the above rule, and then the following windowing based on analysis day (relative to first date of double-blind medication) will be applied:

- Date of diary assessment after scheduled Baseline visit from Analysis Day 6 up to and including Analysis Day 22: Assigned as Week 2;
- Date of diary assessment on or after Analysis Day 23 up to and including the day before the scheduled Week 4 visit: Assigned as Week 4.

For diary data, with the exception of week 12 and week 52 only the latest 10 complete diary day observations leading up to any scheduled visit will be included in the analysis of the diary. For week 12 and week 52, the diary within the latest 10 complete diary day observation will be included if available. If not then the complete diary day observation within the latest 14 days will be included. For both scenarios, there must be 4 or more complete diary days available for the period to be analyzed. Otherwise, if there are less than 4 complete diary days available, the period will be set to missing for the analysis.

**Visit Windowing for Non-Diary Data:**

Except for OAB-q LF, WPAI-US, EQ-5D and Global Impression Items (PGI-Severity, PGI-Control, PGI-Frequency, PGI-Leakage, and PGI-Change), other safety data will be windowed using the rules given in Table 6.5.1 below. For endpoints that present visit-based data, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows will be based on the collection schedule listed in the protocol and variables will be windowed to the closest scheduled visit for that variable. For OAB-q LF, WPAI-US and EQ-5D the analysis visit will be assigned as the scheduled visit performed in the eCRF.

Visits for safety data will be windowed based on the target day of the analysis window, which is relative to Day 1 (the first day of double-blind medication in the RVT-901-3003 trial) and dependent upon treatment received in RVT-901-3003.

### Table 6.5.1: Schedule of Activities for Safety Endpoints

| Visit Name | Nominal Visit | RVT-901-3003 randomized arm | | | |
|---|---|---|---|---|---|
| | | Tolterodine or Vibegron | | Placebo | |
| | | Target Day | Analysis Window | Target Day | Analysis Window |
| 3 | Baseline | 1 | NA | 1 | NA |
| 4 | Week 4 | 29 | [2, 42] | 113 | [86[b],140] |
| 5 | Week 8 | 57 | [43, 70] | NA | NA |
| 6 | Week 12 | 85 | [71, 98[a]] | 169 | [141, 210] |
| 7 | Week 16 | 113 | [99, 140] | NA | NA |
| 8 | Week 24 | 169 | [141, 210] | 253 | [211, 280] |
| 8.5 | Week 32 | NA | NA | 308 | [281, 336] |
| 9 | Week 36 | 253 | [211, 280] | NA | NA |
| 9.5 | Week 40 | NA | NA | 365 | [337, 378] |
| 10 | Week 44 | 308 | [281, 336] | NA | NA |
| 11 | Week 52 | 365 | [337, 378] | NA | NA |
| 12 | Follow-up | 393 | [379, ∞] | 393 | [379, ∞] |

[a] Must have occurred prior to or on the same day as the first dose administered in RVT-901-3004
[b] Must have occurred after the first dose administered in RVT-901-3004

If a patient has multiple values of the same measure in an analysis window, then the value collected closest to the target day will be used. If the visits are equidistant from the nominal day, then the later visit will be used. Values that do not map into the analysis-defined visit windows will be considered unscheduled. These unscheduled values will not be included in by-visit summaries. All values will be listed. All values will be stored in analysis datasets.

A laboratory result based on an inadequate sample will not be used in the presentation of sample statistics if a repeat sample was drawn to replace the sample, but the inadequate sample will be listed.

### 6.6. Pooling of Centers

No investigation of center effects is planned; data from all centers will be pooled.

### 6.7. Subgroups

No subgroup analyses are to be conducted for this study for efficacy endpoints. Vital signs will be summarized by Pre-existing hypertension (Yes or No) and PVR will be summarized by sex (Male or Female) and by BPH (Males with BPH or Males without BPH).

# 7. Demographic, Other Baseline Characteristics and Medication

## 7.1. Patient Disposition and Withdrawals

Patient disposition will be summarized by the combination of randomized treatment in RVT-901-3003 and RVT-901-3004 for Screened and Randomized Sets respectively. The summary table will show the frequency and percentage of patients in each of the analysis sets and those who discontinued the study prematurely along with the primary reasons for discontinuation. A listing of patient disposition will display the number of days from first dose to study discontinuation. For the summary under the Randomized Set, additionally the number of patients dispensed and took at least one dose of study medication, plus the number of patients completed study will also be summarized.

The frequency and percentage of patients with at least one major Protocol Deviation (PD), major PD by classification and reasons/category for PD will be summarized by treatment arm for the FAS-Ext. Inclusion in each of the analysis sets (SAF-Ext, FAS-Ext, FAS-Ext-I, PPS-Ext and PPS-Ext-I), and any reasons for exclusion will be summarized by treatment arm for the Randomized Set. Both will be listed also for the FAS-Ext and Randomized Sets, respectively.

Reasons for discontinuation of study will also be listed, including the date of discontinuation.

Eligibility criteria and informed consent (protocol version, informed consent version date and date signed) will be listed only for all patients screened.

Randomization details will also be listed, including the date of randomization, randomization number and randomization strata (OAB Wet/Dry and Sex).

## 7.2. Demographic and Other Baseline Characteristics

All demographic and baseline characteristic data will be summarized by the combination of randomized treatment in RVT-901-3003 and RVT-901-3004 and by randomized treatment in RVT-901-3004 using descriptive statistics for all patients for each of the following analysis sets: SAF-Ext, FAS-Ext, FAS-Ext-I, PPS-Ext and PPS-Ext-I.

Sex, OAB Type (OAB Wet and OAB Dry), Prior Anticholinergic Use (Yes/No), Prior Beta-3 agonist Use (Yes/No), Benign Prostatic Hyperplasia (BPH) (males only: Yes/No), Diabetes Mellitus (Yes/No), Baseline Hypertension (Yes/No), Pre-existing Hypertension (Yes/No), Child-bearing Potential (females only: Yes/No), Age category 1 (<40, ≥40 to <55, ≥55 to <65, ≥65 to 75, ≥75 years), Age category 2 (<65, ≥65 years), Age category 3 (18 to <65, ≥65 to <85 years, ≥85 years), Ethnicity and Race (white and other) will be summarized by the number and percentage of patients in each category.

Prior Anticholinergic Use and Prior Beta-3 agonist Use are considered prior medications and will be defined as medications documented on the Prior and Concomitant Medications eCRF as having stopped prior to the Run-in Visit.

Baseline Hypertension will be defined from RVT-901-3003 baseline as baseline systolic blood pressure (SBP) ≥140 mmHg or baseline diastolic blood pressure (DBP) ≥90 mmHg, regardless of medical history.

Pre-existing hypertension will be defined from RVT-901-3003 medical history and baseline as having a medical history of hypertension and/or Baseline hypertension (baseline SBP ≥140 mmHg or baseline DBP ≥90 mmHg).

Age (years), height (cm), weight (kg) and BMI captured at Screening will be summarized as a continuous variable.

Unless otherwise stated, percentages will be calculated out of the number of patients in the given Analysis Set.

All demographic data will be listed.

## 7.3. Medical History and Concomitant Diseases

Descriptions of medical history findings from 5 years prior to the Screening Visit will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher. Details related to the patients' prior pelvic floor physiotherapy will be specifically recorded. In addition, for patients randomized to placebo treatment in RVT-901-3003 medical history will also include "ongoing" AEs at Visit #6 (Week 12).

A disease or illness reported as medical history without a start date will be included in medical history without a date assigned.

Medical history will be sorted by descending overall frequency, by SOC and PT in the summary table. Medical history data listings will be sorted by treatment, patient number, start date, SOC and PT.

## 7.4. Other Baseline Characteristics

The data from the last complete voiding diary (micturitions, urge incontinence episodes, urgency episodes, total incontinence episodes, and volume voided) prior to first dose of double-blind medication in RVT-901-3003 will be used as baseline for each patient. The daily averages for micturitions, urgency episodes, and urge urinary incontinence episodes will be calculated as the sum of the event type on Complete Diary Days divided by the number of Complete Diary Days. These will be summarized by treatment group and overall using descriptive statistics for continuous data for all patients in each analysis set SAF-Ext, FAS-Ext, FAS-Ext-I, PPS-Ext and PPS-Ext-I at baseline.

All data will be listed.

