A Phase 4, Double-Blind, Randomized, Placebo-controlled Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Male Subjects with OAB Symptoms while taking the Alpha Blocker Tamsulosin for BPH

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STATISTICAL ANALYSIS PLAN

Final Version 1.00, dated 14-Nov 2017

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Astellas Pharma Inc. (API)

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase (GOT)
BP	Blood pressure
BPH	Benign prostatic hypertrophy
BUN	Blood urea nitrogen
CK	Creatinine kinase
CSR	Clinical Study Report
ECG	Electrocardiogram
FAS	Full Analysis Set
HUS	hours of undisturbed sleep
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPSS	International Prostate Symptom Score
IRT	Interactive Response Technology
ISN	International study number
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measure
OAB	Overactive Bladder
OAB-q	Overactive Bladder questionnaire
OABSS	Overactive Bladder Symptom Score
PD	Protocol deviation
PK	Pharmacokinetic(s)
PPS	Per Protocol Set
PR	Pulse rate
PSA	Prostate-specific antigen
PVR	Post-void residual (volume)
Q1	1st Quartile, 25th Percentile
Q3	3rd Quartile, 75th Percentile
Qave	Average flow rate
Qmax	Maximum urine flow rate
QoL	Quality of Life
QTcF interval	QT interval, corrected for heart rate according to Fridericia's formula
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
Total HRQL score	Total Health-Related Quality of Life score
UFM	Uroflowmetry

Abbreviations	Description of abbreviations
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

List of Key Terms

Terms	Definition of terms
Adverse event	Any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have a causal relationship to the study drug.
Baseline	Observed values/findings that are regarded as the observed starting point for comparison. Visit 2 is the Baseline visit in this study.
Discontinuation	The act of an enrolled subject concluding study participation prior to completion of all protocol-required assessments. Data from discontinued subjects are not necessarily excluded from the data analyses.
Endpoint	A variable that pertains to the trial objectives
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Investigational period	Period of time during which protocol objectives are observed, and when the test drug and comparative drug (sometimes without randomization) is given to subjects, and continues until the last assessment after completing administration of the test drug or comparative drug.
Randomization	The process of assigning study subjects to treatment or control groups, using an element of chance to determine treatment assignments, in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	A potential subject who did not meet one or more criteria required for participation in the trial.
Screening period	Period of time before the investigational period, from the time of informed consent at Visit 1 until just before the test drug or comparative drug is given to the subject at Visit 2.
Study period	Period of time from the first site's initiation date to the last site's completion date.
Subject	An individual who participates in a clinical study, either as a recipient of the study drug or as a control.
Treatment period	For this study, from randomization at Visit 2 through Visit 5 (Week 12/End of Treatment).
Variable	Any quantity that varies; any attribute, phenomenon, or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data. The SAP is finalized and signed prior to unblinding.

This statistical analysis is coordinated by the responsible biostatistician of Astellas Pharma Inc.. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

2 FLOW CHART AND VISIT SCHEDULE

Figure 1 Study Design Flow Chart

Study Schematic Diagram

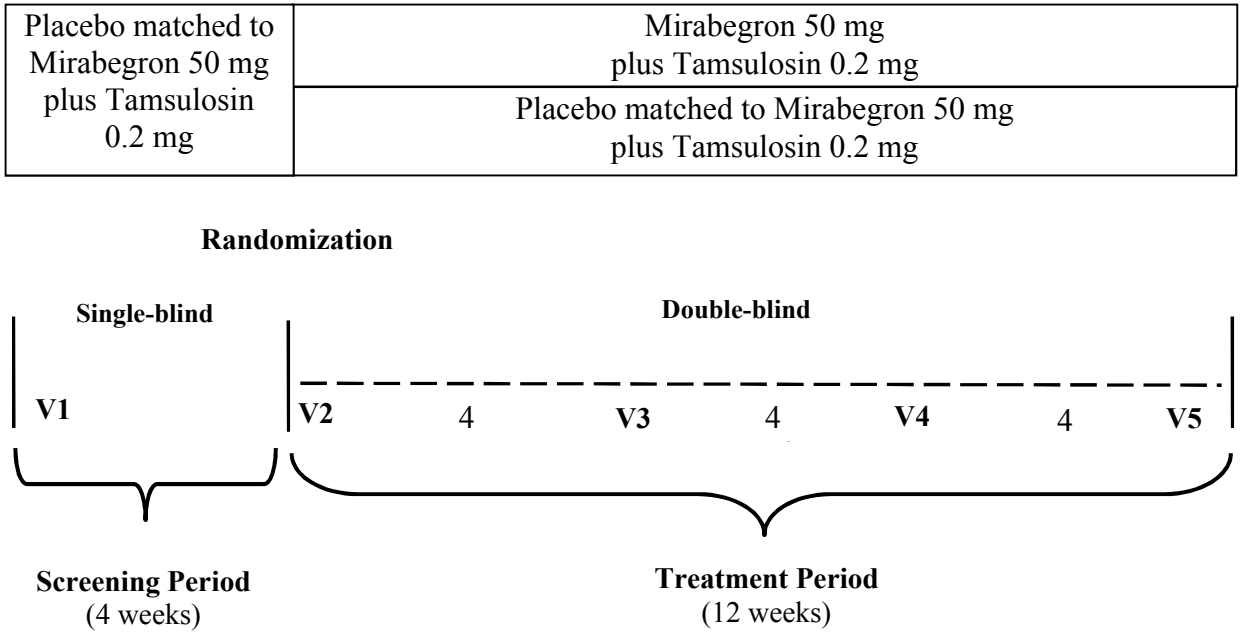

Table 1: Schedule of Assessments

	Screening/ Tamsulosin Screening	**Treatment Period**			
Visit	1	2	3	4	5
Day	-28	1	29	57	85
Week	-4	0	4	8	12
Visit Windows	+/- 7d	-	+/- 7 d	+/- 7 d	+/- 7 d
Visit Windows (Study Days) [a]	-35 to -21	-	22 to 36	50 to 64	78 to 92
Informed Consent	X [b]				
Inclusion/Exclusion Criteria	X	X			
Medical History and OAB History	X				
Demographics	X				
Enter 4-week Tamsulosin Screening [c]	X				
Enrollment	X				
Randomization [d]		X			
Physical Exam	X				
Weight and Height	X				
Vital Signs (includes pulse and blood pressure[e])	X	X	X	X	X
Serum PSA	X				
Prostate volume	X				
Serum chemistry [f], hematology [f], urinalysis	X	X [d]			X
12-Lead ECG (QTcF interval)	X				
Ultrasonography or Bladder Scan (PVR)	X	X	X	X	X
Uroflowmetry [g]	X	X			X
Medication History and OAB Medication History	X				
Concomitant Medications Assessment	X	X	X	X	X
Adverse Event Assessment		X	X	X	X
Dispense Study Drug	X	X	X	X	
Drug Accountability	X	X	X	X	X
Instruct Subject on 3-day Micturition Diary [h]	X	X	X	X	
Subject Completes 3-day Micturition Diary		X [i]	X [i]	X [i]	X [i]
OABSS	X	X	X	X	X
IPSS & IPSS (QoL)	X	X	X	X	X

