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

ISN/Protocol 178-MA-1008

ClinicalTrials.gov Identifier: NCT02757768

Date of Protocol Version 5.2: 22 Jan 2018

Sponsor: Astellas Pharma Global Development, Inc.

Medical Affairs, Americas
1 Astellas Way
Northbrook, IL 60062, USA

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

ISN/Protocol 178-MA-1008

Version 5.2

Incorporating Substantial Amendment 4 [See Attachment 1]

22 January 2018

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EudraCT 2015-004036-36

Sponsor:

Astellas Pharma Global Development, Inc.
Medical Affairs, Americas
1 Astellas Way
Northbrook, IL 60062

Investigator information is on file at Astellas.

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

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)

ISN/Protocol 178-MA-1008 / Version 5.2 / 22 January 2018

Required signatures (e.g. Protocol authors, Sponsor's reviewers and contributors, etc.) are located in **Section 14, Signatures**; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

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)

ISN/Protocol 178-MA-1008 / Version 5.2 / 22 January 2018

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-Investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

North America 24h-Contact for Serious Adverse Events (SAEs)	[redacted] MD [redacted] Astellas Pharma Global Development, Inc. Medical Affairs, Americas 1 Astellas Way Northbrook, IL 60062 USA [redacted]
24h-Contact for Serious Adverse Events (SAEs) reporting See Section 5.5.5	**Please fax the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Product Safety & Pharmacovigilance** [redacted]
Europe 24h Emergency contact	**ESMS 24/7 Medical Support and Emergency Unblinding Services** *Country* / *In Country Number* / *International Back Up Number* [redacted]
Medical Monitor/Medical Expert:	**United States:** [redacted] MD [redacted] Astellas Pharma Global Development, Inc. Medical Affairs, Americas 1 Astellas Way Northbrook, IL 60062 USA [redacted]

	Europe: [redacted]
Clinical Research Contacts:	[redacted] Astellas Pharma Global Development, Inc. Medical Affairs, Americas 1 Astellas Way Northbrook, IL 60062 USA [redacted]

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANCOVA	Analysis of Covariance
APGD	Astellas Pharma Global Development
AST	Aspartate Aminotransferase (GOT)
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the plasma concentration – from time zero to infinity
AUC_{tau}	Area under the plasma concentration – from time zero to tau
AUST	Astellas U.S. Technologies, Inc.
BOO	Bladder Outlet Obstruction
BP	Blood Pressure
BPH	Benign Prostatic Hyperplasia
Bpm	Beats per minute
BPO	Benign Prostatic Obstruction
BUN	Blood Urea Nitrogen
CA	Competent Authority
CBC	Complete Blood Count
Cfu	Colony Forming Unit
CI	Confidence Intervals
CRCL	Creatinine Clearance
C_{max}	Maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
CTD	Clinical Trial Directive
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DILI	Drug-induced Liver Injury
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome

Abbreviations	Description of abbreviations
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT/γ-GT	γ-Glutamyl Transpeptidase (GGT)
HBPM	Home Blood Pressure Monitoring
HCO_3	Bicarbonate
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Study Number
Kg	Kilogram
LA-CRF	Liver Abnormality - Case Report Form
LCE	Leukocyte Esterase
LFT	Liver Function Tests
LOCF	Last Observation Carried Forward
LS	Least Square
LSO	Last Subject Out
LUTS	Lower Urinary Tract Symptoms
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minutes
mL	Milliliter
mmHg	Millimeter of Mercury
msec	Millisecond
N/n	Number
NASH	Non-Alcoholic Steatohepatitis
NA	North America
NDA	New Drug Application
OAB	Overactive Bladder
OAB-q	Overactive Bladder – questionnaire
OCAS	Oral Controlled Absorption System
PBO	Placebo

Abbreviations	Description of abbreviations
PCS	Potentially Clinically Significant
PHI	Personal Health Information
PPBC	Patient Perception of Bladder Condition
PPIUS	Patient Perception of Intensity of Urgency Scale
PR	Pulse Rate
PRO	Patient Reported Outcomes
PTM	Placebo to Match
PTNS	Percutaneous Tibial Nerve Stimulation
PVR	Post-Void Residual Volume
QD	Once Daily
Q_{max}	Maximum urinary flow rate
QoL	Quality of Life
QT	Time interval between QRS complex to end of T wave
QTcF	Fridericia's Correction Formula
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SFL	Screen failure log
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reactions
$t_{½}$	Terminal Elimination Half-Life
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
TLF	Tables, Listings and Figures
TS-VAS	Treatment Satisfaction Visual Analog Scale
TUFS	Total Urgency and Frequency Score
ULN	Upper Limit of Normal
US	United States
UTI	Urinary Tract Infection
YM178	Mirabegron/Myrbetriq/Betmiga

Definition of Key Study Terms

Terms	Definition of terms
Adverse Event	An adverse event is any untoward medical occurrence in a subject 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 subject.
End of Study	The time of the last subject's last protocol-defined assessment.
Enrolled	A screened subject 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 subject goes to bed with the intention to sleep until the time the subject 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 subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Run-In Failure	Screened subject who did not fulfill protocol inclusion and/or exclusion criteria at Visit 2. Subjects who are considered a run-in failure cannot be re-screened into the study at a later date.
Screened	A subject who has signed informed consent and has performed the screening visit.
Screening Failure	Screened subject who did not fulfill protocol inclusion and/or exclusion criteria, or decided not to participate anymore (withdrew consent) prior to Visit 2. Subjects 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.

Terms	Definition of terms
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.
Subject Number	Number assigned to each subject 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.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	22 January 2018/Version 5.2
Sponsor: Astellas Pharma Global Development Inc. (APGD), Medical Affairs, Americas	**Protocol Number:** 178-MA-1008
Name of Study Drug: Mirabegron	**Phase of Development:** 4
Title of Study: 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)	
Planned Study Period: From 2Q2016 to 2Q2018	
Study Objective(s): Primary Objective: To study the efficacy of mirabegron versus placebo in men with OAB symptoms while taking tamsulosin hydrochloride for LUTS due to BPH. Secondary Objective: To assess safety and tolerability of mirabegron versus placebo in men with OAB symptoms while taking tamsulosin hydrochloride for LUTS due to BPH. Other Objectives: To assess patient reported outcomes (PROs) as measured by Symptom Bother and Total Health Related Quality of Life 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).	
Planned Total Number of Study Centers and Location(s): Approximately 100 centers North America and Europe	
Study Population: Men ≥40 years of age with OAB symptoms who take tamsulosin hydrochloride for LUTS due to BPH.	
Number of Subjects to be Enrolled / Randomized: Approximately 985 subjects will be screened to achieve 640 randomized and approximately 544 completed. Subjects will be randomized 1:1. 320 randomized to mirabegron; 320 randomized to placebo	

Study Design Overview:

This is a randomized, double-blind, placebo-controlled, parallel-group, multi-center study.

At Screening (Visit 1), subjects 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, subjects will complete a 3-day diary just prior to Baseline (Visit 2). Approximately 7 days prior to Visit 2 subjects will receive a phone call reminding them about the diary and to answer any questions.

A training diary will be completed in the first 2 weeks of the tamsulosin hydrochloride run-in period. During this evaluation period at least one telephone contact will take place with the subject. Diaries will be completed at home, using the electronic patient-reported outcome (ePRO) device, for 3 consecutive days prior to each visit: Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), and Week 12/End of Treatment (Visit 5). Site staff will contact the subject approximately 7 days prior to the scheduled visit to remind the subject that they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable).

If subjects meet all entry criteria at the end of the tamsulosin hydrochloride run-in period, subjects 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. Those subjects randomized to mirabegron will start at 25 mg and will increase to 50 mg after 4 weeks. Those subjects randomized to placebo 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. Once a subject has increased dose, he will remain on that dose for the remainder of the study unless for safety reasons he is required to discontinue study drug.

Three days before Visits 2 (Baseline), 3 (Week 4), 4 (Week 8), and 5 (Week 12), subjects 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 Home Blood Pressure Monitoring (HBPM). At Visit 1, International Prostate Symptom Score (IPSS) will be completed. At Visits 2, 3, 4, and 5, subjects will complete the IPSS, EQ-5D-5L, OAB-q, PPBC, and TS-VAS. Maximum urinary flow (Q_{max}) will be measured at Visit 1 (Screening/tamsulosin hydrochloride run-in) and Visit 5 (Week 12/End of Treatment). Post-void 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.

Inclusion:

Inclusion Criteria assessed at Visit 1 (Screening):

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) – approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Men ≥40 years of age with history of OAB symptoms (urinary frequency and urgency with or without incontinence) while taking tamsulosin hydrochloride 0.4 mg daily for at least 2 months to treat LUTS due to BPH.
3. Subject has symptoms of OAB (frequency of ≥8 micturitions per day and urgency episodes of ≥2 per day) for ≥3 months prior to Screening.
4. Subject has an IPSS score ≥8.

5. Subject has Prostate-Specific Antigen (PSA) <4 ng/mL OR PSA ≥4 but <10 ng/mL with a prostate biopsy that is negative for cancer in the past two years.
6. Subject is willing and able to complete the 3-day diary (including urine volumes, vital sign measurements), and Quality of Life questionnaires.
7. Subject and their spouses/partners who are of childbearing potential must be using a highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, placement of an IUD or IUS. Birth control must be practiced from Screening and continue throughout the study and for 30 days after the final study drug administration. In addition, sperm donation will not be allowed throughout the study and for 30 days after the final study drug administration.
8. Subject agrees not to participate in another interventional study while on treatment.

Inclusion Criteria assessed at Visit 2 (Baseline) based on the 3-day diary:

9. Subject continues to meet all inclusion criteria of Visit 1 (Screening).
10. Subject must experience an average of 8 or more micturitions per day over the 3-day diary period.
11. Subject must experience an average of 2 or more episodes of urgency per day (grade 3 or 4) over the 3-day diary period.

Waivers to the inclusion criteria will NOT be allowed.

Exclusion:

Exclusion Criteria assessed at Visit 1 (Screening):

1. Subject has PVR >200 mL.
2. Subject has Q_{max} <5.0 mL/second with a minimum voided volume of 125 mL.
3. Subject has hematuria >3 rbc/hpf that has not been fully evaluated.
4. Subject has evidence of Urinary Tract Infection (UTI). Urine culture and sensitivity will be performed for positive leukocytes, nitrites, or turbidity, or at the Investigator's discretion, and will be confirmed with a culture greater than 100,000 cfu/mL. If a subject has a UTI, at Screening (Visit 1) the subject may be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).
5. Subject has neurogenic bladder (spinal cord injury, multiple sclerosis, Parkinson's etc.).
6. Subject has diabetic neuropathy.
7. Previous open, robotic or minimally invasive prostate surgery (including transurethral procedures). Planned (scheduled) pelvic or prostate surgery during the study period.
8. Planned (scheduled) cataract or glaucoma surgery during the study period.
9. Subject with significant stress incontinence as determined by the Investigator.
10. Subject with clinically significant bladder outlet obstruction as determined by the Investigator.
11. Subject has an indwelling catheter or practices intermittent self-catheterization.
12. Subject has experienced 3 or more episodes of recurrent urinary tract infection within the last 12 months.
13. Subject has a symptomatic urinary tract infection, prostatitis, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs (i.e., within the confines of the pelvis including the bladder, prostate and rectum; organs of the lower gastrointestinal tract are not necessarily considered pelvic organs such as the distal ascending colon, the full transverse colon and proximal portion of the descending colon are in the abdomen).
14. Subject has received intravesical injection in the past 12 months with botulinum toxin, resiniferatoxin, or capsaicin.
15. Subject has ever received electro-stimulation therapy for OAB (e.g. sacral nerve stimulation or

Percutaneous Tibial Nerve Stimulation [PTNS]).

