Statistical Analysis Plan

[redacted]

Sponsor Name: Urovant Sciences GmbH

Protocol Number and Title:	**RVT-901-3003** **An International Phase 3, Randomized, Double-Blind, Placebo- and Active (Tolterodine)-Controlled Multicenter Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder**
Protocol Version and Date:	**RVT-901-3003**
<Protocol Amendment numbers and dates>	**v3.0, 15NOV2018** **v2.1, 12FEB2018** **v2.0, 30JAN2018** **v1.2, 01NOV2017** **v1.1, 05OCT2017** **v1.0, 29SEP2017**
[redacted]	[redacted]
Author(s):	[redacted], [redacted], Biostats, Programming & Data Management, Urovant Sciences
	[redacted]
SAP Version:	3.1
SAP Version Date:	06-MAR-2019

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
1.0	30APR2018	[redacted]	Initial Release Version
2.0	20NOV2018		Additions to the efficacy section to include Multiple imputation instead of LOCF Minor changes to content to be in line with protocol version 2.1
3.0	05MAR2019		Updates to shells per Sponsor comments; Addition of section on deviations from Protocol; Minor changes to content to be in line with Protocol version 3.0.
3.1	06MAR2019		Minor update to allow for the possibility to transform data prior to modeling for primary analyses if assumptions for the model are grossly violated.

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

APPROVALS	
[redacted]	
[redacted]	Date (dd-Mmm-yyyy)
[redacted]	Date (dd-Mmm-yyyy)
[redacted], Biostatistics	
Urovant Sciences GmbH	
[redacted]	Date (dd-Mmm-yyyy)
Sponsor Contact [redacted]	
[redacted], Biostats, Programming & Data Management	

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AIC	Akaike's Information Criteria
ANCOVA	Analysis of Covariance
AR	Autoregressive
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
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
C_{24}	24h Concentration
CV	Coefficient of Variation
DBL	Database Lock
DBP	Diastolic Blood Pressure
DRM	Data Review Meeting
ECG	Electrocardiogram
EQ-5D	EuroQual 5 Dimension Questionnaire
FAS	Full Analysis Set
FAS-I	Full Analysis Set 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
MAR	Missing at Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	Minimum

Abbreviation	Description
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
OAB-d Type	eCRF Derived Baseline OAB Categorization
OAB-q	Overactive Bladder Questionnaire
PGI	Patient Global Impression
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PPS	Per-Protocol Set
PPS-I	Per-Protocol Set 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. The population pharmacokinetics (PK) analysis will be conducted independently and is out of the scope of this SAP. Only drug concentrations over time will be summarized.

2.2. Timings of Analyses

The primary analysis of efficacy and the analysis of safety and PK are planned after all patients complete the final study visit 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 efficacy of vibegron compared to placebo in patients with symptoms of overactive bladder (OAB), specifically the frequency of micturitions and frequency of urge urinary incontinence (UUI) episodes.

3.2. Secondary Objective

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

3.3. Safety Objectives

- To evaluate the safety and tolerability of treatment with vibegron.

3.4. Pharmacokinetic Objectives

- To characterize vibegron trough concentrations in patients with symptoms of OAB.

3.5. Exploratory Objectives

[redacted]

3.6. Brief Description

This is an international, Phase 3 randomized, double-blind, placebo-controlled with active control (tolterodine), parallel-group, multicenter study in men and women with OAB, to be conducted in conformance with ICH GCP. The study will assess the safety, tolerability, and efficacy of 75 mg vibegron versus placebo. Patients will be randomized 5:5:4 in a double-blind fashion to one of three treatment arms: vibegron 75 mg, placebo, or tolterodine ER 4 mg, all administered once daily for 12 weeks during the Treatment Period.

Patient participation in the study will be up to 17 weeks post randomization (including authorized windows). This study consists of a Screening Period (1 to 5 weeks), a single-blind Run-in Period (2 weeks), a randomized double-blind Treatment Period (12 weeks) and a Safety Follow-up Period (4 weeks). All patients who complete the Week 12 Visit may be offered the opportunity to enroll in a 40-week double-blind extension study RVT-901-3004 (which will be conducted under a separate protocol), until enrollment in that study is complete. Patients who do not enroll into the optional extension study will

have a Follow-up Visit approximately 28 days after the patient's last dose of Study Treatment (i.e., at Week 16 for patients who complete the Week 12 Visit, or approximately 4 weeks after withdrawal for patients who discontinue the study early). Additionally, Unscheduled Visit(s) may be arranged for patients with study-related safety concerns as needed.

3.7. Patient Selection

A full list of inclusion and exclusion criteria can be found in the RVT-901-3003 Clinical study Protocol Section 5.1.

3.8. Determination of Sample Size

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

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

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

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

Assuming that these endpoints are uncorrelated, this study has 96% power to reject both co-primary hypotheses at a two-sided 0.05 level. These alternative hypotheses are:

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

- **Co-Primary Alternative Hypothesis 2**: In patients with OAB Wet, vibegron 75 mg will have a different mean CFB in the average number of daily UUI episodes than placebo at Week 12.

3.9. Treatment Assignment and Blinding

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

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

Randomization will be stratified based on the investigator-determined baseline categorization of OAB, referred to as OAB Type: Wet or Dry (as defined in the protocol inclusion and exclusion criteria), and Sex (Female vs. Male).

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

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

A double-blind/masking technique will be used: vibegron and its matching placebo and tolterodine ER and its matching placebo will be packaged identically so that treatment blind/masking is maintained. The patient, the Investigator, and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the patients will not be aware of the treatment group assignments.

At the end of the study (including the 28-day Follow-up Period), the official, final database will be frozen and unblinded after medical/scientific review has been performed, and data have been declared final and complete. The Sponsor and [redacted] as designated representative will be granted access to the unblinded database in order to analyze the data. A clinical study report will be prepared after all patients complete the study.

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.

3.10. 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.

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

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.

3.11. Study Procedures and Flowchart

This study consists of a Screening Period (1 to 5 weeks), a single-blind Run-in Period (2 weeks), a randomized double-blind Treatment Period (12 weeks) and a Safety Follow-up Period (4 weeks). The schedule of activities is given in Table 3.11.1.

Table 3.11.1: Schedule of Activities

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

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

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

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

Table Footnotes:

Screening

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

Electronic Diary (eDiary)

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

eDiary Device

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

Patient Voiding Diary and Urine Volume Diary

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

Diary and Visit Reminders

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

Patient Reported Outcomes

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

Post Void Residual Volume

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

Physical/ECG/Vitals

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

Adverse Events

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

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

Prior and Concomitant Medications

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

Labs

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

Dosing/Drug

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

Pharmacokinetics Subset Only

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

Follow-up/Unscheduled

25. Unscheduled Visits and the specific procedures performed at these visits will be determined by the Investigator, as clinically indicated. The procedures indicated in the Schedule of Activities will be performed at these visits, as clinically indicated, based on the purpose of the visit (e.g., follow-up for an adverse event or abnormal laboratory test, study treatment dispensation). The reason for the visit will be captured in the source documents.

26. For Patients who do not enroll into the optional extension study (RVT-901-3004) or patients who withdraw from the study for any reason, a Follow-up Visit should be performed approximately 28 days after the last dose of Study Treatment on Study Day 113 or approximately 28 days after a patient's Withdrawal from the study. When a patient withdraws from the study prior to study completion, all applicable activities scheduled for the Week 12 Visit should be performed at the time of withdrawal.

4. ENDPOINTS

4.1. Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints for this trial are as follows:

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

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 a Complete Diary Day 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. Baseline is defined in Section 6.3.

The number of UUI episodes will be defined as the number of times a patient has checked that they had "urge" as the main reason for the leakage, regardless of whether more than one main 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.

