STATISTICAL ANALYSIS PLAN

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A Phase 4, Open-label, Randomized, Prospective, Interventional Post-authorization Efficacy and Safety Study of Mirabegron 50 mg and 25 mg for the Treatment of Overactive Bladder in Chinese Subjects

Open-label Phase 4 Study with Mirabegron 50 mg and 25 mg in Chinese Subjects with Overactive Bladder

ISN: 178-MA-2295

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
APGD	Astellas Pharma Global Development
ASCM	Analysis Set Classification Meeting
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Intervals
CRF	Case Report Form
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GCMSL	Global Clinical Modeling & Simulation Lead
GD	Global Development
H	High
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
IWRS	Interactive Web Response System
L	Low
LS	Least Squares
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Models Repeated Measures
ms	Millisecond
N	Normal
OAB	Overactive Bladder
OABSS	OAB Symptom Score

Abbreviations	Description of abbreviations
PD	Pharmacodynamic
PD1-x	Protocol Deviation 1-x
PPIUS	Patient Perception of Intensity of Urgency Scale
PT	Preferred Term
PVR	Post Void Residual
QTc	Corrected Q-T Interval
QTcF	QT interval corrected by Fridericia's formula
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures
UA	Urinalysis
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
WHO-DG	World Health Organization Drug Global

List of Key Terms

Terms	Definition of terms
Baseline	The last non-missing observation prior to first administration of IP, unless otherwise specified.
Discontinuation	The act of concluding participation in a trial by an enrolled subject, prior to completion of all protocol required elements. Note: subject discontinuation does not necessarily imply exclusion of subject data from analysis that was collected prior to discontinuation.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a study. Note: once a subject has received the IP or placebo, the protocol applies to the subject.
EoT result	End of treatment result is based on the last available result which is obtained earlier or on the same date as the treatment stop date.
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test product or comparative drug (sometimes without randomization) is given to a subject and continues until the last assessment after completing administration of the test product or comparative drug.
Postinvestigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. NOTE: unequal randomization is used to allocate subjects into groups at a differential rate; for example, 3 subjects may be assigned to a treatment group for every 1 assigned to the control group.
Screening	A process of active consideration of potential subjects for a trial.
Screening period	Period of time before entering the investigational period, usually from the time the subject signed informed consent until just before the first dose of the study drug is given to a subject.
Screening failure	Potential subject who signed the ICF, but did not meet one or more criteria required for participation in the study and was not randomized.
Study period	Period of time from the first site initiation date to the last site completing the study.
Subject	An individual in the population of interest who participates in a clinical trial as recipient of the investigational product.
Treatment emergent adverse event	An adverse event observed after starting administration of the study drug.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes procedures for executing the statistical analysis to fulfil the objectives of the study.

The final SAP will be approved prior to database hard lock. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

Changes from the planned analyses in the final SAP that impact the statistical analyses will be documented in the Clinical Study Report (CSR).

2 STUDY OBJECTIVE(S) AND DESIGN

2.1 Study Objectives

Objectives	Endpoints
Primary	
● To evaluate the efficacy of mirabegron 50 mg for the treatment of OAB in Chinese subjects	● Change from baseline to the end of the 12-week treatment period in mean number of micturitions per 24 hours
Secondary	
● To evaluate the safety of mirabegron for the treatment of OAB in Chinese subjects	● Incidence and severity of AEs ● Clinical laboratory tests (hematology, biochemistry and urinalysis) ● Vital signs (blood pressure and pulse) ● Routine 12-lead ECG ● Post Void Residual (PVR)
● To evaluate other efficacy variables of mirabegron 50 mg for the treatment of OAB	● Change from baseline to the end of the 12-week treatment period: ○ Mean number of grade 3 or 4 (PPIUS) urgency episodes per 24 hours ○ Mean number of daytime incontinence episodes per 24 hours ○ Mean number of nighttime incontinence episodes per 24 hours ○ Mean number of urge incontinence episodes per 24 hours ○ OAB Symptom Score (OABSS) ● Change from baseline to Weeks 4 and 8: ○ Mean number of micturitions per 24 hours ○ Mean number of grade 3 or 4 (PPIUS) urgency episodes per 24 hours ○ Mean number of daytime incontinence episodes per 24 hours ○ Mean number of nighttime incontinence episodes per 24 hours ○ Mean number of urge incontinence episodes per 24 hours ○ OAB Symptom Score (OABSS)
Table continued on next page	

Objectives	Endpoints
● To explore mirabegron starting dose of 25 mg	● Change from baseline to weeks 4, 8, and 12 in: ○ Mean number of micturitions per 24 hours ○ Mean number of grade 3 or 4 (PPIUS) urgency episodes per 24 hours ○ Mean number of daytime incontinence episodes per 24 hours ○ Mean number of nighttime incontinence episodes per 24 hours ○ Mean number of grade 3 or 4 (PPIUS) urge incontinence episodes per 24 hours ○ OAB Symptom Score (OABSS)

AE: adverse event; OAB: overactive bladder; PPIUS: patient perception of intensity of urgency scale; OABSS: OAB Symptom Score

2.1.1 Estimand

The estimand of most clinical importance for this study is defined by the following four attributes:

- Target population: all subjects who took at least 1 dose of the study drug, and in whom a nonmissing measurement for mean number of micturition per 24 hours at baseline and after administration of the study drug is available.
- Outcome measurement: micturition frequency per 24 hours prior to switching (if switching occurs).
- Intercurrent events:
  - Dose escalation.
- Population-based summary: change from baseline to week 12/end of treatment (EoT) in micturition frequency per day within dose groups.

For this study, the treatment estimand is considered appropriate because of the fact that the response of subjects prior to switching is of primary interest. i.e., the estimate for 50 mg of mirabegron should be estimated from subjects who were randomized to 50 mg and the estimate for 25 mg should be estimated from subjects who were randomized to 25 mg while they were treated with 25 mg.

2.2 Study Design

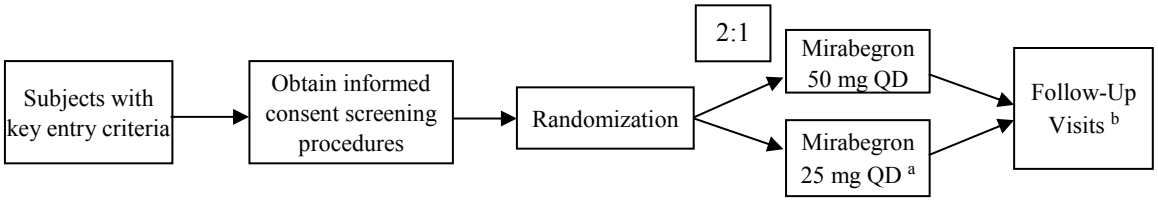
The study follows an open-label, randomized, 12-week, prospective, interventional postauthorization design for the treatment of OAB in approximately 249 Chinese subjects. Each subject will participate in one 12-week treatment period.

This study is designed to support the Imported Drug License (IDL) renewal and mirabegron safety surveillance in China. The data-cut with summaries and the planned primary analysis for the end of this study will be used for IDL renewal. Subjects fulfilling the screening inclusion/exclusion criteria will be randomized in 2:1 ratio to 50 mg mirabegron and 25 mg mirabegron using a computer-generated randomization to reduce selection bias. Treatments will be administered once daily orally after meal during a 12-week, open-label treatment period. Study visits will take place at weeks 4, 8 and 12. For 25 mg mirabegron group, a dose escalation to 50 mg is permitted on visit 3 and visit 4 according to investigators' discretion.

Planned total number of study sites include approximately 10 study sites across China.

Figure 1 presents the study schema.

Figure 1 Study Schema



[a] The investigators may want to assess if 25 mg dose is effective for this group. Subject to their discretions, a dose escalation to 50 mg is permitted on visit 3/week 4 or visit 4/week 8.

[b] Telephone contact or site visit.

The study consists of 3 periods with a total duration of 16 weeks.

- Screening period (2 weeks):
  - This period starts with visit 1/week -2 (screening) and ends with visit 2/week 0 (baseline).
  - After a successful visit 1 /week -1 to -2 (screening), all subjects will start with the completion of a 3-day bladder e-diary recording micturition frequency and incontinence episodes as well as collection of micturition volume over 2 days. The bladder e-diary should be completed over 3 consecutive days, at minimum 3 days, but not more than 7 days, prior to visit 2/week 0 (baseline).
- Open-label, placebo-controlled period (12 weeks):
  - This period starts with the day after visit 2/week 0 (baseline) and ends with visit 5/week 12 (EoT).
  - At visit 2/week 0 (baseline) inclusion and exclusion criteria will be evaluated. Subjects still fulfill the inclusion/exclusion criteria will enter the study. These subjects will be randomized to receive 50 mg or 25 mg of mirabegron using a 2:1 ratio. Daily IP administration will start on day 1 (i.e., the day on visit 2/week 0 [baseline]). IP will be dispensed and collected on visit 2/week 0 (baseline), visit 3/week 4, visit 4/week 8 and visit 5/week 12 (only collected).
  - For 25 mg mirabegron group, a dose escalation to 50 mg is allowed on visit 3/week 4 and visit 4/week 8 by investigator's discretion.
  - Subjects will start with the subsequent 3-day bladder e-diaries minimally 3 days prior to the indicated visit.
- Follow-up period (2 weeks):
  - This period starts the day after visit 5/week 12 (EoT) and ends with visit 6/week 14 (end of study [EoS]). The follow-up period is applicable to all subjects who have been randomized and received IP.
  - At visit 5/week 12 (EoT), IP administration will be stopped and a safety observation period of 2 weeks will start.

