A Phase 4, Double-Blind, Randomized, Placebo-controlled, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Men with Overactive Bladder (OAB) Symptoms While Taking the Alpha Blocker Tamsulosin Hydrochloride for Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH)
PLUS

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Sponsor: Astellas Pharma Global Development, Inc.

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STATISTICAL ANALYSIS PLAN

Final Version 1.2

dated September 27, 2018

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LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviation	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANCOVA	Analysis of Covariance
ARI	Alpha Reductase Inhibitors
AST	Aspartate Aminotransferase (GOT)
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
BPH	Benign Prostatic Hyperplasia
BMI	Body Mass Index
Bpm	Beats per minute
CA	Canada
CFU	Colony Forming Unit
CI	Confidence Intervals
CPMP	Committee for Proprietary Medicinal Products
CS	Classification Specifications
CSR	Clinical Study Report
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoT	End of Treatment
ePRO	Electronic Patient Reported Outcomes
EQ-5D-5L	Measure of health status questionnaire developed by the EuroQol Group
EU	Europe
FAS	Full Analysis Set
FAS-I	Full Analysis Set – Incontinence
FAS-N	Full Analysis Set – Nocturia
FDA	Food and Drug Administration
HBPM	Home Based Blood Pressure Monitoring
HRQL	Health Related Quality of Life
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IPSS	International Prostate Symptom Score
IRT	Interactive Response Technology
Kg	Kilogram
LCE	Leukocyte Esterase
LOCF	Last Observation Carried Forward

Abbreviation	Description of abbreviations
LS	Least Square
LUTS	Lower Urinary Tract Symptoms
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Myocardial Infarction
Min	Minutes
mL	Milliliter
mmHg	Millimeter of Mercury
MMRM	Mixed Model Repeated Measures
NA	North America
N/A	Not Applicable
OAB	Overactive Bladder
OAB-q	Overactive Bladder – questionnaire
OR	Odds Ratio
PD	Protocol Deviation
PSA	Prostate-Specific Antigen
PBO	Placebo
PCS	Potential Clinically Significant
PK	Pharmacokinetics
PPBC	Patient Perception of Bladder Condition
PPIUS	Patient Perception of Intensity of Urgency Scale
PR	Pulse Rate
PRO	Patient Reported Outcomes
PT	Preferred Term
PTM	Placebo to Match
PVR	Post-Void Residual Volume
Q1	First Quartile
Q3	Third Quartile
QD	Once Daily
OAB-q	Overactive Bladder- questionnaire
Q_{max}	Maximum urinary flow rate
QoL	Quality of Life
QTcF	Fridericia's Correction Formula
RAS	Randomized Analysis Set
RR	Response Rate
SBP	Systolic Blood Pressure
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures

Abbreviation	Description of abbreviations
TS-VAS	Treatment Satisfaction Visual Analog Scale
TUFS	Total Urgency and Frequency Score
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

List of Key Terms

Terms	Definition of terms
Adverse Event	An adverse event is any untoward medical occurrence in a patient administered a study drug and which does not necessarily have a causal relationship with this treatment.
Baseline	The baseline value is defined as the last measurement before the first dose of double-blind study drug. For variables based on the electronic diary, the 3 days of the diary recorded prior to the randomization visit will be used to derive these variables at baseline.
Discontinuation	The act of concluding participation, prior to completion of all protocol- required elements, in a trial by an enrolled patient.
End of Study	The time of the last patient's last protocol-defined assessment.
Enrolled	A screened patient who has received the study medication.
Frequency	The complaint of voiding too often during the day.
Incontinence	Any involuntary leakage of urine. For purposes of data analysis specifically for this study, both full void incontinence with or without any urgency as well as partial void incontinence with passed urine in the toilet will be considered as incontinence.
Micturition	Any voluntary micturition (episodes of incontinence only are not included).
Mixed urinary incontinence	The complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.
Nocturia	Waking at night one or more times to void (i.e. any voiding associated with sleep disturbance between the time the patient goes to bed with the intention to sleep until the time the patient gets up in the morning with the intention to stay awake).
Overactive Bladder	Urgency, with or without urgency incontinence, usually with frequency and nocturia, which can be described as the OAB syndrome, urge syndrome or urgency-frequency syndrome.
Randomization	The process of assigning trial patients to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Run-In Failure	Screened patient who did not fulfill protocol inclusion and/or exclusion criteria at Visit 2. Patients who are considered a run-in failure cannot be re- screened into the study at a later date.
Screened	A patient who has signed informed consent and has performed the screening visit.

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Terms	Definition of terms
Screening Failure	Screened patient who did not fulfill protocol inclusion and/or exclusion criteria, or decided not to participate anymore (withdrew consent) prior to Visit 2. Patients who are considered a screen failure at Visit 1 due to an acute condition that resolved (e.g. a treated UTI, an ECG that a cardiologist cleared, discontinuation of a prohibited or restricted medication) may be re-screened into the study at a later date.
Serious Adverse Event	An adverse event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: results in death, is life threatening, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly, or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, or a medically important event.
Stress urinary incontinence	The complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.
Patient Number	Number assigned to each patient by the Interactive Response System after signature of informed consent and prior to any specific procedures.
Treatment-Emergent Adverse Event	An adverse event starting or worsening in the period from first double-blind medication intake until 30 days after last double-blind medication intake.
Urgency	A sudden and compelling desire to pass urine that is difficult to defer.
Urgency Urinary Incontinence	The complaint of involuntary leakage accompanied by or immediately proceeded by urgency.

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 any of the following: study unblinding, database hard lock, interim analysis, or accumulation of substantial amount of data in an open-label study to ensure lack of bias. For operational efficiency an earlier time is usually targeted. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by [redacted] with accountability to the responsible biostatistician of Astellas Pharma Global Development, Inc. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and Tables, Listings, and Figures (TLFs) meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND VISIT SCHEDULE

mirabegron 25 mg QD plus tamsulosin hydrochloride 0.4 mg QD	mirabegron 50 mg QD plus tamsulosin hydrochloride 0.4 mg QD
placebo matched to mirabegron 25 mg QD plus tamsulosin hydrochloride 0.4 mg QD	placebo matched to mirabegron 50 mg plus tamsulosin hydrochloride 0.4 mg QD

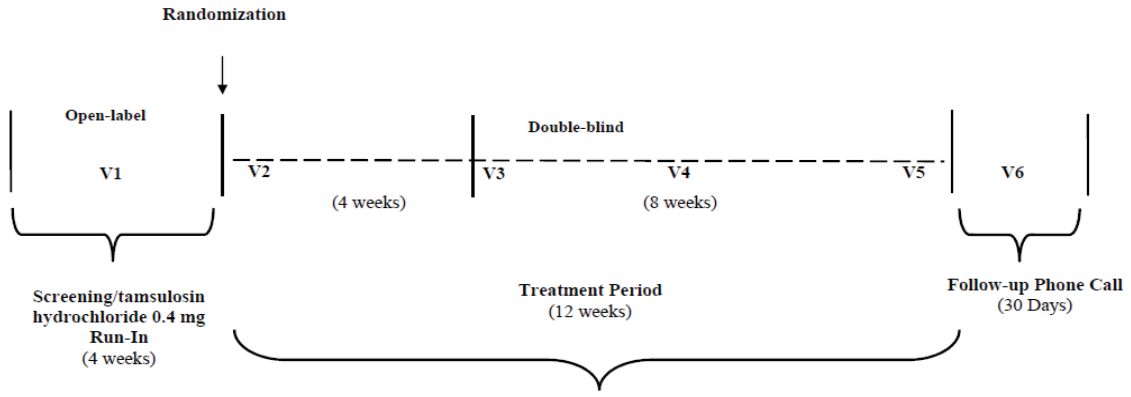

Table 1 Schedule of Assessments

	Screening/ Tamsulosin Hydrochloride Run-In	Treatment Period				Follow-up Phone Call
Visit	1	2	3	4	5	6
Day	-28	1	28	56	84	114
Week	-4	0	4	8	12	16
Visit Windows	+/- 3 d	—	+/- 7 d	+/- 7 d	+/- 7 d	+/- 3 d
Visit Windows (Study Days) [a]	-31 to -25	—	21 to 35	49 to 63	77 to 91	111-117
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Medical History and OAB History	X					
Demographics	X					
Enter 4-week tamsulosin hydrochloride run-in [b]	X					
Reminder Phone Call [c]		X	X	X	X	
Randomization [d]		X				
Physical Exam	X				X	
Weight and Height	X					
Office Visit Vital Signs (pulse and blood pressure)	X	X	X	X	X	
Serum PSA	X					
Serum chemistry, hematology & urinalysis [e, f]	X	X	X	X	X	
12-Lead ECG [g]	X	X	X	X	X	
PVR (Ultrasonography or Bladder Scan)	X	X	X	X	X	
Uroflowmetry (Q_{max}) [h]	X				X	
IPSS	X	X	X	X	X	
Medication History and OAB Medication History [i]	X					
Concomitant Medications Assessment	X	X	X	X	X	X
Adverse Event Assessment [j]	X	X	X	X	X	X
Dispense Study Drug	X	X	X	X		
Drug Accountability		X	X	X	X	
Dose Titration [k]			X			
Instruct Patient on 3-day Diary [l]	X	X	X	X		
Patient Completes 3-day Diary including HBPM		X[m]	X[m]	X[m]	X[m]	
EQ-5D-5L		X	X	X	X	
Table continued on next page						
OAB-q		X	X	X	X	
PPBC		X	X	X	X	
PPIUS		X	X	X	X	
TS-VAS		X	X	X	X	
Review Patient Diary [n]		X	X	X	X	

a. After Visit 1 (Screening/tamsulosin hydrochloride run-in), visit windows/study days will be calculated based on the Visit 2 (Baseline) visit date. Study procedures (e.g. bladder scan) for a particular visit do not need to be completed on the visit date if this is not feasible for the patient, as long as study procedures are performed per protocol within the applicable visit window. Any procedure not done or performed outside the applicable visit window will be noted as a protocol excursion.

b. Patients must take at least 22 days, but no more than 34 days of tamsulosin hydrochloride run-in medication.

c. Reminder Phone Call to complete the diary and to answer any questions is to occur approximately 7 days prior to the visit.

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

e. Blood samples need not be fasting. A central laboratory will be used for all laboratory hematology and biochemistry/PSA assessments. Local laboratories will be used for all urinalysis and urine culture and sensitivity.

f. Urine culture and sensitivity must be performed for positive leukocyte esterase (LCE), nitrites, or turbidity, or at the discretion of the PI. It is not required to send isolated trace positive leukocyte esterase samples for culture. If a patient has a UTI (defined as > 100,000 CFU), the patient may be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).

g. ECGs will be submitted to a central laboratory. Initial inclusion will be based on PI interpretation of ECG eligibility at Screening (Visit 1) and Baseline (Visit 2); however, if the QTcF interval is >450 ms on the printed ECG at Baseline (Visit 2), an expedited central ECG reading (within 24 hours) should be requested and reviewed before the patient is allowed to be randomized. Final central readings must be reviewed by the Investigator for the duration of the study for immediate safety assessment and patient care.

h. Q_{max} can be completed within two weeks of Screening (Visit 1). The patient must void a minimum of 125 mL for the uroflow measurement to be considered adequate.

i. All medications taken within 30 days prior to Screening (Visit 1) must be recorded in the eCRF.

j. Adverse Event collection will begin from the time of informed consent and continue through the Follow-up Phone Call (Visit 6).

k. All patients will be titrated to the 50 mg dose of mirabegron or placebo to match (PTM) after 4 weeks of treatment. Patients will remain on 0.4 mg of tamsulosin hydrochloride for the duration of the study.

l. At the Screening/tamsulosin hydrochloride run-in (Visit 1), all patients will be provided with an ePRO device (electronic diary) that will be used to record the date and time of each micturition, incontinence, urgency episode, measure of urine volume voided, and sleep interruption. Home measurements of am and pm pulse rate and systolic and diastolic blood pressure will be electronically captured in the diary. Additionally, the diary will be used to record medication intake every day during the study, as well as to complete questionnaires. Training on device use must be done at Visit 1 and as necessary throughout the study. Approximately 7 days prior to Visit 2 patients will receive a phone call reminding them about the diary and to answer any questions. Patients will be instructed to begin completing the electronic diary 3 days prior to each in office study visit including Visit 2 (Baseline), Visits 3 - 5 (Treatment Period) and to complete the diary for the full 3 days.

m. For Visits 2, 3, 4 and 5, patients will complete the electronic diary (including am and pm HBPM) for the 3 days prior to the study visit.

n. Investigator, or designee, must review the patient's diary with the patient to ensure completion compliance and discuss data captured.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is to study the efficacy of mirabegron versus placebo (PBO) in men with overactive bladder (OAB) symptoms while taking tamsulosin hydrochloride for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).