4.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints for this study are as follows:

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

- CFB at Week 12 in Coping Score from the OAB-q LF (1-week recall) in all OAB patients
- CFB at Week 12 in average volume voided per micturition in all OAB patients

4.3. Additional Secondary Efficacy Endpoints

The additional secondary efficacy endpoints for this study are as follows:

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

4.4. Safety Endpoints

The following are the safety endpoints of this study:

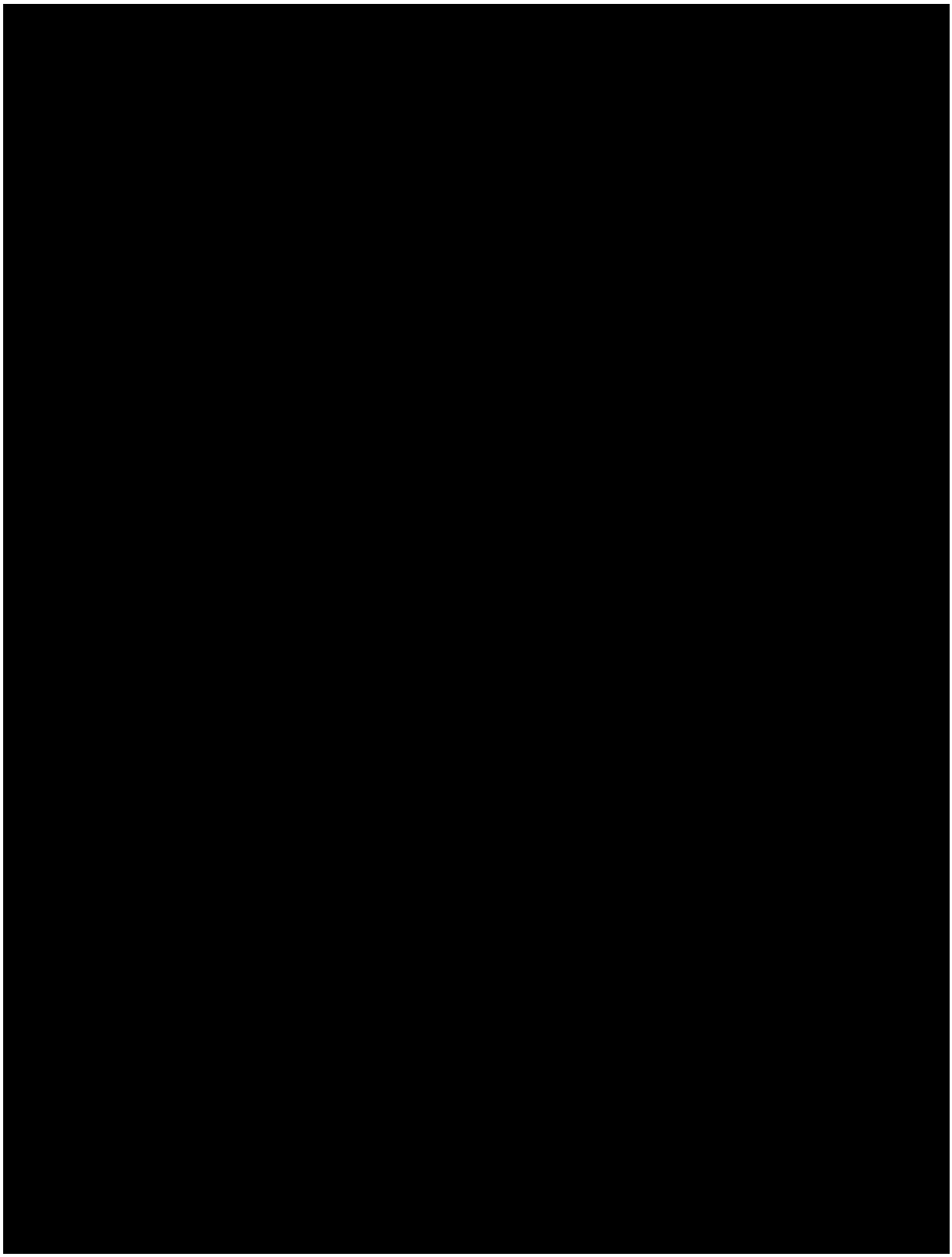
- Incidence of adverse events
- Clinical Laboratory Assessments
- Vital Signs and Physical Examinations

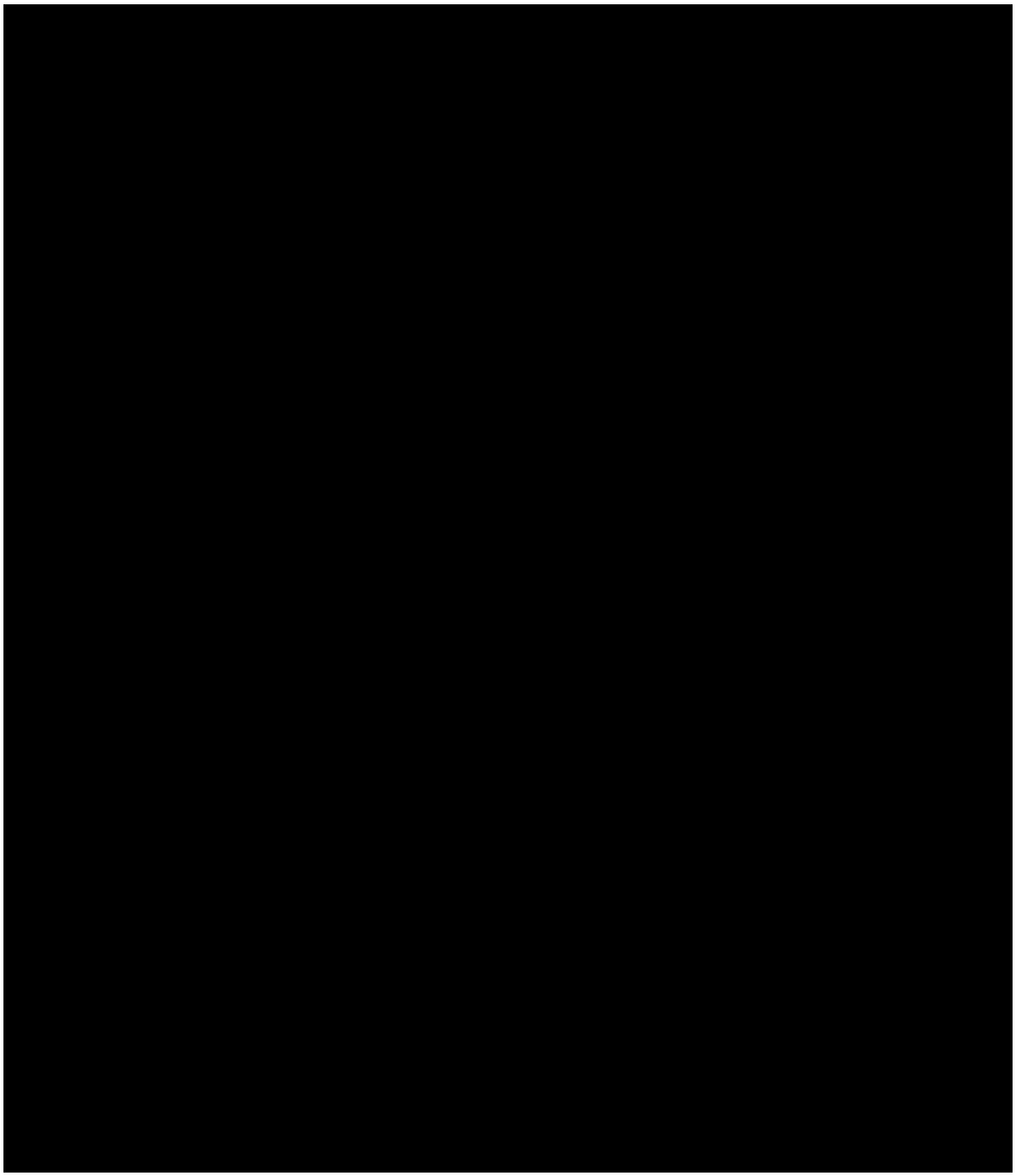
4.5. Pharmacokinetic Endpoints

The PK objective of this trial is to evaluate the trough concentrations of vibegron in patients with symptoms of OAB. These concentrations may be used in combination with other data in a population PK model, which is beyond the scope of the analyses in this SAP. Vibegron concentrations in plasma over time will be summarized.