An independent DSMB can be implemented. A separate charter will describe the responsibilities of the DSMB.

A data cut with summaries and the planned primary analysis for the end of the study may be performed after 50% of subjects planned to be randomized have had their visit 5/week 12/EoT assessment, for regulatory reporting purposes. No decisions regarding conduct of the study (i.e., stopping) will be based on these results.

Details of the schedule of clinical assessments are available in the protocol.

2.3 Randomization

Subjects will be randomized in a 2:1 ratio to 50 mg mirabegron and 25 mg mirabegron using a computer-generated randomization Interactive Web Response System (IWRS). All consented subjects who meet the eligibility criteria will be randomized through IWRS. This service is set up prior to the study to allow the sites real-time allocation of the treatment to the next eligible subject based on the specifications and algorithm provided in the Randomization Specification Document. At visit 2/week 0 (baseline), subjects will be assigned a randomization number in accordance with the randomization code generated by the sponsor's designee.

Subjects will be assigned a subject number at study entry (i.e., signing the Informed Consent Form (ICF)). The subject numbers will be sequential and rising. The subject number will comprise of a 5-digit clinical unit number and 5 digit screening number.

Subjects will be randomized to receive IP according to the randomization schedule obtained via the IWRS system. The study site personnel will dispense the treatment according to the IWRS system's assignment. Specific procedures for randomization through the IWRS system are contained in the study procedures manual.

An enrolled subject who withdraws or discontinues before dosing or before randomization will be considered a screen failure. Randomized subjects who withdraw or discontinue will not be replaced.

3 SAMPLE SIZE

The sample size for this study is based upon change from baseline for mean number of micturitions/24 hours within a single treatment arm. Change from baseline will be tested to determine if the change is different from zero i.e., a change in mean number of micturitions/24 hours. When the sample size is 125, a single group t-test with a 5% two-sided significance level will have 80% power to detect a change of 0.9 micturitions with a SD of 3.562 [Neurourology and Urodynamics, 2015]. Assuming 25% of the subjects will drop out, about 166 subjects will be enrolled to yield 125 evaluable subjects in 50 mg group.

4 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

The determination of whether subjects are included or excluded from the safety and efficacy analysis sets will be made prior to database hard-lock for the primary report.

4.1 All Enrolled Set

The All Enrolled Set consists of all subjects who sign the ICF.

The All Enrolled Set will be used to summarize disposition of subjects who were screened.

4.2 All Randomized Set

The All Randomized Set consists of all randomized subjects, i.e. all those subjects with a randomization number.

The All Randomized Set will be used to summarize disposition of subjects who were randomized to treatment.

4.3 Full Analysis Set

The Full Analysis Set (FAS) consists of subjects who are randomized and receive at least 1 dose of IP and have at least 1 post baseline measurement for mean number of micturitions per 24 hours. The FAS will be analyzed by treatment arm as randomized (i.e., treatment arm based on randomization assignment).

The FAS will be used for summaries of demographic and baseline characteristics and will be the primary analysis set for efficacy analyses.

4.4 Safety Analysis Set

The Safety Analysis Set (SAF) will consist of all subjects who took at least 1 dose of IP. The safety set will be analyzed by treatment arm as treated (i.e., based on the treatment the subject actually received rather than the treatment to which the subject was randomized).

The SAF will be used for summaries of demographic and baseline characteristics and all safety- and tolerability-related variables.

5 EFFICACY ENDPOINTS

Efficacy data will be summarized by treatment group (25 mg and 50 mg) and visit, unless otherwise specified.

Data for the efficacy endpoints will be recorded on an e-diary.
The bladder diary is part of the subject's e-diary which is used to collect micturition frequency, urgency and incontinence episodes as well as volume measurements. In the 3-day bladder e-diary micturition frequency, urgency and incontinence episodes will be recorded as well as collection of micturition volume over 2 days. Diaries will be completed at home by the subject in the week prior to visit 2/week 0 (baseline), visit 3/week 4, visit 4/week 8 and visit 5/week 12 for three consecutive days. Completion of 3-day bladder diaries should start minimally 3 days (but not more than 7 days) prior to the visit.

The following information will be recorded by the patient in the bladder diary:

- Time to awake,
- Time to bed,
- Time of episode,

- Type of episode (micturition and/or incontinence),
- Urgency severity,
- Volume of micturition (mL) [collected prior to Visit 1 only].

The information from the diaries will be used to evaluate the efficacy of treatment or inclusion and/or exclusion from the study (e.g., subjects who have an average total daily urine volume > 3000 mL recorded in a 3-day diary at Visit 1; subjects who have an average of < 8 micturitions/24 hours; or subjects who have an average of <1 episode of grade 3 or 4 (PPIUS) urgency and <1 urgency incontinence/24 hours, during a 3-day micturition diary period). Therefore, patients will receive full instructions and training on how to complete the diary at Screening (Visit 1) and will be counseled on the importance of completing the diaries prior to the next visit. The diaries and questionnaires will be reviewed during each visit after Screening (Visit 1) by the investigator or designee to ensure accuracy of completion.

Voiding episodes will be recorded in one of three ways: “micturition”, “incontinence”, or “micturition and incontinence” in the electronic diary. Micturitions will be counted for “urination” episodes in which the patient fully voids in the toilet. “Incontinence” will be counted for episodes in which the full void was incontinent and the patient did not make it to the toilet to finish urinating. If a patient experienced incontinence and then passed urine into the toilet this should be recorded as “micturition and incontinence”.

Definitions of efficacy variables based on the 3-day micturition diary are presented in Table 1.

Table 1 3-Day Diary Definitions and Calculations

Measurement	Definition	Calculation
Micturition	Any voluntary micturition (excluding incontinence only episodes).	A micturition episode is counted as micturition regardless of whether volume voided was recorded or not. A micturition recorded before midnight of the first day or after midnight on the 3rd day of the 3-day micturition diary period will not be counted. A micturition will also be counted if the patient assessed an episode as both micturition and incontinence.
Valid Diary Day	A diary day in which at least one voluntary micturition episode occurs. A diary day with episodes of incontinence only is not considered a valid diary day.	A diary day is considered valid if at least one micturition was recorded on this calendar day. Days of visits to the clinic will not be counted as valid diary days.
Number of Valid Diary Days	Number of valid diary days per each 3-day micturition diary period.	Count of the valid diary days during the 3-day micturition diary period. Days of visits to the clinic will not be counted as valid diary days.
Valid Diary	A valid diary is a diary with at least 2 valid diary days within the analysis visit window (i.e., minimally 3 days but not more than 7 days prior to the indicated visit). If more than 3 valid diary days are recorded, then the last 3 days will be used in the calculations.	Not applicable.
Incontinence Episode	The complaint of any involuntary leakage of urine.	An incontinence episode is counted if it was recorded in the diary on a valid diary day. An incontinence will also be counted if the patient assessed an episode as both micturition and incontinence.
Number of Incontinence Episodes	Number of times a patient records an incontinence episode during the 3-day micturition diary period.	Total number of incontinence episodes recorded during the 3-day micturition diary period.
Table continued on next page		

Measurement	Definition	Calculation
Severity of Urinary Urgency (based on PPIUS)	Each micturition and/or incontinence episode is graded using the following 5-point scale based on PPIUS: 0 = No urgency, I felt no need to empty my bladder, but did so for other reasons. 1 = Mild urgency, I could postpone voiding as long as necessary, without fear of wetting myself 2 = Moderate urgency, I could postpone voiding for a short while, without fear of wetting myself 3 = Severe urgency, I could not postpone voiding, but had to rush to the toilet in order not to wet myself 4 = Urge incontinence, I leaked before arriving to the toilet.	Not Applicable
Urge Incontinence Episode	The involuntary leakage of urine accompanied by or immediately preceded by urgency.	One urge incontinence episode is counted for each record of the diary in which the following occurs: - incontinence episode is recorded AND - severity of urinary urgency recorded is 3 or 4 NOTE: Only urge incontinence episodes recorded on a valid diary day will be counted.
Number of Urge Incontinence Episodes	Number of times a patient records an urge incontinence episode during the 3-day micturition diary period.	Number of urge incontinence episodes recorded on valid diary days of the 3-day micturition diary period.
Urgency Episodes (severity of 3 or 4)	The complaint of a sudden, compelling desire to pass urine, which is difficult to defer.	One urgency episode is counted for each record of the diary in which the following occurs: - micturition or incontinence episode is recorded AND - severity of urinary urgency recorded is 3 or 4 NOTE: Only urgency episodes recorded on a valid diary day will be counted. If an episode was recorded as both a micturition and an incontinence episode with a urinary urgency of 3 or 4, it will be counted as one urgency episode.