	Screening/ Tamsulosin Screening	Treatment Period			
Visit	1	2	3	4	5
Day	-28	1	29	57	85
Week	-4	0	4	8	12
Visit Windows	+/- 7d	-	+/- 7 d	+/- 7 d	+/- 7 d
Visit Windows (Study Days) [a]	-35 to -21	-	22 to 36	50 to 64	78 to 92
OAB-q	X	X			X
Review Micturition Diary [j]		X	X	X	X

Abbreviations: PSA=Prostate-specific antigen, ECG =electrocardiogram; IPSS = International Prostate Symptom Score; OAB = Overactive bladder; OAB-q = Overactive Bladder questionnaire; OABSS = Overactive Bladder Symptom Score; PVR = Post-void residual (volume); QoL = Quality of Life; UFM = uroflowmetry

a. Visit windows/study days will be calculated based on Day 1 (Visit 2).

b. If a drug for the treatment of BPH is to be changed to tamsulosin to enroll a subject in this clinical study, the change to tamsulosin should be done only after informed consent form signature and a new informed consent is to be obtained at Visit 1 (Screening).

c. Subjects must take tamsulosin for at least 28 days before the Screening period.

d. Randomization is to occur after confirming all eligibility criteria and after performing all other visit procedures at Visit 2.

e. Measured during the patient diary period and at each visit (only at visit for discontinued subjects if there is no entry in the patient diary)

f. Blood samples need not be under fasting conditions.

g. Any UFM results obtained within 28 days prior to the start of the Screening period may be used, with the subject's consent, instead of the Visit 1 data.

h. At the Tamsulosin Screening visit (Visit 1), all subjects will be provided a micturition diary that will be used to record the date and time of each of their micturitions, episodes of incontinence, urgency, and voiding volume. Voiding volumes will be collected at Visit 2 (Baseline) and Visit 5 (Week 12). Additionally, the diary will be used to record daily medication intake and self-

measurement of blood pressure and pulse rate. Subjects will be instructed to begin completing the micturition diary 3 days prior to each in-office study visit, including Visit 2 (Baseline) and Visits 3 through 5 (Treatment Period), and to complete the diary for the full 3 days.

i. For Visits 2, 3, 4, and 5, subjects should complete the micturition diary on the 3 days immediately prior to the study visit, but in any case, on consecutive days within 1 week prior to the study visit.

j. Investigator, or designee, must review the micturition diary with the subject to ensure completion compliance and to discuss the data captured.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

The following objectives are investigated in male patients with overactive bladder (OAB) symptoms while taking the alpha blocker, tamsulosin, for benign prostatic hypertrophy (BPH). The hypothesis being tested is that mirabegron is superior to placebo in the treatment of OAB symptoms.

3.1.1 Primary Objective

To study the efficacy of mirabegron versus placebo in male patients with OAB symptoms while taking the alpha blocker, tamsulosin, for BPH.

3.1.2 Secondary Objective

To assess the safety and tolerability of mirabegron versus placebo in male patients with OAB symptoms while taking the alpha blocker, tamsulosin, for BPH.

3.1.3 Other Objectives

To assess patient-reported outcomes as measured by Symptom Bother, and Total Health-Related Quality of Life scores as assessed by the Overactive Bladder questionnaire (OAB-q) and IPSS (QoL) of mirabegron versus placebo in male subjects with OAB symptoms who are taking the alpha blocker, tamsulosin, for BPH.

3.2 Study Design

This is a randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of treatment with mirabegron for OAB in male subjects at least 40 years of age who are taking tamsulosin for BPH. Eligible subjects must have a history of (on average) at least 2 urgency episodes and 8 or more micturitions in a 24-hour period during the 3 days prior to the start of the Screening period.

The study will consist of a 4-week single-blind Screening period followed by a 12-week double-blind Treatment period. During the Screening period and beginning with Visit 1, all subjects will receive tamsulosin 0.2 mg along with mirabegron 50 mg matching placebo once daily after breakfast.

At the conclusion of the 4-week tamsulosin Screening period, subjects will complete a 3-day micturition diary just prior to Visit 2 (Baseline). Subjects who meet entry criteria at the end of the tamsulosin Screening period will be randomized (at Visit 2) to receive either mirabegron 50 mg or matching placebo for 12 weeks of double-blind treatment, while continuing their treatment with tamsulosin 0.2 mg daily.

For randomization, key efficacy assessments, safety and tolerability assessments of mirabegron administered concomitantly with tamsulosin, refer to section 3.3, 6.1 and 6.2 respectively.

Individual subject participation in the study will be ~16 weeks, which includes the 4-week Screening period and the 12-week double-blind Treatment period.

The study will be conducted in Japan (~50 centers) and Korea (~5 centers). The target enrollment is 550 subjects, with 275 randomized to each treatment group.

3.3 Randomization

Subjects will be randomized 1:1 to receive mirabegron 50 mg or matching placebo once daily during the 12-week treatment period. The randomization will be stratified by site.

Randomization will be performed via Interactive Response Technology (IRT). Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment for each subject.

4 SAMPLE SIZE

The sample size for this study was based on 248 subjects per treatment group (using the Full Analysis Set [FAS]) to provide 90% power to detect a 0.7 reduction in the mean number of micturitions/24 hours in the mirabegron group compared to the placebo group, at a two-sided alpha level of 0.05. A standard deviation (SD) of 2.4 is assumed. Assumptions for the mean reduction and SD are based on data from previous studies. If 90% of the randomized subjects are evaluable for efficacy, 550 subjects should be randomized, with 275 subjects randomized to each treatment group.

5 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 final handling of the analysis sets will be decided with the decisions based on the opinions and advice of medical experts prior to breaking of the randomization code.

Demographics and other baseline characteristics will be summarized by treatment group for the Full Analysis Set, Per Protocol Set (PPS), and Safety Analysis Set (SAF).

The efficacy analysis will be conducted on the FAS, with the PPS as a supportive analysis.

All secondary efficacy analyses will be performed on the FAS.

The safety analysis will be performed on the SAF.

5.1 Full Analysis Set (FAS)

The FAS consists of all subjects who are randomized and receive at least 1 dose of double-blind study drug and have a Baseline micturition measurement and at least 1 post-Baseline micturition measurement.

5.2 Per Protocol Set (PPS)

The PPS includes all subjects of the FAS who do not meet criteria for exclusion from PPS listed in section 5.2.1 of the SAP.

5.2.1 Reasons for Exclusion From PPS

Subjects in FAS who meet any of the following criteria will be excluded from PPS:

1. Those subjects who violated the inclusion criteria.
2. Those subjects who violated the exclusion criteria.
3. Those subjects with drug compliance during the Screening period and Treatment period of less than 80%.
4. Those subjects who took the study drug for less than 42 days from the day following dispensing during the Treatment period. However, subjects who discontinued the study for efficacy-related reasons, such as insufficient therapeutic effect, will be included in the PPS, even if the drug was taken for less than 42 days.
5. Subjects without diary entries for at least 2 of the 3 consecutive days at Visit 2 and the last visit during the Treatment period.
6. Subjects who received any of the prohibited concomitant medications/therapies that may affect the evaluation of efficacy.

5.3 Safety Analysis Set (SAF)

The SAF consists of all subjects who received at least 1 dose of double-blind study medication.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

The primary endpoint is the change from Baseline to End of Treatment in the mean number of micturitions in 24 hours, based on a 3-day micturition diary.