## 7.5. Medication

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug B2 Format, Mar 1st, 2017 version.

Except for Prior OAB medication, the number and percentage of patients taking prior medications and concomitant medications will be summarized overall by ATC (Anatomical Therapeutical Chemical) Levels 2 and 4, in separate tables, for all patients in the SAF-Ext. Prior OAB medications will be summarized by ATC Levels 2, 4 and Preferred Term in the SAF-Ext.

Prior medications, OAB medication and concomitant medications will be listed for all patients in the SAF-Ext.

### 7.5.1. Prior Medication

Prior medications will be defined as medications documented on the Prior and Concomitant Medications eCRF as having stopped prior to the first dose of active medication in either the RVT-901-3003 or RVT-901-3004 studies.

### 7.5.2. Concomitant Medication

Concomitant medications will be defined as medications documented on the Prior and Concomitant Medications eCRF as having started on or after the first dose of active medication in either the RVT-901-3003 or RVT-901-3004 studies or which were started prior to and were ongoing at the date of first dose of active medication in either the RVT-901-3003 or RVT-901-3004 studies. Partial medication start dates will be imputed as detailed in Section 6.3.

### 7.5.3. Other Therapies

Prior OAB medication will be recorded at screening visit. The following criterion will be used for selecting prior OAB medication:

**Table 7.5.3: OAB Medication Selection**

| Class | Variable Selected | Selection |
|---|---|---|
| Anticholinergics | Preferred Term | Darifenacin, fesoterodine, fesoterodine fumarate, hyoscyamine, oxybutynin, oxybutynin hydrochloride, propantheline, solifenacin, solifenacin succinate, tolterodine, tolterodine l-tartrate, trospium, and trospium chloride |
| Beta-3 adrenergic agonists | Preferred Term | Mirabegron, vibegron |

Prior OAB medications will then be defined as per the definition of prior medications in section 7.5.1.

### 7.5.4. Concomitant Procedures

Concomitant procedures will be defined as procedures which started on or after the first dose of active medication in either the RVT-901-3003 or RVT-901-3004 studies or which were started prior to and were ongoing at the date of first dose of active medication in either the RVT-901-3003 or RVT-901-3004 studies. Partial procedure start dates will be imputed as detailed in Section 6.3.

# 8. Efficacy

Throughout the trial, patients were required to fill out an event and volume diary. It was intended for the patients to fill out the voiding diary for 7 days prior to the Baseline (during Run-in), Week 2, 4, 8, and 12 visits (RVT-901-3003) and Week 16, Week 24, Week 44 and Week 52 visits (RVT-901-3004), and to fill out the volume portion of the diary for 1 of the 7 diary days for each visit. Duplicate data entry in diary rows with identical values will not be removed.

The definitions of a “Diary Day”, “Complete Diary Day”, and Baseline are given in Section 6.3.

In order for a patient to have an evaluable change from baseline, the patient must have both a complete baseline diary and a complete post-baseline diary from any post-baseline timepoint (i.e., Week 16, Week 24, Week 44 or Week 52). Change from baseline is defined as the post-baseline assessment minus the baseline assessment.

In general, the Full Analysis Set Extension (FAS-Ext) will be used for all non-incontinence efficacy endpoints. The FAS-Ext-I will be used for all incontinence efficacy endpoints; these are the endpoints related to urge urinary incontinence (UUI) episodes and total incontinence episodes.

Note that for all endpoints the definition of baseline is the baseline value from the RVT-901-3003 study.

## 8.1. Secondary Efficacy Endpoints

### 8.1.1. Change from baseline (CFB) at Week 52 in average number of micturitions per 24 hours in all OAB patients

In this study, the number of micturitions is defined as the number of times a patient has voided in the toilet as indicated on the Voiding diary. 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 a voiding diary, consisting of at least 4 complete diary days. The FAS-Ext will be the analysis population for the micturition endpoint.

A mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation will be used as the primary analysis model for change from baseline in average number of daily micturitions at Week 52. This model includes data from Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, Week 44 and Week 52 and corrects for data that is missing at random (MAR), accounting 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 MAR-free population. This model will be restricted to patients who were randomized to a planned 52-weeks of active treatment. No imputation of missing data is required for this analysis. The analysis model will include terms for treatment, visit, OAB Type (Wet vs Dry), Sex (Female vs Male), baseline score, and interaction of visit by treatment. Only baseline stratification factors (OAB Type, and Sex) found to be statistically significant in RVT-901-3003 will be included in the models. Since this extension study is US only, Region will not be included in the model.

Estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment at each time point.

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 will be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, the following structures will be investigated: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR (1)], heterogeneous compound symmetry (HCS), and compound symmetry (CS). The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used.

An example of the SAS code for the base procedure is given below:

```
proc mixed data = data_active_3003 method = reml ;
      class TRTP1 AVISITN USUBJID OABTYPE SEX ;
      model CHG = TRTP1 AVISITN OABTYPE SEX BASE
            TRTP1*AVISITN / ddfm=KR solution chisq ;
      REPEATED AVISITN / subject=USUBJID type=UN r rcorr ;
      LSMEANS TRTP2*AVISITN / pdiff=all cl alpha=0.05 ;
run ;
```

Where TRTP1 is the planned treatment from RVT-901-3003, AVISITN is the visit number, USUBJID is the unique patient identifier, OABTYPE indicates if the patient is Dry or Wet, SEX is female or male, and BASE indicates baseline value. Data_active_3003 includes only patients who were randomized to active treatment in RVT-901-3003.

#### 8.1.2. CFB at Week 52 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients

The average number of UUI episodes will be defined as the total number of times a patient has checked "urge" as the main reason for accidental urine leakage, regardless of whether more than one reason is checked, on a Completed Diary Day divided by the number of Complete Diary Days in a voiding diary. Average daily urge urinary incontinence episodes at each study visit will be calculated as described above in Section 8.1.1 for the micturition endpoint with the exclusion of the term for OAB type from the model. Estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group at each time point using the method described in Section 8.1.1.

The FAS-Ext-I will be the analysis population for all UUI analyses.

#### 8.1.3. CFB at Week 52 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients

In this study, the number of urgency episodes is defined as the number of times a patient has marked the "need to urinate immediately" on a completed diary day divided by the number of complete diary days in a voiding diary. Average daily urgency episodes at each study visit will be calculated and analyzed in the same manner as described in Section 8.1.1. Estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group at each time point using the method described in Section 8.1.1.

The FAS-Ext will be the analysis population for the urgency episodes endpoint.