In the event that in the 3-day Diary there are two entries with the same collection date and time but with different times of entry on the device, the last entry (time) will be used for analysis, regardless of episode characteristics.

For number of incontinence episodes, diary data will be classified as either "daytime" or "nighttime", where "daytime" is considered to mean "between waking up in the morning and going to sleep later the same day or next day" and "nighttime" means "between going to sleep on a day and waking up on the same or next day. These times are entered on this diary by the subject.
For classifying daytime and nighttime data see Table 2.

Table 2 Daytime and Nighttime

Day	Time Period	Daytime/Nighttime Classification
Day -3, Diary Day 1	Midnight (00:00) to reported wake time	Nighttime
	Reported wake time to reported sleep time	Daytime
	Reported sleep time to midnight (23:59)	Nighttime
Day -2, Diary Day 2	Midnight (00:00) to reported wake time	Nighttime
	Reported wake time to reported sleep time	Daytime
	Reported sleep time to midnight (23:59)	Nighttime
Day -1*, Diary Day 3	Midnight (00:00) to reported wake time	Nighttime
	Reported wake time to reported sleep time	Daytime
	Reported sleep time to midnight (23:59)	Nighttime

*Note: Day -1 is the last valid diary day prior to the visit to the clinic

The procedure for calculating the efficacy endpoints is described below:

Step 1: Take the last valid diary day closest to the visit to the clinic.
Step 2: Take the two prior consecutive diary days (this makes the 3 consecutive diary days that will be used for the calculations).
Step 3: Count the number of valid diary days within these 3 consecutive days.
Step 4: If the number of valid diary days ≥ 2 then go to Step 5, else result of endpoint is missing.
Step 5: Calculate the result for the endpoint as described in Sections 5.1 and 5.2.

Baseline for bladder data will be defined as the last non-missing observation prior to first administration of IP, unless otherwise specified.

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to week 12 in mean number of micturitions per 24 hours.

Number of micturitions per 24 hours will be derived from the Bladder Diary: responses "Pee in toilet" and "Pee in toilet and Leakage".

The mean number of micturitions is equal to the total number of micturitions recorded on valid diary days during the 3-day micturition diary period divided by the number of valid diary days during the 3-day micturition diary period.

For each subject, the mean number of micturitions at Visit x (x=2, 3, 4 and 5), using all available number of micturitions per 24 hours for the valid days in the diary, will be calculated as:

$$\frac{\text{Sum of the number of micturitions (per 24 hrs) over the valid diary days prior to Visit x}}{\text{Number of valid diary days}}$$

Note: Incontinence only episodes will be excluded.

A micturition will also be counted if the subject assessed an episode as both micturition and incontinence (leakage).

If data of more than 3 days prior to a visit are available, only the last 3 days prior to the visit will be used for the analysis.

Subjects without baseline or any post-baseline value will not be included in the change from baseline calculation although they will be included in the summary for either baseline or any post-baseline visit whichever timepoint the data is available.

Change from baseline to visit 5/week 12 is defined as:
Result at visit 5/week 12 – Result at baseline (visit 2/week 0).

5.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints, as derived from the e-diary, are the change from baseline to weeks 4, 8 and 12 in:

- Mean number of micturitions per 24 hours (only week 4 and week 8)
- Mean number of urgency episodes per 24 hours
- Mean number of daytime incontinence episodes per 24 hours
- Mean number of nighttime incontinence episodes per 24 hours
- Mean number of urge incontinence episodes per 24 hours
- OABSS, the sum score of four symptoms (daytime frequency, nighttime frequency, urgency, and urge incontinence)

5.2.1 Mean Number of Micturitions per 24 hours (Week 4 and Week 8)

Derivation of the endpoint is the same described in Section 5.1.

Change from baseline to visit 3/week 4 is defined as:
Result at visit 3/week 4 – Result at baseline (visit 2/week 0).

Change from baseline to visit 4/week 8 is defined as:
Result at visit 4/week 8 – Result at baseline (visit 2/week 0).

5.2.2 Mean Number of Urgency Episodes per 24 hours

Mean number of urgency episodes per 24 hours (see definition in Table 1) is derived from "PPIUS-Urgency of the Micturition" from Bladder Diary.

Scoring PPIUS scale:

- Grade 0: No urgency – I felt no need to empty my bladder, but did so for other reasons
- Grade 1: Mild urgency – I could postpone voiding as long as necessary, without fear of wetting myself
- Grade 2: Moderate urgency – I could postpone voiding for a short while, without fear of wetting myself
- Grade 3: Severe urgency – I could not postpone voiding, but had to rush to the toilet in order not to wet myself
- Grade 4: Urge incontinence – I leaked before reaching the toilet

Let N_{34} equal the number of times that a subject recorded a grade 3 or 4 urgency episode on a diary day. If there are no valid diary days, then N_{34} is missing, while if there are no grade 3 or 4 urgency episodes on a valid diary day, then N_{34} equals 0.
For each subject, the mean number of grade 3 or 4 urgency episodes per 24 hours, at Visit x (x=2, 3, 4 and 5), is the mean of N_{34} over the valid diary days of the Episodic Diary.

$$\frac{\text{Sum of the number of grade } 3-4 \text{ urgency episodes (per 24 hrs) over the valid diary days prior to Visit x}}{\text{Number of valid diary days}}$$

5.2.3 Mean Number of Daytime and Nighttime Incontinence Episodes per 24 hours

Number of Incontinence Episodes per 24 hours will be derived from "Number of Incontinence Episodes During the Day" and "Number of Incontinence Episodes During the Night" collected in the Bladder Diary: responses "Pee in toilet and Leakage" and "Leakage". The number of incontinence episodes during the day includes the episodes from the time when subject wakes up until the time the subject sleeps. The number of incontinence episodes during the night includes the episodes from the time the subject sleeps till the next morning wake up time, see Table 2.

For each subject, the mean number of incontinence episodes per day/night (during the day/night) at Visit x (x=2, 3, 4 and 5) will be calculated using all available number of incontinence episodes for the valid diary days in the Diary for daytime and for nighttime:

$$\text{Mean Number of Daytime Incontinence Episodes at Visit x} = \frac{\text{Total number of "Daytime Leakage Counts" over the Valid Diary Days prior to Visit x}}{\text{Number of Valid Diary Days}}$$

$$\text{Mean Number of Nighttime Incontinence Episodes at Visit x} = \frac{\text{Total number of "Nighttime Leakage Counts" over the Valid Diary Days prior to Visit x}}{\text{Number of Valid Diary Days}}$$

5.2.4 Mean Number of Urge Incontinence Episodes per 24 hour

Number of urge incontinence episodes per 24 hours will be derived from the Bladder Diary: responses "Pee in toilet and Leakage", "Leakage" and a PPIUS score of 3 or 4.

For each subject, the mean number of urge incontinence episodes at Visit x (x=2, 3, 4 and 5), using all available incontinence periods and PPIUS scores for the valid days in the diary, will be calculated as:

$$\frac{\text{Sum of the number of urge ncontinence episodes (per 24 hrs) over the valid diary days prior to Visit x}}{\text{Number of valid diary days}}$$

5.2.5 Overactive Bladder Symptom Score (OABSS)

Baseline for OABSS is defined as the day the subject visits the clinic for visit 2.

The OABSS questionnaire is designed to quantify OAB symptoms as a single score, and contains questions that address 4 symptoms of overactive bladder:

- Daytime frequency,
- Nighttime frequency,
- Urgency,
- Urge incontinence.

The OABSS is composed of 4 questions (one per each symptom) and has a minimum score of 0 and a maximum score of 15. If a subject experiences a more urgent episode the corresponding urgency score is higher and, consequently, the total score will be higher (see [Section 10.7 Appendix 7 Overactive Bladder Symptom Score questionnaire in the protocol]). If one or more of the 4 questions are not answered in the eDiary then the OABSS will be set to missing.

Questionnaires to be completed by the subject at the site in the local language and provided via the e-diary. In case the subject forgets to bring the device, then a back-up device will be used. Results will be directly entered in the e-diary by the subject.

5.2.6 Efficacy Endpoints for the Mirabegron 25 mg Starting Dose

The following efficacy endpoints for the Mirabegron 25 mg starting dose will be evaluated with descriptive statistics:

- Change from baseline to weeks 4, 8, and 12 in mean number of micturition/24 hours;
- Change from baseline to weeks 4, 8, and 12 in mean number of grade 3 or 4 (PPIUS) urgency episodes;
- Change from baseline to weeks 4, 8, and 12 in mean number of incontinence episodes;
- Change from baseline to weeks 4, 8, and 12 in urge incontinence episodes/24 hours;
- Change from baseline to weeks 4, 8, and 12 in OABSS.

5.3 Exploratory Endpoints

There are no exploratory endpoints.