4.6. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for this trial are as follows:





5. ANALYSIS SETS

5.1. Screened Set

The Screened Set comprises all patients who signed the informed consent form (ICF) and have screening data entered into the database. This set includes screen failures, run-in 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 starting the Run-in treatment.

[redacted]

5.2. Run-in Set

The Run-in Set comprises all patients who entered the Run-in period of the study (i.e., were treated with at least one dose of the Run-in treatment). Patients will be considered run-in failures if they enter the run-in period (i.e. have at least one dose of run-in medication) but are not randomized to receive double-blind medication.

[redacted]

5.3. Randomized Set

The Randomized Set comprises all patients who were randomized to receive double-blind treatment after completing the Run-in period.

[redacted]

5.4. Safety Set

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

[redacted]

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

No imputation will be performed for missing safety data (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.

5.5. Full Analysis Set

The Full Analysis Set (FAS) will serve as the primary population for the analysis of efficacy data in this study. Patients will be included in the treatment group to which they are randomized, regardless of which treatment they actually received, for the analysis of efficacy data using the FAS. 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 primary analysis population for incontinence endpoints.

The following FAS populations are defined in the study:

- Full Analysis Set (FAS): all randomized OAB patients who took at least one dose of double-blind study treatment and have at least one evaluable change from baseline micturition measurement
- Full Analysis Set for Incontinence (FAS-I): all randomized OAB Wet patients who took at least one dose of double-blind study treatment and have at least one evaluable change from baseline UUI measurement. The definitions of OAB criteria are presented in Protocol section 5.1.1 (Inclusion criterion 4), and section 6.3 of this document.

[redacted]

5.6. Per-Protocol Set

The Per-Protocol Set (PPS) and Per-Protocol Set for Incontinence (PPS-I) exclude patients from the FAS due to important deviations from the protocol that may substantially affect the results of the primary efficacy endpoints (i.e., Major PDs associated with efficacy). A supportive analysis using the PPS and PPS-I will be performed for the co-primary and key

secondary efficacy endpoints. The final determination on protocol deviations, and thereby the composition of the Per-Protocol 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 treatment group to which they are randomized, regardless of which treatment actually received, for the analyses of efficacy data using the PPS and PPS-I.

5.7. Pharmacokinetic Set

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

5.8. 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 and PPS-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(-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. Summary tables will be provided for all randomized patients. Unless otherwise specified; all demographic and baseline data will be presented by treatment arm and overall. Efficacy and safety data will be presented by treatment arm.

Although the formal analysis will compare vibegron with placebo, the comparisons between tolterodine and placebo will be reported with nominal p-values. No formal comparisons of vibegron vs. tolterodine are planned; all between-treatment analyses between these two groups 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, minimum, Q1, Q3 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 primary population for efficacy analysis will be the FAS for micturition endpoints while the FAS-I will be used for the following incontinence endpoints: UUI, total incontinence episodes, percent of dry diary days. Supportive efficacy analyses based on the PPS and PPS-I will be conducted for the primary and key secondary endpoints. The SAF will be used to conduct analyses of the safety endpoints. All PK data will be based on the PK Analysis set (PKS).

6.2. Testing Strategy and Multiplicity

A stepwise gate-keeping procedure will be used to control the overall Type-I error rate at α=0.05 level (two-sided) over the co-primary and key secondary hypotheses. If significance at the 0.05 level of both co-primary efficacy endpoints is achieved, then the key secondary efficacy endpoints will be tested sequentially in the predefined order given in Section 4.2. Once a key secondary efficacy endpoint is found to be insignificant (i.e., p-value $\geq$ 0.05), the testing procedure will stop. For all subsequent key secondary efficacy endpoints, nominal p-values will be provided but will not be considered a formal test of hypotheses.

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

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

A micturition/void is defined as “Urinated in Toilet” as indicated on the voiding diary.

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.

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

There will be two different definitions of OAB Categorization used for the study: OAB Type and OAB-d Type. OAB Type will be based on the randomization strata and OAB-d Type will be derived based on the baseline diary data, defined below. Details on the derivation of baseline patient voiding diary endpoints are presented further below in this section (Definition of Baseline for Patient Voiding Diary Endpoints).

OAB-d Type (Wet, Dry, Missing) will be categorized based on Baseline diary data, as follows:

OAB Wet: Patients are considered OAB Wet according to the following criteria:

- An average of ≥ 8.0 micturitions per Diary Day; and,
- An average of ≥ 1.0 UUI episodes per Diary Day; and,
- If stress urinary incontinence (SUI) is present, the total number of UUI episodes must be greater than the total number of SUI episodes.

OAB Dry: Patients are considered OAB Dry according to the following criteria:

- An average of ≥ 8.0 micturitions per Diary Day; and,
- An average of ≥ 3.0 urgency episodes per Diary Day; and,
- An average of < 1.0 UUI episodes per Diary Day

OAB-d Type Missing: Patients are considered non-categorized for OAB if neither of the above criteria is achieved.

Where OAB Wet is discussed in this document, it pertains to patients randomized under the strata of OAB Wet; where all OAB Patients are discussed, this relates to all patients randomized as either OAB Wet or OAB Dry. Under the randomization strata, all patients are categorized as OAB Wet or Dry; missing is not present. Unless otherwise stated, for the purposes of the analyses, OAB Type (i.e. as randomized) will be used.

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.

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 post-baseline diaries at Weeks 4 and 8, only complete diary days within 10 days prior to the study visit will be included. For the Week 12/Early Termination 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. 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 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-baseline timepoint, after analysis window has been applied (i.e., Week 2, Week 4, Week 8, or Week 12).

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.

Screening/Washout Period

The Screening/Washout Period covers Day -49 (Screening Visit) to Day -15 (the day before the start of the Run-in Period), which includes a 28-day washout period followed by 7-days of Diary completion. Patients not requiring the 28-day washout period can begin the 7-day Diary the day after the Screening Visit.

Run-in Period

The Run-in Period covers the duration between screening (Day -14) and the day before baseline (Day 1). 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 12.

Safety Follow-up Period

The Safety Follow-up Period continues for 28 days after the last dose of study treatment (Day 85) through Day 113 (Follow-up Visit).

Definition of Study Completion

A patient will be defined as "completed" if she/he completes the Week 12 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 follow-up visit after the Week 12 visit, enrolled into the extension trial 3004, permanently discontinued from the study, or lost to follow-up. When lost to follow-up, the latest date of assessment/event in the database will be used as the last known date of the patient in study.

Day of Study Event (Post-Randomization)

Day of study event = Event Date – Date of Randomization (Day 1) + 1.

Day of Study Event (Pre-Randomization)

Day of study event = Event Date – Date of Randomization (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 the primary analysis of the co-primary endpoints and for all CFB analyses, no imputation of missing data will be performed as the MMRM model accounts for this.

A sensitivity analysis of the co-primary endpoints will be performed using multiple imputation (MI) for missing data and is detailed in Section 8.1.1.2, as well as last observation carried forward (LOCF). For all responder analyses, multiple imputation will be used to impute missing data.