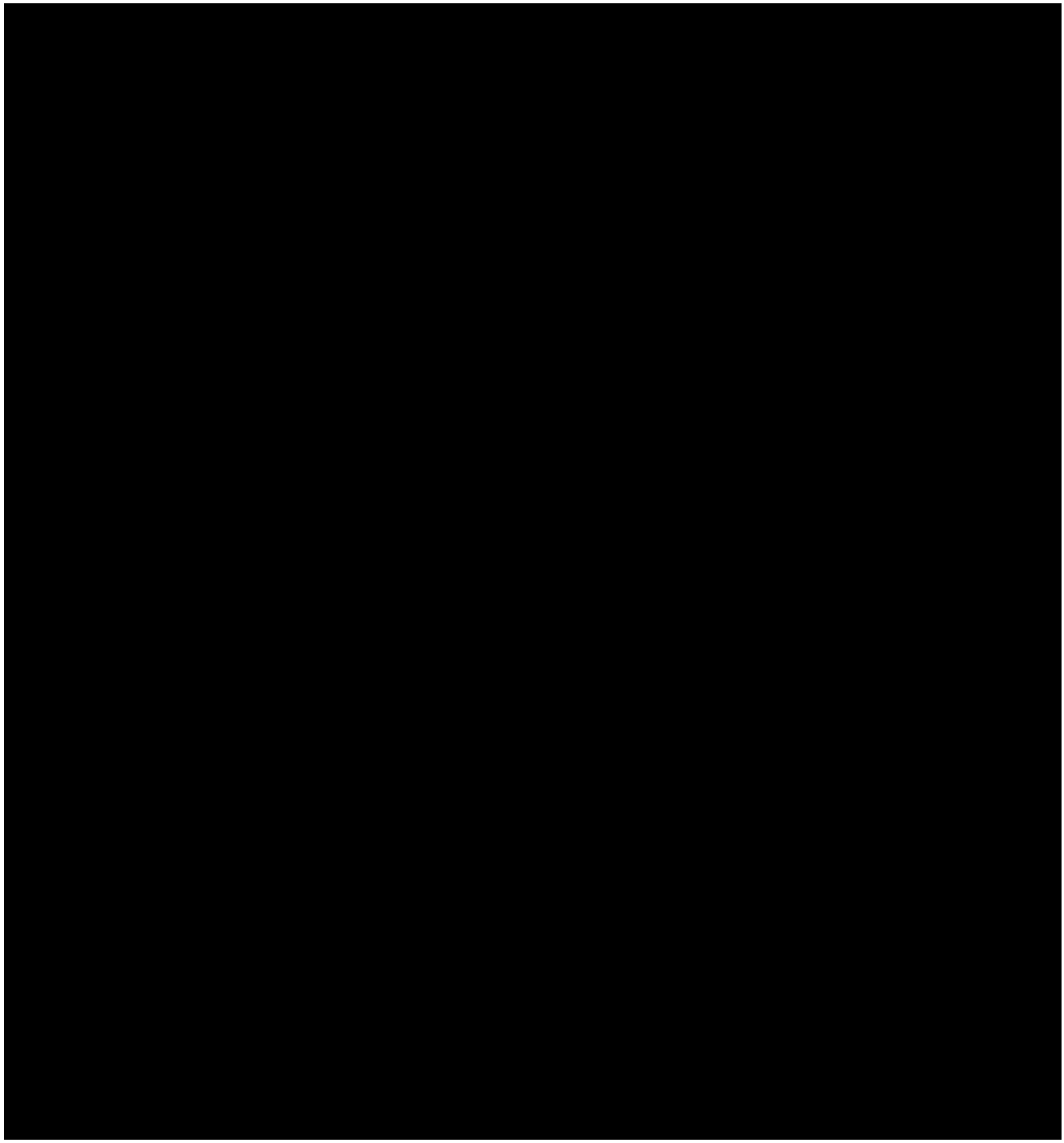
#### 8.1.4. CFB at Week 52 in average number of total urinary incontinence episodes over 24 hours in OAB Wet patients

The number of total incontinence episodes will be defined as the number of times a patient has checked the accidental urine leakage box in the voiding diary. Average daily total incontinence episodes at each

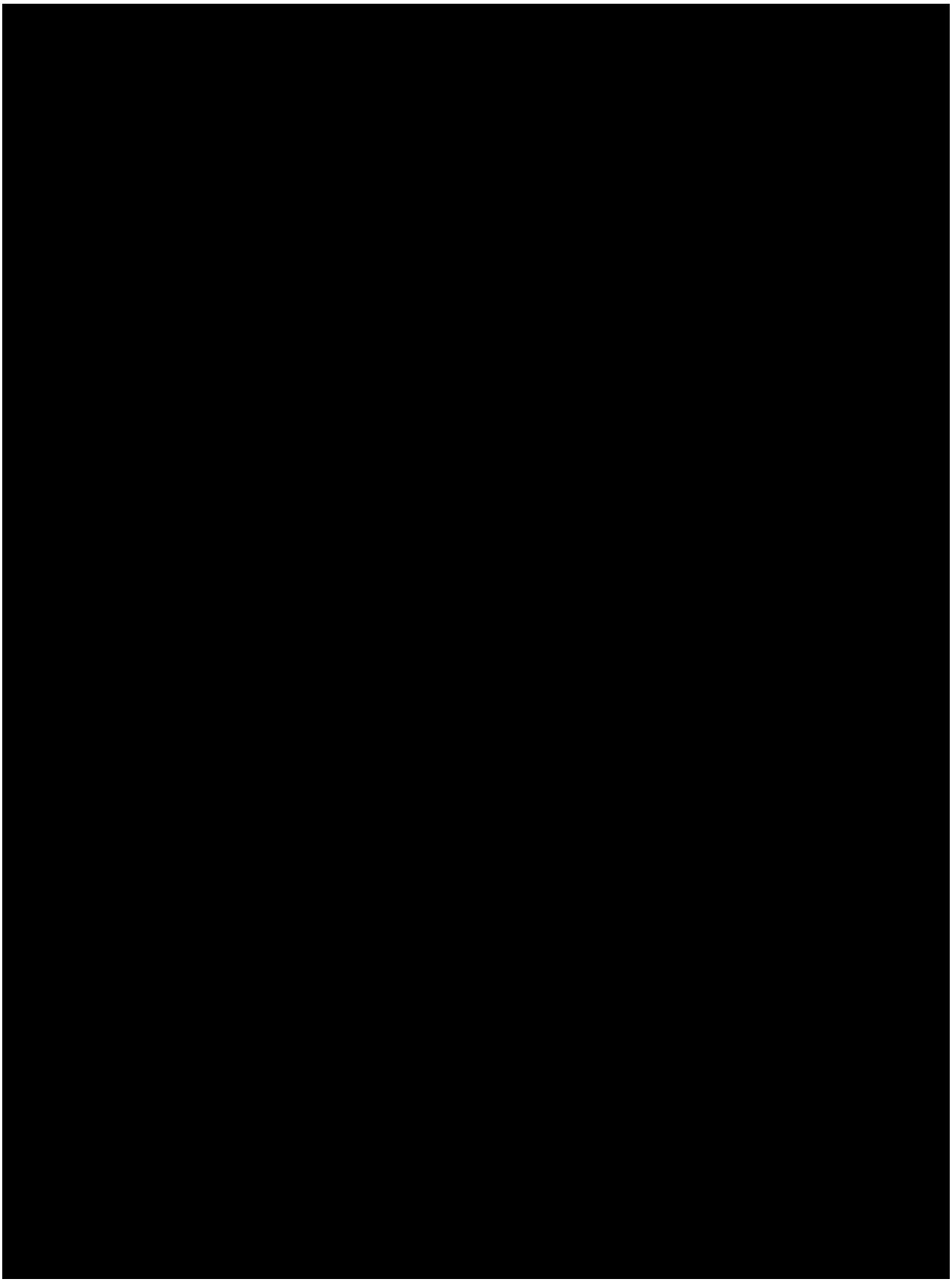
study visit will be calculated and analyzed in the same manner as described in Section 8.1.1. Estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group at each time point using the method described in Section 8.1.1 with the exclusion of the term for OAB type from the model .

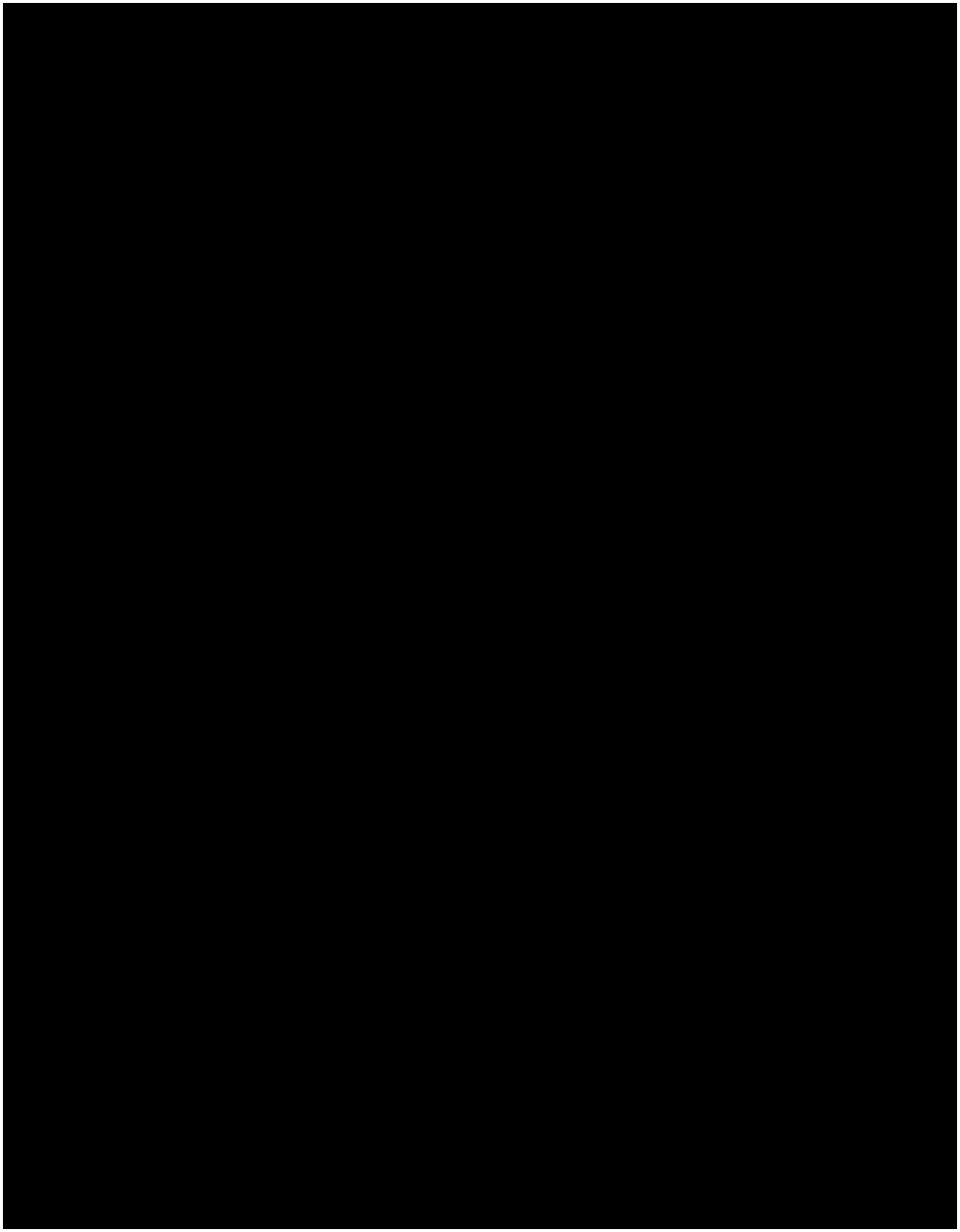
The FAS-Ext-I will be the analysis population for the total incontinence endpoint.