5.4 Safety Endpoints

Safety data will be summarized for both treatment groups ('Mirabegron 50 mg' and 'Mirabegron 25 mg') and visit, unless otherwise specified. Safety data will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
- Clinical laboratory variables (hematology, biochemistry including liver enzymes and total bilirubin, and urinalysis)
- Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature)
- 12-lead electrocardiogram (ECG)
- Post Void Residual Volume (PVR)

The following sequence order will be in effect when more than 1 assessment is required at a time point: routine 12-lead ECG, vital signs, and samples for safety laboratories.

5.4.1 Adverse Events

AEs will be coded using MedDRA. A TEAE is defined as an AE observed after starting administration of the IP until 30 days after the final administration of IP. If the adverse event occurs on Day 1 and the onset check box on the (AE) eCRF is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date).

A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

AEs may be upgraded by the sponsor according to the Important Medical Event process.

A drug-related TEAE is defined as any TEAE with at least a possible relationship to study treatment as assessed by the investigator or with a missing assessment of the causal relationship.

Common TEAEs are defined as preferred terms (PTs) that have been reported by at least 5% of the subjects, in any treatment group.

When an AE start or stop date is missing, the date will be imputed using the rules in Section 6.10.2.2.

Adverse Events of Special Interest

Adverse Events of Special Interest include:

- Increased heart rate and tachycardia
- Increased blood pressure

- Hypersensitivity reactions
- Urinary retention
- QT prolongation

AEs of interest will be identified using all Preferred Terms (PT) from Standardized MedDRA queries (SMQ), version 23.0 or higher, see Table 3, or sponsor-defined list of search terms, see Appendix 9.3 AEs of Interest not covered by Standard MedDRA SMQs v23.0.

Table 3 Standardized MedDRA Queries and PTs

CV - Increased blood pressure	Hypertension SMQ – Narrow search
CV - Increased heart rate and tachycardia	Arrhythmia supraventricular (PT) Atrial tachycardia (PT) Heart rate abnormal (PT) Heart rate increased (PT) Rebound tachycardia (PT) Sinus tachycardia (PT) Supraventricular tachyarrhythmia (PT) Supraventricular tachycardia (PT) Tachyarrhythmia (PT) Tachycardia (PT) Tachycardia paroxysmal (PT) Ventricular tachyarrhythmia (PT) Ventricular tachycardia (PT) Maximum heart rate increased (PT)
Hypersensitivity reactions	Hypersensitivity SMQ – Narrow search
CV - QT prolongation	Torsade de pointes/QT prolongation SMQ – Broad search

5.4.2 Vital Signs

Single blood pressure, pulse and body temperature measurements will be performed at visit 1/screening, visit 2/baseline, visit 3/week 4, visit 4/week 8, visit 5/week 12 (EoT).

Measurements will be per standard clinic practices. Single measurements of blood pressure, pulse, and body temperature will be measured in the sitting position (when possible, otherwise supine, but always in the same position).

Body temperature will be measured with an ear thermometer.

5.4.3 Clinical Laboratory Variables

Hematology, biochemistry and urinalysis assessments will be taken at visit 1/week -2 (screening), and visit 5/week 12 (EoT).

All clinical laboratory assessments will be performed at a local laboratory. Urine pregnancy tests (female subjects of childbearing potential only) will be performed according to the clinical site's preferred method at visit 1/week -2 (screening) and visit 5/week 12 (EoT) except for cases in which the possibility of pregnancy was clearly ruled out by hysterectomy, bilateral oophorectomy or the passage of 2 or more years after last menstruation.

A blood sample will be collected for serology tests (HAV antibodies [IgM], HBc antibodies, HBsAg, HCV antibodies, syphilis and antibodies to HIV types 1 and 2) at screening only.

Additional hematology, biochemistry and urinalysis (UA dipstick) tests may be performed at visit 1/week -2 (screening) and visit 5/week 12 (EoT). If any of the clinical laboratory tests results are outside the normal range at any scheduled time point during the study, the investigator may decide to repeat the test(s) on new samples. The clinical relevance of the abnormal results will be documented. Clinically relevant changes will be recorded as AEs (see Section 7.3 of protocol).

The laboratory parameters that will be assessed during the conduct of the study are listed in Table 4.

Table 4 Laboratory Assessments

Hematology	Biochemistry	Urinalysis	Serology*
Hematocrit Hemoglobin Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Platelets Red blood cell count White blood cell count White blood cell count differential	Albumin Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Corrected serum calcium Creatinine Creatinine kinase Glucose Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Total bilirubin (total and direct) Total protein	Leukocyte esterase Nitrites pH Protein Red blood cells Human chorionic gonadotropin (female subjects only)	HAV antibodies (IgM) HBsAg HBc antibodies HCV antibodies HIV antibodies types 1 and 2 Syphilis

* Serology parameters will be only collected at screening.

The value of each hematology and biochemistry parameter will be compared to its normal range and classified as High, Low or Normal. Urinalysis parameters will be similarly classified as either Normal or Abnormal.

When calculating changes or shifts in a result from baseline, the value from visit 1 will be used as baseline. If the visit 1 value is missing, the latest pre-baseline value will be used (i.e., from Visit 1 or any unscheduled visit conducted between Visit 1 and Visit 2).

5.4.4 Physical Examination

Physical examinations will be performed at visit 1/week -2 (screening) and visit 5/week 12 (EoT) and whenever there is a medical indication and will include assessments of the main body systems.

The physical examination will be performed per clinic standards and clinically significant findings at screening will be recorded as part of the subject's medical history. Any abnormal finding observed at screening must be assessed and documented as not clinically significant if a subject is to be enrolled in the study.

After IP administration, new clinically significant findings or a worsening of an ongoing clinically significant abnormal condition will be recorded as an AE [see Section 7.3 of protocol: Adverse Events and Other Safety Aspects].

5.4.5 12 Lead ECGs

A 12-lead ECG will be performed as single measurement at visit 1/screening and visit 5/week 12 (EoT). ECG traces will be evaluated by the investigator who will give an overall interpretation and may leave a qualifying comment in the eCRF. The overall interpretation will be recorded as:

- Normal, or
- Abnormal - not clinically significant, or
- Abnormal - clinically significant

As well as the overall interpretation, the following ECG variables will be supplied by the local laboratory: PR Interval (msec), RR Interval (msec), QRS Duration (msec), QT interval (msec) and Heart Rate (HR) (beats/min).

5.4.6 Post Void Residual Volume

PVR volume will be assessed by ultrasonography at visit 1/week -2 (screening) and visit 5/week 12 (EoT). For each subject, the same method should be used throughout the study. The bladder should only be emptied when it was initially filled with preferably > 50% of the bladder capacity for age. Every attempt should be made to measure PVR within a minute of voiding. A PVR of ≤ 100 mL is sufficient and the assessment does not have to be repeated. If the PVR is > 100 mL, the PVR assessment should be repeated (filled with preferably > 50% of the bladder capacity for age). If the subject is unable to complete a second measurement, it is up to the investigator to judge whether it can be skipped (and write the reason in the eCRF). The lowest PVR volume result measured should be used to evaluate the exclusion criterion. In case the lowest PVR volume measured is ≥ 100 mL at visit 1/week -2 (screening), the subject should be excluded from the study.

5.5 Other Endpoints

5.5.1 Exposure to Study Drug

The duration of exposure to each dose of study drug (Mirabegron 25 mg and Mirabegron 50 mg) by visit and for the whole period will be calculated using the following information :

- Overall start date and stop date of the study medication.
  The first dose of study drug is to be administered on Day 1, the day on visit 2/week 0 [baseline]. Treatment will be administered once daily orally after meal during a 12-week, open-label treatment period.
- Start date and new dose of study drug at each titration step.
  At visit 3/week 4 or visit 4/week 8 the dose may be up-titrated (from 25 to 50 mg according to investigators' discretion), or may remain the same.
  The study does not allow dose reduction from 50 mg to 25 mg as the former is considered a safe and effective recommended dose.

- Start date and new dose of study drug after each unscheduled dose change.
- At any time during the treatment period, the subject may have an unscheduled dose interruption. At each unscheduled change in dose, the (new) dose, start date and reason are recorded.

In all cases where there is a dose change, either because of dose titration or an unscheduled dose interruption, the first and the last dose of the medication at the old level will be collected at the CRF. In this way, the subject's dosing history can be reduced to a series of unbroken intervals within each of which, the dose level is constant. From these, the subject's exposure at each dose can be calculated.

To illustrate, consider a subject with the following dose information on the eCRF:

- The dates of the very first and very last dose of the study medication given at D_1=1st July 2020, D_{last}=23rd September 2020.
- Up-titration to 50 mg at Visit 3. The first dose at the new level is given at D_2=29th July 2020.
- Study drug interrupted at an unscheduled visit. The date of last dose is given at D_3=1st August 2020.
- Study drug re-started at an unscheduled visit at D_4=5th August 2020.
- Remains at 50 mg till Visit 5 (D_{last}=23rd September 2020).