16. Subject began or has changed a bladder training program or pelvic floor exercises less than 30 days prior to Screening.
17. Subject has postural hypotension or syncope or postural orthostatic tachycardia.
18. Subject has moderate or severe hepatic impairment defined as Child-Pugh Class B or C.
19. Subject has severe renal impairment defined as estimated creatinine clearance less than 29 mL/min/1.73 m^2 as determined by central laboratory calculation of eGFR. A subject with End Stage Renal Disease (ESRD) or undergoing dialysis is also not a candidate for the study.
20. Subject has severe uncontrolled hypertension, which is defined as a sitting systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg.
21. Subject has baseline resting pulse rate <60 BPM or >90 BPM.
22. Subject has evidence of QT prolongation on Screening (Visit 1) or Baseline (Visit 2) electrocardiogram (ECG) defined as QTcF >450 msec.
23. Subject has any clinically significant ECG abnormality, as determined by the Investigator.
24. Subject has AST or ALT >2x upper limit of normal (ULN), or γ-GT >3x ULN and considered clinically significant by the Investigator.
25. Subject has a hypersensitivity to any components of mirabegron, tamsulosin hydrochloride, or any of the inactive ingredients.
26. Subject has a history of angioedema.
27. Subject has any clinically significant condition, which in the opinion of the Investigator makes the subject unsuitable for study participation.
28. Subject has been treated with an experimental device within 28 days or received an investigational agent within 28 days or 5 half-lives, whichever is longer, prior to Screening.
29. Subject has a concurrent malignancy or history of any malignancy (within the past 5 years), except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully.
30. Subject has ongoing alcohol and/or drug abuse.
31. Subject is using prohibited medications defined in Appendix 1, Part A within 30 days prior to Screening (Visit 1) through Follow-Up Phone Call (Visit 6).
32. Subject has stopped, started or changed the dose of a restricted medication (defined in Appendix 1, Part B) within 30 days prior to Screening (Visit 1) through Follow-Up Phone Call (Visit 6).
33. Subject has participated in an interventional trial within 30 days prior to Screening (Visit 1).
34. Subject is involved in the conduct of the study as an employee of the Astellas group, third party associated with the study, or the study site team.
35. Subject has previously received mirabegron in the 6 months prior to Screening (Visit 1).

Exclusion Criteria assessed at Visit 2 (Baseline):

36. Subject was non-compliant during the 4-week tamsulosin hydrochloride run-in period, defined as taking less than 80% or greater than 120% of study medication.
37. Subject had an average total daily urine volume >3000 mL as recorded in the 3-day diary.

Waivers to the exclusion criteria will NOT be allowed.

Test Drug Dose:

Mirabegron 25 mg QD for 4 weeks along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA). Mirabegron 25 mg dose will be titrated to mirabegron 50 mg QD at 4 weeks. Mirabegron 50 mg dose will be maintained for the remaining 8 weeks of the study along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA).

Mode of Administration:

Oral same time each day (with or without food).
Study protocol recommends taking at the same time daily as the tamsulosin hydrochloride capsule (US) / tablet (EU/CA). Tamsulosin hydrochloride should be taken 30 minutes following the same meal each day.

Reference Therapy Dose:

Placebo matched to mirabegron 25 mg QD for 4 weeks along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA).

Dose will be titrated to placebo matched to mirabegron 50 mg at 4 weeks.

Placebo matched to mirabegron 50 mg will be maintained for the remaining 8 weeks of the study along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA).

Mode of Administration:

Oral same time each day (with or without food).
Study protocol recommends taking at the same time daily as the tamsulosin hydrochloride capsule (US) / tablet (EU/CA). Tamsulosin hydrochloride should be taken 30 minutes following the same meal each day.

Drug(s) for Run-In Period:

Tamsulosin hydrochloride capsule (US) / tablet (EU/CA).

Dose:

0.4 mg QD.

Mode of Administration:

Oral taken each day approximately 30 minutes following the same meal.

Concomitant Medication Restrictions or Requirements:

Prohibited Medications (Appendix 1, Part A)

Medications prohibited between Screening/tamsulosin hydrochloride run-in (Visit 1) and Week 16/Follow-up phone call (Visit 6) include other alpha-adrenergic blockers , anticholinergics, antispasmodics, strong and moderate inhibitors of CYP2D6 with narrow therapeutic index, specifically thioridazine, flecainide, propafenone, amitriptyline, paroxetine, and terbinafine, and moderate and strong inhibitors of CYP3A4 (see *Appendix 1*, Part A). These medications must have been discontinued at least 30 days prior to Screening/tamsulosin hydrochloride run-in (Visit 1). Current or previous use of mirabegron within 6 months prior to Screening (Visit 1) is also prohibited.

Restricted medications (Appendix 1, Part B)

Medications restricted between Screening/tamsulosin hydrochloride run-in (Visit 1) and Follow-up Phone Call (Visit 6) include loop diuretics, 5-Alpha reductase inhibitors and PDE5 inhibitors (see *Appendix 1*, Part B). These medications are permitted provided the subject has been taking the medication on a long-term basis, i.e. has not stopped, or started, or changed dose within the 30 days prior to Screening/tamsulosin hydrochloride run-in (Visit 1), no new drug of the same class has been added to the regimen within the 30 days prior to Screening/tamsulosin hydrochloride run-in (Visit 1), and the subject remains on the medication at the same dose during the course of the study.

For 5-alpha reductase inhibitors the subject 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.

Restricted Non-Drug Therapy

Subjects participating in any behavioral modification therapy (i.e. pelvic floor exercises, Kegel exercises, biofeedback, timed voiding, etc.) or other nondrug therapy must have started the therapy within 30 days prior to Screening/tamsulosin hydrochloride run-in (Visit 1) and must continue the same schedule through Follow-Up Phone Call (Visit 6). Neurostimulation for OAB is a strict exclusion criterion.

Duration of Treatment:

Subjects will be randomized to 1 of 2 treatment groups in a 1:1 randomization (mirabegron or placebo) for a maximum of 12 weeks after a 4 week run-in period on tamsulosin hydrochloride. A Follow-up phone call (Visit 6) will be completed 4 weeks after Week 12/End of Treatment (Visit 5). Subject participation will last approximately 20 weeks.

Endpoints for Evaluation:

Primary:

- 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.

Secondary:

- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean volume voided per micturition.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean number of incontinence episodes per day (FAS-I).
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean number of urgency episodes (grade 3 and 4) per day.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in IPSS total score and subscales (Voiding, Storage, and Quality of Life).
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean number of urgency incontinence episodes per day (FAS-I).
- Change from Baseline (Visit 2) to End of Treatment (Visit 5) 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, and Week 12/End of Treatment (Visit 5) as assessed by EQ-5D-5L questionnaire.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in PPBC.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in Total Urgency and Frequency Score (TUFS) using PPIUS (Grade 3 or 4).
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean number of nocturia episodes per day.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in TS-VAS scores.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in the number of protective garments (e.g. absorbent pads, incontinence briefs, disposable underwear).

Exploratory:

- Performance of subgroup analyses by PSA cutoff scores for < 2, 2-4.

Safety Variables:

- Incidence and severity of treatment emergent adverse events (TEAEs) including AEs of special interest.
- Vital signs: sitting systolic and diastolic blood pressure and pulse rate (home blood pressure monitoring [HBPM] and office measurements).
- ECG parameters (heart rate, PR, RR, QRS, QT, QTcF intervals).
- Laboratory parameters (hematology, serum chemistry, including liver function tests, and urinalysis).
- PVR and Q_{max}.

Statistical Methods: ***See Section 7 STATISTICAL METHODOLOGY***

Sample size justification:

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.

A number of 272 evaluable subjects 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 of 2.7 for change from Baseline in micturitions was assumed.

If 85% of the randomized subjects are evaluable, 640 subjects should be randomized. With an expected drop-out rate of 35% by the end of the tamsulosin hydrochloride run-in phase (V2), 985 subjects need to be screened.

Safety:

Safety analyses will be done on the Safety Analysis Set (SAF), which consists of subjects who received at least one dose of double-blind medication. Treatment emergent adverse events will be coded using the MedDRA dictionary and will be summarized by treatment group. The number and percentage of treatment-emergent AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class, preferred term and treatment group. Laboratory variables (biochemistry, hematology, and urinalysis) will be descriptively summarized for Baseline (Visit 2), Week 4, Week 8, and Week 12/End of Treatment and change from Screening to End of Treatment will be summarized by treatment group. Vital sign changes will be summarized by treatment group. Categorical changes in vital signs will also be examined. In addition, post-void residual volumes as measured by bladder sonography and Q_{max} will be summarized by change from baseline. Centrally assessed ECGs will also be summarized by treatment group.

Interim analyses:

Not applicable.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

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

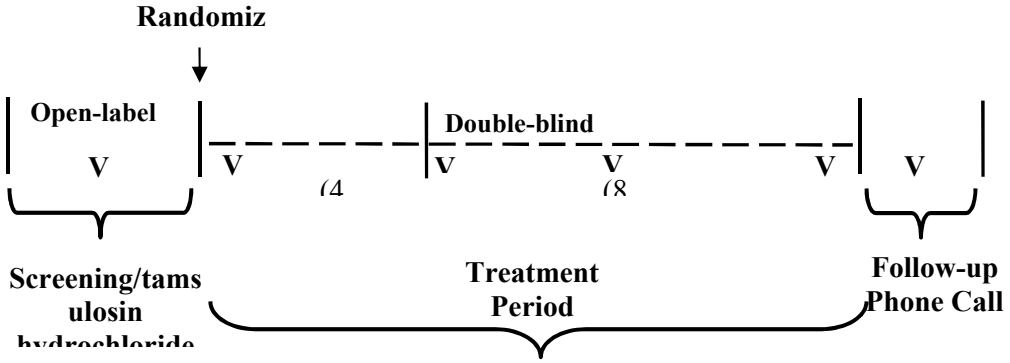

Table 1 Schedule of Assessments

	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 Subject on 3-day Diary [l]	X	X	X	X		
Subject 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

	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
OAB-q		X	X	X	X	
PPBC		X	X	X	X	
PPIUS		X	X	X	X	
TS-VAS		X	X	X	X	
Review Subject 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 subject, 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. Subjects 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 subject has a UTI (defined as > 100,000 CFU), the subject 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 subject 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 subject care.

h. Q_{max} can be completed within two weeks of Screening (Visit 1). The subject 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 subjects 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.

Footnotes continued on next page

l. At the Screening/tamsulosin hydrochloride run-in (Visit 1), all subjects 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, sleep interruption, and protective garments. 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 subjects will receive a phone call reminding them about the diary and to answer any questions. Subjects 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, subjects 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 subject's diary with the subject to ensure completion compliance and discuss data captured.

1 INTRODUCTION

1.1 Background

Overactive bladder (OAB) syndrome is a highly prevalent medical condition. The prevalence of OAB is estimated to be 34 million in the US and 22 million in Europe [Irwin et al, 2009; Kim et al, 2006; Stewart et al, 2003; Milsom et al, 2001]. International Continence Society (ICS) defines OAB as urgency, with or without urge incontinence, usually with frequency and nocturia [Abrams et al, 2003; Lee and Lee, 2014]. Prevalence of OAB symptoms increases with age, and the prevalence of OAB wet (with incontinence) is greater in women than in men [Jaffe and Te, 2005]. In clinical practice, it is recognized that men may experience OAB symptoms concurrent with those of benign prostatic hyperplasia (BPH).