## 8.2. Exploratory Endpoints



[redacted]





# 9. Safety

The SAF-Ext will be used for all safety analyses. Safety will be assessed on the basis of AE reports, clinical laboratory data, extent of exposure and compliance, ECGs, physical examinations, and vital signs.

No inferential statistical testing is planned on the safety data, all data will be summarized and listed only.

No imputation will be performed for missing safety data (except for the case of partially missing dates in order to assign to study periods). Baseline will be defined as the last non- missing value before treatment in RVT-901-3003.

## 9.1. Extent of Exposure

The duration of exposure during the active treatment period will be expressed as the time in days from the first active treatment through to last active treatment day (inclusive). This is given by the following formula:

$$Duration\ (days) = date\ last\ double\ blind\ active\ dose - date\ first\ double\ blind\ active\ dose + 1$$

Duration of exposure will be summarized for the SAF-Ext using summary statistics for continuous variables.

All data will be listed. The treatment period will be dependent upon randomized treatment in RVT-901-3003. Patients randomized to active treatment in RVT-901-3003 will have up to 52-weeks exposure while patients randomized to placebo in RVT-901-3003 and active treatment in RVT-901-3004 will have up to 40-weeks exposure.

## 9.2. Treatment Compliance

During the RVT-901-3003 and RVT-901-3004 studies, when bottles were not returned, sites were instructed to have the patients estimate the quantity dosed (documented in source) and that information was recorded in the drug tracking database (suvoda). When the quantity dosed has been recorded (regardless of whether or not the bottle was returned), the quantity dosed indicated by site is used to calculate the number of doses received. If the bottle was returned and no quantity dosed information has been recorded then the number of doses received is calculated as the number of capsules/tablets dispensed – number of capsules/tablets returned. If no bottles were returned and no quantity dosed information has been recorded then the number of doses received is assumed to be all capsules/tablets dispensed.

Study treatment compliance (%) will be calculated as the actual number of doses received in RVT-901-3004 divided by the expected number of doses in RVT-901-3004, multiplied by 100 and summarized by treatment group.

All data will be listed.

## 9.3. Adverse Events / Adverse Drug Reactions

AEs will be coded using MedDRA version 20.0 or later.

Adverse event datasets for RVT-901-3003 and RVT-901-3004 are to be combined for this analysis. Full details will be specified in the SDTM specification and define documents. For patients randomized to placebo in RVT-901-3003, adverse events occurring during RVT-901-3003 will be reported as medical history. For patients randomized to active treatment in RVT-901-3003, adverse events which are ongoing

at the end of RVT-901-3003 will be combined with information from RVT-901-3004 so that each patient's adverse event is only included once.

All reported AEs (whether treatment emergent or not) will be included in by-patient AE listings. The AE listing will have a column indicating if the onset of the AE by period. Sorting will be by site, patient, onset date of event, SOC, PT and then verbatim description.

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

An AE will be considered treatment emergent (TEAE) if it begins or worsens in severity after the first dose of active Study Treatment through 28 days after the last dose of Study Treatment, or the date of initiation of another investigational agent or surgical intervention, whichever occurs first. Partial AE start dates will be imputed as detailed in Section 6.3.

A Serious Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is another medically important condition

In addition, any illnesses reported before starting active treatment or AE meeting the criteria of seriousness (as defined above) and considered to be possibly related (according to the Investigator) to any study-specific procedure (e.g., laboratory testing procedure, liver biopsy) must be reported as an SAE.

Summary tables will be based on treatment emergent adverse events (TEAEs). The incidence of TEAEs will be presented using counts and percentages of patients with TEAEs and tabulated by SOC and PT. SOC will be sorted in descending frequency and PT within SOC will be sorted by descending frequency based on the incidence across patients overall. If a patient has multiple occurrences (start and stop) of an event associated with a specific SOC or PT within a SOC, a patient will only be counted once in the incidence count for the SOC or PT within SOC respectively.

An overall summary table of AEs by treatment group will be presented detailing the number and percentage of patients, and number of events for the following categories:

- At least one TEAE;
- At least one Treatment-Related TEAE;
- At least one Grade ≥ 3 TEAE;
- At least one Grade ≥ 3 Treatment-Related TEAE;
- At least one Serious TEAE;
- At least one Serious Treatment-Related TEAE;
- At least one TEAE leading to Discontinuation from Study Medication;
- At least one TEAE of Clinical Interest;
- At least one Treatment-Related TEAE of Clinical Interest

The incidence of all TEAEs by SOC and PT will be presented for the following:

- All TEAEs;

- Treatment-Related TEAEs;
- TEAES with Grade ≥ 3;
- Serious TEAEs;
- Serious TEAEs with Grade ≥ 3;
- Treatment Related Serious TEAEs;
- TEAEs leading to Discontinuation from Study Treatment;
- Non-Serious TEAEs ≥ 5% Threshold
- Non-fatal TEAEs
- Hypertension TEAEs by Pre-existing Hypertension (Yes vs No) and Baseline Hypertension (Yes vs. No). Hypertension TEAEs will be selected as any TEAE with Preferred Term of Hypertension.

Treatment listings will include the treatment arm, start and stop dates/times of the AE, and days on study relative to the day of first dose of active study treatment.

A Treatment related AE is defined as an AE for which the investigator classifies the AE as being related to study treatment. To be conservative, the summary table will include events where the relationship to study treatment is missing. Missing severity for TEAEs will be counted as 'Severe'.

For the Non-Serious TEAEs ≥ 5% Threshold, it will include adverse events if the event occurs at an incidence of greater than or equal to 5% in any treatment arm. No rounding is allowed. If an adverse event occurs at an incidence of 4.8%, for example, the incidence will not be rounded up to 5% for the purposes of this table.

Treatment Emergent Adverse Events of Clinical Interest (AECI) and Treatment-Related TEAEs of Clinical Interest will also be summarized by SOC and PT. 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).

The following additional listings will be provided:

- Listing of deaths
- Listing of Serious TEAEs
- Listing of non-treatment-emergent SAEs
- Listing of TEAEs leading to withdrawal or temporary withdrawal of study treatment
- Listing of all AEs with a flag for TEAEs and onset (Prior = prior to first dose of active medication, , or Treatment = on or after first dose of active medication.)