Incomplete/missing start and stop dates will be handled as follows:

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 run-in single-blind medication (or double-blind medication), then the partial date will be imputed as the date of first dose of single-blind medication (or double-blind medication). However, if the date of first dose of single-blind medication and date of first dose of double-blind medication occur in the same month, then the date of first dose of double-blind medication will be imputed. (2) if the partial date is before the date of first dose of run-in single-blind medication, then the start date will be sent as the date of informed consent.

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 run-in single-blind medication (or double-blind medication), then the partial date will be imputed as the date of first dose of single-blind medication (or double-blind medication). However, if the date of first dose of single-blind medication and date of first dose of double-blind medication occur in the same month, then the date of first dose of double-blind medication will be imputed. (2) if the start year is before the year of first dose of run-in single-blind medication, then the start date will be sent as the date of informed consent.

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. If the patient 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 31st of December of year occurance. If the patient died in the same year, then set the imputed date as the death date.

Missing Wake/Bed Time

For a patient 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 patient 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 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, 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:

For any non-diary data involving two scheduled visits (OAB-q-LF, WPAI-US, EQ-5D, Physical Exam and ECG), the analysis visit will be assigned as the scheduled visit performed in the eCRF. For all other non-diary data, analysis visit will be windowed using the rules given in Table 6.5.1 below. These 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.

There is no analysis window for the Screening, Run-in, or Baseline visit; those will be analyzed as collected. Post-baseline visits 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).

Table 6.5.1: Analysis Window

Visit Name	Nominal Visit	Target Day	Analysis Window
Screening	Visit 1	-49 to -15	N/A
Run-in	Visit 2	-14	N/A
Baseline	Visit 3	1	N/A
Week 4	Visit 5	29	[2, 42]
Week 8	Visit 6	57	[43, 70]
Week 12	Visit 7	85	[71, 98]
Follow-up	Visit 8	113	[99, ∞)

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. 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

To determine whether the treatment effect is consistent across various subgroups, the co-primary endpoints will be summarized descriptively for each of the following subgroups:

- Region (US vs. Non-US)
- Age category 1 (<40, ≥40 to <55, ≥55 to <65, ≥65 to < 75, ≥75 years)
- Age category 2 (<65, ≥65 years)
- Age category 3 (<65, ≥65 to < 85, ≥85 years)
- Race (white vs. other)
- Sex (female vs. male)
- Males with BPH vs. males without BPH
- Prior anticholinergic use in the last 12 months (yes vs. no)

- Prior beta-3 agonist use in the last 12 months (yes vs. no)
- OAB Type (OAB Wet vs. OAB Dry)
- OAB-d Type (OAB Wet vs. OAB Dry)

The details of the analysis of subgroups used for statistical inference of the co-primary endpoints are given in Section 8.1.4.

A list of anticholinergics is given in the protocol in Table 4 of Section 7.9.3.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. Patient Disposition and Withdrawals

Patient disposition will be summarized by treatment arm for the Screened, Run-in and Randomized Sets separately. 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. 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 are also 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. Inclusion in each of the analysis sets (SAF, FAS, FAS-I, PPS, PPS-I, and PKS), and any reasons for exclusion will be summarized by treatment arm for the Randomized Set. Both will be listed also for the FAS and Randomized Sets, respectively.

Screen Failure, Run-in and Double-Blind Period disposition, with reasons for discontinuation of study will also be listed, including the date of discontinuation.

Eligibility criteria, screening failures (including date and primary reason for failure), and informed consent (protocol version, informed consent version date and date signed) will be listed for all patients screened.

A summary of randomized patients by country and investigator will be provided.

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

7.2. Demographic Characteristics

All demographic and baseline characteristic data will be summarized by treatment group using descriptive statistics for all patients for each of the following analysis sets: SAF, FAS, FAS-I, PPS and PPS-I.

Sex, Region (US and non-US), OAB Type (OAB Wet and OAB Dry), OAB-d Type (OAB Wet, OAB Dry and Missing), Prior Anticholinergic Use in the Last 12 Months (Yes/No), Prior Beta-3 agonist Use in the Last 12 Months (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 in the Last 12 Months and Prior Beta-3 agonist Use in the Last 12 Months 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 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 as having a medical history of hypertension 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 will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher.

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 during run-in period (micturitions, urge incontinence episodes, urgency episodes, total incontinence episodes, and volume voided) prior to first dose of double-blind medication 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, FAS, FAS-I, PPS and PPS-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. Prior OAB medications will be summarized by ATC Levels 2, 4 and Preferred Term in the SAF.

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

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 Run-in Visit.

7.5.2. Concomitant Medication

Concomitant medications will be summarized separately for the Run-in Period and Double-Blind Period. Concomitant medications will be defined as taken during the Run-in Period if medications were started on or after the first dose of single-blind medication but prior to the first dose of the double-blind medication, or started prior to the first dose of the single-blind medication and were continuing to be taken during the Run-in Period. Concomitant medications will be defined as taken during the double-blind period if medications were started on or after the first dose of double-blind medication but prior to the last dose of the double-blind medication, or started prior to double-blind medication and were ongoing during the Double-Blind Period. Partial medication start dates will be imputed as detailed in Section 6.4.

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, festoterodine 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

8. EFFICACY ANALYSIS

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 Run-in, Baseline, Week 2, Week 4, Week 8, and Week 12 visits, and to fill out the volume portion of the diary for 1 of the 7 diary days for each visit. Duplicate data recorded by the patient in diary rows with identical values will be not 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 post-baseline assessment from any post-baseline value (i.e., Week 2, Week 4, Week 8, or Week 12) for either micturitions for the FAS or UUI for the FAS-I. Change from baseline is defined as the post-baseline assessment minus the baseline assessment.

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

8.1. Co-Primary Endpoint Analysis

8.1.1. CFB in Micturitions at Week 12

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 will be the analysis population for the micturition endpoint.

8.1.1.1. Primary Analysis

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 12. This model includes data from Week 2, Week 4, Week 8 and Week 12 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. 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), Region (US vs non-US), baseline score, and interaction of visit by treatment.

Primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The comparisons between tolterodine and placebo will be reported with nominal p-values. The standard error and 95% CI for the differences will also be presented with the corresponding p-values. Additionally, estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group (placebo, vibegron and tolterodine). The table output will also include treatment group estimates and treatment differences between vibegron and placebo, and tolterodine and placebo at Weeks 2, 4, and 8 from this model.

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:

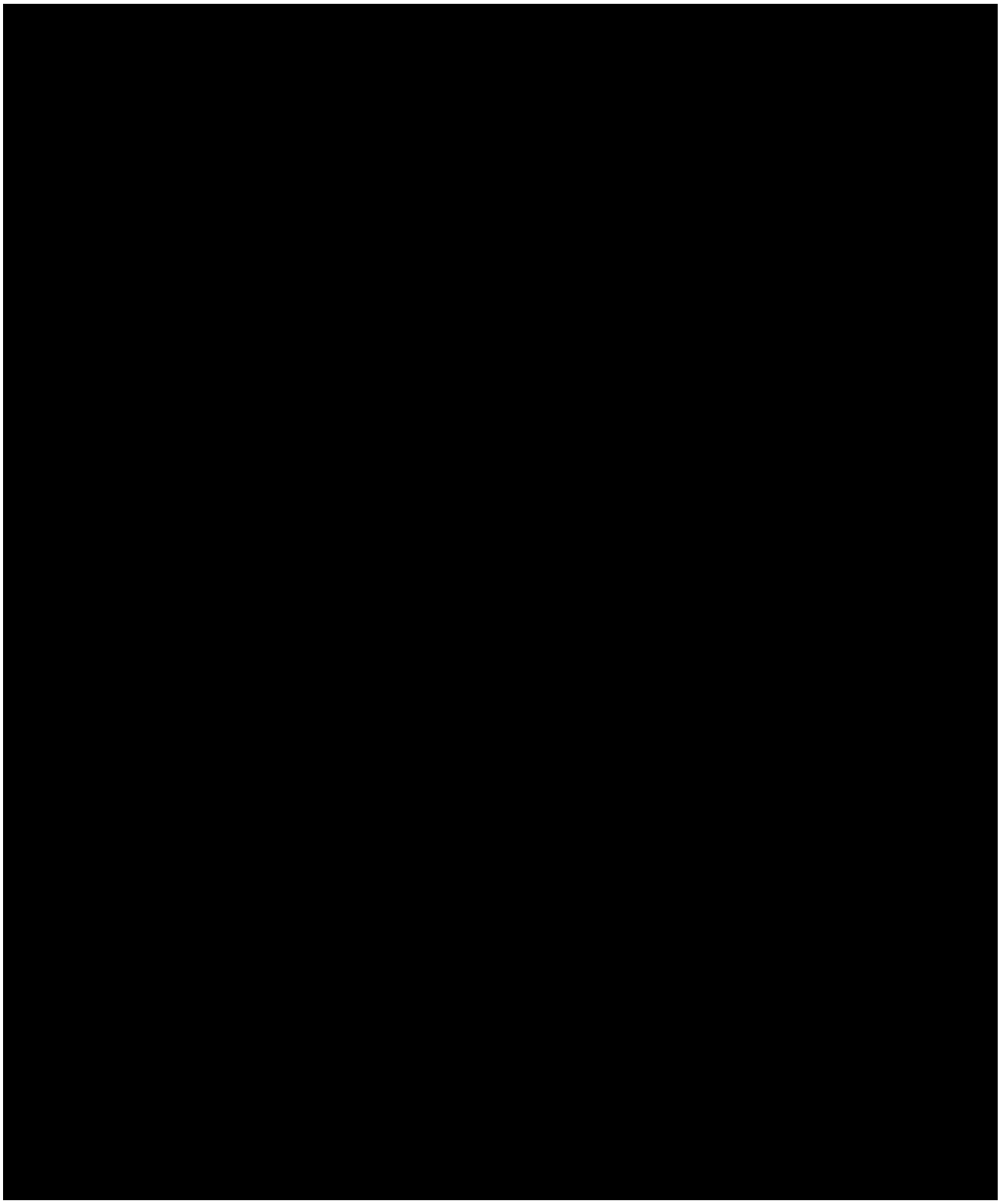
```
proc mixed data = datain method = reml ;
      class TRTP AVISITN USUBJID OABTYPE SEX REGION ;
      model CHG = TRTP AVISITN OABTYPE SEX REGION BASE TRTP*AVISITN
            / ddfm=KR solution chisq ;
      REPEATED AVISITN / subject=USUBJID type=UN r rcorr ;
      LSMEANS TRTP*AVISITN / pdiff=all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

Where TRTP is the planned treatment, 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, REGION indicates if the patient is in the United States or in the non-US countries and BASE indicates baseline value.

Model assumptions will be assessed through inspection of residual plots and normal probability plots. Should gross violations of the assumptions occur, the change from baseline in average daily micturitions will be transformed prior to the modeling.

8.1.1.2. Sensitivity Analysis

[redacted]



[redacted]

8.1.2. CFB in Urge Urinary Incontinence (UUI) at Week 12

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 8.1.1.1 for the micturition endpoint.

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

8.1.2.1. Primary Analysis

The primary analysis model for UUI is similar to the micturition model detailed in Section 8.1.1.1 but excluding the term of OAB Type since the UUI endpoint is only collected for OAB Wet patients. More specifically, the primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The comparisons between tolterodine and placebo will be reported with nominal p-values. The standard error and 95% CI for the differences will also be presented with the corresponding p-values. Additionally, estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group. The table output will also include treatment group estimates and treatment differences between vibegron and placebo, and tolterodine and placebo at Weeks 2, 4, and 8 from this model.

Model assumptions will be assessed through inspection of residual plots and normal probability plots. Should gross violations of the assumptions occur, the change in UUI will be transformed prior to the modeling.

The FAS-I will be the analysis population for the UUI endpoint.

8.1.2.2. Sensitivity Analysis

[redacted]

8.1.3. Multiplicity of Co-Primary Endpoints

No multiplicity adjustment is required for the co-primary endpoints since both endpoints need to be significant at the 0.05 level in order to test the key secondary endpoints.

8.1.4. Subgroup Analysis of Co-Primary Endpoints

For each of the subgroups listed in Section 6.7, a separate MMRM model will be fit on co-primary endpoints, respectively. The same model terms as used for the primary analysis specified in Section 8.1.1.1 for micturition endpoint and Section 8.1.2.2 for the UUI endpoint will be applied with additional terms for subgroup main effect and treatment by subgroup interaction. Only the estimate and p-value for the interaction term from the MMRM will be provided. With the exception of Age Category 2, Race and Sex subgroups, if less than 20% of randomized patients are in a subgroup, then this will not be produced. Descriptive summary statistics will be provided for all subgroups.

The model for each Subgroup is as follows:

- Region (US vs. Non-US)
  - The analysis model for CFB in micturitions will include terms for treatment, visit, OAB Type (Wet vs Dry), Sex (Female vs Male), baseline score, region, interaction of region by treatment, and interaction of visit by treatment.
  - The analysis model for CFB in UUI endpoint will exclude the term of OAB Type.
- Age category 1 (<40, ≥40 to <55, ≥55 to <65, ≥65 to <75, ≥75 years)
  - This category will only be used for descriptive statistics.
- Age category 2 (<65, ≥65 years)
  - The analysis model for CFB in micturitions will include terms for treatment, visit, OAB Type (Wet vs Dry), Sex (Female vs Male), Region (US vs. Non-US), baseline score, age category 2, interaction of age category 2*treatment and interaction of visit by treatment.
  - The analysis model for CFB in UUI endpoint will exclude the term of OAB Type.
- Age category 3 (18 to <65, ≥65 to <85 years, ≥85 years)
  - This category will only be used for descriptive statistics.
- Race (white vs. other)
  - The analysis model for CFB in micturitions will include terms for treatment, visit, OAB Type (Wet vs Dry), Sex (Female vs Male), Region (US vs.Non-US), baseline score, race, interaction of race by treatment, and interaction of visit by treatment.
  - The analysis model for CFB in UUI endpoint will exclude the term of OAB Type.
- Sex (female vs. male)

  - The analysis model for CFB in micturitions will include terms for treatment, visit, OAB Type (Wet vs Dry), Region (US vs Non-US), baseline score, sex, interaction of sex by treatment, and interaction of visit by treatment.
  - The analysis model for CFB in UUI endpoint will exclude the term of OAB Type.

- Males with BPH vs. Males without BPH
  - This category will only be used for descriptive statistics.

- Prior Anticholinergic Use in the Last 12 Months (Yes vs No)
  - This category will only be used for descriptive statistics.

- Prior Beta-3 Agonist Use within the Last 12 Months (Yes vs No),
  - This category will only be used for descriptive statistics.

- OAB Type (OAB Wet vs. OAB Dry)
  - The analysis model for CFB in micturition will include terms for treatment, visit, OAB Type (Wet vs Dry), Sex (Female vs Male), Region (US vs Non-US), baseline score, interaction of OAB Type by treatment, and interaction of visit by treatment.
  - The analysis model for CFB in UUI endpoint will not be applicable for this subgroup analysis.

- OAB-d Type (OAB Wet vs. OAB Dry)
  - The analysis model for CFB in micturition will include terms for treatment, visit, OAB-d Type (Wet vs Dry), Sex (Female vs Male), Region (US vs Non-US), baseline score, interaction of OAB-d Type by treatment, and interaction of visit by treatment.
  - The analysis model for CFB in UUI endpoint will not be applicable for this subgroup analysis.

A forest plot will be provided to present the results from subgroup analyses. Side-by-side 95% confidence intervals will be plotted for each comparison to control within each subgroup, where the 95% confidence intervals are taken from the analysis table described above. The confidence intervals are stacked vertically on the page, with a reference line at zero for mean. All the subgroups should be plotted on a single figure (using multiple pages, if necessary).

8.2. Key Secondary Efficacy Analyses

8.2.1. Multiplicity and Testing Procedure of Key Secondary Endpoints

If statistical significance is found at the 0.05 level for both co-primary endpoints, each key secondary endpoint will be tested sequentially in the order given in Section 4.2. If statistical significance at the 0.05 level is achieved at all previous key secondary endpoints, the next sequential key secondary endpoint will be tested. Once a key secondary endpoint is found to be insignificant (i.e., p-value ≥ 0.05), the testing procedure will stop. For all subsequent key secondary endpoints, nominal p-values will be provided.

Only the endpoints listed in Section 4.1 and Section 4.2 are part of the closed testing procedure. The closed sequential testing procedure, as defined above, maintains the overall Type I error of the study at 0.05.

8.2.2. CFB in Urgency Episodes at Week 12

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 above in Section 8.1.1.1. More specifically, the primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The standard error and 95% CI for the difference will also be presented with the corresponding p-value. Additionally, estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group. The table output will also include treatment group estimates and treatment differences between vibegron and placebo at Weeks 2, 4, and 8, and tolterodine and placebo at Weeks 2, 4, 8 and 12 from this model.

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

8.2.3. UUI Episodes 75% and 100% Responder at Week 12

The FAS-I will be the analysis population for the urgency episodes endpoint described in this section; missing Week 12 data will be analyzed using multiple imputation (See Appendix 1 for further details).

The percent reduction from baseline is calculated as follows:

$$\%\, change = \frac{(aval - base)}{base} * 100$$