For each patient, the mean number of micturitions per 24 hours will be calculated by taking the sum of all marked episodes in the patient diary where the variable ‘Urinated’ is indicated, divided by the number of days on which episodes were marked in the column ‘Urinated’.

A diary day will cover information from 6:00 AM to 5:59 AM the following morning, consequently both date and time of the episodes recorded need to be considered when assessing the number of days on which episodes were marked.

The mean number of micturitions/24 hours in the 3-day diary period before baseline (Visit 2) will be regarded as the baseline value.

6.1.2 Secondary Efficacy Endpoints

The secondary endpoints include the change from Baseline to post-baseline and End of Treatment in:

- Mean number of micturitions/24 hours (except for End of Treatment visit) Calculation is same as the primary endpoint.
- Mean number of urgency episodes/24 hours

Calculation is similar to 'micturition', but sum episodes in the diary where the variable 'Urgency' is indicated. The calculation of days is as per 'micturition'. If there is no urgency episodes on all evaluable days in each visit, then the mean number of urgency episodes/24 hours is equal to zero. Only those subjects whose symptoms were confirmed at baseline (Visit 2) will be analysed, therefore if the mean number of urgency episodes per 24 hours is "0" at baseline, this subject is excluded from the analysis.

- Mean number of urgency incontinence episodes/24 hours
  Calculation is similar to 'micturition', but sum episodes in the diary where both the variables 'Urgency' and 'Urinary incontinence' are indicated. Only those subjects whose symptoms were confirmed at baseline (Visit 2) will be analysed.If there is no urgency incontinence episodes on all evaluable days in each visit, then the mean number of urgency incontinence episodes/24 hours is equal to zero. Therefore if the mean number of urgency incontinence episodes per 24 hours is "0" at baseline, this subject is excluded from the analysis.
- Mean number of incontinence episodes/24 hours
  Calculation is similar to 'micturition', but sum episodes in the diary where the variable 'Urinary incontinence' is indicated. Only those subjects whose symptoms were confirmed at baseline (Visit 2) will be analysed. If there is no incontinence episodes on all evaluable days in each visit, then the mean number of incontinence episodes/24 hours is equal to zero. Therefore if the mean number of incontinence episodes per 24 hours is "0" at baseline, this subject is excluded from the analysis.
- Mean number of nocturia episodes
  Calculation is similar to 'micturition', but sum episodes in the diary where the variable 'Urinated' is indicated during the night time excluding the same time recorded as the time of sleep onset, divided by the number of nights. If the interval between sleep onset time and wake up datetime is more than 24 hours, then the records during the interval will not be used as nocturia.
  Night time is the period between after sleep onset time and the wake-up time the following day (micturitions at the same time as the wake-up time will be excluded). The diary must be completed for at least 2 consecutive days to allow assessment of night time frequency for at least 1 night. Any data collected before the wake-up time on the first day of diary completion and after the sleep onset time on the third day cannot be included in the assessment of night time frequency. Only those subjects whose symptoms were confirmed at baseline (Visit 2) will be analyzed.
  If there is no nocturia episode on all evaluable night time in each visit, then the mean number of nocturia episodes/24 hours is equal to zero. Therefore if the mean number of nocturia episodes per 24 hours is "0" at baseline, this subject is excluded from the analysis.

- Mean volume voided per micturition
  Calculation is similar to 'micturition', but sum urinary volumes where the volume voided is > 0 and where 'Urinary incontinence' is not indicated, rather than count the episodes. The denominator will be the number of micturitions where the volume voided is > 0 and where 'urinary incontinence' is not indicated. Only those subjects whose symptoms were confirmed at baseline (Visit 2) will be analysed.

- Total OABSS score
  For each patient, OABSS total score will be the sum total of the score of each item (Questions 1-4).
- Subscale scores (daytime frequency, nighttime frequency, urgency and urgency incontinence) from OABSS score
  For each patient, OABSS subscale scores will be the score of each item (Questions 1-4).
- Total IPSS score
  For each patient, total IPSS score will be the sum total of the score of each item (Questions 1-7).
- Subscale scores (storage subscale, voiding subscale-1, voiding subscale-2 and quality of life item) and individual scores from IPSS score
  For each patient, IPSS subscale scores will be calculated by following each formula. Storage subscale is derived as sum of scores for questions 2, 4, and 7. Voiding subscale-1 is derived as sum of scores for questions 3, 5, and 6. Voiding subscale-2 is derived as sum of voiding subscale-1 and the score for question 1.
  For each patient, Individual scores and IPSS QoL score will be the score of each item (Questions 1-7 and quality of life item).
- Symptom Bother and Total Health-Related Quality of Life scores (Total HRQL scores), as assessed by OAB-q
  For each patient, OAB-q score (Symptom Bother and Total HRQL score) will be calculated by following each formula.
  Symptom Bother is derived as sum of scores for questions 1-8; lowest possible raw score: 8; highest possible raw score: 48; possible raw score range: 40.

$$\text{Symptom Bother} = \frac{(\text{Actual raw score} - \text{lowest possible raw score})}{\text{Possible raw score range}} \times 100$$

  Higher Symptom Bother is indicative of greater symptom bother.
  Total HRQL score is derived as sum of HRQL subscale scores (not individual items); lowest possible raw score: 25; highest possible raw score: 150; possible raw score range: 125.

$$\text{Total HRQL score} = \frac{(\text{Highest possible raw score} - \text{Actual raw score})}{\text{Possible raw score range}} \times 100$$

  Higher total HRQL score is indicative of better HRQL.
  For the subscale analyses, 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 and the subscale score should be considered missing. If any subscale score (refer to section 6.1.3 for detail) is missing, the HRQL Total score cannot be calculated.

Subjects should be instructed to complete the 3-day micturition diary on the 3 days leading up to the visit for Visit 2 (Day 1), Visit 3 (Day 29 ± 7 days), Visit 4 (Day 57 ±7 days), and Visit 5 (Day 85 ±7 days). If the subject is unable to fill out the diary on the 3 days prior to the visit, then the diary should be completed on any 3 days within the 7 days prior to the visit.

Subjects will complete the OABSS and IPSS/IPSS (QoL) assessments at Visit 1 to Visit 5.

Subjects will complete the OAB-q at Visit 1, Visit 2, and Visit 5.

6.1.3 Exploratory Efficacy Endpoints

The exploratory endpoints will include the change from Baseline to post baseline and End of Treatment in:

- Hours of undisturbed sleep (HUS)
  For each patient, hours of undisturbed sleep (HUS) will be calculated by visit and night. Only those subjects whose symptoms were confirmed at baseline (Visit 2) will be analyzed, therefore if IPSS Q7 score is "0" at baseline, this subject is excluded from the analysis.
  HUS is calculated as time from sleep onset time to time of first micturition episode (the variable 'Urinary incontinence' or 'Urgency' is NOT indicated and after the time of sleep onset time) only if the diary completed for 3 consecutive days is available. On the other hand, for those subjects who have no micturition episode between after sleep onset time and wake up time, HUS is calculated as time from sleep onset time to wake up time.
  If the interval between sleep onset time and wake up time is more than 24 hours, HUS will be calculated as follows:
  HUS is calculated as time from sleep onset time to time of first micturition episode (the variable 'Urinary incontinence' or 'Urgency' is NOT indicated and after the time of sleep onset time) only if the diary completed for 3 consecutive days is available and the time of first micturition episode is before AM.5:59 of the next day of sleep onset. On the other hand, for those subjects who have no micturition episode between after sleep onset time and AM.5:59 of the next day, HUS is null.