A summary of all TEAEs by maximum intensity (mild, moderate, severe, life-threatening, death), SOC, and PT will be presented, where the maximum intensity per patient will be counted at each level of summarization. In addition, a summary of all TEAEs by relationship to study treatment (related, not related), SOC and PT will be presented, where all relationships to study treatment per patient will be counted at each level of summarization. A summary of all TEAEs by PT occurring in at least 2% of subjects in the vibegron arm will be created and sorted by descending frequency in the vibegron arm.

A listing of all Medical History and pre-double-blind treatment adverse events with coded preferred terms belonging to the standard MedDRA query (SMQ) of Hypertension will be created.

## 9.4. Laboratory Evaluations

Laboratory tests will be performed at Screening and periodically throughout the study as described in Section 3.8. Laboratory test data from RVT-901-3003 and RVT-901-3004 will be combined for the subset of patients in RVT-901-3004 for the active treatment period in RVT-901-3003. Only data collected by the central laboratory will be included in the analyses and standard international units will be used for all summaries. Laboratory tests within each category and scheduled visit are given in Table 9.4.1.

**Table 9.4.1: Laboratory Tests**

| Laboratory Category | Laboratory Tests Included (Central Lab) |
|---|---|
| Hematology | Hematocrit, Hemoglobin, RBC, Platelet Count, WBC (total and differential) |
| Chemistry | Albumin, Alkaline Phosphatase, ALT, AST, Bicarbonate, Calcium, Chloride, Creatinine, Glucose (fasting and non-fasting), Potassium, Sodium, Total Bilirubin, Direct Bilirubin, BUN, Total Cholesterol, eGFR |
| Urinalysis[a] | Blood, Glucose, Protein, Specific gravity, Microscopic exam (RBC, WBC, epithelial cells and bacteria), pH, Color, and Urine pregnancy test (β-hCG)b |
| Other | Serum β-human chorionic gonadotropin (β-hCG), where applicable |

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.

Actual (observed) values and changes from baseline in hematology and chemistry laboratory parameters will be summarized by treatment group at each scheduled visit. The number and percentage of subjects with laboratory measurements outside of the central laboratory normal range will also be summarized by treatment group and visit. Shift tables from baseline to maximum post-baseline value, to minimum post-

baseline value, last post-baseline value, and at each post-baseline visit will be provided to display low, normal, high, and missing values by treatment group in a 3-by-3 contingency table. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and baseline.

Actual (observed) values in urinalysis and other laboratory parameters will be summarized by treatment group. The number and percentage of subjects with laboratory measurements outside of the central laboratory normal range will also be summarized by treatment group and visit.

All data will be listed. Any data outside the central laboratory normal reference ranges will be explicitly noted on the listings that are produced.

### 9.5. Vital Signs

The following vital sign data will be collected at all study visits:

- SBP (mmHg)
- DBP (mmHg)
- Pulse Rate (beats/min)
- Respiration Rate
- Temperature
- Weight (Kg)
- Height (cm) measured at Screening Only

For all parameters, actual (observed) values and change from baseline will be presented for scheduled visits using descriptive statistics for continuous variables. The vital sign result at a particular visit for an individual is the mean of the triplicate observations at that visit. This mean value will be used as the individual's result in all summaries.

[redacted]

A shell of this table is given in the SAP shells document. A by-patient listing, sorted by patient identifier, will be presented including all vital sign results (scheduled or unscheduled).

### 9.6. ECG

12-Lead ECG data will be collected at unscheduled assessments. All data collected will be listed.

### 9.7. Physical Examination

Physical examination data will be collected at Visit #12 (Folow-up) and unscheduled assessments. Physical examination results will be listed.

### 9.8. Post-Void Residual (PVR) Urine Volume

PVR Urine volume (mL) data will be summarized at Baseline, Week 12, 24, 40 and 52 by treatment group. Week 12 measurements from RVT-901-3003 will be NA for patients in 40-week treatment groups. The summary will comprise of a continuous summary at each visit, including change from baseline, and a categorical summary of PVR at the following categories: <100 mL, ≥ 100 and < 200 mL, ≥200 and < 350

mL, ≥ 350 mL. The summary will also be presented separately by the following subgroups: Sex (Male vs Female), BPH (Males with BPH vs Males Without BPH). PVR data will also be listed.

# 10. Changes from Analysis Planned in Protocol

ECG measurements are specified in the protocol for Visit #6 (Week 12) and Physical Examinations at Visit #6 (Week 12). These were specified in error and are not conducted. ECG measurements and Physical Examinations are conducted at unscheduled assessments only and will be analyzed per Section 9.6 and 9.7 respectively.

# 11. Reference List

1. Coyne KS, Gelhorn H, Thompson C, Kopp ZS, Guan Z.The psychometric validation of a 1-week recall period for the OAB-q. Int Urogynecol J. 2011;22(12):1555-1563.

2. Matza LS, Thompson C L, Krasnow J, Brewster-Jordan J, Zyczynski T, Coyne K S. Test-retest reliability of four questionnaires for patients with overactive bladder: The overactive bladder questionnaire (OAB-q), patient perception of bladder condition (PPBC), urgency questionnaire (UQ), and the primary OAB symptom questionnaire (POSQ). Neurourol. Urodyn. 2005; 24(3): 215–225.

3. REILLY ASSOCIATES. (2017). WPAI Scoring. Available: http://www.reillyassociates.net/WPAI_Scoring.html . Last accessed 08/28/2017.

4. EuroQol. (2017). EQ-5D Instruments | About EQ-5D. Available: https://euroqol.org/. Last accessed 08/28/2017.

5. Coyne KS, Thompson CL, Lai JS, Sexton C. An Overactive Bladder Symptom and Health-Related Quality of Life Short-Form: Validation of the OAB-q SF. Neurourology and Urodynamics 34:255–263 (2015)

# 12. Programming Considerations

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

## 12.1. General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rtf format.
- Numbering of TFLs will follow ICH E3 guidance .

## 12.2. Table, Listing, and Figure Format

### 12.2.1. General

- All TFLs will be produced in landscape format on American letter size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

### 12.2.2. Headers

- All output should have the following header at the top left of each page:
- Urovant Sciences Protocol RVT-901-3004 ([redacted])

- Draft/Final Run <*date*>
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

12.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

| Severity Rating | N |
|---|---|
| severe | 0 |
| moderate | 8 |
| mild | 3 |

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

| | |
|---|---|
| N | XX |
| Mean | XXX.X |
| Std Dev | X.XX |
| Median | XXX.X |
| Minimum | XXX |
| Maximum | XXX |

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment

group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

#### 12.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.

- Missing data are represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

#### 12.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

### 12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Patient specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

# 13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in [redacted]

[redacted] describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

# 14. Index of Tables

| Header | Table Number | Name | Analysis Set |
|---|---|---|---|
| 14. | | Tables, Figures, and Graphs Referred to but not Included in the Text | |
| 14.1 | | Demographic Data Summary Tables | |
| 14.1.1 | | Patient Disposition | |
| | 14.1.1.1 | Patient Disposition | Screened Set Extension |
| | 14.1.1.2 | Patient Disposition | Randomized Set Extension |
| | 14.1.1.3 | Patient Randomization by Country and Investigator | Randomized Set Extension |
| 14.1.2 | | Protocol Deviations | |
| | 14.1.2.1 | Major Protocol Deviations | FAS-Ext |
| | 14.1.2.2 | Reasons for Exclusion from Analysis Sets | Randomized Set Extension |
| 14.1.3 | | Demographic and Baseline Characteristics | |
| 14.1.3.1 | | Patient Demographic and Baseline Characteristics | |
| | 14.1.3.1.1 | Patient Demographic and Baseline Characteristics | SAF-Ext |
| | 14.1.3.1.2 | Patient Demographic and Baseline Characteristics | FAS-Ext |
| | 14.1.3.1.3 | Patient Demographic and Baseline Characteristics | FAS-Ext-I |
| | 14.1.3.1.4 | Patient Demographic and Baseline Characteristics | PPS-Ext |
| | 14.1.3.1.5 | Patient Demographic and Baseline Characteristics | PPS-Ext-I |
| 14.1.3.2 | | Baseline Disease Characteristics | |
| | 14.1.3.2.1 | OAB Characteristics at Baseline Last Voiding Diary Data Prior to Double-Blind Study Medication | SAF-Ext |
| | 14.1.3.2.2 | OAB Characteristics at Baseline Last Voiding Diary Data Prior to Double-Blind Study Medication | FAS-Ext |
| | 14.1.3.2.3 | OAB Characteristics at Baseline Last Voiding Diary Data Prior to Double-Blind Study Medication | FAS-Ext-I |
| | 14.1.3.2.4 | OAB Characteristics at Baseline Last Voiding Diary Data Prior to Double-Blind Study Medication | PPS-Ext |
| | 14.1.3.2.5 | OAB Characteristics at Baseline Last Voiding Diary Data Prior to Double-Blind Study Medication | PPS-Ext-I |
| 14.1.3.3 | | Medical History | |
| | 14.1.3.3.1 | Medical History | SAF-Ext |
| 14.1.4 | | Medications | |
| | 14.1.4.1 | Prior Medications | SAF-Ext |
| | 14.1.4.2 | Prior OAB Medication | SAF-Ext |