BPH is a condition affecting over 50% of men by age 60 [Bechis et al, 2014]. It is also a common cause of lower urinary tract symptoms (LUTS) such as frequent urination, urgency, nocturia, and the sensation of incomplete bladder emptying [Miller and Tarter, 2009]. In 2008, an estimated 917 million men worldwide were affected by LUTS from BPH [Irwin et al, 2011]. LUTS can be divided into storage and voiding symptoms, with BPH predominantly associated with voiding LUTS symptoms. Patients with voiding symptoms may also have concomitant storage symptoms. Analysis of the general population identified that the combination of storage and voiding LUTS was the most common type of LUTS, affecting 8.9% of the general population sample in a multinational, population-based study (EPIC) [Irwin et al, 2009; Irwin et al, 2006].

Alpha-blockers, such as tamsulosin hydrochloride, are commonly prescribed to manage BPH symptoms but may fail to alleviate storage (OAB) symptoms [Lee and Lee, 2014]. Thus, the American Urological Association (AUA) has identified combination therapy with an α-blocker and anticholinergic as a potential treatment option for patients with BPH and coexisting OAB symptoms [AUA Guidelines, 2010].

The use of antimuscarinics (e.g., tolterodine and solifenancin) as add-on therapy to alpha-blockers such as tamsulosin hydrochloride has been evaluated in a number of clinical studies in men with OAB and BPH [ADAM study by Chapple et al, 2009; VICTOR study by Kaplan et al, 2009; TIME study by Kaplan et al, 2006]. Evaluated add-on therapies were generally found to be well-tolerated and showed an added benefit over alpha-blocker monotherapy in improving OAB-related symptoms.

Mirabegron (Myrbetriq®/Betmiga®) is a potent and selective human beta-3 adrenergic receptor agonist approved for the treatment of OAB with symptoms of urge, urinary incontinence, urgency and urinary frequency [Mirabegron US Package Insert, 2015 and Myrbetriq Canadian Monograph, March 2015, EU SmPC, 2015]. For the mirabegron monotherapy clinical development program, 32 phase 1 studies and 13 phase 2 and 3 studies (10 in patients with OAB, 1 in patients with LUTS/bladder outlet obstruction (BOO) and 2 in patients with type 2 diabetes mellitus) were conducted. Several global phase 3 studies have demonstrated the efficacy, safety and tolerability of once daily mirabegron in patients with OAB. In these clinical trials, the incidence of urinary retention did not increase with

mirabegron, and it was lower than that of placebo and the active control antimuscarinic [Nitti et al, 2013]. In a phase 2 study of 200 men with LUTS and BOO, mirabegron was also found to be safe and generally well-tolerated, with no adverse effects on either the detrusor pressure at maximum flow rate or on the maximum flow rate [Study 178-CL-060].

The use of the beta-3 adrenergic agonist mirabegron to treat OAB symptoms as add-on therapy to tamsulosin hydrochloride will be evaluated for efficacy, safety, and tolerability of the combination therapy. It is anticipated from previous studies of add-on therapies, the combination of mirabegron and tamsulosin hydrochloride will show an added benefit over α-blocker monotherapy in improving OAB-related symptoms.

1.2 Summary of Non-clinical and Clinical Data

Detailed information on the non-clinical studies conducted with mirabegron and tamsulosin hydrochloride can be found in the approved product labeling, Summary of Product Characteristics (SmPC) and US Package Insert for mirabegron and tamsulosin hydrochloride, copies of which will be made available to the Investigator, Institutional Review Boards [IRB], Independent Ethics Committees [IEC] and other bodies as appropriate. Summaries of findings from non-clinical and clinical studies with mirabegron and tamsulosin hydrochloride which may have relevance for the current study are listed below.

1.2.1 Mirabegron (YM178)

Mirabegron was approved for the treatment of OAB in adults in Japan in 2011 and in the US, Canada and Europe in 2012. Mirabegron is a selective human beta-3 adrenergic agonist and the first of a new class of compounds with a different mode of action from the current standard of care, muscarinic receptor antagonists, in the treatment of patients with OAB. Antimuscarinics and mirabegron both reduce micturition frequency and incontinence. Data from the phase 2 study 178-CL-100 showed that mirabegron has a similar effect size to antimuscarinics. Consistent with the Phase 2 data, one phase 3b comparative trial (178-EC-001) between mirabegron and solifenacin in patients dissatisfied with their previous antimuscarinic showed that the two drugs had similar effect sizes for micturition frequency and incontinence.

1.2.1.1 Summary of Non-clinical Studies of Mirabegron

Mirabegron is a potent and selective agonist of the human beta-3 adrenergic receptor. Mirabegron has low intrinsic activity for human beta-1 and beta-2 adrenergic receptors. Mirabegron has no significant affinity for other pharmacological targets in a comprehensive test battery of receptors, ion channels and enzymes. Mirabegron directly relaxes human bladder in vitro through activation of beta-3 adrenergic receptors. Studies in conscious and anesthetized rat models of bladder function demonstrate modulation consistent with a beneficial profile in OAB patients.

Increases in heart rate have been observed following mirabegron administration to rats, dogs, and monkeys. Decreases in blood pressure were observed in dogs but not in rats or monkeys. Assessment of the potential for mirabegron to delay cardiac repolarization demonstrated that mirabegron and its most abundant human metabolites were free from effects on cardiac

repolarization in isolated dog Purkinje fibers and guinea pig papillary muscles. Furthermore, in isolated perfused dog ventricular tissue neither mirabegron nor its metabolites induced electrophysiological changes. Mirabegron and its five most abundant human metabolites did not significantly alter the IKr (hERG), IKs (hKvLOT1/mink), Ito (hKv4.3/KChip2.2), Ina (hNAV1.5), or Ica (hCav 1.2) conductance in in vitro studies at relevant concentrations (>100-fold human C_{max}) at a 100 mg dose.

Single and repeat dose toxicology studies in dogs, monkeys, and rats demonstrate cardiovascular changes at high doses. In a 13-week rat toxicology study, significant increases in plasma alanine aminotransferase (ALT) were observed at doses of 30 mg/kg and higher (22-fold higher than maximum recommended human dose). Modest (less than 2-fold) increases in alkaline phosphatase (ALP) and aspartate aminotransferase (AST) were observed at high doses (72-fold higher than the maximum recommended human dose), together with reversible changes in hepatocytes. Modest elevation of ALT was also observed in monkeys but the changes observed were deemed to be below the level of toxicological significance and there were no changes in liver histopathology. There were no significant changes in liver enzymes or liver histopathology in dogs. Mirabegron was not genotoxic, carcinogenic, or teratogenic in the battery of conventional in vitro and in vivo studies.

1.2.1.2 Summary of the Pharmacokinetics of Mirabegron

After oral administration of mirabegron in healthy volunteers, peak mirabegron plasma concentrations were attained between 3 to 5 hours. The absolute bioavailability increases from 29% at a dose of 25 mg to 45% at a dose of 150 mg under fasted conditions in healthy volunteers. Mean C_{max} and AUC_{inf} increased more than dose proportionality over the recommended dose range. Steady state concentrations were achieved within 7 days of once daily dosing with mirabegron. The C_{max} and AUC_{tau} of mirabegron and its metabolites following multiple oral doses in older adult subjects (≥65 years) were similar in those in younger subjects (18 to 45 years). The C_{max} and AUC_{tau} of mirabegron were approximately 40-60% higher in females than in males. The mean terminal $t_{½}$ is comparable in both sexes. Evaluation of special populations in the phase 1 studies demonstrated that volunteers with severe renal impairment (CrCL 15 to 29 mL/min or eGFR 15 to 29 mL/min per 1.73 m^2) or moderate hepatic impairment (Child-Pugh Class B) had an approximately 2-fold increase in exposure to mirabegron relative to normal healthy volunteers.

The in vitro oxidative metabolism of mirabegron in human liver microsomes is primarily mediated by cytochrome P450 (CYP) 3A4, but a possible role for CYP2D6 could not be excluded. In vitro CYP inhibition studies suggest that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A4.

1.2.1.3 Summary of Clinical Data with Mirabegron

The clinical development program consists of 48 completed clinical studies to date over approximately 10 years and is comprised of 13,640 subjects (1,909 volunteers and 11,731 patients) including patients with OAB, type 2 diabetes mellitus, and lower urinary tract symptoms (LUTS)/bladder outlet obstruction (BOO). A total of 34 phase 1 studies and

14 phase 2 and 3 studies (11 in patients with OAB, 1 in patients with LUTS/BOO and 2 in patients with type 2 diabetes mellitus) have been conducted globally.

Mirabegron has been studied across the dose range of 25 mg to 200 mg once daily in OAB patients. Mirabegron 25 mg, 50 mg, and 100 mg demonstrated statistical superiority compared to placebo for the co-primary endpoints of incontinence episodes and micturition frequency. Both the 50 mg and 100 mg doses also demonstrated superiority compared to placebo for almost all key secondary endpoints defined in the phase 3 program.

Evaluation of the combined safety data from the mirabegron clinical program to date shows mirabegron to be safe and well tolerated. The incidence of Treatment Emergent Adverse Events (TEAEs) in the active treatment group is comparable with the incidence in the placebo group. The most frequently reported TEAE was hypertension which includes reports of blood pressure above the normal range, and BP increased from baseline, occurring predominantly in subjects with baseline hypertension. Most commonly reported adverse reactions (>2% and >placebo) were hypertension, nasopharyngitis, urinary tract infection and headache. Most of the events were mild or moderate in intensity. Other adverse reactions occurring at greater than 1% and greater than placebo include constipation, upper respiratory infection, arthralgia, diarrhea, tachycardia, abdominal pain and fatigue (Table 2). The number of serious TEAEs is low and comparable across mirabegron and placebo treatment groups.

Table 2 Percentage of Patients with Adverse Reactions, Derived from All Adverse Events, Exceeding Placebo Rate and Reported by 1% or More Patients Treated With MYRBETRIQ® 25 mg or 50 mg Once Daily

	Placebo (%)	**MYRBETRIQ® 25 mg (%)**	**MYRBETRIQ® 50 mg (%)**
Number of Patients	1380	432	1375
Hypertension*	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1	1.4	1.2

* Includes reports of blood pressure above the normal range, and BP increased from baseline, occurring predominantly in subjects with baseline hypertension.

In the US Package Insert, mirabegron is contraindicated in patients with hypersensitivity reactions. It has warnings and precautions for increases in blood pressure, angioedema, urinary retention in patients with bladder outlet obstruction, and in patients taking drugs metabolized by CYP2D6.

In the Canadian Monograph, mirabegron is contraindicated in patients with severe uncontrolled hypertension, patients who are pregnant, and patients who are hypersensitive to mirabegron or to any ingredient in the formulation or component of the container. Mirabegron has warnings and precautions for neoplasm, Stevens-Johnson syndrome, increases in serum ALT/AST and bilirubin, QTc prolongation, increases in blood pressure and heart rate, urinary retention, and in patients taking drugs metabolized by CYP2D6. The monograph does not recommend use of mirabegron in patients with severe hepatic impairment, end stage renal disease, pregnant and nursing women, and pediatric patients (<18 years of age).

In the EU Summary of Product Characteristics (EU SmPC), mirabegron is contraindicated in patients with hypersensitivity reactions and for those with uncontrolled hypertension (SBP > 180, or DBP > 110). It has warnings and precautions for increases in blood pressure, QTc prolongation, and urinary retention in patients with bladder outlet obstruction. It recommends not to use in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) or end stage renal disease.

For further information, please refer to the full prescribing information for mirabegron [Mirabegron US Package Insert, 2015 and Myrbetriq Canadian Monograph, March 2015, EU SmPC, 2015].