- First nighttime voided volume

  For each patient, urinary volume at the first nighttime (between after the time of sleep onset and wake up time + 30 minutes) will be calculated. Only those subjects whose symptoms were confirmed at baseline (Visit 2) will be analysed.
  If the interval between sleep onset time and wake up time is more than 24 hours, first nighttime voided volume will be calculated as follows:
  For each patient, urinary volume at the first nighttime (after the time of sleep onset and before AM.5:59 of the next day) will be calculated. On the other hand, for those subjects who have no micturition episode between after sleep onset time and AM.5:59 of the next day, urinary volume at the first nighttime is null. Only those subjects whose symptoms were confirmed at baseline (Visit 2) will be analysed.
- Subscale scores (coping, concern, sleep and social interaction) and individual scores from OAB-q scores
  For each patient, OAB-q subscales will be calculated similar to Total HRQL score. Coping is derived as sum of scores for questions 9, 11, 16, 21, 22, 26, 32, and 33. Concern is derived as sum of scores for questions 12, 13, 14, 19, 23, 25, and 29. Sleep is derived as sum of scores for questions 10, 15, 17, 24, and 30. Social interaction is derived as sum of scores for questions 18, 20, 27, 28, and 31.

- Normalization rate of OABSS
  For each patient, normalization according to OABSS score will be classified by following criteria.
    Normal: OABSS total score <= 2 or the score of Questions 3 <= 1
    Not-normal: OABSS total score >= 3 and the score of Questions 3 >= 2
- Normalization rate of micturition diary (number of episodes of micturition/urgency/urgency incontinence/incontinence/nocturia)
  For each patient, normalization according to symptom derived from the patient diary will be classified by following criteria.
  For micturitions,
    Normal: mean number of micturitions per 24 hours < 8
    Not-normal: mean number of micturitions per 24 hours >= 8
  For urgency episodes, incontinence episodes, urgency incontinence episodes and nocturia,
    Normal: mean number of each symptom per 24 hours is equal to zero.
    Not-normal: mean number of each symptom per 24 hours > 0

6.1.4 Other Efficacy Variables

Not available.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Incidence and severity of treatment emergent adverse events (TEAEs)
- Laboratory parameters (serum chemistry, hematology and urinalysis)
- Vital signs: sitting systolic and diastolic blood pressure and pulse rate (home based self-measurements and office measurements)
- Post-void residual (PVR) urine volume
- Maximum urine flow rate (Qmax)

TEAE is defined as an adverse event observed after starting administration of study drug. If the adverse event occurs on Day 1 and the onset check box is marked “Onset after first dose of study drug for the treatment period” 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 for the treatment period”, then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the screening period and during the treatment 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). All adverse events collected that occur within 7 days after taking the last dose of study drug will also be counted as TEAE.

A drug-related TEAE is defined as any TEAE with at least a possible relationship as assessed by the investigator, with ‘not assessable’ or with missing assessment of the causal relationship to both or either one of Mirabegron/Placebo and Tamsulosin.

6.3 Other Variables

The following variables will be derived for analysis:

- The duration of exposure in treatment period
  For each subject, the Length of Time on study drug in treatment period will be calculated in days, using the following formula:

  ('Date of Last Study Drug Taken in Treatment period'[#] - 'Date of First Study Drug Taken in Treatment period[#]) + 1

  #: These dates can be taken from [Date of Study Drug Taken-page of the Case Report Form]

- The duration of the primary diagnosis (unit: months)
  Duration of the primary diagnosis (months) = 12 * (year of visit date of screening visit (Visit 1) – year of Diagnosis) + month of visit date of screening visit (Visit 1) – month of Diagnosis.
  If the month for diagnosis is missing, then the month will be imputed by January. As a result, if the duration of primary diagnosis is less than 1 month, then it will be assumed to be 1 month.
  If the month and year for diagnosis is missing, then duration of the primary diagnosis is missing.
- Percent overall compliance of the study drug (Mirabegron/Placebo) and Tamsulosin during treatment period
  Overall compliance to the dosing schedule will be examined for subjects whose total tablet count of the study drug (Mirabegron/Placebo) and Tamsulosin is known. Number of tablets which should have been taken depends on the duration of exposure because they should be taken as 1 tablet once daily after breakfast. The following formula can be used for both study drug (Mirabegron/Placebo) and Tamsulosin:

$$\frac{\text{[Total number of tablets consumed during treatment period]}}{\text{[The duration of exposure in treatment period]}} \times 100$$

Where, total number of tablets consumed will be calculated as:
(total number of tablets dispensed) – (total number of tablets returned) – (total number of tablets lost).

- Previous and concomitant medication

Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug in treatment period.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug in treatment period.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

Assessment at Visit 2 (Day 1) will be treated as baseline for efficacy and safety analysis.

The End of Treatment assessment is defined as the last post-Baseline assessment during the double-blind study period for which the primary efficacy data are available.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, minimum, Q1 (25th percentile), median, Q3 (75th percentile) and maximum. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.

Summaries based on FAS and PPS (e.g. disposition, baseline and efficacy data) will be presented by planned treatment group, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented by actual treatment received.

All statistical comparisons will be made using two sided tests at the α=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference, all alternative hypotheses will be two-sided, unless specifically stated otherwise.

All data processing, summarization, and analyses will be performed using Windows SAS® Version 9.4. Specifications for table, figures, and data listing formats can be found in the Tables, Listings and Figures (TLF) specifications for this study.

For the definition of subgroups of interest please refer to section 7.8.

Total and subscale score of OABSS, IPSS and OAB-q are as follows:

Name of score	Subscale score	Calculation	Range
IPSS (Question 1-7 and Quality Life Item)	Storage Subscale	Sum of Question 2,4 and 7	0-15
	Voiding Subscale-1	Sum of Question 3, 5 and 6	0-15
	Voiding Subscale-2	Sum of Question 1, 3, 5 and 6	0-20
	Quality of Life Item	-	0-6
	Total Index Score	Sum of Question 1 to 7	0-35
OABSS (Question 1-4)	Daytime frequency	Question 1	0-2
	Nighttime frequency	Question 2	0-3
	Urgency	Question 3	0-5
	Urgency incontinence	Question 4	0-5
	Total Score	Sum of Question 1 to 4	0-15
OAB-q (Question 1-33)	Symptom bother	Sum of Q1-8	0-100
	Coping	Sum of Q9,11,16,21,22,26,32,33	0-100
	Concern	Sum of Q12,13,14,19,23,25,29	0-100
	Sleep	Sum of Q10,15,17,24,30	0-100
	Social Interaction	Sum of Q18,20,27,28,31	0-100
	Total Health-Related Quality of Life scores	Sum of OAB-q subscale scores (Coping, Concern, Sleep, Social Interaction)t	0-100

The coding dictionary ‘World Health Organization Drug Dictionary (WHO-DD) Enhanced (December 1, 2015)’ and ATC classification will be used for previous and concomitant medication. And the coding dictionary ‘MedDRA (ver.18.1)’ will be used for name of disease (Adverse Event, medical history etc.).