3.1.2 Secondary Objective

The secondary objective is to assess the safety and tolerability of mirabegron versus PBO in men with OAB symptoms while taking tamsulosin hydrochloride for LUTS due to BPH.

3.1.3 Other Objectives

To assess patient reported outcomes (PROs) as measured by Symptom Bother and Total Health Related Quality of Life (QoL) scores as assessed by the Overactive Bladder-questionnaire (OAB-q), EQ-5D-5L, Patient Perception of Bladder Condition (PPBC), Patient Perception of Intensity of Urgency Scale (PPIUS), International Prostate Symptom Score (IPSS), and Treatment Satisfaction-Visual Analog Scale (TS-VAS).

3.2 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multi-center study. Approximately 1317 patients will be screened to achieve 856 randomized and 728 completed patients at up to 100 study centers in North America and Europe.

At Screening (Visit 1), patients will enter into a 4-week open label tamsulosin hydrochloride 0.4 mg QD run-in period prior to being randomized into the 12-week double-blind treatment period (Visit 2). At the conclusion of the 4-week tamsulosin hydrochloride run-in period, patients will complete a 3-day diary just prior to Baseline (Visit 2).

Qualifying patients will be randomized to 1 of 2 treatment groups (Mirabegron or placebo) for 12 weeks of treatment in addition to the continuation of tamsulosin hydrochloride 0.4 mg QD. Three days before Visits 2 (Baseline), 3 (Week 4), 4 (Week 8), and 5 (Week 12), patients will complete a 3-day diary, using the electronic patient-reported outcome (ePRO) device in which they will record micturition frequency, urgency (PPIUS), incontinence and volume voided. In addition the diary will capture morning and evening blood pressure and pulse rate measurements via HBPM. At Visit 1, International Prostate Symptom Score (IPSS) will be completed. At Visits 2, 3, 4, and 5, patients will complete the IPSS, EQ-5D-5L, OAB-q, PPBC, and TS-VAS. Maximum urinary flow (Qmax) will be measured at Visit 1 (Screening/ tamsulosin hydrochloride run-in) and Visit 5 (Week 12/End of Treatment). Postvoid residual volume (PVR) will be assessed at Screening/tamsulosin hydrochloride run-in (Visit 1), Baseline (Visit 2) and at Week 4 (Visit 3), Week 8 (Visit 4) and Week 12/End of Treatment (Visit 5). A follow-up phone call (Visit 6) will be conducted 4-weeks after End of Treatment (Visit 5). Total study participation is approximately 20 weeks.

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3.3 Randomization

After a patient signs informed consent, a patient number will be assigned. To obtain a patient number, the Investigator or designee will utilize a web or phone-based Interactive Response Technology (IRT). Patients who meet all the inclusion and none of the exclusion criteria will enter a 4-week tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA) run-in period (Visit 1). At Visit 2 (Baseline), patients will be randomly assigned to receive mirabegron or placebo using a 1:1 randomization schedule. Randomization will be stratified by geographic region (NA, EU). After submitting certain information about the eligible patient, the randomized drug assignment will be provided by the IRT. Study drug assignment will remain blinded to all staff. Each study drug will be preprinted with a Medication ID number that will be noted in the electronic case report form (eCRF). Once a patient number is assigned, if the corresponding patient does not receive study drug, the patient number will not be used again.

Those patients randomized to mirabegron will start at 25 mg tablet QD along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA) and will increase to 50 mg QD after 4 weeks. Those patients randomized to PBO will start blinded product matched to the mirabegron 25 mg tablet and will increase to blinded product matched to 50 mg mirabegron after 4 weeks of the study along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA). Once a patient has increased dose, they will remain on that dose for the remainder of the study unless for safety reasons that require discontinuation of study drug.

4 SAMPLE SIZE

The primary endpoint for this study is change from baseline to end of treatment in mean number of micturitions per day based on a 3-day diary.

Based on subgroup analysis of prior OAB studies, 544 patients (272 evaluable patients per treatment group) provides 80% power to detect a reduction of 0.65 in the mean number of micturitions per day over placebo in the mirabegron group at an alpha level of 0.05. A standard deviation for change from baseline in micturitions of 2.7 was assumed.

If 85% of the randomized patients are evaluable, 640 patients should be randomized. With an expected drop-out rate of 35% in the tamsulosin hydrochloride run-in phase, 985 patients need to be screened.

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.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of patients to analysis sets will be determined prior to database hard lock.

5.1 Full Analysis Set (FAS)

The FAS will include all patients who meet all of the following criteria:

- Patients who took at least 1 dose of double-blinded study drug after Randomization,

- Reported at least 1 micturition in the baseline diary and at least 1 micturition post-baseline.

The FAS will be used for the summary of all baseline characteristics, including demographics, disease state data and statistical analysis of efficacy endpoints and QoL instruments.

5.2 Full Analysis set – Incontinence (FAS-I)

The FAS-I will include all patients who meet all of the following criteria:

- Patients who took at least 1 dose of double-blinded study drug after Randomization,
- Reported at least 1 micturition in the baseline diary and at least 1 micturition post-baseline,
- Reported at least 1 incontinence episode in the baseline diary.

The FAS-I will be used for the analysis of incontinence episodes.

5.3 Full Analysis set – Nocturia (FAS-N)

The FAS-N will include all FAS patients who reported at least 1 nocturia episode in the baseline diary.

The FAS-N will be used for the analysis of Nocturia episodes.

5.4 Safety Analysis Set (SAF)

The SAF will consist of all randomized patients who received at least one dose of double-blind study medication. The SAF will be used for summarizing demographic and baseline OAB characteristics and safety data.

5.5 Randomized Analysis Set (RAS)

The Randomized Analysis Set (RAS) will consist of all randomized patients. The RAS will be used to summarize disposition of patients who were randomized to double-blind treatment.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

- Change from Baseline (Visit 2) to Week 12/End of Treatment (Visit 5) in mean number of micturitions per day based on a 3-day diary.

6.1.2 Secondary Efficacy Endpoints

- Change from Baseline (Visit 2) to Week 4 and Week 8 in mean number of micturitions per day based on a 3-day diary.
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in mean volume voided per micturition.

- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in mean number of incontinence episodes per day (FAS-I).
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in mean number of urgency episodes (grade 3 and 4) per day.
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in IPSS total score and subscales (Voiding, Storage, and Quality of Life).
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in mean number of urgency incontinence episodes per day (FAS-I).
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in Symptom Bother Total Health Related Quality of Life and subscale (coping, concern, sleep, social interaction, and symptom bother) scores as assessed by OAB-q questionnaire.
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in PPBC.
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in Total Urgency and Frequency Score (TUFS) using PPIUS (Grade 3 or 4).
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in mean number of nocturia episodes per day (FAS-N).
- Change from Baseline (Visit 2) to Week 4, Week 8, Week 12, and End of Treatment in TS-VAS scores.

6.1.2.1 Patient Diary - Micturition and Incontinence

During the study, patients will be requested to complete a ″3-day diary", which will be implemented on an electronic handheld device. This diary will collect data on micturition and incontinence, sleep interruption, vital sign measurements and the Patient Perception of Intensity of Urgency Scale (PPIUS) prior to Visits 2, 3, 4, and 5. The information from the diaries will be used to evaluate the efficacy of treatment. Therefore, patients will receive full instructions and training on how to complete the diary at Screening/tamsulosin hydrochloride run-in (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/tamsulosin hydrochloride run-in (Visit 1) by the Investigator or designee to ensure accuracy of completion.

Diaries will be completed at home for 3 consecutive days prior to each visit: Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5), and End of Treatment.

A diary day starts at midnight and ends at midnight the following day. Time to bed with intention to sleep, time to awake with intention of staying awake, type of episode (urination/incontinence/both), time of episode, urgency severity, and measure of urine volume voided, and sleep interruption will be recorded by the patient in the micturition diary.

At Baseline (Visit 2), diary data, including frequency of micturition (urination episodes) and urgency episodes (grade 3 and 4) with or without incontinence will be reviewed to confirm inclusion criteria.

Voiding episodes will be recorded in one of three ways: “urination”, “incontinence”, or “both” 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 “both”. During analysis, “both” will be counted towards micturition and incontinence. In addition to micturition information, the electronic diary will also collect time of medication intake and vital signs along with sleep interruption.

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

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Table 3. Micturition 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 (determined by the date of questionnaire completion) 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. If more than 3 valid diary days are recorded then the last 3 days will be used in the calculations. If there is no 'go to bed time' on the last day, that day will be deleted.	Not applicable.

Measurement	Definition	Calculation
Mean Number of Micturitions per day	Average number of times a patient urinates (excluding incontinence only episodes and excluding duplicate records [same time and episode characteristics]) per day during the 3-day micturition diary period.	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.
Urinary Incontinence Episode or 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.
Mean Number of Incontinence Episodes per day	Average number of times a patient records an incontinence episode per day during the 3-day micturition diary period.	Number of incontinence episodes 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.
Mean Volume Voided per Micturition	Mean volume voided (mL) per micturition during 3 days of the 3-day micturition diary period.	Sum of each volume voided for each record with volume voided > 0 on valid diary days divided by the total number of records with a volume voided > 0 on valid diary days during 3 days with volume measurements in the 3-day micturition diary period.

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 = Urgency incontinence, I leaked before arriving to the toilet.	Not applicable.
Urgency Urinary Incontinence Episode or Urgency Incontinence Episode	The involuntary leakage of urine accompanied by or immediately preceded by urgency.	One urgency 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 urgency incontinence episodes recorded on a valid diary day will be counted.

Measurement	Definition	Calculation
Number of Urgency Incontinence Episodes	Number of times a patient records an urgency incontinence episode during the 3-day micturition diary period.	Number of urgency incontinence episodes recorded on valid diary days of the 3-day micturition diary period.
Mean Number of Urgency Incontinence Episodes per day	Average number of times a patient records an urgency incontinence episode per day during the 3-day micturition diary period.	Number of urgency incontinence episodes 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.
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.
Mean Number of Urgency Episodes (severity of 3 or 4) per day	Average number of times a patient records an urgency episode (severity of 3 or 4) with or without incontinence per day during the 3-day micturition diary period.	Sum of each record with an urgency episode (severity of 3 or 4) recorded on a valid diary day divided by the number of valid diary days during the 3-day micturition diary period.

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Measurement	Definition	Calculation
Nocturia	Waking at night one or more times to void (i.e. any voiding associated with sleep disturbance between the date/time the patient goes to bed with the intention to sleep until the date/time the patients gets up in the morning with the intention to stay awake). A "night time" episode is considered as a nocturia episode. A "night time" episode of incontinence only that are not associated with urgency is not considered as a nocturia episode.	A nocturia episode is counted for each micturition record which occurred between the date/time of going to bed with the intention to sleep (exclusive) and the date/time of getting up with the intention to stay awake (exclusive) on a valid diary day and which was accompanied by a sleep interruption. Nocturia will only be determined for patients who are not night-shift workers.
Number of Nocturia Episodes	Number of nocturia episodes during the 3-day micturition diary period.	Sum of each nocturia episode recorded.
Mean number of Nocturia Episodes per day	Average number of times a patient records a nocturia episode per day during the 3-day micturition diary period.	Number of nocturia episodes 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.