1.2.2 Tamsulosin Hydrochloride

Tamsulosin hydrochloride was registered in Japan in 1993, in the European Community in 1995 and in the USA in 1997. In the US, tamsulosin hydrochloride is indicated for treatment of the signs and symptoms of BPH and in the EU, for lower urinary tract symptoms (LUTS) associated with BPH. Since the launch of tamsulosin hydrochloride, a worldwide exposure of more than 24 million patient years has demonstrated that tamsulosin hydrochloride is effective and safe in the treatment of LUTS associated with BPH. The most common adverse event is dizziness and weakness. Intra-operative Floppy Iris syndrome during cataract and glaucoma surgery has been associated with tamsulosin hydrochloride use. The initiation of tamsulosin hydrochloride in patients with scheduled cataract or glaucoma surgery is not recommended (see US Package Insert, 2014 and EU SmPC, 2013).

1.2.2.1 Summary of Non-clinical Studies of Tamsulosin Hydrochloride

Tamsulosin hydrochloride is an antagonist of alpha$_{1A}$ adrenoceptors in the prostate. The symptoms associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic

component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of alpha$_1$ adrenoceptors. Antagonism of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH.

Tamsulosin hydrochloride, an alpha$_1$ adrenoceptor blocking agent, exhibits selectivity for alpha$_1$ receptors in the human prostate. At least three discrete alpha$_1$ adrenoceptor subtypes have been identified: alpha$_{1A}$, alpha$_{1B}$, and alpha$_{1D}$; their distribution differs between human organs and tissue. Approximately 70% of the alpha$_1$ receptors in the human prostate are of the alpha$_{1A}$ subtype.

1.2.2.2 Summary of the Pharmacokinetics of Tamsulosin Hydrochloride

The pharmacokinetics of tamsulosin hydrochloride have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 mg to 1 mg. Absorption of tamsulosin hydrochloride from capsules of 0.4 mg is essentially complete (90%) following oral administration under fasting conditions. Tamsulosin hydrochloride exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of a once-a-day dosing. The time to maximum concentration (T_{max}) is reached by 4 to 5 hours under fasting conditions and by 6 to 7 hours when administered with food. Taking capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions.

Tamsulosin hydrochloride is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. In vitro results indicate the CYP3A4 and CYP2D6 are involved in the metabolism of tamsulosin hydrochloride as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic drug-metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride.

1.2.2.3 Summary of Clinical Data with Tamsulosin Hydrochloride

Four placebo-controlled clinical studies and one active-controlled clinical study enrolled a total of 2296 patients (1003 received 0.4 mg capsules tamsulosin hydrochloride once daily, 491 received 0.8 mg capsules tamsulosin hydrochloride once daily, and 802 were control patients) in the US and Europe.

In the two US placebo-controlled, double-blind, 13-week, multi-center studies [Study 1 (US92-03A) and Study 2 (US93-01)], 1486 men with the signs and symptoms of BPH were enrolled. In both studies, patients were randomized to either placebo, tamsulosin hydrochloride capsules 0.4 mg once daily, or tamsulosin hydrochloride capsules 0.8 mg once daily. Patients in tamsulosin hydrochloride capsules 0.8 mg once daily treatment groups received a dose of 0.4 mg once daily for one week before increasing to the 0.8 mg once daily dose. The primary efficacy assessments included: 1) total American Urological Association

(AUA) Symptom Score questionnaire, which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms, where a decrease in score is consistent with improvement in symptoms; and 2) peak urine flow rate, where an increased peak urine flow rate value over baseline is consistent with decrease urinary obstruction.

Mean total AUA Symptom Scores for both tamsulosin hydrochloride capsules 0.4 mg and 0.8 mg once daily groups showed a rapid decrease starting at one week after dosing and remained decreased through 13 weeks in both studies.

For further information, please refer to the full prescribing information for tamsulosin hydrochloride [Flomax® (tamsulosin hydrochloride) Capsules, 0.4 mg US Package Insert, 2014, Flomax Relief® MR, 2014, and Tamsulosin hydrochloride, EU SmPC, 2013].

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Summary of Key Safety Information for Mirabegron

Mirabegron was first approved in Japan on 1 July 2011, and was launched to market on 16 September 2011 under the trade name Betanis®. On 28 June 2012, mirabegron received approval in the United States (trade name: Myrbetriq®). The approved indication is the treatment of OAB with symptoms of urinary incontinence, urgency, and urinary frequency. On 20 December 2012, mirabegron received marketing approval in the EU under the trade name Betmiga®. On 6 March 2013, mirabegron received approval in Canada (trade name: Myrbetriq®). As of September 3, 2015, mirabegron has regulatory approval in 58 countries.

The safety of mirabegron treatment has been well characterized in 5,863 subjects in the phase 2/3 studies, including 5,648 subjects with OAB, treated with mirabegron at doses ranging from 25 to 200 mg once daily. Of the 5,648 subjects with OAB who received mirabegron, 1,572 subjects received mirabegron continuously for at least 6 months, 1,482 subjects for at least 9 months, and 622 for at least 1 year.

Important potential risks include QT prolongation with supratherapeutic doses or in high-risk populations, increased heart rate, increased blood pressure, non-immediate cutaneous hypersensitivity reactions and exposure in utero. The potential risks of QT prolongation, increased heart rate, or increased blood pressure are greater with increasing exposure. The expected adverse drug reactions for mirabegron are presented in Table 2. The approved therapeutic dose of mirabegron in the United States and Canada is 25 mg once daily which may be increased to 50 mg once daily based on individual patient efficacy and tolerability [Mirabegron US Package Insert, 2015 and Myrbetriq Canadian Monograph, March 2015]. In the EU the approved starting dose of mirabegron is 50 mg once daily [EU SmPC, 2015]. The favorable benefit risk profile of mirabegron is not expected to change over time.

A mean increase of approximately 1 bpm for pulse rate was observed in OAB patients who received mirabegron 50 mg. This magnitude of change was similar for both 12-week and long-term studies, for men and women, and in both the mirabegron and tolterodine (active control) treatment groups. In patients with OAB, categorical increases in pulse rate were noted more frequently with mirabegron and tolterodine than with placebo, with similar

changes observed for mirabegron 50 mg and tolterodine. Pulse increases were more pronounced in young subjects in comparison to older adults (age 55 years and greater) subjects. Changes in pulse were reversible upon discontinuation of treatment.

An approximate mean increase in 1 mmHg from baseline for SBP/DBP was observed in OAB patients who received mirabegron 50 mg compared with placebo. This magnitude of change was similar for both 12-week and long-term studies, for men and women, and in both the mirabegron and tolterodine treatment groups. TEAE and SAE related to hypertension were similar for mirabegron 50 mg, placebo, and tolterodine in the 12-week studies, and were similar for mirabegron and tolterodine in the long-term study. Blood pressure increases were more pronounced in young subjects in comparison to older adult (age 55 years and greater) subjects. Changes in blood pressure were reversible upon discontinuation of treatment. Please refer to the product insert for expected adverse drug reactions (ADR).

Detailed information on the clinical safety profile for mirabegron can be found in the full prescribing information [Mirabegron US Package Insert, 2015, Myrbetriq Canadian Monograph, March 2015, and EU SmPC, 2015].

According to current package inserts, no dose adjustment is necessary for older adult patients. The pharmacokinetics of mirabegron is not significantly influenced by age. The C_{max} and AUC of mirabegron following multiple oral doses in older adult volunteers (≥ 65 years) were similar to those in younger volunteers (18 to 45 years). Of 5,648 patients who received mirabegron in the phase 2 and 3 studies, 2,029 (35.9%) were 65 years of age or older, and 557 (9.9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in the studies [Mirabegron US Package Insert, 2015 and Myrbetriq Canadian Monograph, March 2015, EU SmPC, 2015].

1.3.2 Summary of Key Safety Information for Tamsulosin Hydrochloride

In the phase 3 trials (178-CL-046, 178-CL-047, 178-CL-074), 308 men were on tamsulosin hydrochloride across treatment groups. There were no differences in rates of hypertension or elevated heart rate between men on and off tamsulosin hydrochloride.

1.3.3 Summary of Key Safety Information for Combination of Mirabegron and Tamsulosin Hydrochloride

Study 178-CL-080 was an open-label, 2-treatment arm, 2-sequence study to investigate the cardiovascular (CV) interactions between mirabegron (100 mg) and tamsulosin hydrochloride (0.4 mg as a single dose) in healthy male volunteers. Under the conditions of the study, the CV results suggest there is no clinically relevant pharmacodynamic interaction between tamsulosin hydrochloride and mirabegron. Combination treatment of mirabegron and tamsulosin hydrochloride did not appear to affect the safety profiles of either drug. In this interaction study, there were no serious adverse events and no events of syncope in either treatment arm.

In Japanese men with OAB induced by benign prostatic obstruction, addition of mirabegron to tamsulosin hydrochloride was shown to be more effective for ameliorating storage symptoms compared to tamsulosin hydrochloride monotherapy [Ichihara et al, 2014].

1.4 Risk-Benefit Assessment

Subjects randomized to placebo treatment are unlikely to benefit from the study beyond the benefits they receive from tamsulosin hydrochloride alone. However, OAB is not a life-threatening disease and it is not expected that a 12-week exposure to placebo treatment will have a negative impact on disease progress, given that subjects will have been on tamsulosin hydrochloride prior to study entry and it will be continued. Subjects receiving mirabegron are likely to benefit from at least a partial relief of symptoms during the study.

There is extensive clinical experience with tamsulosin hydrochloride monotherapy in the treatment of BPH. Clinical equipoise is maintained in the study because an alpha blocker is considered standard treatment of men with BPH and because the subjects are continuing on their usual prescribed dose as opposed to being placed on a tamsulosin hydrochloride placebo.

Mirabegron has a distinct mechanism of action (beta-3 adrenergic agonist) compared with the current standard of care, primarily antimuscarinics, for the treatment of symptoms of OAB. Antimuscarinics have been studied concomitantly with alpha blockers and appear to be efficacious without added risk. Muscarinic antagonists and beta-3 adrenergic agonists modulate bladder function through distinct molecular pathways. Thus concomitant use of tamsulosin hydrochloride and mirabegron offers the possibility of enhancing efficacy in the treatment of men with BPH who have co-existing OAB.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

The primary objective is to study the efficacy of mirabegron versus placebo in men with OAB symptoms while taking tamsulosin hydrochloride for LUTS due to BPH.

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

Other objectives are to assess patient reported outcomes (PROs) as measured by Symptom Bother and Total Health Related Quality of Life 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).

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multi-center study. Approximately 985 subjects will be enrolled at up to 100 study centers in North America and Europe.

At Screening (Visit 1), subjects 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, subjects will complete a 3-day diary just prior to Baseline (Visit 2). Approximately 7 days prior to Visit 2 subjects will receive a phone call reminding them about the diary and to answer any questions.

A training diary will be completed in the first 2 weeks of the tamsulosin hydrochloride run-in period. During this evaluation period at least one telephone contact will take place with the subject. Diaries will be completed at home, using the electronic patient-reported outcome (ePRO) device, for 3 consecutive days prior to each visit: Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), and Week 12/End of Treatment (Visit 5). Site staff will contact the subject approximately 7 days prior to the scheduled visit to remind the subject that they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable).

If subjects meet all entry criteria at the end of the tamsulosin hydrochloride run-in period, subjects 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. Those subjects randomized to mirabegron will start at 25 mg and will increase to 50 mg after 4 weeks. Those subjects randomized to placebo 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. Once a subject has increased dose, he will remain on that dose for the remainder of the study unless for safety reasons he is required to discontinue study drug.

Three days before Visits 2 (Baseline), 3 (Week 4), 4 (Week 8), and 5 (Week 12), subjects 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, subjects will complete the IPSS, EQ-5D-5L, OAB-q, PPBC, and TS-VAS. Maximum urinary flow (Q_{max}) will be measured at Visit 1 (Screening/tamsulosin hydrochloride run-in) and Visit 5 (Week 12/End of Treatment). Post-void 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.