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number of subjects with informed consent, discontinued before randomization and randomized (overall only);
- Number and percentage of subjects discontinued before screening period by primary reason (overall only);
- Number and percentage of subjects discontinued in screening period by primary reason (overall only);

Screenig failure is all subjects who signed informed consent but discontinued before randomization.

- Number and percentage of subjects randomized in each analysis set, by treatment group and overall;
- Number and percentage of subjects who completed or discontinued the study, by primary reason for study discontinuation for randomized subjects and by treatment group; and
- Number and percentage of subjects excluded from PPS by reason for exclusion defined in section 5.2.1. by treatment group for FAS.

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations (*Unique to Korea*)) will be assessed for all randomized subjects. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment group and total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation (PD) criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Screening examination was performed before informed consent.

PD2 - Did not obtain updated informed consent from.

PD3 - No efficacy data after administration

PD4 - Violate the inclusion Criteria or exclusion criteria assessed at Visit 1 (Screening)

PD5 - Violate the inclusion Criteria or exclusion criteria assessed at Visit 2 (Baseline)

PD6 - Drug compliance during the Screening period and Treatment period of less than 80%

PD7- Duration of fixed dose period administration was less than 42 days

PD8 - Lack of diary entries at Visit 2 or the last visit during the Treatment period

PD9 - Receive of the prohibited concomitant medications/therapies

PD10 - Antihistamines, ephedrine hydrochloride, and methylephedrine hydrochloride for common cold, etc.

PD11-Lack of diary entries during go out

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics by treatment group for the SAF, FAS and PPS.

Number and percentage of subjects in each country will be presented by treatment group for the SAF, FAS and PPS.

Descriptive statistics for age, duration of the primary diagnosis, body weight, body mass index (BMI), height, prostate volume, PSA and QT interval, corrected for heart rate according to Fridericia's formula (QTcF interval), IPSS (total/, QOL,), OABSS-total, OAB-q (Symptom Bother, total), Qmax, Qave, PVR at visit 1 will be presented. Also, IPSS (total/, QOL,), OABSS-total, OAB-q (Symptom Bother, total), Qmax, Qave, PVR, Micturition diary(Micturitions, Urgency, Urgency Incontinence, Incontinence, Volume voided per Micturitons, Nocturia) at visit 2 will be presented. Frequency tabulations for sex, race, ethnicity, age group (defined in section 7.8, medical condition of primary diagnosis, status of urinary incontinence, duration of the primary diagnosis group (defined in section 7.8). This will be done for the SAF, FAS and PPS by treatment group. Additionally, to detect the difference of distribution between treatment groups, 2-sample t-test will be used for numerical data and Fisher's exact test will be used for categorical data (Two-sided significance level of 0.05 will be used as a measure).

Complication is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group for the SAF, FAS and PPS. The definition of complication is all medical history that is ongoing at Visit 1.

7.2.4 Previous and Concomitant Medications

Previous and concomitant medications are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by treatment group for the SAF, FAS and PPS.

As with previous medication, concomitant medication will be summarized for each treatment group by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF, FAS and PPS. Subjects taking the same medication multiple times will be counted once per medication. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

If the start day of concomitant medications/therapy is missing, then the day will be imputed by 1st of the months. As a result, if the start day of concomitant medications/therapy is earlier than the first administration date of the study drug for treatment period, then the onset date will be re-imputed by the same date as the first administration date of the study drug for treatment period. If the end day of concomitant medications/therapy is missing, then the day will be imputed by last of the months. As a result, if the end date of concomitant medications/therapy is earlier than the first

administration date of the study drug for treatment period, the end date will be re-imputed by the same date as the first administration date of the study drug for treatment period.

7.3 Study Drugs

7.3.1 Exposure

The following information on drug exposure will be presented for each treatment group for the SAF, FAS and PPS:

Duration of exposure in treatment period 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:
    - 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 84 days
    - 84 days or more
    - Unknown.

Counts and percentages of subjects in each of these categories will be summarized for each treatment group for the SAF, FAS and PPS.

7.3.2 Treatment Compliance

Overall compliance of the study drug (Mirabegron/Placebo) and Tamsulosin with the dosing schedule will be examined for subjects whose total study drug and Tamsulosin count and first and last days of treatment are known for the SAF, FAS and PPS.

Percent overall compliance of the study drug and Tamsulosin during treatment period will be summarized in two ways for the SAF, FAS and PPS:

- Descriptive statistics will be presented by treatment group.
- Percent compliance will be categorized according to the following categories by treatment group:
    - less than 50%
    - at least 50%, less or equal to 80%
    - greater than 80%
    - Unknown.

7.4 Analysis of Efficacy

Continuous variables will be summarized using descriptive statistics, including mean, standard deviation, minimum, Q1, median, Q3 and maximum. Categorical variables will be described using absolute and relative frequency.

7.4.1 Analysis of Primary Endpoint(s)

7.4.1.1 Primary Analysis of Primary Endpoint

The primary efficacy endpoint, change from Baseline to End of Treatment in the mean number of micturitions per 24 hours, will be analyzed using an Analysis of Covariance

(ANCOVA), including treatment group and region as fixed factors and baseline as a covariate for the FAS. Within the framework of the ANCOVA model, point estimates and two-sided 95% confidence intervals (95% CI) for the mean change from Baseline both within and between treatment groups (point estimate will be calculated as [Mirabegron + Tamsulosin] minus [PLACEBO + Tamsulosin]) will be calculated. The two-sided significance level will be set at 5%.

The SAS code used to implement ANCOVA will be similar to that shown below:

```
PROC GLM;
   CLASS treatment region;
   MODEL chg = treatment region base / SS3;
   LSMEANS treatment / ALPHA=0.05 CL PDIFF=CONTROL("PLACEBO + Tamsulosin");
RUN;
```

Here, variables in the MODEL statement are:

- chg: Change from baseline to End of Treatment in the mean number of micturitions per 24 hours
- treatment: Treatment group (PLACEBO + Tamsulosin/Mirabegron + Tamsulosin)
- region: Region (Japan/Korea)
- base: Baseline mean number of micturitions per 24 hours

The hypotheses for the treatment group comparisons are as follows:

H_0: The change from Baseline to End of Treatment in the mean number of micturitions over 24 hours is the same in subjects who received mirabegron compared to those who received placebo.

H_1: The change from Baseline to End of Treatment in the mean number of micturitions over 24 hours is not the same in subjects who received mirabegron compared to those who received placebo.

The End of Treatment assessment will be analyzed.

Separately, ANCOVA including the interaction between treatment and other covariates will be investigated in order to present information of significance of interactions.

The SAS code used to implement ANCOVA including the interaction will be similar to that shown below:

```
PROC GLM;
   CLASS treatment region;
   MODEL chg = treatment region base treatment*region treatment*base / SS3;
RUN;
```

Here, variables in the MODEL statement are same as those for ANCOVA not including the interaction.

7.4.1.2 Sensitivity Analysis of Primary Endpoint

An analysis of the primary endpoint will be conducted on the PPS. The method used for this analysis will be identical to the primary analysis described in section 7.4.1.1.