From these dates we calculate the following:

- The duration of exposure to the treatment can be calculated as $E_{TOT}=D_{last}-D_1+1-(D_4-D_3-1)$ =82 days.
- Between Visits 2 and 3, the subject is on 25 mg. If the last dose at 25 mg collected in CRF is given on D_2-1, the day before the subject has the first dose at the new level (50 mg), then the exposure at 25 mg between Visits 2 and 3 is, therefore, $(D_2-1)-D_1+1$=28 days
- Between Visits 3 and 5, the study drug is temporarily suspended and then restarted. The subject will be considered to be exposed to the 50 mg dose from D_2 until D_3, i.e. D_3-D_2+1=4 days.
- For the calculation of the exposure, suspension of the study drug is accounted. The dose will be considered interrupted between D_3+1 to D_4-1, i.e., $(D_4-1) - (D_3+1) + 1$ = 3 days.
- The study drug is at 50 mg from D_4 to D_{last}, the date of the last dose on Visit 5, i.e., $(D_{last}-D_4+1)$=50 days.
- The total exposure at 50 mg is E_{50}=54 days, and at 25 mg total exposure is E_{25}=28 days.

5.5.2 Compliance to Study Drug

Compliance will be calculated according to the number of tablets of study medication dispensed, the number of tablets used and the duration of exposure between the applicable visits and overall.

The total number of tablets used between Visits i and j (i=2 [baseline], 3, 4, and j=i+1) is calculated as:

N_{used} = Total number of tablets dispensed at Visit i - Total number of tablets returned at Visit j

If some tablets (or part of kits) of IP are lost by the subject or returned later than expected, investigator will document the reason and IP compliance will be calculated based on actual tablets taken by subjects and IP accountability log.
When a strip with study drug is not returned/not reconciled, then for the calculations it is assumed that all tablets were taken from that strip.

The amount of expected study drug intake depends on the number of days of study drug treatment and the number of prescribed daily tablets. Since subjects are supposed to take 1 tablet per day, the total number of expected tablets to be used between Visits i and j (i=2 {baseline], 3, 4, and j=i+1) is calculated as described below.

For the compliance calculations it is assumed that on the visit day at Visit 3 (week 4), Visit 4 (week 8) and Visit 5 (week 12), the tablet is taken at home before going to the clinic. For the baseline visit (Visit 2) the subject takes the tablet at the clinic (Day 1).
For the period from:

- Baseline to Week 4 the expected number of tablets taken is equal to: Date of drug returned at Week 4 – Date of drug dispensed at Baseline visit + 1.
- Week 4 to Week 8 and from Week 8 to Week 12 the expected number of tablets taken is equal to: Date of drug returned Week (i+4) – Date of drug dispensed (Week i), where i=4 or 8.

Between Visits i and j the compliance to study medication will be calculated as follows:

$$\text{Compliance} = (N_{used} / N_{prescribed}) \times 100\%.$$

For the whole study period, the total amount of study drug used ($TOTN_{used}$) is equal to the sum of the values of N_{used} at each applicable visit. Similarly, the total amount of study drug prescribed ($TOTN_{prescribed}$) is equal to the sum of the values of $N_{prescribed}$ at each applicable visit. Using these total values, the subject's compliance over the whole study period will be calculated as 100% x ($TOTN_{used}$ / $TOTN_{prescribed}$).

6 STATISTICAL METHODOLOGY

6.1 General Considerations

Continuous data will be summarized descriptively including the number of subjects (n), mean, standard error of the mean (SEM) (efficacy data), standard deviation (SD), median, minimum and maximum. Categorical data will be summarized by frequencies and percentages. Percentages by categories will be based on the number of subjects with no missing data, i.e., the percentages for the non-missing categories will add up to 100%.

All statistical comparisons will be conducted using 2-sided tests at the 5% significance level unless stated otherwise. All null hypotheses will be of no treatment difference, all alternative hypotheses will be two-sided, unless specifically stated otherwise.

All data summarization and analyses will be performed using SAS® Version 9.4 or higher on Linux. Specifications for table, figures, and data listing formats can be found in the TLF specifications.

6.2 Study Population

All study population summaries will be presented showing two treatment groups as:

- Mirabegron 25 mg (Total)
- Mirabegron 50 mg (As-Randomized)
- Total Mirabegron, i.e., the sum of the Mirabegron 25 mg (Total) and of Mirabegron 50 mg (As-Randomized)

6.2.1 Disposition of Subjects

The following subject data will be presented by treatment arm, unless stated otherwise:

- Number of subjects with informed consent, discontinued before randomization, randomized (total only) (All Enrolled Set)
- Number and percentage of subjects randomized in each analysis set, by treatment group and total (All Randomized Set)
- Number and percentage of subjects completed and discontinued the screening (including COVID-19 reasons), by primary reason for study discontinuation (total only) (All Enrolled Set)
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation (including COVID-19 reasons), and by treatment group and total (All Randomized Set)
- Number and percentage of subjects who completed the Week 0, Week 4, Week 8 and Week 12 visit by treatment group and total (All Randomized Set)
- Number and percentage of subjects completed and discontinued the follow-up period, by primary reason for post-study period discontinuation (including COVID-19 reasons), and by treatment group and total (All Randomized Set)
- Number and percentages of subjects screened and randomized to each treatment group under each protocol version (All Subjects With Informed Consent).

A listing of inclusion and exclusion criteria, listing of first and last evaluations as well as a listing of subjects who were excluded from at least 1 analysis set will be provided for the All Enrolled Set.

6.2.2 Protocol Deviations

The number and percentage of subjects with the following protocol deviation criteria will be summarized for each criterion and total by treatment group and total as well as by investigative site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion.

The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria

PD2 - Developed withdrawal criteria during the study and was not withdrawn

PD3 - Received wrong treatment or incorrect dose

PD4 - Received excluded concomitant treatment

PD5 – Issues related to missing or invalid baseline Diary/OABSS

6.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics. Summaries will be presented by treatment group and total.

For the SAF and FAS, descriptive statistics for age will be presented as well as frequency tabulations for sex, ethnicity, race ('Chinese' or 'Other') and prior OAB treatment (Yes/No).

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by treatment group for the SAF.

Demographic data and other baseline characteristics (including medical history) will be provided in listing format by site and subject for the All Randomized Set.

6.2.4 Previous and Concomitant Medications

Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

Previous medications are defined as medications that patients started and ended prior to first administration of study medication. Concomitant medications are defined as any medications that subjects took after the first dose of study medication and through Follow-up period (EoS). Medications that started prior to first administration of study drug and continued while study drug was given will be counted in both previous and concomitant medications.

Previous and concomitant medications are coded with WHO-Drug Global data and will be provided in listing format by site and subject for the All Randomized Set.

6.3 Study Drug Exposure and Compliance

As per study schedule, all subjects will be assigned to either 'Mirabegron 25 mg' or 'Mirabegron 50 mg' at visit 2/week 0.

At visit 3/week 4 or visit 4/week 8 subjects can be up-titrated from 'Mirabegron 25 mg' to 'Mirabegron 50 mg' until the end of the study. Once up-titrated the dose cannot be adjusted back down. Study drug exposure will be summarized for the following groups:

- Mirabegron 25 mg
  - Never Up-Titrated
  - Later Up-Titrated to 50 mg
  - Total
- Mirabegron 50 mg
  - as Randomized

- Up-Titrated from 25 mg
- Total

6.3.1 Exposure

The following information on drug exposure will be presented by treatment groups described in Section 6.3 for the SAF:

- Descriptive statistics for cumulative amount of the drug to which the subject was exposed; and
- Number and percent of subject with dose increases or interruptions.

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented by treatment group.
- Exposure time will be categorized according to the following categories by treatment group:
  - at least 1 day, less than 7 days
  - at least 7 days, less than 14 days
  - at least 14 days, less than 28 days
  - at least 28 days, less than 56 days
  - at least 56 days, less than 83 days
  - 84 days or more
  - Unknown.
- Counts and percentages of cumulative exposure will be categorized according to the following categories by treatment group for the SAF:
  - ≥ 7 days
  - ≥ 14 days
  - ≥ 28 days
  - ≥ 56 days
  - ≥ 84 days

Exposure details will be listed for each subject by study visit and total for all randomized subjects.

6.3.2 Treatment Compliance

Total compliance with the dosing schedule will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent total compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by treatment group.
- Percent compliance will be categorized according to the following categories by treatment group:
  - less than 70%
  - at least 70%, less than 80%
  - at least 80%, less than 120%
  - at least 120%

- Unknown.

Treatment compliance details, including all data relevant to the calculation, will be listed for each subject by study visit and total for all randomized subjects.

6.4 Analysis of Efficacy

Efficacy analysis of the data from Mirabegron 50 mg group will be conducted on the FAS, and interpretation of results from statistical tests will be based on the FAS as well.

No multiplicity adjustment will be necessary in this study.

Efficacy data will be summarized by visit (week 0, 4, 8 and 12) and by EoT values unless otherwise specified.