2.2.2 Dose Rationale

The approved dose in the treatment of overactive bladder in the United States and Canada is mirabegron 25 mg daily, which may be increased to 50 mg daily based on individual efficacy and tolerability [Mirabegron US Package Insert, 2015 and Myrbetriq Canadian Monograph, March 2013]. The recommended dose of mirabegron in the European SmPC is 50 mg [EU SmPC, 2015]. The dosing regimen for the study is starting with mirabegron 25 mg with an obligatory increase to mirabegron 50 mg after 4 weeks of treatment which is intended to reflect a pragmatic and clinically plausible regimen. The treatment effect size at Week 4 in the phase 3a program approaches the maximum treatment response for incontinence and micturition.

2.3 Endpoints

2.3.1 Primary Endpoints

The primary endpoint is:

- 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.

2.3.2 Secondary Endpoints

The secondary endpoints are:

- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean volume voided per micturition.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean number of incontinence episodes per day (FAS-I).
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean number of urgency episodes (grade 3 and 4) per day.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in IPSS total score and subscales (Voiding, Storage, and Quality of Life).
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean number of urgency incontinence episodes per day (FAS-I).
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) 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, and Week 12/End of Treatment (Visit 5) as assessed by EQ-5D-5L questionnaire.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in PPBC.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in Total Urgency and Frequency Score (TUFS) using PPIUS (Grade 3 or 4).
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in mean number of nocturia episodes per day.

- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in TS-VAS scores.
- Change from Baseline (Visit 2) to Week 4, Week 8, and Week 12/End of Treatment (Visit 5) in the number of protective garments (e.g. absorbent pads, incontinence briefs, disposable underwear).

2.3.3 Exploratory Endpoint

The exploratory endpoint is:

- Performance of subgroup analyses by PSA cutoff scores for < 2, 2-4.

2.3.4 Safety Variables

The safety variables are:

- Incidence and severity of treatment emergent adverse events (TEAEs) including AEs of special interest (see Section 5.4.3.2).
- Vital signs: sitting systolic and diastolic blood pressure and pulse rate (home blood pressure monitoring [HBPM] and office measurements).
- ECG parameters (heart rate, PR, RR, QRS, QT, QTcF intervals).
- Laboratory parameters (hematology, serum chemistry, including liver function tests, and urinalysis).
- Change in PVR and Qmax.

3 STUDY POPULATION

3.1 Selection of Study Population

The study will enroll men at least 40 years of age who have symptoms of overactive bladder while taking the α-blocker tamsulosin hydrochloride for Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH). Six hundred forty (640) subjects will be randomized to 1 of 2 treatment groups in a 1:1 randomization (mirabegron or placebo); 320 randomized to mirabegron; 320 randomized to placebo.

3.2 Inclusion Criteria

Inclusion Criteria assessed at Visit 1 (Screening).

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Men ≥40 years of age with history of OAB symptoms (urinary frequency and urgency with or without incontinence) while taking tamsulosin hydrochloride 0.4 mg daily for at least 2 months to treat LUTS due to BPH.

3. Subject has symptoms of OAB (frequency of ≥8 micturitions per day and urgency episodes of ≥2 per day) for ≥3 months prior to Screening.
4. Subject has an IPSS score ≥8.
5. Subject has Prostate-Specific Antigen (PSA) < 4 ng/mL OR PSA ≥4 but <10 ng/mL with a prostate biopsy that is negative for cancer in the past two years.
6. Subject is willing and able to complete the 3-day diary (including urine volumes, vital sign measurements), and Quality of Life questionnaires.
7. Subject and their spouses/partners who are of childbearing potential must be using a highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, placement of an IUD or IUS. Birth control must be practiced from Screening and continue throughout the study and for 30 days after the final study drug administration. In addition, sperm donation will not be allowed throughout the study and for 30 days after the final study drug administration.
8. Subject agrees not to participate in another interventional study while on treatment.

Inclusion Criteria assessed at Visit 2 (Baseline) based on the 3-day diary:

9. Subject continues to meet all inclusion criteria of Visit 1 (Screening).
10. Subject must experience an average of 8 or more micturitions per day over the 3-day diary period.
11. Subject must experience an average of 2 or more episodes of urgency per day (grade 3 or 4) over the 3-day diary period.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Exclusion Criteria assessed at Visit 1 (Screening).

Subject will be excluded from participation if any of the following apply:

1. Subject has PVR >200 mL.
2. Subject has Q_{max} <5.0 mL/second with a minimum voided volume of 125 mL.
3. Subject has hematuria >3 rbc/hpf that has not been fully evaluated.
4. Subject has evidence of Urinary Tract Infection (UTI). Urine culture and sensitivity will be performed for positive leukocytes, nitrites, or turbidity, or at the Investigator's discretion, and will be confirmed with a culture greater than 100,000 cfu/mL. If a subject has a UTI, at Screening (Visit 1) the subject may be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).
5. Subject has neurogenic bladder (spinal cord injury, multiple sclerosis, Parkinson's etc.).
6. Subject has diabetic neuropathy.

7. Previous open, robotic or minimally invasive prostate surgery (including transurethral procedures). Planned (scheduled) pelvic or prostate surgery planned during the study period.
8. Planned (scheduled) cataract or glaucoma surgery during the study period.
9. Subject with significant stress incontinence as determined by the Investigator.
10. Subject with clinically significant bladder outlet obstruction as determined by the Investigator.
11. Subject has an indwelling catheter or practices intermittent self-catheterization.
12. Subject has experienced 3 or more episodes of recurrent urinary tract infection within the last 12 months.
13. Subject has a symptomatic urinary tract infection, prostatitis, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs (i.e., within the confines of the pelvis including the bladder, prostate and rectum; organs of the lower gastrointestinal tract are not necessarily considered pelvic organs as the distal ascending colon, the full transverse colon and proximal portion of the descending colon are in the abdomen).
14. Subject has received intravesical injection in the past 12 months with botulinum toxin, resiniferatoxin, or capsaicin.
15. Subject has ever received electro-stimulation therapy for OAB (e.g., sacral nerve stimulation or Percutaneous Tibial Nerve Stimulation [PTNS]).
16. Subject began or has changed a bladder training program or pelvic floor exercises less than 30 days prior to Screening.
17. Subject has postural hypotension or syncope or postural orthostatic tachycardia.
18. Subject has moderate or severe hepatic impairment defined as Child-Pugh Class B or C.
19. Subject has severe renal impairment defined as estimated creatinine clearance less than 29 mL/min/1.73 m^2 as determined by central laboratory calculation of eGFR. A subject with End Stage Renal Disease (ESRD) or undergoing dialysis is also not a candidate for the study.
20. Subject has severe uncontrolled hypertension, which is defined as a sitting systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg.
21. Subject has baseline resting pulse rate <60 BPM or >90 BPM.
22. Subject has evidence of QT prolongation on Screening (Visit 1) or Baseline (Visit 2) electrocardiogram (ECG) defined as QTcF >450 msec.
23. Subject has a clinically significant ECG abnormality, as determined by the Investigator.
24. Subject has AST or ALT >2x upper limit of normal (ULN), or γ-GT >3x ULN and considered clinically significant by the Investigator.

25. Subject has a hypersensitivity to any components of mirabegron, tamsulosin hydrochloride, or any of the inactive ingredients.
26. Subject has a history of angioedema.
27. Subject has any clinically significant condition, which in the opinion of the Investigator makes the subject unsuitable for study participation.
28. Subject has been treated with an experimental device within 28 days or received an investigational agent within 28 days or 5 half-lives, whichever is longer, prior to Screening.
29. Subject has a concurrent malignancy or history of any malignancy (within the past 5 years), except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully.
30. Subject has ongoing alcohol and/or drug abuse.
31. Subject is using prohibited medications defined in Appendix 1, Part A within 30 days prior to Screening (Visit 1) through Follow-Up Phone Call (Visit 6).
32. Subject has stopped, started or changed the dose of a restricted medication (defined in Appendix 1, Part B) within the 30 days prior to Screening (Visit 1) through Follow-Up Phone Call (Visit 6).
33. Subject has participated in an interventional trial within 30 days prior to Screening (Visit 1).
34. Subject is involved in the conduct of the study as an employee of the Astellas group, third party associated with the study, or the study site team.
35. Subject has previously received mirabegron in the 6 months prior to Screening (Visit 1).

Exclusion Criteria assessed at Visit 2 (Baseline):

36. Subject was non-compliant during the 4-week tamsulosin hydrochloride run-in period, defined as taking less than 80% or greater than 120% of study medication.
37. Subject had an average total daily urine volume >3000 mL as recorded in the 3-day diary.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

Mirabegron will be supplied as 25 mg and 50 mg OCAS (Oral Controlled Absorption System) modified release tablets. Mirabegron OCAS tablets contain the following excipient: Polyethylene Oxide 2000000 NF, Polyethylene Glycol 8000 NF, Hydroxypropyl Cellulose NF, Butylated Hydroxytoluene NF, and Magnesium Stearate NF. The tablets are film coated

using Opadry® 03F43159 (25 mg) and 03F42192 (50 mg). The opadry formulation contains: Hypromellose USP, Polythylene Glycol 8000, Yellow Ferric Oxide NF and Red Ferric Oxide NF.

The mirabegron tablets are packaged in blisters and must be stored at room temperature, 25°C (77°F); excursion permitted to 15°-30°C (59°-86°F).

The clinical trial material of mirabegron OCAS tablets have been manufactured for Astellas by Astellas Pharma Technologies, Inc.

All investigational materials must be kept in a secure area inaccessible to unauthorized individuals.

4.1.2 Concomitant Medication

Tamsulosin hydrochloride will be supplied as 0.4 mg capsules (US) / tablets (EU/CA) in either commercial blister packs or commercial bottles. All storage and handling information can be found in the product package insert or the Summary of Product Characteristics (SPC).

4.1.3 Placebo

The placebo to match (PTM) mirabegron OCAS tablets contain Polyethylene Oxide 2000000 NF, Polyethylene Glycol 8000 NF, Hydroxypropyl Cellulose NF, Butylated Hydroxytoluene NF, and Magnesium Stearate NF. The tablets are film coated using Opadry® 03F42192 which contains: Hypromellose USP, Polyethylene Glycol 8000, Yellow Ferric Oxide and Red Ferric Oxide NF.

The PTM mirabegron OCAS tablets have been manufactured for Astellas by Astellas Pharma Technologies, Inc.

The mirabegron PTM tablets are packaged in blisters. The blisters must be stored at room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled in accordance with AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

All Investigational Medicinal Products will bear a label conforming to regulatory guidelines, Good Manufacturing Practice and local laws and regulations which identifies the contents as investigational drug.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the Investigator to ensure that study drug deliveries from the Sponsor are received by the Investigator/or designee and

- that such deliveries are recorded,
- that study drug is handled and stored according to labeled storage conditions,
- that study drug is only dispensed to study subjects in accordance with the protocol, and

- that any unused study drug is returned to the Sponsor or standard procedures for the alternative disposition of unused study drug are followed.

The supplied study drug should **not** be stored at a temperature outside the temperature range specified on the study drug label. Any temperature excursion outside the temperature range should be evaluated by the Sponsor.

Drug inventory and accountability records for the study drugs will be kept by the Investigator/or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The Investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The Investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the Investigator to dispense these test drugs.
- A study drug inventory will be maintained by the Investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the Investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the Sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

4.4.1 Blinding Method

This is a randomized, double-blind, placebo-controlled, parallel group study. Randomization will be stratified by geographic region (NA, EU). Subjects will be assigned to a treatment group in the order which they meet the criteria for randomization. After the completion of the 4-week open label tamsulosin hydrochloride run-in period, subjects will be randomized to either 25 mg mirabegron or PTM for 4 weeks of treatment and then an obligatory increase to mirabegron 50 mg or 50 mg PTM for the remainder of the study. Subjects will receive their allocated treatment according to a computer-generated randomization schedule prepared by the Sponsor or designee prior to the start of the study. The subject, Investigator and Sponsor will not be aware of the treatment regimen.