7.4.1.3 Subgroup Analysis of Primary Endpoint

The analyses described in section 7.4.1.1 will be conducted by subgroups defined in section 7.8. The SAS code used to implement ANCOVA by subgroups will be similar to that shown below:

```
PROC GLM;
    BY grouping variables;
    CLASS treatment region;
    MODEL chg = treatment region base / SS3;
    LSMEANS treatment / ALPHA=0.05 CL PDIFF=CONTROL("PLACEBO + Tamsulosin");
RUN;
```

7.4.1.4 Secondary Analysis of Primary Endpoint

The primary efficacy endpoint will also be analyzed using a Mixed Model Repeated Measure (MMRM). MMRM analysis will be conducted for change from baseline in the mean number of micturition episodes per 24 hours to post-baseline visits using the baseline the mean number of micturition episodes per 24 hours as a covariates, analysis visits and region as a fixed effect, subject as random effect and including interaction of [treatment group x visit] for FAS and PPS. For MMRM, Restricted Maximum Likelihood (REML) approach will be used, KENWARD-ROGER approximation will be used to estimate of degree of freedom of denominator, and 'Unstructured" will be assumed as structure of variance-covariance matrix. Though, when the calculation will not be converged, other covariance structures will be selected in the following order; "Unstructured Correlations", "Heterogeneous Toeplitz", "Heterogeneous First-Order Autoregressive", "Toeplitz", "First-Order Autoregressive", "Compound Symmetry", and "Variance Components" instead. Within the framework of MMRM, point estimates and two-sided 95% CIs for the mean change from Baseline both within and between treatment groups (point estimate will be calculated as [Mirabegron + Tamsulosin] minus [PLACEBO + Tamsulosin]) will be calculated.

The SAS code used to implement MMRM will be similar to that shown below:

```
PROC MIXED method=REML;
    CLASS treatment region visit usubjid;
    MODEL chg = treatment region base visit treatment*visit / ddfm=KENWARDROGER;
    REPEATED visit / type=UN subject=usubjid r;
    LSMEANS treatment*visit / CL PDIFF=CONTROL("PLACEBO + Tamsulosin");
RUN;
```

Here, variables in the MODEL statement are:

- chg: Change from baseline to End of Treatment in the mean number of micturitions per 24 hours
- treatment: Treatment group (PLACEBO + Tamsulosin/Mirabegron + Tamsulosin)
- region: Region (Japan/Korea)
- base: Baseline mean number of micturitions per 24 hours
- visit: Post-baseline visit (Week 4. Week 8, Week 12)
- usubjid: Subject Identifier

7.4.2 Analysis of Secondary Endpoints

The secondary endpoints are actual value and the change from Baseline to post-baseline and End of Treatment in:

- Mean number of micturitions/24 hours (except for End of Treatment visit)
- Mean number of urgency episodes/24 hours
- Mean number of urgency incontinence episodes/24 hours
- Mean number of incontinence episodes/24 hours
- Mean number of nocturia episodes
- Mean volume voided per micturition
- Total OABSS score
- Subscale scores (daytime frequency, nighttime frequency, urgency and urgency incontinence) from OABSS score
- Total IPSS score
- Subscale scores (storage subscale, voiding subscale and quality of life item) and individual scores from IPSS score
- Symptom Bother and total Health-Related QoL scores, as assessed by the OAB-q questionnaire.

For the changes in mean number of incontinence and urge incontinence episodes, the analysis will be based on those subjects who have at least 1 incontinence episode at Baseline.

For the change in the mean number of nocturia episodes, the analysis will be based on those subjects who had at least 1 nocturia episode at Baseline.

Concerning actual value and the change from baseline to post-baseline of the secondary endpoints, descriptive statistics will be calculated by treatment group at each visit and at the End of Treatment for FAS and PPS.

Mean (+/- SD) plot for actual value and change from baseline to post-baseline will be presented by treatment group for FAS. In addition, for mean number of micturitions/24 hours, this plot will be presented by subgroups defined in section 7.4.4 for FAS.

Radar charts of the mean of actual value for OABSS and IPSS will be made to present relationship between each question by treatment group for FAS.

For individual score from OABSS score and IPSS score, frequency tabulations of scores will be presented for each treatment group at each visit and at the End of Treatment for FAS and PPS.

Except for the changes in mean number of micturitions, incontinence and urge incontinence episodes, change from Baseline to End of Treatment of these endpoints will be analyzed using an ANCOVA (refer to section 7.4.1.1 for detail) for FAS and PPS.

The changes from Baseline to End of Treatment in mean number of incontinence and urge incontinence episodes will be analyzed using a Stratified Rank Analysis of Covariance (RANCOVA), including the rank score for change from Baseline to End of Treatment stratified by region as the dependent variable, treatment group and region as fixed factors and the rank score for baseline stratified by region as a covariate for FAS

and PPS. The rank score is defined as fractional ranks by dividing each rank by the number of data + 1 and mid-ranks will be assigned for ties.

The SAS code used to implement RANCOVA will be similar to that shown below:

```
PROC RANK out=rank TIES = MEAN NPLUS1;
    BY region;
    VAR chg base;
    RANKS cr br;
RUN;
PROC GLM data=rank;
    CLASS region;
    BY region;
    MODEL cr = br / SS3;
    OUTPUT out = out residual = residual;
RUN;
PROC FREQ data = out;
    TABLE region*treatment*residual / CMH2;
RUN;
```

Here, variables in the MODEL statement are:

- chg: Change from baseline to End of Treatment in the mean number of micturitions per 24 hours
- base: Baseline mean number of micturitions per 24 hours stratified
- treatment: Treatment group (PLACEBO + Tamsulosin/Mirabegron + Tamsulosin)
- region: Region (Japan/Korea)
- cr: The rank of change from baseline to End of Treatment in the mean number of micturitions per 24 hours by region
- br: The rank score of baseline mean number of micturitions per 24 hours stratified by region

7.4.3 Analysis of Exploratory Endpoints

The exploratory endpoints include actual value and the change from Baseline to post-baseline and End of Treatment in:

- HUS
- First nighttime voided volume
- Subscale scores (coping, concern, sleep, social interaction) and individual scores from OAB-q

Concerning actual value and the change from baseline to post-baseline of these endpoints, descriptive statistics will be calculated by treatment group at each visit and at the End of Treatment for FAS.

Mean (+/- SD) plot for actual value and change from baseline to post-baseline will be presented for FAS.

For HUS, similar analysis will be done only for those subjects who have at least one micturition episode between sleep onset time and wake up time at baseline (e.x., IPSS Q7 > 0) or/and post-baseline. Descriptive statistics for HUS will be derived as the average of 2 consecutive nighttime diary. For example, if subject has only one night time episode in the 2 consecutive nighttime diary, average of HUS (time from sleep onset time to time of

first micturition episode) and HUS (time from sleep onset time to wake up time) will be calculated.

Kaplan-Meier curves will also be used to estimate the distribution of HUS for FAS. Median duration will be estimated using the corresponding 50th percentile of Kaplan-Meier estimates. A two-sided 95% confidence interval will be provided for this estimate. The 25th and 75th percentiles of Kaplan-Meier estimates, and the range of HUS (minimum, maximum) will be presented as well. The range will be determined including censored observations.

Conventions of censoring of HUS will be defined as; those subjects who have no micturition episode between sleep onset time and wake up time will be censored at wake up time. Also, similar analysis will be done treating them as subjects who have an event at the wake up time.

Radar charts of the mean of actual value for OAB-q will be made to present relationship between subscale scores by treatment group for FAS.

For individual score from OAB-q, frequency tabulations of scores will be presented for each treatment group at each visit and at the End of Treatment for FAS.