| Header | Table Number | Name | Analysis Set |
|---|---|---|---|
| | 14.1.4.3 | Concomitant Medications Double Blind Period | SAF-Ext |
| 14.1.5 | | Treatment Compliance | |
| | 14.1.5.1 | Treatment Compliance Double-Blind Period | SAF-Ext |
| | 14.1.5.2 | Treatment Compliance Double-Blind Period | FAS-Ext |
| 14.2 | | Efficacy Data Summary Figures and Tables | |
| 14.2.1 | | Secondary Efficacy Parameters | |
| 14.2.1 | | Secondary Efficacy Parameter 1 – Change from baseline (CFB) at Week 52 in average number of micturitions per 24 hours in all OAB patients | |
| | 14.2.1.1 | Average Daily Number of Micturitions Descriptive Statistics | FAS-Ext |
| | 14.2.1.2 | Change from Baseline in Average Daily Number of Micturitions (MMRM) | FAS-Ext |
| | 14.2.1.3 | Average Daily Number of Micturitions Descriptive Statistics | PPS-Ext |
| | 14.2.1.4 | Change from Baseline in Average Daily Number of Micturitions (MMRM) | PPS-Ext |
| 14.2.2 | | Secondary Efficacy Parameter 2 – CFB at Week 52 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients | |
| | 14.2.2.1 | Average Daily Number of UUI Episodes Descriptive Statistics | FAS-Ext-I |
| | 14.2.2.2 | Change from Baseline in Average Daily Number of UUI Episodes | FAS-Ext-I |
| | 14.2.2.3 | Average Daily Number of UUI Episodes Descriptive Statistics | PPS-Ext-I |
| | 14.2.2.4 | Change from Baseline in Average Daily Number of UUI Episodes | PPS-Ext-I |
| 14.2.3 | | Secondary Efficacy Parameter 3 - CFB at Week 52 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients | |
| | 14.2.3.1 | Average Daily Number of Urgency Episodes Descriptive Statistics | FAS-Ext |
| | 14.2.3.2 | Change from Baseline in Average Daily Number of Urgency Episodes | FAS-Ext |
| | 14.2.3.3 | Average Daily Number of Urgency Episodes Descriptive Statistics | PPS-Ext |
| | 14.2.3.4 | Change from Baseline in Average Daily Number of Urgency Episodes | PPS-Ext |
| 14.2.4 | | Secondary Efficacy Parameter 4 - CFB at Week 52 in average number of total urinary incontinence episodes over 24 hours in OAB Wet patients | |
| | 14.2.4.1 | Average Number of Total Urinary Incontinence Episodes Descriptive Statistics | FAS-Ext-I |
| | 14.2.4.2 | Change from Baseline in Average Number of Total Urinary Incontinence Episodes | FAS-Ext-I |
| | 14.2.4.3 | Average Number of Total Urinary Incontinence Episodes Descriptive Statistics | PPS-Ext-I |

| Header | Table Number | Name | Analysis Set |
|---|---|---|---|
| | 14.2.4.4 | Change from Baseline in Average Number of Total Urinary Incontinence Episodes | PPS-Ext-I |
| 14.2.5 | | Exploratory Efficacy Parameters | |
| | | [redacted] | |
| 14.3 | | Safety Data Summary Tables | |
| 14.3.1 | | Adverse Events | |
| | 14.3.1.1 | Overall Summary of Treatment Emergent Adverse Events | SAF-Ext |
| | 14.3.1.2 | Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.3 | Summary of Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.4 | Summary of Treatment Emergent Adverse Events with Grade ≥ 3 by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.5 | Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.6 | Summary of Serious Treatment Emergent Adverse Events with Grade ≥ 3 by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.7 | Summary of Serious Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term | SAF-Ext |

| Header | Table Number | Name | Analysis Set |
|---|---|---|---|
| | 14.3.1.8 | Summary of Treatment Emergent Adverse Events Leading to Discontinuation from Study Treatment by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.9 | Summary of Treatment Emergent Adverse Events of Clinical Interest by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.10 | Summary of Related Treatment Emergent Adverse Events of Clinical Interest by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.11 | Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity | SAF-Ext |
| | 14.3.1.12 | Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship | SAF-Ext |
| | 14.3.1.13 | Summary of Treatment Emergent Adverse Events Occurring in >2% of the Vibegron arm by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.14 | Summary of Treatment Emergent Adverse Events by Preferred Term | SAF-Ext |
| | 14.3.1.15 | Summary of Treatment Emergent Adverse Events Occurring in >2% of the Vibegron Arm by Preferred Term | SAF-Ext |
| | 14.3.1.16 | Summary of Non-Serious Treatment Emergent Adverse Events Occurring in >=5% Threshold by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.17 | Summary of Non-Fatal Treatment Emergent Adverse Events by System Organ Class and Preferred Term | SAF-Ext |
| | 14.3.1.18 | Summary of Hypertension Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Pre-Existing Hypertension Category | SAF-Ext |
| | 14.3.1.19 | Summary of Hypertension Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Baseline Hypertension Category | SAF-Ext |
| | 14.3.1.20 | Post Void Residual Urine Volume (mL) Descriptive Statistics | SAF-Ext |
| | 14.3.1.21 | Post Void Residual Urine Volume (mL) by Subgroups Descriptive Statistics | SAF-Ext |
| 14.3.2 | | Listings of Deaths, Other Serious and Significant Adverse Events | SAF-Ext |
| | 14.3.2.1 | Listing of Deaths | SAF-Ext |
| | 14.3.2.2 | Listing of Serious Treatment Emergent Adverse Events | SAF-Ext |
| | 14.3.2.3 | Listing of Treatment Emergent Adverse Events Leading to Temporary or Permanent Withdrawal of Study Medication | SAF-Ext |

| Header | Table Number | Name | Analysis Set |
|---|---|---|---|
| 14.3.3 | Not to be used for any Tables | Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events | Completed by Medical Writer |
| 14.3.4 | | Abnormal Laboratory Value | |
| 14.3.4.1 | | Clinical Laboratory Data | |
| 14.3.4.1.1 | | Hematology Data | |
| | 14.3.4.1.1.1 | Hematology: Summary by Visit and Change from Baseline | SAF-Ext |
| | 14.3.4.1.1.2 | Hematology: Proportion of Abnormal Results by Study Visit | SAF-Ext |
| | 14.3.4.1.1.3 | Hematology: Shift from Baseline Grade/Toxicity to Maximum Grade/Toxicity | SAF-Ext |
| 14.3.4.1.2 | | Clinical Chemistry Data | |
| | 14.3.4.1.2.1 | Clinical Chemistry: Summary by Visit and Change from Baseline | SAF-Ext |
| | 14.3.4.1.2.2 | Clinical Chemistry: Proportion of Abnormal Results by Study Visit | SAF-Ext |
| | 14.3.4.1.2.3 | Clinical Chemistry: Shift from Baseline Grade/Toxicity to Maximum Grade/Toxicity | SAF-Ext |
| 14.3.4.1.3 | | Urinalysis Data | SAF-Ext |
| | 14.3.4.1.3.1 | Urinalysis: Summary by Visit and Change from Baseline | SAF-Ext |
| | 14.3.4.1.3.2 | Urinalysis: Proportion of Abnormal Results by Study Visit | SAF-Ext |
| 14.3.4.2 | | Vital Signs | SAF-Ext |
| | 14.3.4.2.1 | Summary of Vital Sign Parameters | SAF-Ext |
| | 14.3.4.2.2 | Summary of Vital Sign Parameter Change from Baseline | SAF-Ext |
| | 14.3.4.2.4 | Summary of Vital Sign Parameter Change from Baseline by Pre-Existing Hypertension Category | SAF-Ext |
| | 14.3.4.2.4 | Summary of Vital Sign Parameter Change from Baseline by Baseline Hypertension Category | SAF-Ext |
| 14.3.4.3 | | Extent of Exposure | SAF-Ext |
| | 14.3.4.3.1 | Summary of Extent of Exposure to Study Drug | SAF-Ext |
| | 14.3.4.3.2 | Summary of Extent of Exposure to Study Drug | FAS-Ext |