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

Mirabegron and mirabegron PTM tablets will be used in this study. The mirabegron PTM will be identical in size, color and appearance to the mirabegron 25 mg and mirabegron 50 mg tablets.

4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

Study drug treatment may be revealed only for reasons relating to the subject's safety and when critical therapeutic decisions are contingent on knowing the assigned study drug.

Withdrawal of a subject from the study (refer to Section 6.1) is not a sufficient reason to break the study blind. Any decision to break the blind should be discussed with the Astellas Study Physician (refer to Section II for contact information).

If the blind is broken for a subject, the reason is to be documented as a written entry in the source document. Key information will be recorded at the time when the blind is broken. This includes the date the blind was broken, the reason, the person who requested the breaking of the blind, the name of the person who broke the blind, and the name of the Astellas representative contacted.

4.4.4 Breaking the Treatment Code for Emergency

In order to break the treatment code (unblinding) for a subject, the assigned study medication information is accessible through the IWRS. The Sponsor must be notified immediately if the blind is broken. The date, time, and reason the blind was broken must be recorded in the source documents and on the appropriate Electronic Case Report Form (eCRF) if applicable.

Breaking the treatment code, or unblinding of an individual subject's treatment assignment, may be done only for reasons relating to subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment.

4.4.5 Breaking the Treatment Code by the Sponsor

The Sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff, who are responsible to break the codes for all SUSAR cases for reporting purposes.

4.5 Assignment and Allocation

After a subject signs informed consent, a subject number will be assigned. To obtain a subject number, the Investigator or designee will utilize a web or phone-based Interactive Response Technology (IRT), available seven days a week and 24 hours a day.

Subjects 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), subjects will be randomly assigned to receive mirabegron or placebo using a 1:1 randomization schedule. Randomization will be stratified by geographic region (NA, EU).

To obtain the randomization treatment, the Investigator or designee will utilize a web or phone-based IRT, available seven days a week and 24 hours a day. After submitting certain information about the eligible subject, 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. The Medication ID number assigned to the subject will be noted in the electronic case report form (eCRF) for study drug.

Once a subject number is assigned, if the corresponding subject does not receive study drug, the subject number will not be used again.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

Subjects will be randomized to one of two treatment groups in a 1:1 ratio to either mirabegron or placebo (PTM). Those subjects randomized to mirabegron will start at 25 mg tablet QD for 4 weeks along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA). Mirabegron dose will be titrated to mirabegron 50 mg QD at 4 weeks. Mirabegron 50 mg dose will be maintained for the remaining 8 weeks of the study along with tamsulosin hydrochloride capsule 0.4 mg (US) / tablet (EU/CA). Oral mirabegron can be taken with or without food, but during the course of the study will be taken the same time each day as the concomitant tamsulosin hydrochloride medication.

Those subjects randomized to placebo will start placebo to match (PTM) mirabegron 25 mg tablet QD for 4 weeks along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA). PTM mirabegron 25 mg will be increased to PTM mirabegron 50 mg and will be maintained for the remaining 8 weeks of the study along with tamsulosin hydrochloride 0.4 mg capsule (US) / tablet (EU/CA). Subjects will be instructed to take PTM at the same time each day as the concomitant tamsulosin hydrochloride medication.

Subjects will be instructed to take oral tamsulosin hydrochloride 0.4 mg approximately one-half hour following the same meal each day.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

The study design employs a dose increase from 25 mg mirabegron to 50 mg mirabegron at Week 4 (Visit 3). 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.

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

5.1.3.1 Previous Medication (Drugs and Therapies)

The Investigator must record the use of previous (all medication taken within 30 days prior to Screening [Visit 1]) and current concomitant treatment, both drug and non-drug therapies, prescribed and over-the-counter and all alternative medicines, in the eCRFs. This also includes drugs used on a chronic and as-needed basis.

Subjects must be instructed not to start any new medication, both prescribed and over-the-counter, without consulting the Investigator, unless the new medication is required for emergency use. Subjects must be instructed to notify the Investigator immediately if medications were required for emergency use.

5.1.3.2 Concomitant Medication (Drugs and Therapies)

Concomitant medications will be captured from Screening/tamsulosin hydrochloride run-in (Visit 1) through the Follow-Up Phone Call (Visit 6).

Prohibited Medications (Appendix 1, part A)

Medications prohibited between Screening/tamsulosin hydrochloride run-in (Visit 1) and Week 16/Follow-up phone call (Visit 6) include other alpha-adrenergic blockers, anticholinergics, antispasmodics, strong and moderate inhibitors of CYP2D6 with narrow therapeutic index, specifically thioridazine, flecainide, propafenone, amitriptyline, paroxetine, and terbinafine, and moderate and strong inhibitors of CYP3A4 (see Appendix 1, Part A). These medications must have been discontinued at least 30 days prior to Screening/tamsulosin hydrochloride run-in (Visit 1). Current or previous use of mirabegron within 6 months prior to Screening (Visit 1) is also prohibited.

Restricted Medications (Appendix 1, part B)

Medications restricted between Screening/tamsulosin hydrochloride run-in (Visit 1) and Week 16/Follow-up Phone Call (Visit 6) include loop diuretics, 5-Alpha reductase inhibitors and PDE5 inhibitors (see Appendix 1, Part B). These medications are permitted provided the subject has been taking the medication on a long-term basis, i.e. has not stopped, or started, or changed dose within the 30 days prior to Screening/tamsulosin hydrochloride run-in (Visit 1), no new drug of the same class has been added to the regimen within the 30 days prior to Screening/tamsulosin hydrochloride run-in (Visit 1), and the subject remains on the medication at the same dose during the course of the study. For 5-alpha reductase inhibitors the subject 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.

Restricted Non-Drug Therapy

Subjects participating in any behavioral modification therapy (i.e., pelvic floor exercises, Kegel exercises, biofeedback, timed voiding, etc.) or other nondrug therapy must have started the therapy within 30 days prior to Screening/tamsulosin hydrochloride run-in (Visit 1) and must continue the same schedule through Follow-Up Phone Call (Visit 6). Neurostimulation for OAB is a strict exclusion criterion.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study

period. Compliance will be verified by the accounting of each study drug at each monthly visit starting with the Baseline (Visit 2).

If compliance during the tamsulosin hydrochloride run-in period is less than 80% or greater than 120% of study medication the subject is considered non-compliant and will be excluded from the study.

If compliance for blinded treatment is less than 80%, the Investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects who are less than 80% compliant with the dosage regimen for any two consecutive visit periods during the study should be withdrawn from the study.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

The subject's date of birth (or age, if local regulations do not allow recording of subject's date of birth), gender, race, ethnicity, height, and weight will be recorded at Screening/tamsulosin hydrochloride run-in (Visit 1).

5.2.2 Medical History

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

5.2.3 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 subject will be obtained at Screening/tamsulosin hydrochloride run-in (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.

5.3 Efficacy Assessment

5.3.1 Patient Diary – Micturition and Incontinence

During the study, subjects 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, protective garments, 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, subjects 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.

A training diary will be completed in the first 2 weeks of the tamsulosin hydrochloride run-in period. The purpose of this training diary is to familiarize the subject with using the electronic handheld device and for the Investigator to assess the ability and willingness of the subject to complete the diary. During these 2 weeks the Investigator will remotely evaluate diary completion and will provide additional instructions if necessary. During this evaluation period at least one telephone contact will take place with the subject. The diary that is completed during the last 3 days before randomization will be used to establish Baseline data. Therefore, it is very important to ensure that any compliance or completion issues are discussed during the 2-week training diary.

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), and Week 12/End of Treatment (Visit 5). Site staff will contact the subject approximately 7 days prior to the scheduled visit to remind the subject they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable).

A diary day starts at midnight and ends at midnight the following day. Time to bed with intention to sleep, time to wake with intention of staying awake, type of episode (urination/incontinence), time of episode, urgency severity (see Section 5.3.2), measure of urine volume voided, and sleep interruption will be recorded by the subject 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 subject fully voids in the toilet. “Incontinence” will be counted for episodes in which the full void was incontinent and the subject did not make it to the toilet to finish urinating. If a subject 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 and protective garment use (see Table 1, Schedule of Assessments).

5.3.2 Patient Perception of Intensity of Urgency Scale (PPIUS)

The Patient Perception of Intensity of Urgency Scale (PPIUS) will be completed as part of the micturition diary.

For each micturition and/or incontinence episode, subjects will be asked to rate the degree of associated urgency according to the following validated 5-point 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), and Week 12/End of Treatment (Visit 5).

5.3.3 Total Urgency and Frequency Score (TUFS)

The Total Urgency and Frequency Score (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 [Chapple et al, 2014].

5.3.4 International Prostate Symptom Score (IPSS)

The International Prostate Symptom Score (IPSS) consists of seven questions concerning urinary symptoms and one question concerning quality of life.

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

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

OAB has significant effects on health-related quality of life (QoL) of afflicted subjects. This has been quantified in various empirical studies [Wall et al, 1993]. QoL is determined by socio-demographic, clinical, psychological and social factors. This underlies the importance of assessing the perceptions of subjects 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.

5.3.5.1 Overactive Bladder-questionnaire (OAB-q)

OAB symptoms and QoL in relation to OAB will be assessed by the Overactive Bladder-questionnaire (OAB-q) [Coyne et al, 2002]. This questionnaire has validated psychometric properties, has been used extensively in QoL-research in respondents with OAB, and has been shown to be responsive in treatment studies [Coyne et al, 2002]. The OAB-q is a self-reported questionnaire with 33 items, which contain the dimensions Coping, Concern, Sleep, Social Interaction, and a Symptom Bother scale with eight symptoms [Garely et al, 2007].

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

5.3.5.2 Patient Perception of Bladder Condition (PPBC)

The Patient Perception of Bladder Condition (PPBC) is a validated, global assessment tool using a 6-point Likert scale that asks subjects to rate their subjective impression of their current bladder condition [Coyne et al, 2006]. The PPBC questionnaire will be assessed at Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), and End of Treatment (Visit 5).

5.3.5.3 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., no problems, slight problems, moderate problems, severe problems, and 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), and End of Treatment (Visit 5).

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

The Treatment Satisfaction – Visual Analog Scale (TS-VAS) is a visual analog scale that asks subjects 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). The TS-VAS will be assessed at Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), and End of Treatment (Visit 5).

5.4 Safety Assessment

The safety evaluation including vital signs, adverse event recording, clinical laboratory assessments and physical examination will be performed according to Table 1, Schedule of Assessments.

Requirements related to the evaluation, reporting and analysis of Drug-Induced Liver Injury (DILI) information are found in Appendix 2 (Liver Safety Monitoring and Assessment). In the event of a confirmed, marked hepatic abnormality as defined in Appendix 2, it is the Investigator's responsibility to ensure contact with the Sponsor/delegated CRO by telephone or fax immediately (i.e., within 24 hours of awareness).

5.4.1 Vital Signs

Vital signs, including pulse rate and blood pressure, will be measured in the diary for 3 days prior to each visit and at all in-office visits according to Table 1, Schedule of Assessments. The Investigator responsibility for reporting the Treatment Emergent Adverse Event (TEAE) of hypertension will be based on office visit measurements and not on diary review.

For office based vital signs the patient should be seated comfortably for at least 5 minutes with the back supported, feet on the floor, arm supported in a horizontal position, and the

blood pressure cuff at heart level for each blood pressure measurement. The Investigator will use the same device and cuff size throughout the study. The same arm should be used throughout the study.