6.1.2.2 Patient Perception of Intensity of Urgency Scale (PPIUS)

The PPIUS is a scale that will be completed as part of the micturition diary.

For each micturition and/or incontinence episode, patients will be asked to rate the degree of associated urgency according to the following validated 5-point categorical scale. The categories are recommended by the Committee for Proprietary Medicinal Products [CPMP/EWP/18/01, Final].

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 at the toilet.

The PPIUS will be completed at Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5), and End of Treatment.

6.1.2.3 Total Urgency and Frequency Score (TUFS)

The TUFS is calculated by adding the PPIUS scores of every void in a patient's 3-day diary, and dividing this by the number of days recorded in the diary.

6.1.2.4 International Prostate Symptom Score (IPSS)

The IPSS consists of seven questions concerning urinary symptoms and one question concerning quality of life and it can be divided into voiding symptoms (incomplete emptying, intermittency, weak stream, and straining) and storage symptoms (frequency, urgency, and nocturia) (See Table 4 below). The IPSS classification ranges from mild (0 to 7) to moderate (8-19), or severe (20-35).

Table 4. Calculation of IPSS Subscale Scores and IPSS Total Score Scale

Scale	Sum Item Values	Lowest and Highest Possible Scores
Voiding	1+3+5+6	0, 20
Storage	2+4+7	0, 15
IPSS Total	1+2+3+4+5+6+7	0, 35
Quality of Life	8	0, 6

The IPSS will be completed at Screening (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5), and End of Treatment.

An example of the IPSS questionnaire is given in section 10.2 (Appendix 2).

6.1.2.5 OAB Symptoms, Quality of Life, Bladder Health and Treatment Benefit

OAB has significant effects on health-related QoL of the afflicted patients. This has been quantified in various empirical studies [Wall et al, 1993]. QoL is determined by socio-demographic, clinical, psychological and social factors. This underlines the importance of assessing the perceptions of patients themselves when evaluating the effects of medical or pharmacological treatment [Palmtag 2004]. In this study, the Overactive Bladder-questionnaire (OAB-q), EQ-5D-5L, the Patient Perception of Bladder Condition (PPBC), and Treatment Satisfaction – Visual Analog Scale (TS-VAS) will be utilized.

6.1.2.5.1 Overactive Bladder-questionnaire

The OAB-q consists of a total of 33 items/questions, each with response options based on a 6-point Likert scale (1 through 6) and with a recall period of the past four weeks. The items are grouped into Symptom Bother and each subscale of Health Related Quality of Life (HRQL) as described below.

Symptom Bother Answers on questions 1 through 8 will be summed which means the lowest and highest possible raw scores are 8 and 48, respectively, with a possible raw score range of

40. The following formula will be used to transform the Symptom Bother score which will range from 0 to 100 (=worst severity):

$$\text{Transformed Score} = \frac{(\text{Actual Raw Score} - \text{Lowest Possible Raw Score})}{\text{Possible Raw Score Range}} \times 100$$

A negative change from baseline to a scheduled visit in symptom bother score indicates an improvement.

For the HRQL subscales (coping, concern, sleep and social interaction), raw scores will be calculated using the items described in the table below. The HRQL total score will be calculated by adding each individual HRQL subscale score together [Coyne et al, 2007], where a higher score indicates better HRQL.

The OAB-q will be assessed at Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5), and End of Treatment.

Table 5. Calculation of HRQL Subscale Scores and HRQL Total Score Scale

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Coping	9+11+16+21+22+26+32+33	8, 48	40
Concern	12+13+14+19+23+25+29	7, 42	35
Sleep	10+15+17+24+30	5, 30	25
Social interaction	18+20+27+28+31	5, 30	25
HRQL Total	Sum of HRQL subscales	25, 150	125

The raw scores will be transformed by the following formula with higher transformed scores indicating better quality of life [Coyne et al, 2007]:

$$\text{Transformed Score} = \frac{(\text{Highest Possible Score} - \text{Actual Raw Score})}{\text{Possible Raw Score Range}} \times 100$$

A positive change from baseline to a scheduled visit for a HRQL score indicates improvement.

For the symptom bother score and the subscale analysis, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing. If a subscale score for calculation of HRQL Total is missing, the HRQL Total score will not be calculated.

An example of the OAB questionnaire is given in section 10.3 (Appendix 3).

6.1.2.5.2 Patient Perception of Bladder Condition (PPBC)

The PPBC is a validated, global assessment tool using a 6-point Likert scale that asks patients to rate their subjective impression of their current bladder condition [Coyne et al, 2006].

The PPBC has the following response options, where a higher value equates a worse condition:

- 1 = My bladder condition does not cause me any problems at all
- 2 = My bladder condition causes me some very minor problems
- 3 = My bladder condition causes me some minor problems
- 4 = My bladder condition causes me (some) moderate problems
- 5 = My bladder condition causes me severe problems
- 6 = My bladder condition causes me many severe problems

The PPBC questionnaire will be assessed at Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5), and End of Treatment.

6.1.2.5.3 EQ-5D-5L

The EQ-5D-5L is an international standardized non-disease specific (i.e., generic) instrument for describing and valuing health status. It has a multidimensional measure of health-related QoL, capable of being expressed as a single index value and specifically designed to complement other health status measures [Euroqol, 1990; Herdman et al, 2011].

The EQ-5D-5L has five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has 5 response levels (e.g., 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems/unable to perform the activity). In addition, it has a visual analog scale that elicits a self-rating by the respondent of his health status.

EQ-5D-5L will be assessed at Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12, and End of Treatment.

An example of the EQ-5D-5L questionnaire and visual analog scale is given in sections 10.4 and 10.5 (Appendix 4a &4b).

6.1.2.5.4 Treatment Satisfaction – Visual Analog Scale (TS-VAS)

The TS-VAS is a visual analog scale that asks patients to rate their satisfaction with the treatment by placing a vertical mark on a line that runs from 0 (No, not at all) to 10 (Yes, completely satisfied). The TS-VAS will be assessed at Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5), and End of Treatment.

6.1.3 Other Efficacy Variables

The exploratory endpoint is:

- Performance of subgroup analyses by PSA cutoff scores for < 2, 2-4.
- Performance of subgroup analyses by 5-alpha reductase inhibitor (5-ARI) use at baseline (Yes or No use)

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
- Adverse Events of Possible Hepatic Origin (See Section 10.1 - Appendix 1)
- Acute Urinary Retention (urinary retention requiring catheterization)
- Benign prostatic obstruction (BPO) requiring surgery
- Urinary Tract Infections
- Clinical laboratory variables (hematology, serum chemistry including liver function tests, and urinalysis)
- Cardiovascular events, vital signs (sitting systolic and diastolic blood pressure and pulse rate: home blood pressure monitoring [HBPM] and office measurements), MI, stroke, dysrhythmias, and uncontrolled hypertension.
- Physical Examination
- 12-lead electrocardiogram (ECG)
- Change in Post-Void Residual Volume (PVR) and Q_{max}

TEAE is defined as an adverse event observed after starting administration of the test drug/comparative drug. If the adverse event occurs on Day 1 and the onset check box 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 patient experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as a TEAE only if it has worsened in severity (i.e. it is reported with a new start date). All adverse events collected that begin within 30 days after taking the last dose of study drug will also be counted as TEAEs.

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

6.3 Other Variables

6.3.1 Duration of Exposure

For each patient the duration of exposure on double-blind treatment will be calculated in days using the following formula:

(Date of last dose of study drug – Date of first dose of study drug) + 1

where the dates of the first and last known double-blind treatment are recorded on the study drug dosing eCRF pages. If they are missing, then imputed dates as per Subsection 7.10.1.2

will be used. Any gaps in dosing will be included in the total number of days on double-blind treatment.

For each patient the duration of exposure on Tamsulosin will be calculated in days using the following formula:

(Date of last dose of Tamsulosin – Date of first dose of Tamsulosin) + 1

where the dates of the first and last known Tamsulosin treatment are recorded on Tamsulosin dosing eCRF pages.

6.3.2 Percent Overall Compliance

During the double-blind treatment period, patients are supposed to take a 25mg tablet once daily and will increase to 50mg after 4 weeks. Overall compliance to the dosing schedule will be examined for patients in the safety population whose total tablet count and duration of exposure is known. The percent compliance is defined as the total number of tablets consumed divided by the total number of tablets that should have been taken times 100.

(Total number of tablets consumed) x 100% / [(Overall duration of exposure) + (Duration of exposure on 50mg)]

where total number of tablets consumed will be calculated as:

Total number of tablets dispensed – Total number of tablets returned

The quantity of study drug dispensed to and returned by the patient will be counted and recorded on the study drug dosing eCRF pages.

Overall compliance of Tamsulosin will be computed in a similar pattern using the following formula:

(Total number of tablets consumed) x 100% / (Overall duration of Tamsulosin exposure)

6.3.3 Previous, Prohibited, and Concomitant Medication

6.3.3.1 Previous Medication

Previous medication is defined as medication with at least one dose taken within 30 days prior to screening (i.e. first or last medication intake is prior to first tamsulosin hydrochloride run-in dose date (exclusive)). All previous OAB medications, regardless of when they were taken, will be collected on the eCRF. Previous non-OAB medications will only be collected on the eCRF if taken within 30 days prior to screening.

6.3.3.2 Prohibited Medication

Use of these medications in any formulation is not permitted between Screening (Visit 1) and Week 16/Follow-up phone call (Visit 6). Current or previous use of mirabegron within 6 months prior to Screening (Visit 1) is also prohibited. This list is not exhaustive. In case of doubt, the Investigator must contact the local study monitor. These medications must have been discontinued at least 30 days prior to Screening (Visit 1).

Table 5. Part A –Prohibited Medications

Alpha1 and Nonselective Adrenergic Blockers		
Alfuzosin	Prazosin	Doxazosin
Terazosin	Silodosin	Trazodone
Phenoxybenzamine	Phentolamine	Tolazoline
Typical/atypical antipsychotics		
Anticholinergics/Antispasmodics		
Atropine	Baclofen	Biperiden
Clomipramine	Cyclobenzaprine	Darifenacin
Dicyclomine/Dicycloverine	Emepronium	Glycopyrronium/Glycopyrrolate
Fesoterodine	Flavoxate	Hyoscine
Hyoscyamine	Ipratropium	Isopropamide
Orphenadrine	Oxybutynin	Oxyphencyclimine
Propantheline	Propiverine	Scopolamine/(Butyl)hyoscine
Tolterodine	Trospium	Otilonium
Tiotropium	Solifenacin	
Potent and Moderate CYP3A4 Inhibitors		
Indinavir	Nelfinavir	Ritonavir
Clarithromycin	Itraconazole	Ketoconazole
Nefazadone	Saquinavir	Telithromycin
Cimetidine	Clotrimazole	Cyclosporine
Erythromycin	Fluconazole	Itraconazole
Ketoconazole	Macrolide antibiotics	
Strong and Moderate Inhibitors of CYP2D6 Substrates and those with Narrow Therapeutic Index		
Aripiprazole (neuroleptic)	Amitriptyline/ Nortriptyline (TCA)	Donepezil (Acetylcholinesterase inhibitor)
Thioridazine (anti-psychotic)	Flecainide (anti-arrhythmic)	Propafenone (anti-arrhythmic)
Imipramine/Desipramine (TCA)	Tramadol (analgesic)	Venlafaxin/Desvenlaxafine (SNRI)
Paroxetine	Terbinafine	

Part B -Medications Permitted With Restrictions

Medications restricted between Screening (Visit 1) and Follow-Up Phone Call (Visit 6) include loop diuretics, PDE5 inhibitors and 5-Alpha reductase inhibitors. All medications in Part B of Appendix 1 are permitted provided the patient has been taking this medication on a long-term basis, i.e. has not stopped, or started or changed dose within the 30 days prior to Screening (Visit 1), no new drug of the same class has been added to the regimen within the 30 days prior to Screening (Visit 1), and the patient remains on the medication at the same dose during the course of the study. For 5-alpha reductase inhibitors the patient must have been taking the medication for at least 6 months. No alpha-blockers other than tamsulosin hydrochloride are allowed. Intermittent use of PDE5 inhibitors (e.g. tadalafil) for treating erectile dysfunction (ED) is allowed. PDE5 inhibitors that are taken on a daily basis for the management of LUTS are not allowed.