In addition, exploratory endpoints also include several normalization rates. The percentage of subjects normalized will be calculated excluding the subjects who were normalized at Baseline. The definition of normalization is as follows:

- OABSS: 1 point or less on Question 3, or a total score of ≤2 points
- Micturition episodes: mean number per 24 hours of <8
- Urgency episodes: mean number per 24 hours of zero
- Urgency incontinence episodes: mean number per 24 hours of zero
- Incontinence episodes: mean number per 24 hours of zero
- Nocturia episodes: mean number per 24 hours of zero

The number and percentage of subjects who achieve normalization at the each visit and at the End of Treatment will be summarized along with 2 sided 95% CI (calculated by Clopper-Pearson method) for FAS.

7.4.4 Subgroup Analysis of Efficacy Endpoints

All efficacy endpoints (for continuous variables) will be summarized using descriptive statistics, including mean, standard deviation, minimum, Q1, median, Q3 and maximum for each treatment groups by subgroups defined in section 7.8.

7.5 Analysis of Safety

All analysis of safety will be presented by treatment group for SAF, unless specified otherwise.

7.5.1 Adverse Events

Following definitions of AE will be used for analysis.

As for definition of TEAE and drug-related adverse events, refer to section 6.2.

"Adverse event leading to permanent discontinuation of study drug" are events selected "DRUG WITHDRAWN" checkbox as both or either one of "Action Taken for Study Drug (Mirabegron/Placebo)" and "Action Taken for Study Drug (Tamsulosin)".

"Death" is event checked "Death" checkbox as detail of serious adverse event.

If the onset day TEAE is missing, then the day will be imputed by 1st of the months. As a result, if the onset date of TEAE is earlier than the first administration date of the study drug for treatment period, then the onset date will be re-imputed by the same date as the first administration date of the study drug for treatment period. If the end date TEAE is missing, then the date will be imputed by last day of the giving months. And if, the month TEAE is missing, then the date will be imputed by 31DEC. As a result, if the end date of TEAE is earlier than the first administration date of the study drug for treatment period, then the onset date will be re-imputed by the same date as the first administration date of the study drug for treatment period. The imputed onset day and end day will be used for summary of AE with time interval (section 7.5.1.4).

7.5.1.1 Adverse events

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage with two-sided 95% CI of subjects with TEAEs,
- Number of drug related TEAEs (Mirabegron/Placebo, Tamsulosin, Both),
- Number and percentage with two-sided 95% CI of subjects with causally drug related TEAEs (Mirabegron/Placebo, Tamsulosin, Both),
- Number of serious TEAEs,
- Number and percentage with two-sided 95% CI of subjects with serious TEAEs,
- Number of serious drug related TEAEs (Mirabegron/Placebo, Tamsulosin, Both),
- Number and percentage with two-sided 95% CI of subjects with serious drug related TEAEs (Mirabegron/Placebo, Tamsulosin, Both),
- Number of TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both),
- Number and percentage with two-sided 95% CI of subjects with TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both),
- Number of drug related TEAEs leading to permanent discontinuation of study drug* (Mirabegron/Placebo, Tamsulosin, Both),
- Number and percentage with two-sided 95% CI of subjects with drug related TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both),
- Number of serious TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both),
- Number and percentage with two-sided 95% CI of subjects with serious TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both),
- Number of serious drug related TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both),

- Number and percentage with two-sided 95% CI of subjects with serious drug related TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both) and
- Number of deaths.

*: Categorization of drug related TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both) will be defined as events matching to the category for both relationship to study drug and action taken for study drug at the same time.

The treatment groups will be compared using Fisher's Exact test, with a two-sided 95% exact unconditional CI (point estimate will be calculated as [Mirabegron + Tamsulosin] minus [PLACEBO + Tamsulosin]) and 5% significance level.

7.5.1.2 Adverse events by SOC and/or PT

The coding dictionary for this study will be MedDRA (ver.18.1), which will be used to summarize AEs by SOC and PT.

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 (Mirabegron/Placebo, Tamsulosin, Both),
- serious TEAEs,
- drug related serious TEAEs (Mirabegron/Placebo, Tamsulosin, Both),
- TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both),
- drug related TEAEs leading to permanent discontinuation of study drug (Mirabegron/Placebo, Tamsulosin, Both),
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 2.0% in any treatment group, and
- Common TEAEs that equal to or exceed a threshold of 2.0% in any treatment group.

The treatment groups will be compared using Fisher's Exact test, with a two-sided 95% exact unconditional CI and 5% significance level.

7.5.1.3 Severity of AE

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. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity, then the subject will be counted only once with the worst severity, however, if any of the severity values are missing then the subject will be counted only once with missing severity. In the adverse event count, the adverse events will be presented in each category they were classified to. Drug related TEAEs (Mirabegron/Placebo, Tamsulosin, Both) will be presented in a similar way.

7.5.1.4 Relationship of AE

The number of TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by relationship to study drug (Mirabegron/Placebo, Tamsulosin). In the subject count, if a subject has multiple TEAEs

with the same SOC or PT, but with differing relationship, then the subject will be counted only once with the highest degree of relationship. In the adverse event count, the adverse events will be presented in each category they were classified to.

7.5.1.5 Onset/Prevalence/First Onset of AE (Time Intervals)

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized in the following categories for each treatment group by time interval.

- Onset of AE: For each adverse event in a particular interval, a subject will be counted if there is an onset of a treatment-emergent adverse event regardless of onset in other intervals.
- Prevalence of AE: For each adverse event in a particular interval, a subject will be counted if the adverse event started, continued, or stopped during that interval.
- First Onset of AE: For each adverse event only the earliest onset will be counted if there is more than one onset of that adverse event.

Time intervals will be categorized according to the following categories:

  - 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 84 days; and
  - 84 days or more.

7.5.1.6 Subgroup Analysis of AE

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment group by subgroups defined in section 7.8.

7.5.1.7 AEs Reported During Screening Period by SOC and/or PT

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

- AEs,
- serious AEs.

7.5.1.8 Severity of AEs Reported During Screening Period

The number of TEAEs and the number and percentage of subjects with AEs reported during screening period, as classified by SOC and PT will also be summarized by severity. The method used for this analysis will be identical to the analysis described in section 7.5.1.3.

7.5.1.9 AEs of Special Interest

Following AEs of special interest are defined:

- Cardiovascular events
- Blood pressure
- Urinary retention

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

7.5.2 Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to initial study drug administration. Quantitative clinical laboratory variables, i.e. hematology, biochemistry, and urinalysis will be summarized using descriptive statistics for each treatment group at each visit and at the End of Treatment. Additionally, 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 for each treatment group at each visit and at the End of Treatment.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented for each treatment group at each visit and at the End of Treatment.

For hematology and biochemistry, shift tables of reference range changes from baseline to Week 12 and End of Treatment will be presented for each treatment group. For urinalysis (qualitative), shift table will also be presented for each treatment group in the same way.

For coagulation, only listing will be presented for each treatment group.

The following data will be presented graphically by treatment group:

- Laboratory test results using box plot,
- Change from baseline in laboratory test results using box plot,
- Qualitative laboratory test results using bar chart,
- Shift scatter plot of maximum laboratory test results on treatment versus baseline,
- Laboratory test results using spaghetti plot.