All inferential statistics will be presented by the following treatment groups:

- Mirabegron 25 mg (Total)
- Mirabegron 50 mg (As-Randomized)

All summary descriptive statistics will be presented by the following treatment groups:

- Mirabegron 25 mg
  - Never Up-Titrated
  - Later Up-Titrated to 50 mg
  - Total
- Mirabegron 50 mg
  - as Randomized
  - Up-Titrated from 25 mg
  - Total

6.4.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline to week 12 in mean number of micturitions per 24 hours in Mirabegron 50 mg group.

6.4.1.1 Primary Analysis for Primary Efficacy Endpoint

The primary estimator for the primary estimand as defined in [Section 2.1.1 Estimand] will be calculated according to the evaluation of the primary efficacy endpoint. The primary efficacy endpoint will be analyzed using a Mixed Models Repeated Measures (MMRM). The MMRM model will include visit (the repeated term), treatment group (25 mg [total] or 50 mg [as-randomized]), pooled site, sex and the interaction between treatment group and visit as fixed effects and baseline measurement (the mean number of micturitions per 24 hours) as covariate. The algorithm to pool sites will be generated and documented prior to data base lock (Appendix 9.1). If the inclusion of pooled sites creates modeling problems, then dropping that factor will be considered. Subject will be identified as subject in the repeated statement.

The hypothesis for comparisons is given as follows:

H_0: The adjusted mean change from baseline at week 12 in mean number of micturitions per 24 hours in the 50 mg group is not different from zero.

H_1: The adjusted mean change from baseline at week 12 in mean number of micturitions per 24 hours in the 50 mg group is not equal zero.

Statistical testing will be done 2-sided at a 5% significance level.

The MMRM model results will be presented by treatment least squares (LS) means (± standard error [SE]) along with 2-sided 95% confidence intervals (CIs) and associated p-value for mean changes from baseline at weeks 4, 8 and 12 (the primary endpoint).
Data from subjects who switch from 25 to 50 mg mirabegron will not be included in MMRM model. Data from those subjects prior to switching will still be included in the MMRM model with treatment equal to 25 mg.

Model fitting will be visually assessed. A scatter plot of residuals versus predicted values, along with histogram and normal probability plots will be produced.

6.4.1.2 Graphical Summary of Data from Primary Efficacy Endpoint

Mean number of micturitions per 24 hours at each visit and change from baseline in mean number of micturitions per 24 hours will be plotted for FAS: mean (SEM) values will be presented for each visit.
LS Mean change from baseline in mean number of micturitions per 24 hours at each visit and change from baseline in mean number of micturitions per 24 hours will be plotted for FAS: mean (95% CI) values will be presented for each visit.

6.4.1.3 Subgroup Analysis for Primary Efficacy Endpoint

For the primary efficacy endpoint, descriptive statistics (n, mean, SD, minimum, median, maximum) and the statistical comparison within each group will be calculated for mean change from baseline at each visit using the same MMRM model described in Section 6.4.1.1 for the following subgroup: Prior OAB treatment (Yes vs. No).

Appendix 9.2 reports a non-exhaustive list of prior OAB treatment (not allowable during the study period).

6.4.2 Analysis of Secondary Efficacy Endpoints

6.4.2.1 Analysis of Secondary Efficacy Endpoints at Week 12

The same primary efficacy analysis (MMRM, with corresponding baseline measurement for the endpoint as the covariate) as for the primary endpoint (except for the covariate, i.e., mean number of micturitions at baseline) will be applied to change from baseline at the end of the 12-week treatment period in Mirabegron 50 mg subjects for:

- Mean number of grade 3 or 4 (PPIUS) urgency episodes per 24 hours
- Mean number of daytime incontinence episodes per 24 hours
- Mean number of nighttime incontinence episodes per 24 hours

- Mean number of urge incontinence episodes per 24 hours
- OAB Symptom Score

For each of the endpoints above, the covariate included in the model will be the respective variable of interest at the baseline, e.g., OAB Symptom Score at baseline for change from baseline to week 12 for the OABSS endpoint.

Data of these secondary efficacy endpoints will be analyzed for the FAS.

6.4.2.2 Analysis of Secondary Efficacy Endpoints at Weeks 4 and 8

For each treatment group, separately, least squares (LS) means (± standard error [SE]) along with 2-sided 95% Cis, from the same analysis model described in Section 6.4.2.1, will be presented for changes from baseline at Weeks 4 and 8.

6.4.2.3 Analysis of Secondary Efficacy Endpoints for Mirabegron 25 mg Starting Dose

Secondary efficacy endpoints presented in Section 5.2.6 will be summarized for Mirabegron 25 mg starting dose by visit (week 0, 4, 8 and 12) following the same statistical methods described in Sections 6.4.2.1 - 6.4.2.2 and will be conducted on the FAS.

6.4.2.4 Graphical Summary of Data from Mean Number of Grade 3 or 4 (PPIUS) Urgency Episodes and Urge Incontinence Episodes per 24 hours

Mean number of grade 3 or 4 (PPIUS) urgency episodes per 24 hours at each visit and mean number of urge incontinence episodes per 24 hours at each visit will be plotted for FAS: mean (SEM) values will be presented for each visit.

6.5 Analysis of Safety

Safety analysis will be conducted on the SAF. Safety endpoints will be summarized by treatment group and visit, if applicable. Descriptive statistics will be presented.

All safety summaries (except for shift tables in Sections 6.5.2 and 6.5.4) will be presented by the following:

- Mirabegron 25 mg
  - Never Up-Titrated
  - Later Up-Titrated to 50 mg (at visit 3 or 4)
  - Total
- Mirabegron 50 mg
  - as Randomized
  - Up-Titrated from 25 mg (at visit 3 or 4)
  - Total
- Total Mirabegron, i.e., the sum of the Mirabegron 25 mg (Total) and of Mirabegron 50 mg (As-Randomized)

6.5.1 Adverse Events

Summaries and listings of SAEs and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms or upgraded according to the Important Medical Event process, if any upgrade was done.

The coding dictionary for this study will be MedDRA. It will be used to summarize AEs by System Organ Class (SOC) and Preferred Term (PT).

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to withdrawal of treatment,
- Number and percentage of subjects with TEAEs leading to withdrawal of treatment,
- Number of drug-related TEAEs leading to withdrawal of treatment,
- Number and percentage of subjects with drug-related TEAEs leading to withdrawal of treatment,
- Number of TEAEs leading to death,
- Number and percentage of subjects with TEAEs leading to death,
- Number of drug-related TEAEs leading the death,
- Number and percentage of subjects with drug-related TEAEs leading to death, and
- Number and percentage of subjects who died.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment group. Summaries will be provided for:

- TEAEs,
- Drug related TEAEs,
- Serious TEAEs,
- Drug related serious TEAEs,
- TEAEs leading to withdrawal of treatment,
- Drug related TEAEs leading to withdrawal of treatment,
- Frequently Reported (>=5% in Any Treatment Group) TEAEs Excluding SAEs

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized for each treatment group.

The number of TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by severity and by relationship to study drug. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity or relationship, then the subject will be counted only once with the worst severity

and highest degree of relationship, however, if any of the severity or relationship values are missing then the subject will be counted only once with missing severity or relationship. In the adverse event count, the adverse events will be presented in each category they were classified to. Drug related TEAEs will be presented in a similar way by severity only.

Adverse events of interest will be tabulated by PT.

AEs will be provided in listing format by site and subject for the SAF.

6.5.2 Clinical Laboratory Evaluation

The baseline value will be the last non-missing value taken on or prior to first dose of study drug. In the "Schedule of Assessment" table in the protocol (Table 1) this "baseline" assessment will be done at screening (Visit 1).

In the eCRF both Blood Urea and Blood Urea Nitrogen (BUN) are presented. In the event that Blood Urea is measured and not BUN, then for summary statistics the BUN value will be obtained using the following formulae: BUN(mmol/L) = 2.1428 x Urea(mmol/L)
Note: BUN values will be summarized and in the listing both Blood Urea and BUN values will be presented.

When corrected serum calcium is not measured, the corrected serum calcium will be calculated as (depending on the units used for calcium and albumin):
Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 [40 (g/L) – albumin (g/L)])

For each local laboratory, separately, the quantitative clinical laboratory variables, i.e., hematology, biochemistry, and urinalysis, will be summarized using mean, standard deviation, median, minimum and maximum by treatment group and visit [visits 1 and 5] and for EoT values.

In addition, data from the local laboratories will be normalized to a single laboratory for the purpose of combining all laboratories and providing an overall summary. For normalizing the data of a laboratory parameter a common reference range for this parameter has to be determined. In this study the common reference range is the normal range coming from the site with the highest number of treated subjects.

Calculating the normalized value of a laboratory parameter: first all data from the parameter assessed in the local laboratories will be transformed into SI units. Next the data will be transformed according to the transformation formula below. Let x be the value of the laboratory parameter from the local laboratory, ULNL the upper limit of the normal range of the local laboratory, and ULNC the upper limit of the common reference range, then the transformed value (t) from the local laboratory is:

$$t = x.\frac{ULNC}{ULNL}$$ (Scale normalization, Karvanen et al.)

This value t will be used for reporting normalized laboratory values. Both the observed and normalized values (where applicable) will be reported in listings.