Table 5. Part B – Medications Permitted With Restrictions

Loop Diuretics		
Furosemide	Bumetanide	Piretanide
5-alpha Reductase Inhibitors (minimum 6 months duration)		
Dutasteride	Finasteride	
PDE5 Inhibitors (only intermittent use for ED is allowed, daily use for BPH/LUTS is prohibited)		
Sildenafil	Tadalafil	Vardenafil

6.3.3.3 Concomitant Medication

Concomitant medication during the tamsulosin hydrochloride run-in period is defined as medication with at least one dose taken between the date of first dose (inclusive) of run-in study medication and the date of first dose (not inclusive) of double-blind study drug.

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

For above variables, imputation methods will be used in case of missing medication intake dates.

6.3.4 Demographics

The patient's age, sex, race, ethnicity, height, and weight will be recorded at Screening (Visit 1).

6.3.5 Medical History

Medical history (other than for overactive bladder), including smoking history will be obtained at Screening (Visit 1) from each patient. All relevant past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.6 Diagnosis of the Target Disease, Severity, and Duration of Disease

A detailed history of OAB and lower urinary tract symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH) for each patient will be obtained at Screening (Visit 1). This includes date of onset of OAB symptoms, OAB symptoms at time of diagnosis and at Screening, OAB

non-drug therapy and medication history for OAB and reason for treatment termination. In addition information regarding the history of BPH and LUTS will be collected.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

In general, baseline is defined as the last measurement before the first dose of double-blind study drug. For variables based on the micturition electronic diary, the 3 days of the diary recorded prior to the baseline visit will be used to derive these variables at baseline just as the 3 diary days before each post-baseline visit will be used to derive these variables at these visits.

The End of Treatment (EoT) visit is defined as the last post-baseline visit during the double-blind treatment period for which data is available. The EoT visit value for diary variables is the average or number of the diary measurements for Week 12, as applicable. If no Week 12 diary data measurements are available, then the last available earlier post-baseline average or number of the diary measurements within a designated visit window will be used (LOCF). Data from the EoT visit will be analyzed to account for patients prematurely terminating the study and is regarded as the primary visit. The EOT visit will be Week 12/EoT (Visit 5) for patients who complete the study.

For continuous variables, descriptive statistics will include the number of patients (n), mean, standard deviation (SD), median, minimum and maximum. When needed, the use of other percentiles (e.g. 10%, 25%, 75% and 90%) will be mentioned in the relevant section. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of patients with no missing data, i.e. will add up to 100%.

All statistical comparisons will be made using a two-sided test at $\alpha = 0.05$ significance level and confidence intervals will be reported with a coverage consistent with this significance level.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

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

7.1.1 Last Observation Carried Forward (LOCF)

For the efficacy diary data the EoT value will be calculated as the average or the count of the valid diary measurements reported in the last 3 valid diary days of the analysis visit window prior to EoT. For patients who withdraw before week 12, the last available post-baseline average of the diary data measurements will be carried forward as the EoT value (LOCF).

For the non-diary efficacy data and safety data, the EoT value will be the last measurement within the week 12 visit day windows. For patients who withdraw before week 12 the last measurement within the analysis visit window of the last available post-baseline visit will be carried forward as the EoT value (LOCF).

7.1.2 Model Structure - Analysis of Covariance (ANCOVA)

Changes from baseline to a post-baseline visit for variables for which a normal distribution is assumed will be analyzed using the following ANCOVA model:

$$Ch_{ijks} = \beta_0 + \beta_1 Base_{ijks} + Trt_i + Region_j + AgeGrp_k + \epsilon_{ijks}$$

Where Ch_{ijks} is the change from baseline for patient s from treatment group i, geographic region (NA/EU) group j, and age group k. β_0 and β_1 are the intercept and the slope of Ch_{ijks} as a function of the baseline value and ϵ_{ijks} is the residual for each patient.

The ANCOVA model results will be presented with least squares (LS) means and two-sided 95% confidence intervals (CIs) for mean changes from baseline within each treatment group. Differences in LS means between Mirabegron versus placebo will be derived together with two-sided 95% CIs. T-statistics corresponding to the Type III sums of squares for the differences in the LS means will be used to obtain p-values for the comparisons. Distribution assumptions underlying the analysis will be assessed by residual plots.

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

```
PROC MIXED data=dataset COVTEST NOCLPRINT METHOD=ML;
CLASS Trt Gender Region AgeGrp;
MODEL Ch=Base Trt Region AgeGrp / SOLUTION CL;
LSMEANS Trt / CL OM AT MEANS PDIFF;
ESTIMATE 'Mirabegron versus placebo' Trt 1 -1 /EST CL;
RUN;
```

SAS code used to implement the stratified rank ANCOVA will be similar to that shown below:

```
PROC RANK data=dataset NPLUS1 TIES=MEAN OUT=RANK1;
VAR Base Ch ;
RANKS BASERANK CHRANK ;
BY Region ;
RUN ;

PROC MIXED data=RANK1 METHOD=ML /RESIDUAL OUTP=OUT
     (KEEP= Region CHRANK BASERANK Trt Resid);
BY Region;
MODEL CHRANK = BASERANK;
RUN ;

PROC FREQ data= out ;
TABLES Region*Trt*Resid /noprint CMH2 ;
ODS OUTPUT CMH = out2 ;
RUN ;
```

7.1.3 Mixed Model Repeated Measures (MMRM)

Changes from baseline to each post-baseline visit "t" (e.g. in mean number of micturitions per day, PRO values, Vital signs etc.,) will be analyzed using the following MMRM model:

$$Ch_{ijkst} = \beta_0 + \beta_1 Base_{ijks} + Trt_i + Region_j + AgeGrp_k + Time_t + Trt*Time_{it} + Co\text{-}variance_{it} + \epsilon_{ijkst}$$

Where Ch_{ijkst} is the change from baseline (i.e. time = 0 week) for patient *s* from treatment group *i*, geographic region group *j*, age group *k and for given time point t (i.e. time = 4, 8 and 12 weeks).* β_0 and β_1 are the intercept and the slope of Ch_{ijks} as a function of the baseline value and ϵ_{ijkst} is the residual for each patient. $Trt*Time_{it}$ is the time-by-treatment interaction effect and unstructured co-variance matrix will be used to adjust for the within-patient error variance co-variance.

The MMRM model results will be presented with LS means, standard errors and two-sided 95% CIs for mean change from baseline at all time points (4, 8 and 12 weeks) within each treatment group. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. In addition, differences in LS means between Mirabegron versus placebo at each time point will be derived together with two-sided 95% CIs. T-statistics corresponding to the Type III sums of squares for the differences in the LS means will be used to obtain p-values for the comparisons.

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

```
PROC MIXED data=dataset COVTEST NOCLPRINT METHOD=ML;
      CLASS ID Trt Time Gender Region AgeGrp;
      MODEL ch=Base Trt Region AgeGrp Time Time*Trt / SOLUTION CL
      DDFM=KenwardRoger;
      REPEATED Time /SUBJECT = ID TYPE = UN R RCORR;
      LSMEANS Trt*Time / CL PDIFF;
      ESTIMATE 'Mirabegron versus placebo' Trt 1 -1 /EST CL;
RUN;
```

In case of non-convergence of the above model or memory space issues, the same model but with Satterthwaite approximation (replacement of Kenward-Roger method) will be preferred.

7.1.4 Logistic Regression.

For the responder analyses, a logistic regression model for the response rate (*RR)* at a specified visit will be modeled with the logit link as follows:

$$logit(E(RR_{ijks})) = \beta_0 + \beta_1 Base_{ijks} + Trt_i + Region_j + AgeGrp_k + \epsilon_{ijks}$$

where $(E(RR_{ijks}))$ is the probability that a patient *s* from treatment group *i*, geographical region group *j*, and age group *k* demonstrates a response.

The odds ratio (OR) as well as its two-sided wald 95% CIs and p-value for Mirabegron versus placebo use will be derived.

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

```
PROC GENMOD data=dataset order=data;
      CLASS Trt Region AgeGrp;
```

```
      MODEL Responder(event='1') =Base Trt Region AgeGrp/ DIST=bin
      LINK=logit
      LRCI type3 wald;
      ESTIMATE 'Mirabegron versus placebo' Trt 1 -1/ EXP;
      LSMEANS Trt / DIFF CL CORR PDIFF;
RUN;
```

7.1.5 Mixed Effects Poisson (negative binomial) Regression Model

The analysis for count data ($Count_{ijks}$) at a specified visit e.g., the number of incontinence episodes (Includes nocturia episodes) prior to EoT will be performed using a Mixed Effects Poisson (Negative Binomial) regression model for a patient s from treatment group i, geographic region group j, age group k. The count data will be modeled with the log link function as follows:

$$log(E(Count_{ijks})) = log(Day_{ijks}) + \beta_0 + \beta_1 Base_{ijks} + Trt_i + Region_j + AgeGrp_k + \epsilon_{ijks}$$

where the offset variable $log(Day_{ijks})$ is the log of the number of valid diary days of each patient with a slope=1.

The RR as well as its two-sided 95% CIs and p-value for treatment over placebo will be derived.

To fix the final model (whether Poisson or Negative Binomial), the below steps will be followed.

Step 1: model fit for equi-dispersion (conditional mean = conditional variance) for Poisson will be assessed using scaled deviance or Scaled Pearson chi-square (χ^2) under "Criteria for Assessing Goodness of Fit". Poisson model will be fixed in case the deviance value is approximately 1. Or else Step 2 will be followed.

Step 2: In case the deviance value >1 (over dispersion), negative binomial (NB) regression model will be fixed instead Poisson.

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

```
PROC GENMOD data=dataset order=data;
      CLASS Trt Region AgeGrp;
      MODEL Count= Base Trt Region AgeGrp/ type3 LINK=log DIST=negbin
      offset=lday;
      ESTIMATE 'Mirabegron versus placebo' Trt 1  -1 / EXP;
      LSMEANS Trt / DIFF CL CORR PDIFF;
RUN;
```

NOTE: DIST should be Poisson (DIST =Poisson) in case data fits to Poisson model

7.2 Study Population

7.2.1 Disposition of Patients

The following patient data will be presented:

- Number of patients with informed consent, discontinued before randomization, randomized (overall only);
- Number and percentage of patients randomized in each analysis set, by treatment group and overall;
- Number and percentage of patients completed and discontinued treatment, by primary reason for treatment discontinuation for randomized patients, by treatment group;
- Number and percentage of patients completed and discontinued the study, by primary reason for study discontinuation for randomized patients and by treatment group;

7.2.2 Protocol Deviations

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

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

Protocol Deviation (PD)1 - 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.

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics by treatment group.

Number and percentage of patients randomized in each country and site will be presented by treatment group for FAS and SAF.

Those patients randomized to Mirabegron will start at 25 mg and will increase to 50 mg after 4 weeks. Those patients randomized to PBO will start blinded product matched to the Mirabegron 25 mg tablet and will increase to blinded product matched to 50 mg after 4 weeks. Once a patient has increased dose, he will remain on that dose for the remainder of the study unless for safety reasons that require discontinuation of study drug.

Descriptive statistics for age (in years), weight, body mass index (BMI) and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (≥40-<65, ≥65 and ≥40-<75, ≥75) and race will be presented. This will be done for the SAF and FAS by treatment group.

Demographic variables are based on the last available value prior to first dose of double-blind treatment.