All laboratory parameter's unit for analysis will be used Japan original unit. If there would be some gap between Korean unit and Japan unit, transpose to Japan original unit to use analysis.

7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

Parameter	Criteria
ALT	> 3xUpper limit of normal (ULN)
	> 5xULN
	> 10xULN
	> 20xULN
AST	> 3xULN
	> 5xULN
	> 10xULN

	> 20xULN
ALT or AST	> 3xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzyme and total bilirubin tests during the investigational period will be presented by treatment group.

7.5.3 Vital Signs

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs were measured during each visit at the clinical site. In addition, patients were required to measure vital signs for 3 days prior to the visit at home, both in the morning and in the afternoon.

7.5.3.1 Vital signs (at the clinical site)

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) at the clinical site will be summarized using descriptive statistics by treatment group and at each visit and at the End of Treatment. Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and at each visit and at the End of Treatment.

Following data will be presented graphically by treatment group:

- Vital sign results using mean (+/- 95% CI) plot,
- Change from baseline in vital sign results using mean (+/- 95% CI) plot,
- Shift scatter plot of maximum vital sign results on treatment versus baseline.

7.5.3.2 Vital signs (at home)

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) at home will be summarized using descriptive statistics by treatment group and at each visit and at the End of Treatment. Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and at each visit and at the End of Treatment.

Following data will be presented graphically by treatment group:

- Vital sign results using mean (+/- 95% CI) plot,
- Change from baseline in vital sign results using mean (+/- 95% CI) plot,
- Shift scatter plot of maximum vital sign results on treatment versus baseline.

The value for using table and figure are the average of results for 3 days prior to the visit at home, both waking up and bedtime. And the value for using listing is the average of results for 3 days prior to the visit at home by waking up and bedtime.

7.5.4 Pregnancies

A detailed listing of all pregnancies will be provided.

7.5.5 Other Safety-Related Observations

The other safety endpoints are as follows:

- Post-void residual urine volume
- Qmax
- Average flow rate (Qave)

Concerning actual value and the change from baseline to post-baseline of the secondary endpoints, descriptive statistics will be calculated by treatment group at each visit and at the End of Treatment.

7.6 Analysis of PK

Not applicable to this study.

7.7 Analysis of PD

Not applicable to this study.

7.8 Subgroups of Interest

All efficacy endpoint and TEAEs will be summarized by the treatment group for the subgroups defined on the basis of the categorized variables listed below:

Grouping variable	Subgroups
Region*	Japan
	Korea
Age1	< 65 years
	>=65 years
Age2	< 65 years
	>=65 - < 75 years
	>=75 years
BMI	< 25 kg/m^2
	>= 25 kg/m^2
Duration of the Primary Diagnosis**	<12months
	>=12 months
	Unknown
Urgency Incontinence at Baseline	0
	> 0
PVR	<Median
	>=Median
Qmax	<15 ml/sec
	>=15 ml/sec

*: For subgroup analysis for primary efficacy endpoint, “region” will be excluded from ANCOVA model.

**: If the month for diagnosis is missing and year of visit date of screening visit (Visit 1) – year of Diagnosis <= 1, then excluded from the subgroup analyses.

“Unknown” will be used only for demographic analysis, not used for subgroup analysis.

For more details refer to section 7.4.1.3, 7.4.4 and 7.5.1.

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

No formal interim analysis is planned.

7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Refer to the data specification document in which more details are provided.

7.10.1 Missing Data

The final handling of missing data will be decided by the time of database lock, and will be based on the opinion and advice of a medical expert.

As a general principle, no imputation of missing data for other 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.

7.10.2 Outliers

The final handling of outliers will be decided by the time of database lock, and will be based on the opinion and advice of a medical expert.

7.10.3 Visit Windows

The day of prescription of the study drug for the treatment period is defined as Day 1, and the following day is defined as Day 2.

As indicated in Section 7.10.2, the final handling of outliers will be decided by the time of database lock, and will be based on the opinion and advice of a medical expert. However, the policy described below will be followed as a general rule:

If multiple observed values have been obtained within the same visit window for a subject, the value closest to the scheduled date will be used. If there are similar deviations from the scheduled date, the value obtained on the later date will be used.

Data obtained as early as possible within the allowable range for each visit and within a 7-day period from the final dose will be used.

Micturition Diary:

The mean number of: micturition episodes per 24 hours, urgency episodes per 24 hours, urinary incontinence episodes per 24 hours, urgency incontinence episodes per 24 hours, as well as mean volume voided per micturition and mean number of nocturia episodes will be calculated on the basis of the micturition diary and handled as follows:

The information in the diary (recorded within 3 days before each visit, in principle) measured and recorded in the time windows specified below will be used as the data for that time point.

Time Point	Scheduled Day	Acceptable Time Range

Diary retrieved at Visit 2	1	Day -7 to Day 1 (AM 5:59)
Diary retrieved at Visit 3	29	Day 19 to Day 36 (AM 5:59)
Diary retrieved at Visit 4	57	Day 47 to Day 64 (AM 5:59)
Diary retrieved at Visit 5	85	Day 75 to Day 92 (AM 5:59)
Diary retrieved at the final evaluation in the Treatment period	The final diary must be completed within 7 days after the last dose of study drug.	
If the subject cannot complete the diary during the 3 days immediately prior to the visit, the diary entries must be recorded for any 3 days within 7 days prior to the visit.		

If for some reason, information cannot be recorded in the diary during the 3 days before a given visit, data will be assessed based on the diary entries recorded within 7 days before the visit and within the above-specified time windows.

OABSS, IPSS, IPSS (QoL), and OAB-q*
The information measured and recorded within the time windows specified below will be used as the data for that time point.

Time Point	Scheduled Day	Acceptable Time Range
Completed at Visit 1	-28	Day -35 to Day -21
Completed at Visit 2	1	-
Completed at Visit 3	29	Day 22 to Day 36
Completed at Visit 4	57	Day 50 to Day 64
Completed at Visit 5	85	Day 78 to Day 92
Questionnaires are to be completed at the final evaluation during the Treatment period.	Final diary must be completed within 7 days after the last dose of study drug.	

*OAB-q not performed at Visit 3 and Visit 4.

Safety Assessments
The time windows for the analysis of residual urine volume, laboratory tests*, and measurement of blood pressure (BP) and pulse rate (PR) are described below:

Time Point for Evaluation	Scheduled Day	Acceptable Time Range
Visit 1	-28	Day -35 to Day -21
Visit 2	1	-
Visit 3	29	Day 22 to Day 36
Visit 4	57	Day 50 to Day 64
Visit 5	85	Day 78 to Day 92
Final evaluation during the Treatment period	Final evaluation must be performed within 7 days after the last dose of study drug.	

* Performed only at Week -4, Week 0, and Week 12/early termination

The time windows for the analysis of self-measurement of BP and PR are described below:

Time point	Scheduled day	Acceptable time range
Diary retrieved at Visit 2	1	Day -7 to Day -1
Diary retrieved at Visit 3	29	Day 19 to Day 35
Diary retrieved at Visit 4	57	Day 47 to Day 63
Diary retrieved at Visit 5	85	Day 75 to Day 91
The diary is to be retrieved at the final evaluation during the Treatment period.	The final diary must be completed within 7 days after the last dose of study drug.	

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	DD-MMM-2017	NA	Document finalized

9 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)

10 APPENDICES

10.1 Appendix 1: Key Contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

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