Additionally, for groups with both a baseline and week 12 measurement (i.e., Mirabegron 25 mg [Never Up-Titrated], Mirabegron 50 mg [As-Randomized] and Total Mirabegron) a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

The number and percentage of subjects below and above reference range will be summarized by treatment group and visit.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented by treatment group and visit.

Summary shifts of reference range (low, normal, high) changes from baseline to week 12 will be presented by the following treatment groups:

- Mirabegron 25 mg (Total)
- Mirabegron 50 mg (As-Randomized)
- Total Mirabegron, i.e., the sum of the Mirabegron 25 mg (Total) and of Mirabegron 50 mg (As-Randomized).

These shifts are categorized as:

  - "Shift to Low": shift from normal or high to low
  - "Shift to High": shift from normal or low to high
  - "Categorized Increase": shift from low to normal or from normal to high
  - "Categorized No Change": value stays in the same reference range
  - "Categorized Decrease": shift from high to normal or from normal to low.

All clinical laboratory data collected during the study and variables derived from it will be listed using SAF.

6.5.2.1 Liver Safety Assessment

The liver safety assessments will be summarized by the categories below based on the measurements from Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination. These parameters will be based on measurements from the local laboratory.

The subject's highest value during the investigational period will be used.

- ALT >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- AST >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- ALT or AST >3xULN, >5xULN, >10xULN, >20xULN
- ALP >1.5xULN
- Total Bilirubin >2xULN
- (ALT or AST >3xULN) and (Total Bilirubin >2xULN or INR > 1.5)
- (ALT or AST >3xULN) and ALP <2xULN and Total Bilirubin >2xULN

Note: ALT, AST, ALP and Total Bilirubin results will be classified using the reference ranges supplied by the local laboratories.

The last 2 criteria where 2 or more parameters are evaluated will be with the measurements on the same day or up to 1 day apart (Samples to be taken simultaneously or within a maximum of 24 hours).

The denominator for each criterion will be the number of subjects who have at least one value during the investigational period. The number and percentage of subjects meeting the criteria during the investigational period will be summarized by treatment group.

A scatter plot of Peak AST or ALT data vs. Peak Total Bilirubin data will be presented for mirabegron subjects. Data will be presented as fractions of the ULN (of the local laboratories). In this scatter plot the area for Hy's Law will be presented, where ALT or AST >3xULN and Total bilirubin
>2xULN (ALT, ALT and Total Bilirubin from same blood sample or within a maximum of 24 hours). The area for hyperbilirubinemia (ALT and AST <3xULN and Total bilirubin >2xULN), Temple's corollary (ALT or AST >3xULN and Total bilirubin < 2xULN) will also be presented in this scatter plot.

Laboratory data will be provided in listing format by site and subject for the SAF.

6.5.3 Vital Signs

The baseline value will be the last non-missing value taken on or prior to first dose of study drug (Visit 2).

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate and measurement for temperature) will be listed and summarized by treatment group and visit using mean, standard deviation, median, minimum and maximum. Additionally, for groups with both a baseline and a post-baseline 12 measurement, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group, total and visit. Summary of vital signs will be presented for each visit [visits 1, 2 (Baseline), 3, 4, and 5], and for EoT values.

Vital signs data will be provided in listing format by site and subject for the SAF.

6.5.4 Electrocardiograms

The baseline value will be the last non-missing value taken on or prior to first dose of study drug. In the "Schedule of Assessment" table in the protocol (Table 1) this "baseline" assessment will be done at screening (Visit 1).

ECG variables will be summarized using mean, standard deviation, median, minimum, and maximum by treatment group total and visit, including changes from baseline for groups with both a baseline and week 12 measurement. Summary of ECG variables will be presented for each visit [visits 1 and 5], and for EoT values. In addition to the ECG variables mentioned in Section 5.4.5, QTcF (msec) (=QT (msec)/([RR (msec)/1000]$^{1/3}$) will be summarized.
Note: unit for QT and RR reported in CRF is msec.

Normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12 lead ECG along with shift tables will be presented for changes from baseline to Week 12 including local interpretation categories by the following treatment groups:

- Mirabegron 25 mg (Never Up-Titrated)
- Mirabegron 50 mg (As-Randomized)
- Total Mirabegron.

The QTc interval will be summarized using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below.

Category	QTc Interval Criteria Value (msec)
Normal	≤ 450
Borderline	> 450
Prolonged	> 480
Clinically significant	> 500

Note that these categories are cumulative in that subjects satisfying criterion for more extreme category will also be counted in each applicable less extreme category.

The corrected QT interval (i.e., QTcF) will also be summarized by treatment group and visit showing the frequencies of subjects with the following changes from baseline:

Variable	Change from Baseline
QTc Interval (msec)	< 0 ≥ 0 and < 30 ≥ 30 and < 60 ≥ 60

ECG data will be provided in listing format by site and subject for the SAF.

6.5.5 Pregnancies

A detailed listing of all pregnancies will be provided if any occur using All Enrolled Set.

6.5.6 Other Safety-Related Assessments

6.5.6.1 Post Void Residual Volume

The baseline value will be the last non-missing value taken on or prior to first dose of study drug. In the "Schedule of Assessment" table in the protocol (Table 1) this "baseline" assessment will be done at screening (Visit 1).

PVR will be summarized by treatment group and visit using mean, standard deviation, median, minimum, and maximum at each treatment visit, including changes from baseline (for groups with both a baseline and week 12 measurement). In case of 2 measurements at the same visit, the lowest (instead of mean) PVR volume will be used for the calculations. Summary of PVR values will be presented for each visit [visits 1 and 5], and for EoT values.

PVR data will be provided in listing format by site and subject for the SAF.

6.6 Analysis of Pharmacokinetics

Not applicable.

6.7 Analysis of Pharmacodynamics

Not applicable.

6.8 Other Analyses

Not applicable.

6.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

There is no planned interim analysis but a data cut with summaries (e.g., after 50% of subjects planned to be randomized have had their week 12/EoT assessment) and the planned primary analysis for the end of the study may be generated at a specific timepoint during the study for regulatory reporting purposes. No decisions regarding conduct of the study (i.e., stopping) will be based on these results.

6.10 Additional Conventions

6.10.1 Analysis Windows

The study protocol gives the total study schedule and the permissible intervals for these visits expressed as the number of days relative to visit 2/baseline. The total time each subject will be in the study will not exceed 16 weeks with a maximum of a screening period of 2 weeks, a maximum of 12 weeks for the investigational period and a maximum of a follow-up period of 2 weeks.

Analyses will not exclude subject data due to the subject's failure to comply with the visit schedule, see Table 5.

The data summary by visits will be done following the analysis windows specified in Table 5.

For Bladder e-diary data. using the Subject Visit (SV) domain: for each diary record find the date from SV that satisfies the condition (Date from SV-7) <= Diary Date < Date from SV. Using the corresponding relative day of that date, assign the analysis visit as specified in Table 5.

Table 5 Visit Windows for Efficacy and Safety Parameters

Analysis Visits	Target day relative to Baseline (Visit 2, Day 1)	Analysis Window (day)
Bladder e-diary		
Baseline	Day -1	Day -12 to Day -1
Week 4	Day 28	Day 7 to Day 42
Week 8	Day 56	Day 43 to Day 70
Week 12	Day 84	Day 71 to Day 97
EoT	Day 84	Day 2 to ≤ Last dose of study drug

Analysis Visits	Target day relative to Baseline (Visit 2, Day 1)	Analysis Window (day)
OABSS questionnaire		
Baseline	Day 1	Day -12 to Day 1
Week 4	Day 28	Day 2 to Day 42
Week 8	Day 56	Day 43 to Day 70
Week 12	Day 84	Day 71 to Day 97
EoT	Day 84	Day 2 to ≤ Last dose of study drug
Vital signs*		
Week -2	Day -14	Day -17 to Day -4
Week 0/ Baseline	Last value prior to first dose	Day -3 to Day 1 (prior to first dose)
Week 4	Day 28	Day 2 to Day 42
Week 8	Day 56	Day 43 to Day 70
Week 12	Day 84	Day 71 to Day 97
EoT	Day 84	Day 1 to ≤ Last dose of study drug
ECG, Clinical Laboratory Tests (including Pregnancy Test) and PVR*		
Week -2/ Baseline	Day -14	Day -17 to Day 1 (prior to first dose)
Week 12	Day 84	Day 2 to Day 97
EoT	Day 84	Day 1 to ≤ Last dose of study drug

* if an Early Discontinuation visit occurs within any specified visit window, all data collected during this visit will be assigned to the respective analysis visit.

For non-diary data, if a subject has more than one non-missing value within a visit window, the non-missing assessment which is closest to the target day within a window will be used. If two or more values are equally close and on different days, the latest non-missing value will be used. If two or more values are equally close and on the same day, the mean will be used for continuous variables or the worst observed case for categorical variables.

For diary data, the assessment date for the whole diary will be considered to be the date of the last valid day of the diary. If more than one diary has an assessment date within the same window, and if this results in more than one non-missing value of a diary variable, the non-missing value with the diary assessment day that is closest to the target day will be used. In case of ties on different days, the later non-missing value will be used. In case of ties located on the same side of the target day (i.e., more than one value for the same day), the mean of the values will be used for continuous variables and the worst value for categorical variables.