Where *aval* is the value at Week 12 and *base* is the baseline value. The achievement of at least a 75% reduction in UUI episodes (and similarly, a 100% reduction in UUI episodes) is a binary variable of 0 (endpoint is not attained) or 1 (endpoint is attained). The difference in proportion responding between vibegron and placebo, and tolterodine and placebo along with the associated 95% confidence interval and p-value, will be calculated using the Cochran-Mantel-Haenszel risk difference estimate stratified by Sex (Female vs Male)., with weights proposed by Greenland and Robins, which is calculated as follows:

$\hat{\delta}_{MH} = \frac{\sum_{i=1}^{u} w_i \cdot \hat{\delta}_i}{\sum_{i=1}^{u} w_i}$, where

$\hat{\delta}_i = \frac{x_i}{n_i} - \frac{y_i}{m_i}$ denotes the risk difference in stratum $i, i = 1, \cdots, u$

$w_i = \frac{n_i \cdot m_i}{n_i + m_i}$ denotes the weight of stratum $i, i = 1, \cdots, u$

x_i denotes the number of patients with event in treatment_1 in stratum i, $i = 1, \cdots, u$

y_i denotes the number of patients with event in treatment_2 in stratum i, $i = 1, \cdots, u$

n_i denotes the number of patients on treatment_1 in stratum i, $i = 1, \cdots, u$

m_i denotes the number of patients on treatment_2 in stratum i, $i = 1, \cdots, u$

The estimated variance of $\hat{\delta}_{MH}$ is calculated as:

$$\widehat{var}\left(\hat{\delta}_{MH}\right) = \frac{\sum_{i=1}^{u} L_i}{\left(\sum_{i=1}^{u} w_i\right)^2}$$

where $L_i = \frac{x_i(n_i - x_i)\, m_i^3 + y_i(m_i - y_i)\, n_i^3}{n_i \cdot m_i \cdot (n_i + m_i)^2}$, $i = 1, \cdots, u$

Assuming a normal distribution of $\hat{\delta}_{MH}$, an approximate 95% CI is given as follows, where $z_{0.975}$ is the 97.5% quantile of the standard normal distribution:

$$CI = \left[\hat{\delta}_{MH} \pm z_{0.975} \cdot \sqrt{\widehat{var}\left(\hat{\delta}_{MH}\right)}\right]$$

Also, the approximate p-value can be calculated using the following:

$$\text{pvalue} = 2 \cdot \Pr\left[Z > \left|\frac{\hat{\delta}_{MH}}{\sqrt{\widehat{var}\left(\hat{\delta}_{MH}\right)}}\right|\right], \text{where } Z \sim N(0,1)$$

If there is a stratum for a treatment group that has 0 patients in it, the 0 count will be replaced by 0.5 in order to prevent dividing by 0 in the above equations, as suggested in Greenland & Robins.

The primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The table output will show the number and percent of patients attaining the endpoint for all treatment arms, the CMH estimated risk difference between vibegron and placebo, and tolterodine and placebo with 95% CI and p-value using the above formula at Week 12. The table output will also include this summary at Weeks 2, 4, and 8.

To further characterize meaningful change from baseline at Week 12 in urgency episodes as defined by various anchor levels of PGI-Severity, PGI-Control, and PGI-Frequency. Cumulative function (CDF) plots and kernel density plots of percent change from baseline at Week 12 in average daily urgency episodes will be categorized by the following anchor levels. The anchor levels of PGI-Severity, PGI-Control, and PGI-Frequency are shifts from baseline to Week 12, separately. The number of patients and mean percent CFB at Week 12 in average daily urgency episodes will be presented on the plots.

- ≥2 categories worse
- One-category worse
- No change
- One-category improvement
- Two-categories improvement
- ≥3 categories improvement

To further evaluate clinical meaningful improvement in the PGI-Control and PGI-Frequency items, the described CDF and kernel density plots will be provided for the subset of patients with severe symptoms at baseline (e.g., patients with “no control” over OAB symptoms’ in PGI-Control; patients experiencing OAB symptoms “very often” in PGI-Frequency). These are further described in the Exploratory Efficacy Endpoints section.

8.2.4. Urgency Episodes 50% Responder at Week 12

The FAS will be the analysis population for the urgency episodes responder endpoint described in this section; missing Week 12 data will be analyzed using multiple imputation (See Appendix 1 for further details).

The percent reduction from baseline is calculated in the usual fashion. The achievement of at least a 50% reduction in urgency episodes is a binary variable of 0 (endpoint is not attained) or 1 (endpoint is attained). This endpoint will be analyzed in the same manner as described above in Section 8.2.3. More specifically, the primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The table output will show the number and percent of patients attaining the endpoint for all treatment arms, the CMH estimated risk difference between vibegron and placebo with 95% CI and p-value using the above formula at Week 12. The table output will also include this summary at Weeks 2, 4, and 8. The CMH risk difference between tolterodine and placebo will also be shown along with the 95% CI and related p-value at Weeks 2, 4, 8 and 12.

The CDF plots and kernel density plots of percent change from baseline at Week 12 in average daily urgency episodes will be provided. These are further described in the Exploratory Efficacy Endpoints section.

8.2.5. CFB in Total Incontinence at Week 12

Total incontinence is defined as having any reason for "Accidental Urine Leakage" and/or "Accidental Urine Leakage" is 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.

The average number of daily incontinence episodes at each study visit will be calculated and analyzed in the same manner as described above in Section 8.1.1.1. More specifically, the primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The standard error and 95% CI for the difference will also be presented with the corresponding p-value. Additionally, estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group. The table output will also include treatment group estimates and treatment differences between vibegron and placebo at Weeks 2, 4, and 8, as well as differences between tolterodine and placebo at Weeks 2, 4, 8 and 12 from this model.

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

8.2.6. CFB in OAB-q LF Coping Score at Week 12

The OAB-q LF is a validated PRO and has been shown to have sound psychometric properties. It was developed with patient input from both the OAB-wet and OAB-dry

populations, and there is strong evidence to support the measure's content validity in both target patient populations. In addition, the OAB-q has been shown to have excellent measurement properties, including validity and reliability. See Appendix 2 for a complete list of questions.

The first 8 questions of the OAB-q LF ask patients much they are bothered by their bladder symptoms during the last week. Each question has a response ranging from "Not at all" which is scored as a 1 to "A very great deal" which is scored as a 6. These questions make up the symptom bother scale.

Questions 9 through 33 ask patients how much their symptoms have affected their life over the last week. Each question has a response ranging from "None of the time" which is scored as a 1 to "All of the time" which is scored as a 6. There are 4 subscales and one total score derived from these questions as follows:

To transform the raw scores to a unified score ranging from 0 to 100, the following algorithms are used.

For the Symptom Bother Score, the transformed score is:

$$score = \frac{(actual\ score - lowest\ possible\ )}{range} = \frac{(actual\ score - 8)}{40} \text{ x } 100$$

For Symptom Bother, higher scores correspond to the symptoms having a larger bother and lower scores represent a lower amount of bother due to symptoms.

For the Coping, Concern, Sleep, Social Interaction, and Total HRQL Scores, the transformed score is:

$$score = \frac{(highest\ possible - actual\ score\ )}{range} \text{ x } 100$$

Where the highest possible score and range come from the corresponding row of Table 8.2.6.1. In this case, higher scores correspond to a higher quality of life and lower scores represent a lower quality of life.

It is recommended that if <50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing[5].

The CFB analysis for the Coping Score will be calculated at Week 12 and analyzed in a similar manner as the primary endpoints, but with only one post-baseline assessment. More specifically, the primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12 using a mixed model. The standard error and 95% CI for the difference will also be presented with the corresponding p-value. Additionally, estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group and the difference between tolterodine and placebo will also be presented. The mixed model for this will use the same terms as the primary analysis, but without any repeated measures. An example of the SAS code for the base procedure is given below:

```
proc mixed data = datain method = reml ;
      class TRTP USUBJID OABTYPE SEX REGION ;
      model CHG = TRTP OABTYPE SEX REGION BASE
            / ddfm=KR solution chisq ;
      LSMEANS TRTP / pdiff=all cl alpha=0.05 ;
run ;
```

Where `TRTP` is the planned treatment, , `USUBJID` is the unique patient identifier, `OABTYPE` indicates of the patient is Dry or Wet, `SEX` is female or male, `REGION` indicates if the patient is in the United States or in non-US countries and `BASE` indicates baseline value.

The FAS will be the analysis population for the all of the OAB-q LF endpoints.

8.2.7. CFB in Average Volume Voided per Micturition at Week 12

Patients are asked to fill out a volume voided question for 1 day of the patient voiding diary. On this day, patients will use a graduated collection device to measure the volume of urine voided. Patients will collect this for every void on this 1 day. The average

volume voided at a visit will be the arithmetic mean of all voids for which a patient has recorded the volume. The CFB will be derived and analyzed in the same manner as described above in Section 8.1.1.1. More specifically, the primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The standard error and 95% CI for the difference will also be presented with the corresponding p-value. Additionally, estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group. The table output will also include treatment group estimates and treatment differences between vibegron and placebo at Weeks 2, 4, and 8, as well as differences between tolterodine and placebo at Weeks 2, 4, 8 and 12 from this model.

The FAS will be the analysis population for the volume voided endpoint.

8.3. Additional Secondary Efficacy Endpoints and Analyses

8.3.1. CFB in OAB-q LF Scores at Week 12

The OAB-q LF Total HRQL Score is detailed in Section 8.2.6. The CFB analysis for the Total HRQL Score at Week 12 will be calculated and analyzed in the same manner as described above in Section 8.2.6. More specifically, the primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The standard error and 95% CI for the difference will also be presented with the corresponding p-value; these will also be presented for the difference between tolterodine and placebo. Additionally, estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group.

The OAB-q LF Symptom bother Score is detailed in Section 8.2.6. The CFB analysis for the Symptom Bother Score at Week 12 will be calculated and analyzed in the same manner as described above in Section 8.2.6. More specifically, the primary inference will be drawn from the treatment difference between vibegron and placebo at Week 12. The standard error and 95% CI for the difference will also be presented with the corresponding p-value; these will also be presented for the difference between tolterodine and placebo. Additionally, estimates of least-squares means, standard errors, and 95% CIs will be presented for each treatment group.

The FAS will be the analysis population for the all of the OAB-q LF endpoints.

8.3.2. Responder Endpoints

The following are additional secondary responder endpoints:

- Percent of all OAB patients with average daily number of micturitions < 8 at Week 12

- A patient is defined as having an average of < 8 daily micturitions if the arithmetic mean of the number of micturitions per day in the void diary is less than 8 in a voiding diary.
- The FAS is the analysis set for this endpoint. Imputation of missing data will be performed using MI.

- Percent of OAB Wet patients with at least a 50% reduction from baseline in average daily number of incontinence episodes at Week 12
  - This endpoint is derived in the same manner as Section 8.2.3 but uses all events marked as having leakage, regardless of cause, or where "Accidental Leakage" is checked.
  - The FAS-I is the analysis set for this endpoint. Imputation of missing data will be performed using MI.

All of the above endpoints will be analyzed in the same manner as described above in Section 8.2.3.

8.3.3. Patient Global Impression of Severity and Control

The Patient Global Impression (PGI) questions are designed to assess a patient's overall impression of OAB, additional details are given in the Appendix 3. The PGI-Severity and PGI-Control questions are ordinal assessments going from lower impact of disease to highest impact of disease with scales ranging from 1 to 4 for severity and 1 to 5 for control. These questions will be analyzed as categorical variables with count and percent for each category at Baseline, Week 4, Week 8, and Week 12. These questions will also be summarized descriptively as numerical variables of score and change from baseline at visits of Baseline, Week 4, Week 8, and Week 12. Finally, the change from baseline will be analyzed in the same manner using the MMRM described above in Section 8.1.1.1.

The FAS will be the analysis set for the PGI analyses. For the MMRM analysis of change from baseline, no imputation of missing data will be performed.

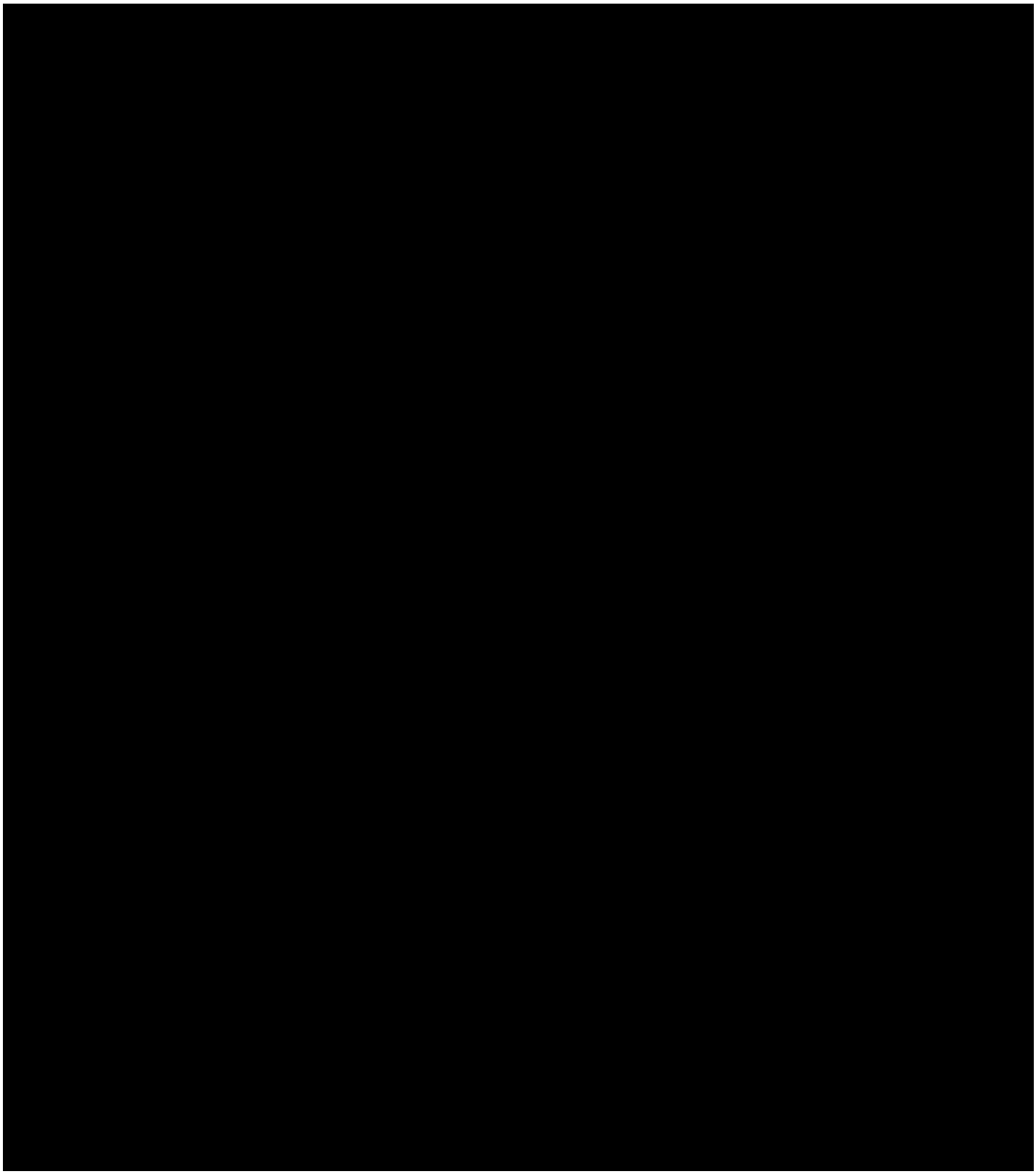
8.4. Exploratory Efficacy Endpoints and Analyses Not Related to Primary/Secondary Endpoints

[redacted]

8.5. Exploratory Efficacy Endpoints and Analyses Not Related to Primary/Secondary Endpoints

[redacted]

[redacted]



[redacted]

8.6. ANALYSIS OF PHARMACOKINETICS

The full population PK analysis is beyond the scope of this SAP; only drug trough concentrations will be summarized.

Pharmacokinetic samples for PK Analysis will be collected from a subset of patients (approximately 25% of enrolled patients). Blood samples will be collected pre-dose at Week 4), Week 8, and Week 12 (at any time during the visit). Plasma PK concentrations will be listed and summarized by study visit using the PK population. Only concentrations collected between 22 and 26 hours post dose will be included in the summary statistics.

Missing concentration data for all patients who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

- Concentration values below the assay's limit of quantification (BLQ) for pre-dose samples will be treated as zero.
- The sampling time relative to dosing for pre-dose samples will also be treated as zero.
- If the actual sampling time is missing, the planned time will be used.
- Samples taken far outside the sampling windows may be excluded from by-time point summary statistics. No further imputation will be applied to any missing values.

8.6.1. Listing and Presentation of individual PK data

The following presentations of patient plasma PK concentration data will be provided for each analyte for the PK Population using nominal times:

- Data listing, including patient, time point (actual, planned, deviation time), duration of actual sampling time to the last dose prior to the visit and treatment;