BMI is calculated as BMI (kg/m^2) = weight (kg) / $height^2$ (m).

OAB related baseline characteristics summarized in Table 6 and recorded on the eCRF from the Screening Visit will be summarized for the FAS by treatment group.

Duration of the OAB symptoms in months is calculated as the number of months from onset date of OAB symptoms at diagnosis to the informed consent date at the screening.

(*Date of Informed Consent* - *onset date of OAB symptoms at diagnosis* + 1) / 30.44

Table 6 OAB Related Baseline Characteristics from eCRF

Characteristic	Summarized as	Categories
Duration of OAB symptoms (in months)	Continuous	N/A
OAB Severity at Baseline Based on Number of Micturition per day	Categorical	• <10 • ≥10 - ≤15 • >15
OAB Severity at Baseline Based on Number of Incontinence Episodes per day	Categorical	• >0 - ≤2 • >2 - ≤4 • >4
IPSS at Screening	Categorical	Total IPSS Score • Mild (1-7) • Moderate (8-19) • Severe (20-35)
	Continuous	Storage Voiding Total Score QoL
Previous OAB Medication	Categorical	• Yes • No
Previous non-drug treatment for OAB (prior to screening)	Free Text	• Yes →Biofeedback →Exercises →Electrical Stimulation →Behavioral →Pessaries →Implants →Surgery →Other (if available) • No
5-ARI use from the prior/con meds (dustasteride and finasteride)	Categorical	• Yes • No

OAB related baseline characteristics derived from the 3-day micturition diary prior to the Run-in Visit and the Randomization Visit will be summarized as continuous variables overall for FAS with following listed characteristics in Table 7. Only patients with a baseline value > 0 will be included in each individual summary.

Table 7 OAB Related Baseline Characteristics from 3-Day Micturition Diary

Characteristic	Summarized as	Categories
Number of incontinence episodes reported during the 3-day diary	Continuous	N/A
Mean number of incontinence episodes per day	Continuous	N/A
Number of urgency incontinence episodes reported during the 3-day diary	Continuous	N/A
Mean number of urgency incontinence episodes per day	Continuous	N/A
Mean number of micturitions per day	Continuous	N/A
Mean number of urgency episodes (grade 3 or 4) per day	Continuous	N/A
Number of nocturia episodes reported during the 3-day diary	Continuous	N/A
Mean number of nocturia episodes per day	Continuous	N/A

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 FAS.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with World Health Organization – Drug Dictionary (WHO-DD), and will be summarized by therapeutic subgroup (Anatomical Therapeutic Chemical (ATC) 2nd level) and chemical subgroup (ATC 4th level) and preferred World Health Organization (WHO) name by treatment group for the FAS.

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

7.3 Study Drugs

7.3.1 Exposure

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

- Descriptive statistics for number of days treatment was received will be presented by treatment group
- Number and percent of patients with dose increase from 25mg to 50mg by treatment group.

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented by treatment group.
- Counts and percentages of exposure time will be categorized according to the following categories by treatment group:
    - 1 to 6 days
    - 7 to 13 days

- 14 to 27 days
- 28 to 55 days
- 56 to 83 days
- 84 days or more
- Unknown.

- Counts and percentages of cumulative exposure will be categorized according to the following categories by treatment group:
  - ≥7 days
  - ≥14 days
  - ≥28 days
  - ≥56 days
  - ≥84 days

Counts and percentages of patients in each of these categories will be summarized for each treatment group for the SAF.

7.3.2 Treatment Compliance

Overall compliance will be examined for patients in SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways for SAF:

- Descriptive statistics will be presented by treatment group.
- Percent compliance will be categorized according to the following categories by treatment group:
  - <80%
  - >=80% to <120%
  - >=120%
  - Unknown.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary analysis

The primary analysis set for efficacy analyses will be FAS. The primary efficacy variable is change from baseline to end of treatment in mean number of micturitions per day based on a 3-day electronic diary.

<u>Mean number of micturitions per day</u>

The hypothesis being tested for the mean number of micturitions per day can be stated as:

> H_0: Difference between mirabegron and placebo in change from baseline to end of treatment in mean number of micturitions per day based on a 3-day electronic diary is 0.
>
> H_1: Difference between mirabegron and placebo in change from baseline to end of treatment in mean number of micturitions per day based on a 3-day electronic diary is not equal to 0.

Change from baseline to end of treatment in mean number of micturitions per day will be tested using an ANCOVA model. The response variable will be the mean change in number of micturitions episodes per day from baseline to the end of the study with treatment group, geographic region, and age group (≥40-<65, ≥65) as fixed factors and baseline mean number of micturitions episodes per day as the covariate in the model. As part of the ANCOVA results, LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided. Differences in LS means between Mirabegron and placebo will be derived together with 95% CIs and p-values.

7.4.1.2 Secondary Analysis of Primary Endpoint

Residual plots will be produced to check the assumptions of the underlying statistical models for mean number of micturitions episodes per day. If the fit of the models is questionable, the dependent variable may be logarithmically transformed in order to improve the fit or a non-parametric analysis could be applied as a secondary analysis. Outliers are defined and handled per section 7.10.2. If outliers are present, then additional sensitivity analyses will be performed with the outliers excluded to assess their impact on the results.

The primary analysis will be repeated for completers only, i.e. without utilizing LOCF imputation for patients with missing values for end of treatment (Week 12). Additionally, Week 4 and Week 8 values will be analyzed similarly to End of Treatment (i.e. the statistical tests applied will be the same as the test applied to the ones described in Section 7.4.1)

An analysis of change from baseline in mean number of micturitions per day using a Mixed Model Repeated Measures (MMRM) with age group, geographic region, time (visit), and a time-by-treatment interaction as factors and the number of micturition episodes at baseline as covariate will serve as another sensitivity analysis. The repeated measures model will present LS means and two-sided 95% CIs for changes from baseline within each treatment group.

7.4.1.3 Sub-group Analysis

Sub-group analysis of the primary endpoint will be conducted using an ANCOVA model.

The sub-groups to be considered for the analysis will include;

- Geographic region (NA, EU)
- Age group (≥40-<65, ≥65 and ≥40-<75, ≥75)
- Previous OAB medication (Yes, No)
- 5-ARI use at baseline (Yes, no): only for diary variables

- Race, a category to be included in case of at least 25 patients within that category

The models for the sub-group analysis will have the treatment arm as a fixed factor and baseline values as the covariate in the model. LS means, two-sided 95% CIs, and p-values for mean changes from baseline within each subgroup will be provided.

7.4.2 Analysis of Secondary Endpoints

The secondary efficacy variables are:

- Change from baseline to week 4 and week 8 in mean number of micturitions per day
- Change from baseline to end of treatment in mean incontinence episodes per day (FAS-I)
- Change from baseline to end of treatment in mean volume voided per micturition,
- Change from baseline to end of treatment in mean number of urgency episodes (grade 3 and 4) per day
- Change from baseline to end of treatment in IPSS total score and subscales (Voiding, Storage, and Quality of Life)
- Change from baseline to end of treatment in mean number of urgency incontinence episodes per day (FAS-I)
- Change from baseline to end of treatment in symptom bother and total health related quality of life scores as assessed by OAB-q questionnaire and subscales (coping, concern, sleep, social interaction, and symptom bother), and
- Change from baseline to end of treatment in mean number of nocturia episodes per day (FAS-N)
- Change from baseline to end of treatment in TUFS using PPIUS (grade 3 or 4), PPBC, and TS-VAS.

Change from baseline to end of treatment in mean incontinence episodes per day

Analysis of mean change in number of incontinence episodes per day from Baseline to End of Treatment will be performed on the FAS-I using ANCOVA model, p-values will be calculated by stratified ranking ANCOVA. The response variable is standardized ranks on change from Baseline, with treatment group, age group (<65, >=65 years) and geographic region as fixed factors and baseline value as a covariate.

Poisson (or negative binomial) regression for count variables

The analysis for count data ($Count_{ijklms}$) at EoT e.g., the number of incontinence episodes prior to EoT will be performed using a Mixed Effects Poisson (Negative Binomial (NB)) regression model for a patient *s* from treatment group *i*, sex group *j*, age group *k*, previous OAB treatment group *l* and geographic region *m*. The count data will be modeled with the log link function as follows:

$$log(E(Count_{ijklms})) = log(Day_{ijklms}) + \beta_0 + \beta_1 Base_{ijklm} + Trt_i + Sex_j + AgeGrp_k + OABtrt_l + Region_m + \epsilon_{ijklms}$$

where the offset variable $log(Day_{ijklms})$ is the log of the number of valid diary days of each patient with a slope=1.

The RR as well as its two-sided 95% CIs and p-value for Mirabegron vs placebo will be derived.

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

```
DATA dataset;
 SET dataset;
   logt = log(number of valid diary days);
RUN;

PROC GENMOD data=dataset  order=data;
   CLASS Trt Sex AgeGrp OABtrt Region;
   MODEL Count= Base Trt Sex AgeGrp OABtrt Region / type3 LINK=log
DIST=negbin  OFFSET = logt  ;
```

Other efficacy analysis

Other secondary efficacy variables will be analyzed using the same ANCOVA model as described for micturitions (refer to section 7.4.1.1). Other planned utility indices and analyses will be calculated in a separate report from the Statistical Analysis Plan and Clinical Study Report.

Shift tables for IPSS scores: by category mild/moderate/severe (Score: 1-7: Mild; 8-19: Moderate; 20-35: Severe)

Shift tables that include number and percent of patients from one category at baseline to another (Mild/Moderate/Severe) category at week 4, 8, and 12/EOT by treatment group will be presented for IPSS total score and subscale scores.

IPSS has Lower urinary tract symptoms (LUTS) are categorized as storage (urgency, frequency, nocturia) (items 2, 4, 7), voiding (sensation of incomplete emptying, hesitancy, weak stream and straining (items 1, 3, 5, 6) and QOL (item 8). Storage and voiding symptoms will be summarized separately.

Responder analysis

Responder analyses will be performed for:

Number of patients with ≥50% reduction in micturition frequency at End of Treatment,

Number of patients with less than 8 micturitions per day at End of Treatment,

Number of patients with 0 incontinence episodes per day at End of Treatment,

Number of patients with ≥50% reduction in incontinence at End of Treatment,

Number of patients with ≥50% reduction in grade 3 or 4 urgency episodes at End of Treatment,

Number of patients with 4 point decrease in IPSS score at End of Treatment,

Number of patients with IPSS scores less than 8 at End of Treatment,

Number of patients with greater than or equal to 10 points improvement in Symptom Bother Total HRQL scores and each HRQL subscale scores at End of Treatment,

Number of patients with greater than or equal to 1 point decrease in PPBC score at End of Treatment,

Number of patients with greater than or equal to 2 point decrease in PPBC score at End of Treatment,

Number of patients with ≥50% reduction in number of nocturia episodes at End of Treatment,

Number of patients with less than 2 nocturia episodes per day at End of Treatment.

Sensitivity Analysis

An analysis of change from baseline in PRO values using an MMRM with geographic region, age group, time (visit), and a time-by-treatment interaction as factors and PRO value at baseline as a covariate will serve as a sensitivity analysis. The repeated measures model will present LS means and two-sided 95% CIs for changes from baseline within each treatment group.

7.4.3 Analysis of Exploratory Endpoints

Subgroup analyses by PSA cut-off scores for <2, 2-4 and 5-ARI use at baseline will be performed on all applicable primary and secondary efficacy endpoints, which were analyzed using ANCOVA or ranking ANCOVA (refer to section 7.4.1.1).

7.5 Analysis of Safety

Safety analysis will be performed for adverse events (AEs) and vital signs using the SAF. No inferential comparison between treatment groups will be performed for the safety analysis in this study.

7.5.1 Adverse Events

Summaries and listings of serious adverse events (SAEs) and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of 'Always Serious' terms if any upgrade was done.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be listed.