For analyzing diary data the labels of the study visits will not be used, they will be assigned based on the dates of assessment.

A two-day window around the visit date will be applied for the assignment of study period for exposure data.

6.10.2 Imputation Rules for Incomplete Dates

As a general principle, no imputation of missing data for variables will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to

determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

6.10.2.1 Imputation Rules for Diary Dates

Not Applicable.

6.10.2.2 Imputation Rules for Adverse Events

For AEs, a missing or incomplete onset date will be imputed according to the following conventions.

If an onset date is missing or only the year is known, the imputed onset date will be the date of first dose of study drug.

If only the year is known for the AE onset date, the imputed onset date will be the latest of the following non-missing dates:

- Date of first dose of study drug
- January 1 of the year of AE onset date

If only the month and year is known for the onset date, set the surrogate onset date to the first day of that month and then apply the following rules.

- If the month and year of the onset date is prior to the month and year of the first dose of study drug, then the surrogate onset date will be the imputed onset date.
- If the month and year of the onset date is on or after the month and year of the first dose of study drug, then the imputed onset date will be the **latest** of the following non-missing dates:
    - Date of first dose of study drug
    - Surrogate onset date

If the imputed onset date is after the adverse event end date, the imputed onset date will be the same as the adverse event end date.

6.10.2.3 Imputation Rules for Concomitant Medications

In case of missing partial start and stop dates for concomitant medications, the following rules will be used:

If the start date is missing or partial:

- if the month is missing, use January
- if the day is missing, use the first day of the month under consideration
- if the year is missing, use year of the informed consent date
- if the entire date is missing, use informed consent date

If the stop date is missing or partial:

- if the month is missing, use December
- if the day is missing, use the last day of the month under consideration

- if the year or the entire date is missing, set the stop date to December 31st, 2099

If the imputed start date is after the stop date, then the imputed start date will be 1 day prior to the stop date.

6.10.3 Outliers

All values will be included in the planned analyses. A sensitivity analysis excluding outliers may be performed as an additional secondary analysis, if considered appropriate by the study statistician or the medical expert.

7 REVISION AND RATIONALE

7.1 List of Changes in SAP Version 2.0 from Version 1.0

The changes from the approved SAP Version 1.0 (Dated 09-Dec-2020) to Version 2.0 that impact analyses are listed with the rationale in the table below.

SAP Sections	Description	Rationale
5	Table for classifying assessments as daytime or nighttime is added	Added for clarification
	Text for procedure for calculating efficacy endpoints	Added for clarification
5.1	Second paragraph: "total number of" should be "mean number of"	Corrected the definition of mean number of micturitions
5.2	Summary of efficacy data will also be done for EoT values	Added to be consistent with other studies.
	The success rate of efficacy variables in each treatment group initiated with either 50 mg or 25 mg dose will NOT be evaluated at each treatment visit	Not applicable
5.2.4	Section 5.2.4 was added to explain how the number of urge incontinence episodes are calculated	Was missing in Version 1
5.2.5	Text added how to deal if not all questions for OABSS are answered. Definition of baseline assessment was added.	Added for clarification
5.4.1	Corrected definition of TEAE	To be consistent with protocol
	Common TEAEs are defined as preferred terms (PTs) that have been reported by at least 5% of the subjects, in any treatment group.	Added "in any treatment group" to be consistent with other studies.
	Table 3 was updated	Based on new information
5.5.2	Text on compliance is updated	For clarification
6.4.1.3	Text on the "statistical comparison within each group" was added	To be consitent with analysis of micturition data.
6.5.1	Text regardind "upgraded according to the Important Medical Event process" was added.	Text added to be consistent with other studies
6.4, 6.5.2 – 6.5.4, and 6.5.6.1	Summary of efficacy, Lab, ECG, Vital signs and PVR data will also be done for EoT values	Added for clarification.

SAP Sections	Description	Rationale
6.5.2	Text adjusted for local laboratories and how to deal with Blood Urea and BUN results	To clarify how these data will be processed
	Text added on normalizing local lab data	To clarify how this will be done
6.5.4	Definition of QTcF was added	Added for clarification
6.10.1	Table 5 is updated	For bladder and questionnaire data no gaps in the windows are allowed, see new SAP template
9.1	The algorithm for pooling sites is added	This should be defined before Database Lock.

7.2 List of Changes in SAP Version 3.0 from Version 2.0

The changes from the approved SAP Version 2.0 (Dated 06-May-2021) to Version 3.0 that impact analyses are listed with the rationale in the table below.

SAP Sections	Description	Rationale
6.2.3	Results of Prior OAB Treatment will be summarized	Added for clarification
	Medical History data will be summarized	Addional request
6.4.1.2	Text added that 2 additional figures will be presented	Added for clarification
6.4.2.4	Section added to describe that for two secondary endpoints a figure will be presented	Additional request

8 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

Neurourology and Urodynamics. 2015;34:685–92.

Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15:241-3.

9 APPENDICES

9.1 Pooling of Sites Algorithm

Two hundred and forty-nine (249) subjects were randomized at 15 sites. When "site" is included as a factor in a statistical model, sites that have less than 8 FAS subjects in total will be identified and then combined for statistical analysis purposes according to the following algorithm:

- Step 1: Divide the sites into two groups with Group 1 including all sites that have at least 8 FAS subjects and Group 2 including all remaining sites. Sort each group in ascending order by total sample size and site number.
- Step 2: Starting at the top of the Group 2 list (i.e., the first site with the smallest total sample size), combine the minimum number of sites required to achieve a "pooled site" that has at least 8 FAS subjects in total. Continue forming "pooled sites" in this manner until all Group 2 sites have been grouped or it is no longer possible to form a "pooled site" with at least 8 FAS subjects in total.
- Step 3: If there is a site (or several sites) left after step 2, combine the site(s) with the last "pooled site" that is created. For the situation where no previous "pooled site" is created, combine the site(s) with the first site on the sorted Group 1 list.
- "Pooled site" will be assigned names PoolSite01, PoolSite02, etc. For sites not needing to be pooled, the original site name will be used such as Site001. For all sites that have been combined into pooled sites, the assigned pooled site will be used instead of the original site identification in all statistical models that include "site" as a factor. However, the original site identification will be used in all summaries of subject disposition or discontinuation by site and in all data listings.

9.2 List of Excluded Concomitant Medications

Any medication used for the management of OAB (including tricyclic antidepressants, 1st generation H1-antagonists and alpha-blockers) and any drugs that are sensitive CYP2D6 substrates with a narrow therapeutic index and sensitive P-gp substrates.

Use of these medications is not permitted during the study phase. This list is not exhaustive.

Anticholinergics/antimuscarinics	**Tricyclic/heterocyclic antidepressants**	**1st generation H1-antagonists†**
Darifenacin	Alimemazine / Trimipramine	Tripelennamine
Dicyclomine/Dicycloverine	Amitriptyline	Dimenhydrinate
Fesoterodine	Amoxapine	Clemastine
Flavoxate	Clomipramine	Bromazine
Isopropamide	Desipramine	Orphenadrine
Oxybutynin	Dosulepin/ Dothiepin	Doxylamine
Oxyphencyclimine	Doxepine	Carbinoxamine
Propantheline	Imipramine	Diphenhydramine
Propiverine	Lofepramine	Cyclizine
Tolterodine	Maprotiline	Chlorcyclizine
Trospium	Mianserin	Hydroxyzine
Solifenacin	Mirtazapine	Meclizine
	Nortriptyline	
	Protriptyline	
Alpha-blockers	**CYP2D6 with narrow therapeutic index**	**Sensitive P-gp substrates**
Tamsulosin	Thioridazine	Digoxin
Alfuzosin	Flecainide	Dabigatran
Doxazosin	Propafenone	
Terazosin	Imipramine	
Silodosin	Desipramine	
Strong CYP3A4 inhibitors	**Other**	
Itraconazole	Mirabegron (except for study drug)	
Ketoconazole	Botulinum toxin	
Ritonavir	Opioids	
Clarthromycin		

†Incidental use for motion sickness is accepted. P-gp: P-glycoprotein

9.3 AEs of Interest not covered by Standard MedDRA SMQs v23.0

The following is a list AE terms to programmatically flag subjects with AE's of interest (see Section 5.4.1).

Type	Term	Code	AE of Interest	MedDRA 23.0 Search Criteria
LLT	Acute retention of urine	10001055	Acute urinary retention	Selected LLT (non-SMQ)
PT	Residual urine volume	10050832	Urinary retention	Selected PT's (non-SMQ)
PT	Residual urine volume increased	10067758	Urinary retention	Selected PT's (non-SMQ)
PT	Urinary retention	10046555	Urinary retention	Selected PT's (non-SMQ)

9.4 Key Contributors

Name, Degree And Title And Function	Department
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9.5 Author and Approver Signatures

Signatures

Prepared by: _____ Date: _____

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