An AE of hypertension will be recorded, independent of Investigator assessment of clinical significance or relatedness, if one of the following criteria is met on 2 or more consecutive 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 subjects who were normotensive (average systolic blood pressure <140 mmHg AND average diastolic blood pressure <90 mmHg) [WHO-ISH, 2013] 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 subjects 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 (see Appendix 4).

An AE of tachycardia should be considered if resting heart rate (pulse rate) is > 100 bpm (see Appendix 5). The Investigator responsibility for reporting the TEAE will be based on office visit measurements and not on diary review.

5.4.2 Patient Diary – Subject Measurement Vital Signs

During Visit 1, the Investigator should instruct the subject on how to perform and document in the electronic diary the self-measurement of BP and PR. The subject will have an opportunity to familiarize himself with the self-measurement of BP and PR and recording of the data.

The electronic diary will capture HBPM vital signs. It will be completed in both the morning and evening for 3 consecutive days prior to each visit: Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12/End of Treatment (Visit 5).

Validated devices for measuring BP and PR will be provided to subjects along with detailed operating instructions. At home, according to the "The ABCD's of Blood Pressure Measurement" [American Heart Association, April 2012], the subject should rest for at least 5 minutes before taking the measurements. The subject should be quiet and relaxed, sitting in a chair with their feet on the floor, legs should not be crossed, and arms should be bare and supported at heart level. The cuff should be put on according to the instructions of the Investigator. The subject should not move and should remain silent during the reading as moving and talking can affect the reading. The subject should measure his BP and PR in triplicate during the 3 consecutive days prior to the next visit, on the arm chosen from the Screening measurements.

Measurement should be taken after waking up in the morning and again in the evening. The subject should ensure that the morning measurements of vital signs are taken BEFORE breakfast and BEFORE study medication intake. The evening BP measurement is not specified in relation to either a meal or the time study drug was taken. It is recommended to be taken after 4 pm and before going to bed.

Three readings at each occasion should be taken, each about 2 minutes apart. Date, time, systolic and diastolic BP, and PR will be documented in the electronic diary. The subject should take care to have a 30 minute rest after exercise or smoking or intake of caffeine or alcohol, prior to taking a measurement.

5.4.3 Adverse Events

Adverse Event collection will begin from the time of informed consent and continue through the Follow-up Phone Call (Visit 6). See **Section 5.5 Adverse Events and Other Safety Aspects** for information regarding adverse event collection and data handling.

5.4.3.1 Adverse Events of Possible Hepatic Origin

See Appendix 2 Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in the study and receiving study drug is accompanied by increases in liver function testing (LFT, e.g.: AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.4.3.2 Adverse Events of Special Interest

Adverse Events of Special Interest include:

- Blood pressure and pulse rate (defined in Section 5.4.1, analysis in Section 7.5.3)
- Acute urinary retention (urinary retention requiring catheterization)
- Benign prostatic obstruction (BPO) requiring surgery.

5.4.4 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study. See Table 1 Schedule of Assessments for study visit collection dates. For this study, 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.

Table 3 Laboratory Assessments

Screening/tamsulosin hydrochloride run-in (Visit 1) Baseline (Visit 2) Week 4 (Visit 3) Week 8 (Visit 4) Week 12/End of Treatment (Visit 5)	Hematology	CBC Hemoglobin Hematocrit
Screening/tamsulosin hydrochloride run-in (Visit 1) Baseline (Visit 2) Week 4 (Visit 3) Week 8 (Visit 4) Week 12/End of Treatment (Visit 5)	Biochemistry/PSA	Serum PSA (Visit 1 only) Sodium Potassium Calcium Chloride Glucose Creatinine Alkaline phosphatase HCO_3 BUN AST ALT GGT Total bilirubin Total protein Albumin INR
Screening/tamsulosin hydrochloride run-in (Visit 1) Baseline (Visit 2) Week 4 (Visit 3) Week 8 (Visit 4) Week 12/End of Treatment (Visit 5)	Urinalysis (Microscopic)	Protein Glucose pH Blood WBC RBC Epithelial cells LCE Nitrites Bacteria Urine Culture*

*Urine culture and sensitivity must be performed for positive leukocyte esterase (LCE), nitrites, or turbidity, or at the discretion of the Investigator. Urine culture and sensitivity at the discretion of the Investigator will be performed at a local laboratory. It is not required to send isolated trace positive leukocyte esterase samples for culture.

Clinical significance of out-of-range laboratory findings is to be determined and documented by the Investigator/sub-Investigator who is a qualified physician.

Before the start of the study, sampling and shipment procedures will be provided in a laboratory manual. The Investigator may decide to repeat the tests, should the results be outside normal ranges and considered clinically relevant, or if the original sample could not be analyzed.

If the blood sample at Visit 1 cannot be analyzed, the test results are considered a lab error or the test results are increased related to a temporary condition unrelated to OAB and likely to resolve at short notice, it is acceptable to repeat the laboratory tests to check eligibility criteria. The subject should be requested to come for an unscheduled visit between Visit 1

and Visit 2. If the repeat test results are still exclusionary, the subject should not be randomized. Repeat test to check eligibility criteria can only be repeated once before Visit 2.

Any changes in laboratory values are to be evaluated by the Investigator. Clinically relevant changes must be recorded as AEs in the eCRF (see Section 5.5.1).

5.4.5 Physical Examination

The subject will have a physical examination performed at Screening/tamsulosin hydrochloride run-in (Visit 1) and at Week 12 (Visit 5). This includes examination of main body systems. Date of physical examination and any clinically relevant adverse findings not documented in the medical history will be recorded as an AE in the eCRF (see Section 5.5.1).

5.4.6 Electrocardiogram (ECG)

A single 12-lead ECG will be recorded at Screening/tamsulosin hydrochloride run-in (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), and End of Treatment (Visit 5). ECG will be taken with the subject in the supine position (subject is allowed to be sitting if unable to be supine).

ECGs will be submitted to a central laboratory to allow for central reading (ECG recordings will be performed according to ICH guidelines E14 to make them readable and interpretable for potential later assessment by an independent cardiologist). Recordings will be made at a speed of 25 mm/s and all leads have to include at least four complexes. This is according to the standard setting on the machines.

The ECGs should be transmitted from the machine to the central laboratory (following the steps indicated in the user manual). In addition, one print copy of the original ECG traces should be maintained in the study file. These should be clearly marked with the subject identification number (in such a way that they are anonymized), visit date, and visit number, and should be kept with the source documents.

The ECG machine will produce automatically calculated interval duration measurements and an evaluation on the printed ECG. The manually read analysis reports of the central ECG readings will be made available to the Investigators (within 72 hours). The final ECG reports sent by the central laboratory must be reviewed by the Investigator and should be used for immediate safety assessment and subject care since there might be slight changes from the initial analysis produced by the ECG machines.

If the QTcF interval is >450 ms on the printed ECG at Visit 2, an expedited central ECG reading (within 24 hours) should be requested. In this case the final ECG report should be received/reviewed before the subject is allowed to be randomized.

The ECG report itself should not be captured on the eCRF, but will be captured in the central ECG laboratory database. Only the visit, ECG date, automated QTc, overall ECG interpretation and relevant comments will be captured in the eCRF.

If specific concerns regarding the cardiac safety of a subject exist, a dual approach is recommended:

- On-site evaluation of the ECGs should be conducted by a local cardiologist,
- In addition, the central ECG laboratory can be contacted (24 hours a day) to provide the final centrally read ECG analysis results within a shorter timeframe than the usual 72 hours (for contact details see the ECG Study Manual provided by the central ECG laboratory).

Any abnormalities (based on the Central Reading Interpretation) must be evaluated in clinical context (based on subject's medical history and concomitant medication) and the Investigator should determine if it is clinically significant and record with Potentially Clinically Significant (PCS). Any clinically significant abnormality should be reported as an AE.

5.4.7 Post-Void Residual Volume (PVR)

Post-Void Residual (PVR) volume will be assessed by ultrasonography or bladder scan at Screening/tamsulosin hydrochloride run-in (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), and Week 12/End of Treatment (Visit 5).

5.4.8 Uroflowmetry

Maximum flow rate (Q_{max}) will be assessed at Screening/tamsulosin hydrochloride run-in (Visit 1) and Week 12/End of Treatment (Visit 5). The subject must void a minimum of 125 mL for the uroflow measurement to be considered adequate.

5.4.9 Follow-up Phone Call to Patients

Subjects will be contacted 4 weeks after Week 12/End of Treatment (Visit 5) by telephone for a Follow-up Phone Call (Visit 6) to assess concomitant medications and any adverse events that may have occurred following the end of treatment.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the Investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the (e)CRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the Investigator.

5.5.2 Definition of Serious Adverse Events (SAEs)

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 (an adverse event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- 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 (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Stroke, myocardial infarction, dysrhythmias, and uncontrolled hypertension will also be examined.

In addition to AEs special situations (SS) (with or without an associated AE) occurring on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)

- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)

All of the events of interest noted above should be recorded on the eCRF. Any SS that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and the SAE worksheet and submitted to Astellas.

The Sponsor has a list of events that they classify as "always serious" events. If an adverse event is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

The following standard with 3 grades is to be used to measure the severity of adverse events, including abnormal clinical laboratory values.

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

5.5.5 Reporting of Serious Adverse Events (SAEs)

The reference safety information for mirabegron to be used for this study is the Company Core Data Sheet (CCDS) for mirabegron, Section 4.8- Undesirable Effects.

Please refer to the reference safety information for details of prescribing information (contraindications, special warnings and precautions).

In the case of a serious adverse event (SAE), the Investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness).

The Investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor by fax immediately (within 24 hours of awareness). If the faxing, scanning or emailing of an SAE Worksheet is not possible within 24 hours, the local drug safety contact should be informed by phone. Please fax the SAE Worksheet to:

Astellas Pharma Global Development, Inc. – United States
Product Safety & Pharmacovigilance
North America telefax numbers: [redacted]
International telefax number: [redacted]
Email: [redacted]

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records and on the eCRF.

The following minimum information is required:

- ISN/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e., IND Safety Reports) to the regulatory agencies (i.e., FDA) as necessary, and will inform the Investigators of such regulatory reports. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (i.e., EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor or Sponsor's designee will notify all Investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements to the IRB/IEC/head of the study site.

The heads of the study sites/Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

For Suspected Unexpected Serious Adverse Reactions (SUSAR) from a blinded trial, unblinded CIOMS-I report will be submitted to the authorities and IRB/IEC where required.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the adverse event progresses to an ″SAE″, or if a subject experiences a new SAE, the Investigator must immediately report the information to the Sponsor.

5.5.7 Monitoring of Common Serious Adverse Events

Common serious adverse events are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are provided in Appendix 3 **Most Common Serious Adverse Events** for reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common serious adverse events” as specified in Appendix 3 **Common Serious Adverse Events**. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in **Section 5.5.5 Reporting of Serious Adverse Events.**

5.5.8 Procedure in Case of Pregnancy

If during the conduct of a clinical trial, a male subject impregnates his partner, the subject should report the pregnancy to the Investigator. The Investigator will report the pregnancy to the Sponsor or delegated CRO as an SAE.

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected overdose, refer to the approved Package Insert, SPC, or local product information supplied by the manufacturer for each agent.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all Investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.6 Test Drug Concentration

Not applicable.

5.7 Other Measurements, Assessments or Methods

Not applicable.