The number and percentage of TEAEs, serious TEAEs, and discontinuations due to a TEAE will be summarized by System Organ Class, Preferred Term, and treatment group. In addition, TEAEs will be summarized by relationship to study drug as determined by the Investigator and by severity for each treatment group.

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of patients with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of patients with causally drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of patients with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of patients with serious drug related TEAEs,
- Number of TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of patients with TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of patients with urinary tract infection, and
- Number of deaths.

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

- TEAEs
- Common TEAEs (≥2% in one group)
- Common TEAEs (≥1% in one group)
-

- Drug related TEAEs,
- Severe TEAEs
- Serious TEAEs,
- Drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- Drug related TEAEs leading to permanent discontinuation of study drug,
- Non-serious TEAEs over 5% in any one treatment group
- TEAEs by subgroup as indicated in section 7.8

The number and percentage of patients with TEAEs, as classified by PT only, will be summarized for each treatment group and by the subgroups of interest found in Section 7.8.

The number of TEAEs and the number and percentage of patients with TEAEs, as classified by SOC and PT will also be summarized by severity. In the patient count, if a patient has multiple TEAEs with the same SOC or PT, but with differing severity, then the patient will be counted only once with the worst severity, however, if any of the severity values are missing then the patient will be counted only once with missing severity. In the adverse event count, the adverse events will be presented in each category to which they were classified. Drug related severe TEAEs will be presented in a similar way.

Additional summaries will be provided for the following AEs of special interest:

- Vital signs (systolic and diastolic blood pressure and pulse rate),
- Acute urinary retention (urinary retention requiring catheterization)
- Benign prostatic obstruction (BPO) requiring surgery.

7.5.2 Clinical Laboratory Evaluation

Laboratory variables (biochemistry, hematology, and urinalysis) will be descriptively summarized for baseline (Visit 2), Week 4, Week 8 and Week 12/EOT and change from Screening to EOT will be summarized by treatment group.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, and urinalysis will be summarized using mean, standard deviation, minimum, maximum, Q1, Q3, and median for each treatment group at each visit. Additionally, a within-patient change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

For each hematology and biochemistry laboratory parameter, laboratory test results will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. Shift tables of reference range changes from Screening to Week 12/EOT and most extreme value during the double-blind treatment period by treatment group will be summarized for all laboratory values.

Laboratory abnormalities will be evaluated based on the Potentially Clinically Significant (PCS) laboratory criteria. For each laboratory PCS criterion, the number and percent of

patients who have a laboratory value meeting the PCS criteria during the double-blind treatment period will be summarized by treatment group. The directions of changes (high or low) in PCS will be indicated in the tables. The pre-defined criteria for PCS laboratory values are presented below.

Potentially Clinically Significant Laboratory Criteria			
Laboratory Parameter	**Unit**	**Low PCS Criterion**	**High PCS Criterion**
Hematology			
Hemoglobin	g/L	< 80	>180
Hematocrit	Fraction	< 0.25	> 0.55
Erythrocyte (Red Blood Cell Count)	$x10^{12}$/L	< 2.5	> 7.0
Platelet Count	$x10^{9}$ /L	< 120	> 500
Leukocyte (White Blood Cell Count)	$x10^{9}$ /L	< 2.5	> 18
Potassium	Meq/L	< 3.0	> 6.0

7.5.2.1 Liver function tests

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The patient'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 patients with potentially clinically significant values in liver function 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.

Pulse rate, systolic blood pressure, and diastolic blood pressure will be summarized by treatment group, by Home Based Blood Pressure Monitoring (HBPM) and office based, and the subgroups of interest found in Section 7.8 using descriptive statistics (mean, standard deviation, minimum, maximum, and median) for baseline value, specified post-baseline time point values (Week 4, Week 8, and Week 12/EoT), and change from baseline to each specified post-baseline time point. For HBPM, a visit is defined as a set of 3 (or less) valid diary days prior to each visit. Morning and evening blood pressure will be reported separately. The first reading of HBPM from each time period will be discarded and the subsequent two readings for each time period will be averaged over the 3-day diary. If only 2 measurements were recorded on one day, both measurements will be kept. Average change from baseline to end of treatment for each vital sign variable for HBPM and office based will be analyzed using the ANCOVA model with treatment group and geographic region as fixed factors and baseline vital sign value as covariate. Age group (≥40-<65, ≥65; ≥40-<75, ≥75) will be included as the stratification factor. It should be noted that age group was omitted from the description of the analysis in the protocol. As part of the ANCOVA results, LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided. Differences in LS means between mirabegron and placebo will be derived together with 95% CIs.

An analysis of change from baseline of vital signs using an MMRM model with geographic region, age group, time (visit), and a time-by-treatment interaction as factors and the baseline values as covariate will serve as another sensitivity analysis. The repeated measures model will present LS means and two-sided 95% CIs for changes from baseline within each treatment group.

For measurement based on HBPM, the averaging approach described above will be applied. Hypertension events from the HBPM will be identified, but won't be summarized as AE. An AE of hypertension will be recorded if one of the following criteria is met on 2 or more consecutive office-based visits. :

1. If the average systolic blood pressure is > 140 mmHg AND/OR the average diastolic blood pressure is > 90 mmHg at two consecutive visits after Baseline (Visit 2) in patients who were normotensive (average systolic blood pressure < 140 mmHg and average diastolic blood pressure < 90 mmHg [WHO-ISH, 2003]) at Baseline (Visit 2).
2. If the average systolic blood pressure is increased > 20 mmHg AND/OR the average diastolic blood pressure is increased > 10 mmHg at two consecutive visits as compared to Baseline (Visit 2) in patients with hypertension at Baseline (Visit 2).
3. If treatment with antihypertensive drugs is initiated for treatment of hypertension or if the dose of prior antihypertensive drugs is increased due to an increase in blood pressure.

An AE of "increased" Blood Pressure should be considered if the above conditions are not met, but a high blood pressure is recorded."

An AE of tachycardia should be considered if resting heart frequency (pulse rate) is > 100 bpm.

An AE of white coat hypertension will be recorded if the office measurement is more than 10% greater than last measurement for the preceding home based diary. An AE of masked hypertension will be recorded if last home based measurement is more than 10% greater than the following office measurement. The percentage of patients with white coat hypertension, masked hypertension or no difference at 1 visit or two or more visits will be summarized.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest value obtained during treatment for each patient for each treatment group.

Number and percentage of patients with more than 2/5/10/15/20 mmHg increase from baseline in SBP, more than 2/5/10/15 mmHg increase in DBP or more than 5/10/15 bpm increase from baseline in pulse rate, on 2 consecutive post-baseline visits will be summarized by treatment group. Number and percentage of patients with vital sign variables shifting between JNC-7 defined risk categories will be summarized by treatment group. These categories are listed below:

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal	< 120	<80
Prehypertension	120-139	80-89
Hypertension Stage 1	140-159	90-99
Hypertension Stage 2	≥160	≥100

Number and percentage of patients with a PR > 100 bpm at any office visit or by HBPM will be summarized by treatment group separately.

The following Vital Sign data will be presented graphically by treatment group across visits:

- Change from baseline in vital sign results using mean (± 95% CI) plot
- Scatter plot of maximum vital sign results on treatment versus baseline value (separate plot for SBP, DBP, and pulse).

7.5.4 Electrocardiograms (ECGs)

ECG variables (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval) will be summarized using descriptive statistics or frequencies and percentages for each treatment group at Baseline, Week 4, Week 8, and Week 12/EOT, including changes from baseline to EOT.

Number and percent of patients with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by local investigator for the 12 lead ECG will be tabulated by treatment group at each treatment visit.

Shift tables that include number and percent of patients will be presented for 12 lead ECG reading changes from normal at baseline to abnormal at week 4, 8, and 12/EOT by treatment group.

The QTcF interval will be summarized using frequency tables for each treatment group and time point for values of clinical importance using the range criteria below. It will be summarized by FDA Guidance categories.

	QTcF Interval Criteria Value (msec)
FDA Categories	≤ 450 > 450 > 480 > 500

The QTcF interval will also be summarized by the frequencies of patients with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment group and time point.

Variable	**Change from Baseline**
QTcF Interval (msec)	<30 >= 30 >30-<60 >=60

7.5.5 PVR Volume

PVR volume in mL and corresponding change from baseline values will be summarized by treatment group and visit (baseline and Week 12) for continuous values as well as using the following categories:

- <= 200 mL
- >200-<= 250 mL
- >250-<= 300 mL
- >300 mL

A shift table for changes from baseline to each post-baseline visit for PVR volume based on these categories above will be performed for each treatment group.

7.5.6 Q_{max}

Q_{max} will be analyzed from change from baseline (collected at the beginning of the run-in period) and summarized by treatment group and visit. Numbers and percentages of patients who shift to Q_{max} < 5.0 mL/s will be tabulated.

In addition, Qmax will also be summarized after outliers were removed as defined in section 7.10.2.

7.5.7 Weight, Height, and BMI

A descriptive summary for values of height (baseline only), weight in kg and BMI in kg/m2 at each post-baseline visit and the changes from baseline will be provided at each visit. A listing will also be provided.

7.6 Analysis of Pharmacokinetics (PK)

Not applicable

7.7 Analysis of Pharmacodynamics (PD)

Not applicable

7.8 Subgroups of Interest

Primary efficacy endpoint and selected safety variables (treatment emergent adverse events and vital signs) will be summarized by treatment group for the subgroups defined on the basis of the categorized variables listed below in case of at least 25 patients for each treatment group within that category:

Grouping variable	**Subgroups**
Geographic Region	North America
	Europe
Age group	≥40-<65 years
	≥65 years
	≥40-<75 years
	≥75 years
Previous OAB medication	Yes
	No
PSA cut-off (exploratory endpoint)	<2
	2-4
5-ARI at baseline	Yes
	No
Hypertension at baseline (for vital signs)	Yes
	No
Race	White
	Black or African American
	Asian
	American Indian/Alaskan Native
	Hawaiian or Other Pacific Islander
	Other

7.9 Other Analyses

Not applicable

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

7.10.1 Missing Data

Missing primary and secondary efficacy endpoints will be handled by LOCF for continuous variables, and non-responder imputation for binary variables.

For all OAB-q scales and subscales, if <50% of the items are missing, the scale/subscale 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/subscale score should be calculated, the scale/subscale score should be considered missing.

As a general principle, imputation of missing dates for variables will not be done. Exceptions are for start and stop dates of study drug intake, AEs and concomitant medications. The imputed dates will be used to determine whether the medication was taken prior to or during the double-blind treatment period. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

7.10.1.1 Imputation of Study Drug Start Dates and Study Drug End Dates

Imputation of Study Drug Start Dates

Run-In Period

For patients who are not Screen Failures, the first dose date of tamsulosin hydrochloride run-in will be imputed if both of the following criteria are met:

- There is a missing or partial date for the first dose of tamsulosin hydrochloride run-in study drug AND
- The number of tablets dispensed at the Screening Visit does not equal the number of tablets returned (including missing values).

If both criteria are met, then the first dose date of tamsulosin hydrochloride run-in study drug is defined as the first non-missing date in the following order:

1. Dispense date at Screening Visit +1 day
2. Date of the Screening Visit +1 day

Double-Blind Treatment Period

For patients who are randomized to double-blind treatment, the first dose date of double-blind treatment study drug will be imputed if both of the following criteria are met:

- There is a missing or partial date for the first dose of double-blind treatment AND
- The number of tablets dispensed at the Randomization Visit does not equal the number of tablets returned (including missing values) AND
- Dispensed date is non-missing.

If all the above criteria are met, then the first dose date of double-blind treatment is defined as:

Dispense date at the Randomization Visit +1 day

Imputation of Study Drug End Dates

Run-In Period

For patients who are not Screen Failures, the last dose date of tamsulosin hydrochloride run-in will be imputed if both of the following criteria are met:

- There is a missing or partial date for the last dose of tamsulosin hydrochloride run-in study drug AND
- The number of tablets dispensed at the Screening Visit does not equal the number of tablets returned (including missing values).