- Summary of prior-dose plasma PK concentrations-time data by treatment at each visit (population sample size (N), number of patients with available data (n), number of patients with imputed value (BLQ assigned to zero), mean, SD, coefficient of variation (%CV), median, minimum and maximum).

  Where the %CV is calculated as:
  - %CV = 100 * (SD/Mean).

9. SAFETY

The SAF 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.

9.1. Extent of Exposure

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

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

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

All data will be listed.

9.2. Treatment Compliance

Study treatment compliance (%) will be calculated as the actual number of doses divided by the expected number of doses, multiplied by 100 and summarized by treatment group and study period (Run-in and Double-Blind Treatment).

These numbers will be determined by the number of tablets dispensed and returned unused by the patient. Where no treatment bottle is returned, and thus the actual number of doses is unknown, it will be assumed that the patient took all medication available in the bottle.

All data will be listed.

9.3. Adverse Events

AEs will be coded using MedDRA version 20.0 or later.

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 country, site, patient, date of event, SOC, PT and then verbatim description.

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

An AE will be considered treatment emergent (TEAE) if it begins or worsens in severity after the first dose of the double-blind Study Treatment through 28 days after the last dose of Study Treatment, or the date of initiation of another investigational agent or surgical intervention or rollover to the extension study, whichever occurs first. Partial AE start dates will be imputed as detailed in Section 6.4.

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 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 single-blind medication, Run-in = on or after first dose of single-blind medication but prior to first dose of double-blind medication, or Treatment = on or after first dose of double-blind 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 patients in the

vibegron arm and greater than the placebo 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 of hypertension will be created.

9.4. Laboratory Evaluations

Laboratory tests will be performed at Screening and periodically throughout the study as described in the Flowchart, Section 3.11. 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 and Scheduled Study Visits

Laboratory Category	Laboratory Tests Included (Central Lab)
Hematology	Hematocrit, Hemoglobin, Platelet Count, WBC (total and differential), RBC
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	Blood, Glucose, Protein, Specific gravity, Microscopic exam (RBC, WBC, epithelial cells and bacteria), pH, Color, and Urine pregnancy test (β-hCG)
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.
c. eGFR will be calculated and reported by the central lab.
d. If total bilirubin is elevated above the upper limit of normal.

Laboratory summaries will be based on the central laboratory data.

A sample for the 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.

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 patients 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 for hematology and chemistry parameters 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 patients 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 patients 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.

[redacted]

[redacted]

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 the screening visit. All data collected will be listed.

9.7. Physical Examination

Physical examination data will be collected at scheduled visits, as described in the Flowchart, Section 3.11. Physical examination results will be listed.

9.8. Post-Void Residual (PVR) Urine Volume

PVR Urine volume (mL) data will be summarized at Baseline and Week 12 by treatment group. 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. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The following changes to the analyses specified in the Protocol are enacted. Where specified, the section relates to the section of the SAP.

[redacted]

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 TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs 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 TLFs, 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 TLFs. 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-901-3003

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be 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 TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be 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 table contents.

- 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 should be 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, vibegron, tolterodine 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 should be 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 should be 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 any 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 should be included.

- An Unknown or Missing category should be added to any 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 should be printed out to 1 more significant digit than the original values, and standard deviations should be 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 should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be 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 should be 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% should be presented as 100%, without any decimal places.

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence over all treatment groups 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) should be 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 should be 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 should be 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 should be 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 should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be 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 must 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 average 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 should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may 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. [redacted] provide an overview of the development of such SAS programs.

[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. APPENDICES

[redacted]


[redacted]

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 Frequency (PGI-Frequency)

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