# 15. Index of Figures

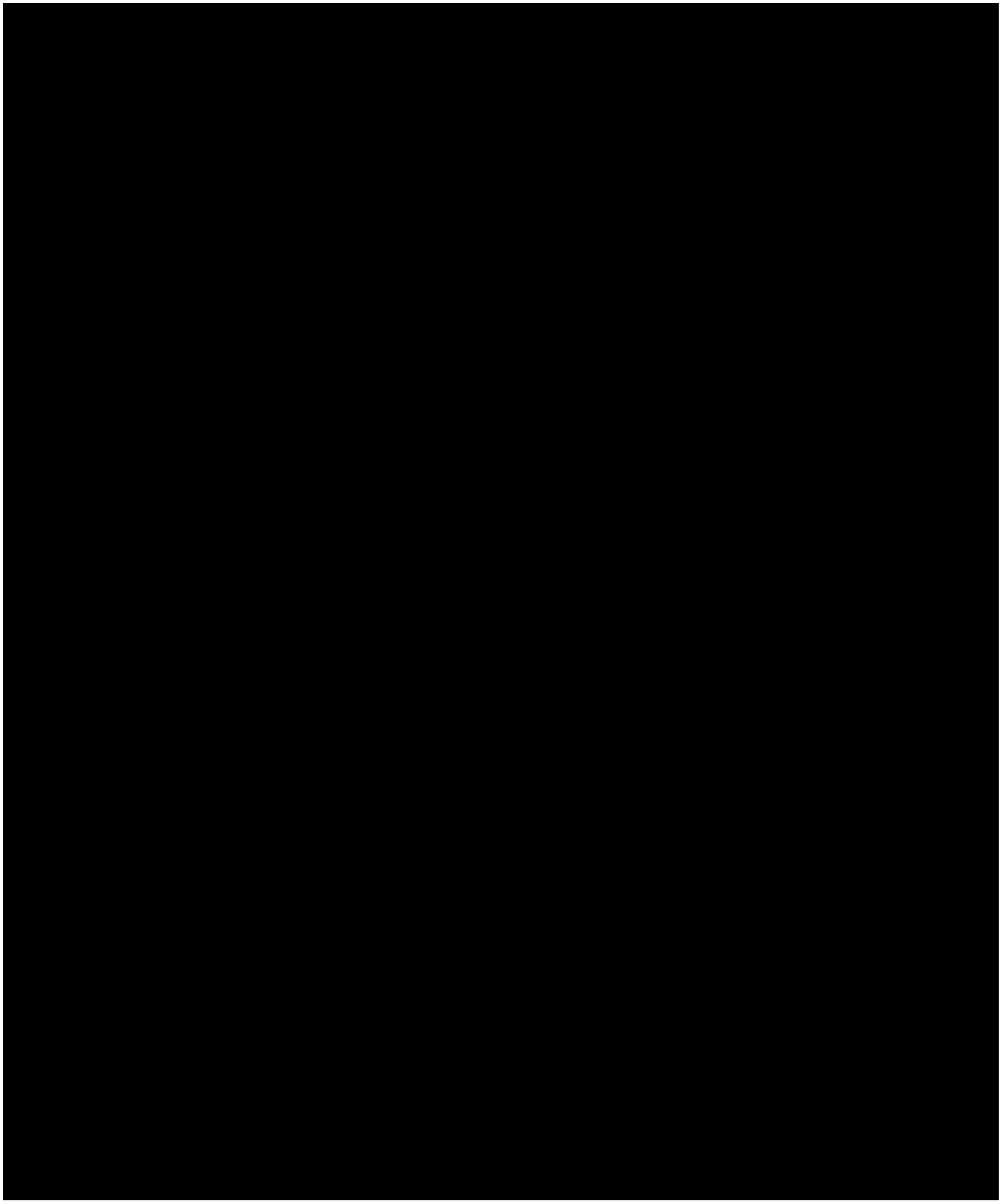
| Header | Table Number | Name | Analysis Set |
|---|---|---|---|
| 14. | | Tables, Figures, and Graphs Referred to but not Included in the Text | |
| 14.2.1 | | Secondary Efficacy Parameters | |
| 14.2.1 | | Secondary Efficacy Parameter 1 – Change from baseline (CFB) at Week 52 in average number of micturitions per 24 hours in all OAB patients | |
| | 14.2.1.5 | Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Micturitions | FAS-Ext |
| 14.2.2 | | Secondary Efficacy Parameter 2 – CFB at Week 52 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients | |
| | 14.2.2.5 | Plot of LS Means (SE) of Change from Baseline in Average Daily Number of UUI Episodes | FAS-Ext-I |
| 14.2.3 | | Secondary Efficacy Parameter 3 - CFB at Week 52 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients | |
| | 14.2.3.5 | Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Urgency Episodes | FAS-Ext |
| 14.2.4 | | Secondary Efficacy Parameter 4 - CFB at Week 52 in average number of total urinary incontinence episodes over 24 hours in OAB Wet patients | |
| | 14.2.4.5 | Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Total Incontinence | FAS-Ext-I |