If both criteria are met, then the last dose date of tamsulosin hydrochloride run-in study drug is defined as the first non-missing date in the following order:

1. Date of the day before the first dose of double-blind treatment in the double-blind treatment period,
2. Day of the dispense date at the randomization visit
3. Day of the randomization visit (Visit 2)
4. Date of the first dose of Tamsulosin Hydrochloride run-in study drug + 1 day
5. Dispensed date at the Screening Visit + 1 day
6. Date of the Screening Visit + 1 day

Double-Blind Treatment Period

For patients who are randomized to double-blind treatment, the last dose date of double-blind treatment study drug will be imputed if all the following criteria are met:

- There is a missing or partial date for the last dose of double-blind treatment AND
- The number of tablets dispensed at the Randomization Visit does not equal the number of tablets returned (including missing values).

If only the day is missing for the last dose date of double-blind treatment, the last day of the month under consideration will be used.

If the month and/or year are missing for the last dose date of double-blind treatment, then the last dose date of double blind treatment is defined as the first non-missing date in the following order:

1. Last dispense date of the double-blind period + 1 day
2. Date of the first dose of double-blind treatment in the double-blind treatment period + 1 day

3. Date of the randomization visit + 1 day.

For imputing the last dose date of tamsulosin hydrochloride run-in study drug and double-blind treatment study drug, an imputed first dose date should not be used but the next imputation rule should be used instead.

7.10.1.2 Imputation of Adverse Event Onset Date

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 **latest** of the following non-missing dates:

- Date of first dose of double-blind treatment
- Date of randomization visit + 1 day
- Date of last dose of single-blind run-in study drug + 1 day

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

1. If the month and year of the onset date is prior to the month and year of the first dose of double-blind treatment, then the surrogate onset date will be the imputed onset date.
2. If the month and year of the onset date is on or after the month and year of the first dose of double-blind treatment or if the first dose of double-blind treatment is missing, then the imputed onset date will be the **latest** of the following non-missing dates:

- Date of first dose of double-blind treatment
- Date of randomization visit + 1 day
- Date of last dose of single-blind run-in study drug + 1 day
- Surrogate onset date

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

7.10.1.3 Imputation of Concomitant Medication and Non-Drug Treatment Start and End Date

Start and stop dates for all concomitant medications and non-drug treatment are collected on the eCRF. However, in case of missing or partial information in these dates, the following rules will be used:

If start date is missing or partial:

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

- if entire date is missing, use informed consent date

If stop date is missing or partial and the medication is not ongoing:

- if month is missing, use December
- if day is missing, use the last day of the month under consideration
- if year or the entire date is missing, set to December 31st, 2099

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

If the medication or non-drug treatment is ongoing, the stop date will remain missing.

7.10.1.4 Imputation of OAB Symptoms Onset Date

If the onset date of OAB symptoms is partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year.
- Missing year, but day and month are present: No imputations will occur, and the patient will be excluded from all summaries related to duration of OAB symptoms.
- Missing day, month and year: No imputations will occur, and the patient will be excluded from all summaries related to duration of OAB symptoms.
- If any such imputed date falls after the informed consent date, then the onset date will be same as the informed consent date.

7.10.2 Outliers

An outlier is defined as an observation for which the residual is more than three interquartile ranges above the 75th percentile or below the 25th percentile. Outliers will be identified based on diagnostics performed for the co-primary and secondary efficacy variables by using standardized residuals from ANCOVA model (Section 7.4.1.2). If outliers are present, then additional sensitivity analyses will be performed with the outliers excluded to assess their impact on the results.

7.10.3 Visit Windows

Patients do not always adhere strictly to the visit timing in the protocol. Therefore, the designation of visits during the double-blind treatment period will be based on the day of evaluation relative to the start of the double-blind treatment period (day of first dose of double-blind treatment in double-blind treatment period = Day 1 of double-blind treatment period) rather than the nominal visit recorded in the CRF.

To assign a measurement to a study visit during the double-blind treatment period, the first step consists of selecting all measurements falling within the double-blind treatment period

as defined above. To further determine the study visit measurement, mutually exclusive relative day windows are used.

If a patient has more than one visit with a measurement included within a window, the assessment closest to the scheduled day will be used. In case of ties between observations located on different sides of the scheduled day, the later assessment will be used. In case of ties located on the same side of the scheduled 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.

It should be noted that if more than one measurement for a parameter is recorded within the same visit window, the above conventions may not lead to the most conservative approach for the by-visit summaries of categorical or numerical variables. The worst individual categorical or numerical value within a visit window may not be identified as the value representative for the analysis visit due to the rules above. However, the worst individual categorical or numerical value will be accounted for in tables summarizing the worst individual categorical or numerical value reported during the double-blind treatment period. All individual values will be provided in a listing.

7.10.3.1 Analysis Visit Windows for Efficacy and Safety Variables

All the efficacy and safety assessments for a treatment period will be allocated based on the tables below.

Efficacy:

Analysis visit	Target day	Actual assessment day
Screening/Tamsulosin Hydrochloride Run-In	Day -28	-31 to -25
Baseline	Day 1	Day 1[a]
Week 4	Day 28	21-35
Week 8	Day 56	49-63
Week 12	Day 84	77-91
End of Treatment	Day 84	2-91 (Last day of post-baseline assessment)
Week 16/Follow-up Phone Call	Day 114	111 to 117

a. After screening/tamsulosin hydrochloride run-in, visit windows/study days will be calculated based on the Baseline (Visit 2) date.

Safety:

Analysis visit	Target day	Actual assessment day
Screening/Tamsulosin Hydrochloride Run-In	Day -28	-31 to -25
Baseline	Day 1	Day 1[a]
Week 4	Day 28	21-35
Week 8	Day 56	49-63
Week 12/End of Treatment	Day 84	77-91
Week 16/Follow-up Phone Call	Day 114	111 to 117

a. After screening/tamsulosin hydrochloride run-in, visit windows/study days will be calculated based on the Baseline (Visit 2) date.

For efficacy variables recorded in the 3-day micturition diary, the following rules will apply:

- As micturition diary data are to be recorded from midnight 3 days prior to a visit to midnight 1 day prior to a visit, micturition diary records which have the same date as a visit date should be excluded from the analysis. Non-micturition questionnaire assessment dates will be compared to the eDiary dates and used to flag which diary records should be excluded.
- Any diary days which are > 7 days after the last dose of double-blind treatment will not be included in the analysis.
- Average values or number of episodes for count data will only be calculated if at least 2 valid diary days are available within the specified window. In the case that only 1 valid diary day is available, then no value will be calculated.
- If there are more than 3 valid diary days available for a visit, the average will be based on the last 3 days prior to the scheduled visit.
- Duplicate records (same time and episode characteristics) per day during the 3-day micturition diary period will be excluded.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	15-July-2016	NA	Final Version 1.0
1.1	22-Aug-2016	Updated based on sponsor's comments	Final Version 1.1
1.2	27-Sep-2018	Updated based on sponsor's comments	Final Version 1.2

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10 APPENDICES

10.1 Appendix 1: Adverse Events of Possible Hepatic Origin

MedDRA Hepatic Disorders SMQ

DocUUID : f1c70a60-c521-4b7f-ac81-17461fb8bee9

- Congenital, familial, neonatal and genetic disorders of the liver (SMQ)
  - Accessory liver lobe
  - Alagille syndrome
  - Cerebrohepatorenal syndrome
  - Congenital absence of bile ducts
  - Congenital cystic disease of liver
  - Congenital hepatic fibrosis
  - Congenital hepatobiliary anomaly
  - Congenital hepatomegaly
  - Cystic fibrosis hepatic disease
  - Dilatation intrahepatic duct congenital
  - Glycogen storage disease type I
  - Glycogen storage disease type III
  - Glycogen storage disease type IV
  - Glycogen storage disease type VI
  - Hepatitis neonatal
  - Hepatocellular damage neonatal
  - Hepato-lenticular degeneration
  - Hepatosplenomegaly neonatal
  - Hereditary haemochromatosis
  - Neonatal cholestasis
  - Neonatal hepatomegaly
  - Polycystic liver disease
  - Porphyria acute
  - Hyperbilirubinaemia neonatal
  - Jaundice neonatal
  - Kernicterus
  - Porphyria non-acute
- Drug related hepatic disorders - comprehensive search (SMQ)
  - Cholestasis and jaundice of hepatic origin (SMQ)
    - Bilirubin excretion disorder
    - Cholaemia
    - Cholestasis
    - Cholestatic liver injury
    - Cholestatic pruritus
    - Drug-induced liver injury
    - Hepatitis cholestatic
    - Hyperbilirubinaemia
    - Icterus index increased
    - Jaundice
    - Jaundice cholestatic
    - Jaundice hepatocellular
    - Mixed liver injury

- Ocular icterus
- Deficiency of bile secretion
- Yellow skin

Drug related hepatic disorders - severe events only (SMQ)

- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
  - Acute hepatic failure
  - Acute yellow liver atrophy
  - Ascites
  - Asterixis
  - Bacterascites
  - Biliary cirrhosis
  - Biliary cirrhosis primary
  - Biliary fibrosis
  - Cholestatic liver injury
  - Chronic hepatic failure
  - Coma hepatic
  - Cryptogenic cirrhosis
  - Diabetic hepatopathy
  - Drug-induced liver injury
  - Duodenal varices
  - Gallbladder varices
  - Gastric varices
  - Gastric varices haemorrhage
  - Hepatectomy
  - Hepatic atrophy
  - Hepatic calcification
  - Hepatic cirrhosis
  - Hepatic encephalopathy
  - Hepatic encephalopathy prophylaxis
  - Hepatic failure
  - Hepatic fibrosis
  - Hepatic hydrothorax
  - Hepatic infiltration eosinophilic
  - Hepatic lesion
  - Hepatic necrosis
  - Hepatic steatosis
  - Hepatitis fulminant
  - Hepatobiliary disease
  - Hepatocellular foamy cell syndrome
  - Hepatocellular injury
  - Hepatopulmonary syndrome
  - Hepatorenal failure

Hepatorenal syndrome
Hepatotoxicity
Intestinal varices
Liver and small intestine transplant
Liver disorder
Liver injury
Liver operation
Liver transplant
Lupoid hepatic cirrhosis
Mixed liver injury
Nodular regenerative hyperplasia
Non-alcoholic steatohepatitis
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Peripancreatic varices
Portal hypertension
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal triaditis
Portal vein dilatation
Portopulmonary hypertension
Renal and liver transplant
Retrograde portal vein flow
Reye's syndrome
Reynold's syndrome
Splenic varices
Splenic varices haemorrhage
Subacute hepatic failure
Varices oesophageal
Varicose veins of abdominal wall
Anorectal varices
Anorectal varices haemorrhage
Intrahepatic portal hepatic venous fistula
Peritoneovenous shunt
Portal shunt
Small-for-size liver syndrome
Spider naevus

Hepatitis, non-infectious (SMQ)
Acute graft versus host disease in liver
Allergic hepatitis
Autoimmune hepatitis
Chronic graft versus host disease in liver
Chronic hepatitis

- Graft versus host disease in liver
- Hepatitis
- Hepatitis acute
- Hepatitis cholestatic
- Hepatitis chronic active
- Hepatitis chronic persistent
- Hepatitis fulminant
- Hepatitis toxic
- Ischaemic hepatitis
- Lupus hepatitis
- Non-alcoholic steatohepatitis
- Radiation hepatitis
- Granulomatous liver disease
- Liver sarcoidosis

Liver neoplasms, benign (incl cysts and polyps) (SMQ)

- Benign hepatic neoplasm
- Focal nodular hyperplasia
- Haemangioma of liver
- Haemorrhagic hepatic cyst
- Hepatic adenoma
- Hepatic cyst
- Hepatic cyst ruptured
- Hepatic haemangioma rupture

Liver neoplasms, malignant and unspecified (SMQ)