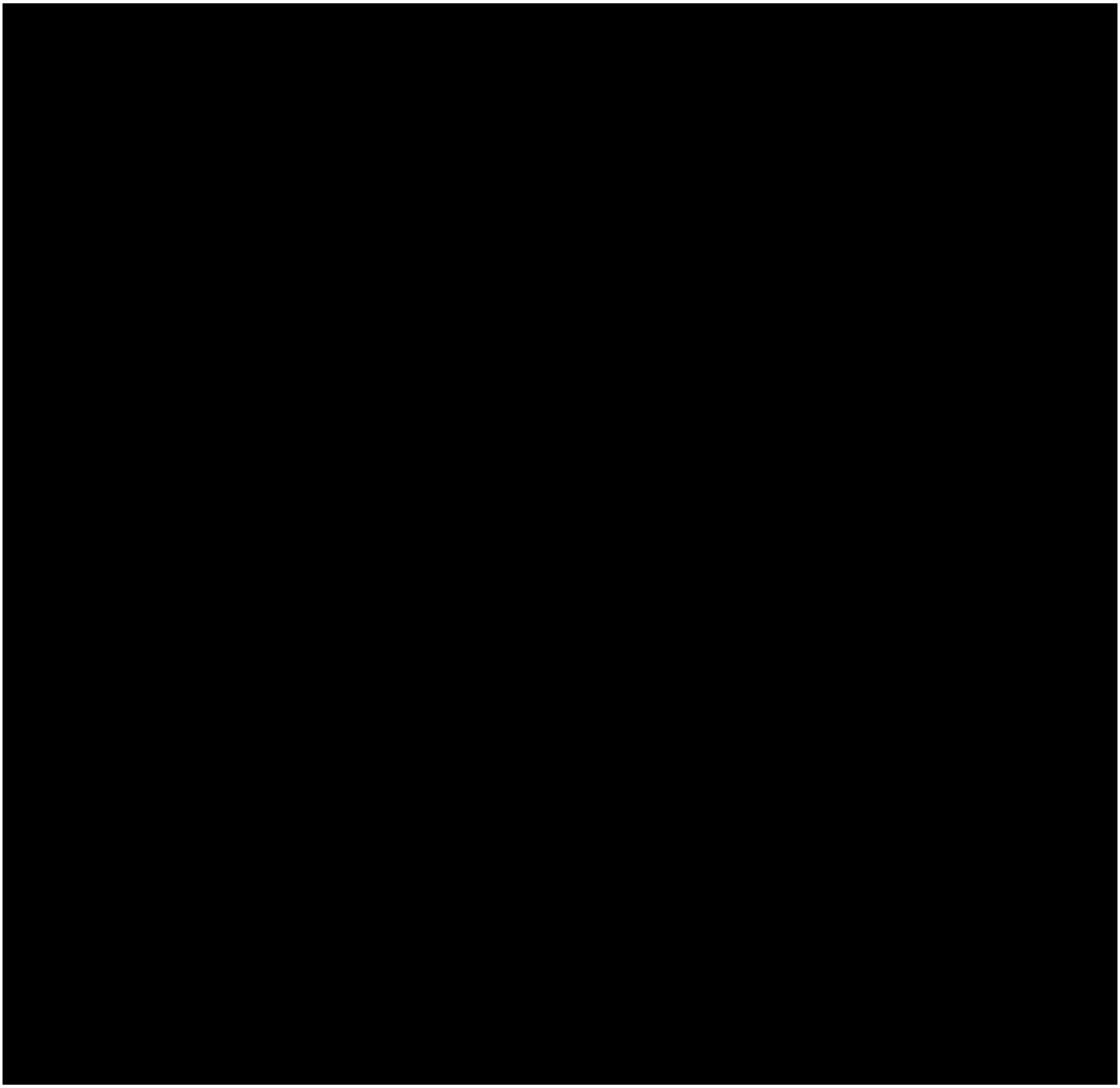
# 16. Index of Listings

| Header | Table Number | Name | Analysis Set |
|---|---|---|---|
| 16.2 | | Patient Data Listings | |
| 16.2.1 | | Discontinued Patients | |
| | 16.2.1.1 | Patient Disposition | Screened Set Extension |
| | 16.2.1.2 | Patient Disposition | Randomized Set Extension |
| 16.2.2 | | Protocol Deviations | |
| | 16.2.2.1 | Protocol Deviations | FAS-Ext |
| 16.2.3 | | Patients Excluded from the Efficacy Analysis | |
| | 16.2.3.1 | Inclusion Criteria | Screened Set Extension |
| | 16.2.3.2 | Exclusion Criteria | Screened Set Extension |
| | 16.2.3.3 | Exclusions from Analysis Sets | Randomized Set Extension |
| 16.2.4 | | Demographic Data | |
| | 16.2.4.1 | Demographics and Baseline Characteristics | SAF-Ext |
| | 16.2.4.2 | Medical History | SAF-Ext |
| | 16.2.4.3 | Prior Medications | SAF-Ext |
| | 16.2.4.4 | Concomitant Medications | SAF-Ext |
| | 16.2.4.5 | Prior OAB Medication in the Last 12 Months | SAF-Ext |
| | 16.2.4.6 | Concomitant Procedures | SAF-Ext |
| 16.2.5 | | Compliance Data | SAF-Ext |
| | 16.2.5.1 | Randomization and Treatment Administration | SAF-Ext |
| | 16.2.5.2 | Study Drug Accountability | SAF-Ext |
| | 16.2.5.3 | Study Drug Compliance | SAF-Ext |
| 16.2.6 | | Individual Efficacy Response Data | |
| | 16.2.6.1 | Derived Average Daily Diary Parameters | FAS-Ext |
| | 16.2.6.2 | Patient Urine Volume Chart | FAS-Ext |
| | 16.2.6.3 | Patient Diary Data | FAS-Ext |
| | 16.2.6.4 | Secondary Efficacy Endpoint: OAB-q LF | FAS-Ext |
| | 16.2.6.5 | Secondary Efficacy Endpoints: Global Impression Items | FAS-Ext |
| | 16.2.6.6 | Secondary Efficacy Endpoint: WPAI-US | FAS-Ext |
| | 16.2.6.7 | Secondary Efficacy Endpoint: EQ-5D-5L | FAS-Ext |
| 16.2.7 | | Adverse Event Listings | |
| | 16.2.7.1 | Listing of All Adverse Events | SAF-Ext |
| | 16.2.7.2 | Listing of All Adverse Events of Clinical Interest (AECI) | SAF-Ext |
| 16.2.8 | | Listing of individual laboratory measurements by patient | |
| | 16.2.8.1 | Clinical Laboratory Data | |
| | 16.2.8.1.1 | Listing of Hematology Laboratory Parameters | SAF-Ext |

| Header | Table Number | Name | Analysis Set |
|---|---|---|---|
| | 16.2.8.1.2 | Listing of Clinical Chemistry Laboratory Parameters | SAF-Ext |
| | 16.2.8.1.3 | Listing of Urinalysis Laboratory Parameters | SAF-Ext |
| | 16.2.8.1.4 | Listing of Other Laboratory Parameters | SAF-Ext |
| | 16.2.8.2 | Other Safety Data | |
| | 16.2.8.2.1 | Listing of Vital Signs | SAF-Ext |
| | 16.2.8.2.2 | Listing of Electrocardiogram (ECG) parameters | SAF-Ext |
| | 16.2.8.2.3 | Listing of Physical Examination | SAF-Ext |
| | 16.2.8.2.4 | Post Void Residual Volume | SAF-Ext |

# 17. Appendices





## Appendix 2. OAB-q-1 wk English-US-original

### Overactive Bladder Questionnaire (OAB-q)

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

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

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

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

## Overactive Bladder Questionnaire (OAB-q)

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

## Overactive Bladder Questionnaire (OAB-q)

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

## Appendix 3. Global Impression Items

### Patient Global Impression of Severity (PGI-Severity)

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

☐ None

☐ Mild

☐ Moderate

☐ Severe

### Patient Global Impression of Control (PGI-Control)

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

☐ Complete control

☐ A lot of control

☐ Some control

☐ Only a little control

☐ No control

### Patient Global Impression of Symptom Freq uency (PGI-Freq uency)

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

☐ Never

☐ Rarely

☐ Sometimes

☐ Often

☐ Very often

### Patient Global Impression of Urgency-Related Leakage (PGI-Leakage)

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

☐ Never

☐ Rarely

☐ Sometimes

☐ Often

☐ Very often

**Patient Global Impression of Change (PGI-Change)**

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

☐ Much better

☐ Moderately better

☐ A little better

☐ No change

☐ A little worse

☐ Moderately worse

☐ Much worse

## Appendix 4. Cover Note for Listings

For the following listings, the given questions are represented by numbers within the listing. The relevant mapping is shown below.

Listing 16.2.6.4
OAB-q LF Questions

During the past week, how bothered were you by…

1. Frequent urination during the daytime
2. An uncomfortable urge to urinate?
3. A sudden Urge to Urinate with little or no warning
4. Accidental loss of small amounts of urine?
5. Nighttime urination?
6. Waking up at night because you had to urinate?
7. An uncontrollable urge to urinate?
8. Urine loss associated with a strong desire to urinate?

During the past week how often have your bladder symptoms…

9. Made you carefully plan your commute?
10. Caused you to feel drowsy or sleepy during the day?
11. Caused you to plan “escape routes” to restrooms in public places?
12. Caused you distress?
13. Frustrated you?
14. Made you feel like there is something wrong with you?
15. Interfered with your ability to get a good night’s rest?
16. Caused you to decrease your physical activities (exercising, sports, etc.)?
17. Prevented you from feeling rested upon waking in the morning?
18. Frustrated your family and friends?
19. Caused you anxiety or worry?
20. Caused you to stay home more often than you would prefer?
21. Caused you to adjust your travel plans so that you are always near a restroom?
22. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?
23. Made you frustrated or annoyed about the amount of time you spend in the restroom?
24. Awakened you during sleep?
25. Made you worry about odor or hygiene?
26. Made you uncomfortable while traveling with others because of needing to stop for a restroom?
27. Affected your relationships with family and friends?
28. Caused you to decrease participating in social gatherings, such as parties or visits with family or friends?
29. Caused you embarrassment?
30. Interfered with getting the amount of sleep you needed?
31. Caused you to have problems with your partner or spouse?
32. Caused you to plan activities more carefully?
33. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?

Listing 16.2.6.4
EQ-5D Answers

Mobility

1. I have no problems walking about
2. I have some problems walking about
3. I am confined to bed

Self-Care

4. I have problems with self-care
5. I have some problems with washing or dressing myself
6. I am unable to wash or dress myself

Usual Activities

1. I have no problems with performing my usual activities
2. I have some problems with performing my usual activities
3. I am unable to perform my usual activities

Pain/ Discomfort

1. I have no pain or discomfort
2. I have moderate pain or discomfort
3. I have extreme pain or discomfort

Anxiety/ depression

1. I am not anxious or depressed
2. I am moderately anxious or depressed
3. I am extremely anxious or depressed