- Liver malignant tumours (SMQ)
  - Hepatic angiosarcoma
  - Hepatic cancer metastatic
  - Hepatic cancer stage I
  - Hepatic cancer stage II
  - Hepatic cancer stage III
  - Hepatic cancer stage IV
  - Hepatoblastoma
  - Hepatoblastoma recurrent
  - Hepatocellular carcinoma
  - Mixed hepatocellular cholangiocarcinoma
- Liver tumours of unspecified malignancy (SMQ)
  - Hepatic neoplasm
  - Hepatobiliary neoplasm

Liver related investigations, signs and symptoms (SMQ)

- Alanine aminotransferase abnormal
- Alanine aminotransferase increased
- Ammonia abnormal
- Ammonia increased

Ascites
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
Bacterascites
Bile output abnormal
Bile output decreased
Bilirubin conjugated abnormal
Bilirubin conjugated increased
Biopsy liver abnormal
Blood bilirubin abnormal
Blood bilirubin increased
Blood bilirubin unconjugated increased
Bromosulphthalein test abnormal
Child-Pugh-Turcotte score increased
Foetor hepaticus
Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gamma-glutamyltransferase abnormal
Gamma-glutamyltransferase increased
Guanase increased
Hepaplastin abnormal
Hepaplastin decreased
Hepatic artery flow decreased
Hepatic congestion
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic function abnormal
Hepatic hydrothorax
Hepatic mass
Hepatic pain
Hepatic sequestration
Hepatic vascular resistance increased
Hepatobiliary scan abnormal
Hepatomegaly
Hepatosplenomegaly
Hyperammonaemia
Hyperbilirubinaemia
Hypercholia
Hypertransaminasaemia
Kayser-Fleischer ring
Liver function test abnormal
Liver induration

Liver palpable subcostal
Liver scan abnormal
Liver tenderness
Mitochondrial aspartate aminotransferase increased
Molar ratio of total branched-chain amino acid to tyrosine
Oedema due to hepatic disease
Perihepatic discomfort
Retrograde portal vein flow
Total bile acids increased
Transaminases abnormal
Transaminases increased
Ultrasound liver abnormal
Urine bilirubin increased
X-ray hepatobiliary abnormal
5'nucleotidase increased
Blood alkaline phosphatase abnormal
Blood alkaline phosphatase increased
Blood cholinesterase abnormal
Blood cholinesterase decreased
Deficiency of bile secretion
Glutamate dehydrogenase increased
Haemorrhagic ascites
Hypoalbuminaemia
Leucine aminopeptidase increased
Periportal oedema
Peritoneal fluid protein abnormal
Peritoneal fluid protein decreased
Peritoneal fluid protein increased
Pneumobilia
Portal vein flow decreased
Portal vein pressure increased
Retinol binding protein decreased
Urobilinogen urine decreased
Urobilinogen urine increased

Liver-related coagulation and bleeding disturbances (SMQ)

Antithrombin III decreased
Blood fibrinogen abnormal
Blood fibrinogen decreased
Blood thrombin abnormal
Blood thrombin decreased
Blood thromboplastin abnormal
Blood thromboplastin decreased
Coagulation factor decreased

- Coagulation factor IX level abnormal
- Coagulation factor IX level decreased
- Coagulation factor V level abnormal
- Coagulation factor V level decreased
- Coagulation factor VII level abnormal
- Coagulation factor VII level decreased
- Coagulation factor X level abnormal
- Coagulation factor X level decreased
- Hypocoagulable state
- Hypofibrinogenaemia
- Hypoprothrombinaemia
- Hypothrombinaemia
- Hypothromboplastinaemia
- International normalised ratio abnormal
- International normalised ratio increased
- Protein C decreased
- Protein S abnormal
- Protein S decreased
- Prothrombin level abnormal
- Prothrombin level decreased
- Prothrombin time abnormal
- Prothrombin time prolonged
- Prothrombin time ratio abnormal
- Prothrombin time ratio increased
- Thrombin time abnormal
- Thrombin time prolonged

Hepatic disorders specifically reported as alcohol-related (SMQ)

- Alcoholic liver disease
- Cirrhosis alcoholic
- Fatty liver alcoholic
- Hepatitis alcoholic
- Zieve syndrome

Liver infections (SMQ)

- Acute hepatitis B
- Acute hepatitis C
- Adenoviral hepatitis
- Asymptomatic viral hepatitis
- Chronic hepatitis B
- Chronic hepatitis C
- Congenital hepatitis B infection
- Cytomegalovirus hepatitis
- HBV-DNA polymerase increased
- Hepatic amoebiasis

Hepatic candidiasis
Hepatic cyst infection
Hepatic echinococciasis
Hepatic infection
Hepatic infection bacterial
Hepatic infection fungal
Hepatic infection helminthic
Hepatitis A
Hepatitis A antibody abnormal
Hepatitis A antibody positive
Hepatitis A antigen positive
Hepatitis A virus test positive
Hepatitis B
Hepatitis B antibody abnormal
Hepatitis B antibody positive
Hepatitis B core antibody positive
Hepatitis B core antigen positive
Hepatitis B DNA assay positive
Hepatitis B DNA increased
Hepatitis B e antibody positive
Hepatitis B e antigen positive
Hepatitis B surface antibody positive
Hepatitis B surface antigen positive
Hepatitis B virus test positive
Hepatitis C
Hepatitis C antibody positive
Hepatitis C RNA increased
Hepatitis C RNA positive
Hepatitis C virus test positive
Hepatitis D
Hepatitis D antibody positive
Hepatitis D antigen positive
Hepatitis D RNA positive
Hepatitis D virus test positive
Hepatitis E
Hepatitis E antibody abnormal
Hepatitis E antibody positive
Hepatitis E antigen positive
Hepatitis E virus test positive
Hepatitis F
Hepatitis G
Hepatitis H
Hepatitis infectious

- Hepatitis infectious mononucleosis
- Hepatitis mumps
- Hepatitis non-A non-B
- Hepatitis non-A non-B non-C
- Hepatitis post transfusion
- Hepatitis syphilitic
- Hepatitis toxoplasmal
- Hepatitis viral
- Hepatitis viral test positive
- Hepatobiliary infection
- Hepatosplenic candidiasis
- Herpes simplex hepatitis
- Liver abscess
- Schistosomiasis liver
- Viral hepatitis carrier
- Withdrawal hepatitis
- Gianotti-Crosti syndrome
- Portal pyaemia
- Weil's disease

Pregnancy-related hepatic disorders (SMQ)

- Acute fatty liver of pregnancy
- Cholestasis of pregnancy

10.2 Appendix 2: International Prostate Symptom Score - questionnaire

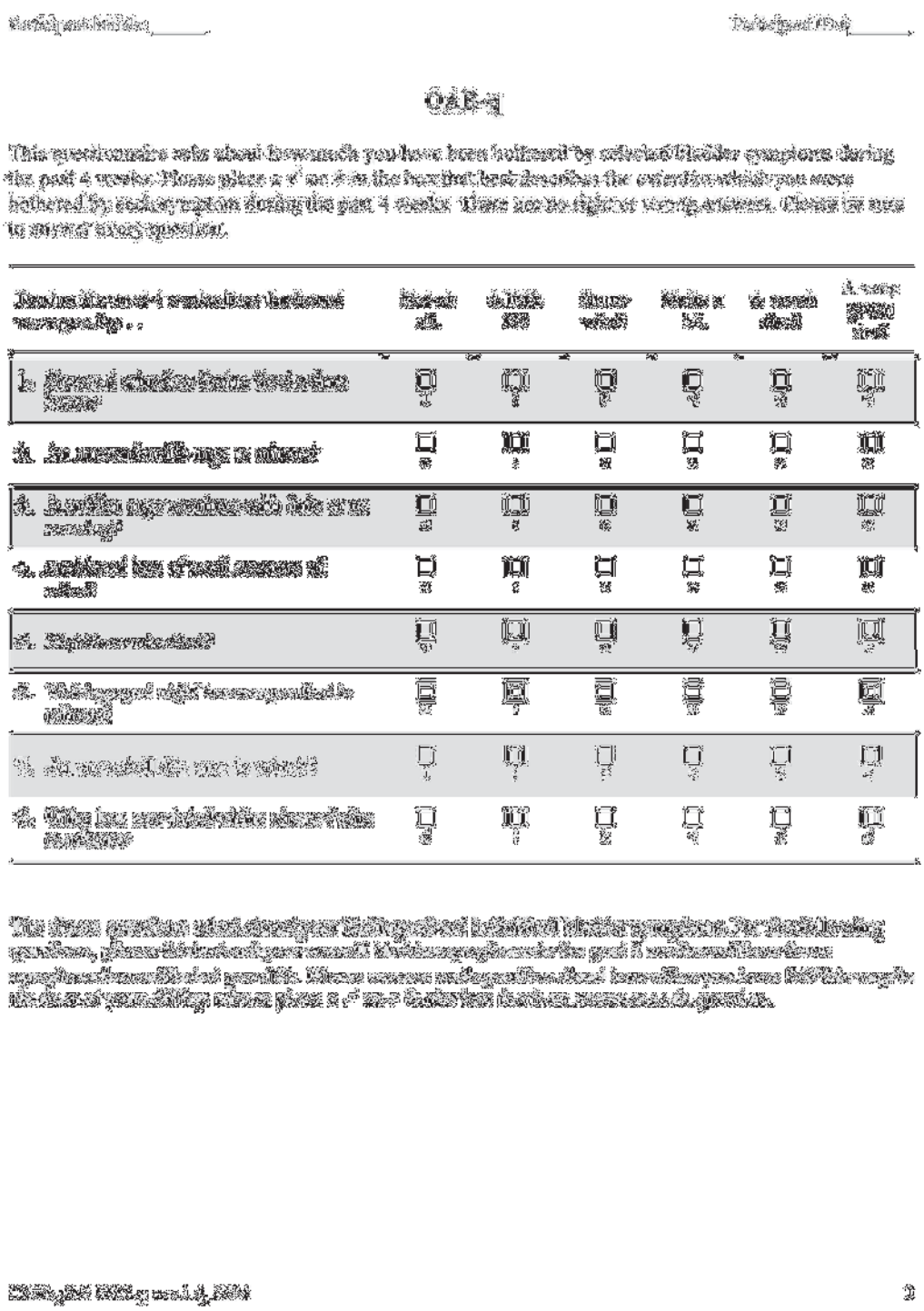
Patient Name: _____ Date of birth: _____ Date completed _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

10.3 Appendix 3: Overactive Bladder Questionnaire



[illegible] ______ [illegible] ______

During the past 4 weeks, how often have your bladder symptoms . . .	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						
[illegible]						

[illegible] 9

[illegible] [illegible]

During the past 4 weeks, how often have your bladder symptoms…	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
[illegible]	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐	☐

[illegible]

[illegible]

10.4 Appendix 4a: EQ-5D-5L Questionnaire

EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

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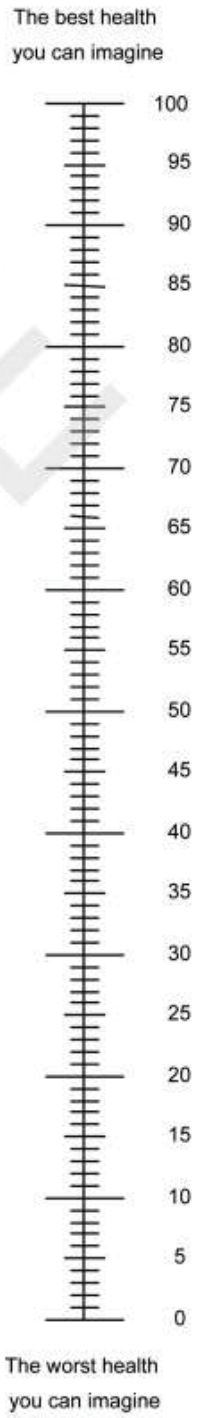
10.5 Appendix 4b: EQ-5D-5L – Visual analog scale

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



10.6 Appendix 5: Signatures