5.8 Total Amount of Blood

Blood samples will be taken for the purposes of hematology, biochemistry and PSA analysis at Screening/tamsulosin hydrochloride run-in (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), and Week 12/End of Treatment (Visit 5). It is anticipated the total amount of blood taken will not exceed 50 mL throughout the duration of the study.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the Investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Subjects will be discontinued if they meet any of the following criteria:

- ALT or AST >3x ULN and total bilirubin >2x ULN
- ALT or AST >8x ULN on one occasion
- ALT or AST >5x ULN for more than 2 consecutive weeks
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

Subjects may also be discontinued for:

- Medically important adverse event(s)
- Protocol deviation(s) (e.g., subject took prohibited medication that in the Investigator’s opinion, after discussion with the Medical Monitor, may negatively impact the subject’s safety or demonstrated lack of cooperation in following protocol-specified procedures/instructions)
- Withdrawal of consent
- Investigator and/or Sponsor feel it is in the subject’s best interest

6.2 Discontinuation of the Site

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of Astellas. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before database softlock at the latest. Any deviations from the analysis planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to Database Lock, a Final Review of Data and 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.

In general, baseline 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 Visit 2/Baseline (Week 0) 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 study 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 subjects prematurely terminating the study and is regarded as the primary visit. The EOT visit will be Week 12/EOT (Visit 5) for subjects who complete the study.

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

All efficacy and safety variables will be summarized using descriptive statistics. Continuous variables will be summarized using the descriptive statistics number of non-missing observations (N), mean, standard deviation (SD) or standard error (SE), minimum, median, and maximum unless specified otherwise. Categorical variables will be described using N and percent.

7.1 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 subjects (272 evaluable subjects 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 subjects are evaluable, 640 subjects should be randomized. With an expected drop-out rate of 35% by the end of the tamsulosin hydrochloride run-in phase (V2), 985 subjects need to be screened.

7.2 Analysis Set

Three main analysis populations will be defined: Full Analysis Set (FAS), Full Analysis Set - Incontinence (FAS-I), and Safety Analysis Set (SAF).

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set

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

- Subjects 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 demographic, disease state data, prior medications, prior medical history and a statistical analysis of efficacy endpoints and QoL instruments.

7.2.2 Full Analysis Set - Incontinence (FAS-I)

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

- Subjects 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.

7.2.3 Safety Analysis Set (SAF)

The SAF will consist of all randomized subjects 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.

7.3 Demographics and Other Baseline Characteristics

Demographic and OAB baseline characteristics will be summarized using descriptive statistics by treatment group, mirabegron and placebo.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS. Incontinence episodes will be analyzed with the FAS-I. The interpretation of results from statistical tests will be based on the FAS.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

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. The primary analysis will be performed for the FAS at the EOT visit, i.e. Week 12 for subjects who complete the study or last post-baseline visit during the double-blind study period for subjects who discontinue early.

The hypothesis for comparison is as follows:

H0: 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.

H1: 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 analyzed using Analysis of Covariance (ANCOVA). The response variable will be the mean change in number of micturition episodes per day from baseline to end of the study with treatment group, geographic region, and age group as fixed factors and baseline as a covariate. Within the framework of this ANCOVA model, LS means and two-sided 95% CIs for the mean change 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. Further details may be found in the SAP.

7.4.1.2 Secondary Analysis

The primary analysis will be repeated for completers only, i.e. without utilizing LOCF imputation for subjects with missing Week 12 values. Additionally, Week 4 and Week 8 values will be analyzed similarly to End of Treatment.

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 Subgroup Analysis

Subgroup analyses will include analyses by geographic region, age group, by previous OAB medication, and reason for treatment termination if previously treated. If sample sizes are sufficient, subgroup analyses by race will be performed. More details on subgroup analyses will be provided in the SAP.

7.4.2 Analysis of Secondary Endpoints

Secondary variables are change to end of treatment in mean incontinence episodes per day, mean volume voided per micturition, mean number of urgency episodes (grade 3 and 4) per day, IPSS total score and subscales (Voiding, Storage, and Quality of Life), Symptom Bother and Total Health related quality of life scores as assessed by OAB-q questionnaire (and subscales), TUFS, PPBC, EQ-5D-5L, and TS-VAS.

An analysis of change from baseline in PRO values using a Mixed Model Repeated Measures (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.

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 to End of Treatment, with Baseline standardized ranks as covariates and geographic region as a stratum. Standardized ranks are used to adjust for differences in the number of subjects at each geographic region. Further details may be found in the Statistical Analysis Plan.

The number of incontinence episodes and protective garment use during the 3-day diary period will be analyzed using a mixed effects Poisson regression model with treatment group, age group, and geographic region as factors and number of incontinence episodes at baseline as a covariate. Differences in LS means between mirabegron and placebo will be calculated together with 95% CI.

Other secondary efficacy variables will be analyzed using the same ANCOVA model as described for micturitions (refer to Section 7.4.1.1). Descriptive analyses of the EQ-5D-5L will be in the Clinical Study Report. Other planned utility indices and analyses will be calculated in a separate report from the Statistical Analysis Plan and Clinical Study Report.

Responder analyses will be performed for 50% reduction in micturition frequency and for number of subjects with less than 8 micturitions per day at End of Treatment.

7.4.3 Analysis of Exploratory Endpoints

Subgroup analyses by PSA cutoff scores for < 2, 2-4 will be performed.

7.5 Analysis of Safety

7.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of treatment-emergent AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class, preferred term and treatment group. The number and percentage of TEAEs by severity and relationship to study drug will also be summarized. All AEs will be listed.

7.5.2 Laboratory Assessments

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.

For each hematology and biochemistry laboratory parameter, laboratory test results will be classified as low (L), normal (N), or high (H) 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.

7.5.3 Vital Signs

Pulse rate, systolic blood pressure, and diastolic blood pressure will be summarized by treatment group using descriptive statistics (mean, standard deviation, minimum, maximum and median) for baseline value, post-baseline time point values (Week 4, Week 8, and Week 12/EOT), and change from baseline to each post-baseline time points. The average change from baseline to end of treatment for each vital sign variable will be analyzed using the ANCOVA model with treatment group and geographic region as fixed factors and baseline vital sign value as covariate. Results will be summarized separately for office based measurements and HBPM. No p-values will be calculated.

An analysis of change from baseline of vital signs using a Mixed Model Repeated Measures (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.

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

7.5.4 Physical Examination

Physical examination will be listed by treatment group.

7.5.5 ECGs

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

The overall ECG interpretation from the local Investigator (normal, abnormal – not clinically significant, abnormal – clinically significant) will be summarized by treatment group and visit. Also a shift table will be produced for showing the shift from baseline by treatment group and visit. Parameters from central ECG readings (QT, QTcB, QTcF, HR, PR, QRS, RR, coded abnormalities and overall conclusion) and their change from baseline will be summarized using descriptive statistics by treatment group and visit. Numbers and percentages of subjects with QTcF values >450 ms, >480 ms or >500 ms or with changes from baseline in QTcF ≥30 msec or ≥60 msec will be summarized by treatment group.

7.5.6 PVR

PVR volume and its change from baseline will be summarized by treatment and visit. Shifts in PVR from baseline to each visit and from baseline to worst post-baseline value will be produced. Number and percentages of subjects with a PVR > 200 ml will be tabulated.

7.5.7 Q_{max}

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

7.6 Analysis of Pharmacokinetics

Not applicable.

7.7 Analysis of Pharmacodynamics

Not applicable.

7.8 Protocol Deviations and Other Analyses

Protocol deviations as defined in Section 8.1.6 Protocol Deviations will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

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

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

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

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

Any other analyses will be specified in the Statistical Analysis Plan (SAP).

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

No formal interim analysis is planned.

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

For efficacy variables and vital sign data, analysis at End of Treatment will take into account subjects who withdraw before Week 12 and therefore do not have efficacy measurements available for that visit. The End of Treatment analysis is a Last Observation Carried Forward (LOCF) approach. As a secondary analysis, a mixed model repeated measures analysis will be performed for selected variables as described in Sections 7.4.1 and 7.4.2

Other imputation rules to account for missing data will be described in the SAP.

Subjects do not always adhere strictly to the visit timing the protocol. Visit windows around the target days for each visit will be defined in the SAP.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The Investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The Investigator or designee will enter data collected using an Electronic Data Capture (EDC) system.

Laboratory tests are performed and sent to a Central Lab for testing. The Central Lab will compile the results and send to data file to Astellas or designee for inclusion in the clinical database.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

For screening failures, the minimum demographic data (sex, birth date or age, race and informed consent date) and reason for screening failure will be collected in the screen failure log (SFL), if applicable. This information can be entered into the study database.

Subject diaries will be completed by the subjects on an electronic device. The information completed by the subjects on the electronic device will be automatically uploaded into a central website. The Investigator or site designee should review the diary data on the website for correct completion while the subject is at the site. The diary data will be transferred electronically to Sponsor or designee at predefined intervals during the study. The vendor will provide Sponsor or designee with a complete and clean copy of the data.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the Investigator/sub-Investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The Investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2 "Specification of Source Documents") when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the CRO appointed by the Sponsor in accordance with the CRO's standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively. Data analysis will be performed according to Astellas data standards.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The Investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an Investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the Investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the Investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the Investigator must contact the Sponsor immediately.

The Investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and

communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last Visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure (IB), the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The Investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the Investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding one year. The Investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-Sponsored studies, or for APEB/APEL-Sponsored studies within one year after last subject out (LSO) or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject or his guardian or legal representative, and answer all questions regarding this study. Prior to any study related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the Investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The Investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. The Investigator must update their ICF and submit it for approval to the IRB/IEC. The Investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The Investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The Investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure (IB) and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The Investigator may use this information for the purpose of the study only. It is understood by the Investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical Investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The Investigator will archive all study data (e.g., Subject Identification Code List, source data, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). It is recommended, however, that records be retained for at least five years in the event follow-up is necessary to help determine any potential hazards to subjects who took part in the study. The Sponsor will notify the site/Investigator if the NDA is approved or if the IND is discontinued. The Investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered into the EDC system for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC/CA approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the Investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the Sponsor and the Investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the

protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating Investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB) | Monitoring Committee | Other Evaluation Committee(s)

Not applicable.

10.2 Other Study Organization

10.2.1 Cardiovascular Adjudication Committee

A cardiovascular adjudication committee is in place to assess all serious adverse events of potential cardiovascular nature occurring in the study. The committee will consist of three independent members of appropriate expertise who are not directly involved in the clinical study and who are blinded to the treatment allocation. Event related information of the cases will be sent to the committee for blinded assessment. The assessments will be captured on paper CRFs, and entered into a clinical database. A separate charter describes the classification of those events to be adjudicated (including but not limited to cardiac

arrhythmia and thromboembolic events) and the specification of the event-related documents, listing, data flow, method(s) for data collection and data transfer.

10.2.2 Neoplasm Adjudication Committee

A neoplasm adjudication committee is in place to assess all potential neoplasm events occurring in the study. The committee will consist of three independent reviewers of appropriate expertise who are not directly involved in the clinical study and who are blinded to the treatment allocation. Event related information of the cases will be sent to the committee for blinded assessment. The assessments will be captured on paper CRFs, and entered into a clinical database. A separate charter describes the classification of those events to be adjudicated and the specification of the event-related documents, listings, data flow, method(s) for data collection and data transfer.

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12 APPENDICES

12.1 Appendix 1: List of Prohibited and Restricted Concomitant Medications

Part A – Prohibited Medications

Use of these medications in any formulation is not permitted between Screening (Visit 1) and Week 16/Follow-Up Phone Call (Visit 6) and must have been discontinued at least 30 days prior to Screening. 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.

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)	Venlafaxine/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 Appendix 1: List of Prohibited and Restricted Concomitant Medications are permitted provided the subject has been taking this medication on a long-term basis, i.e. has not stopped, or started or changed dose within 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 subject remains on the medication at the same dose during the course of the study.

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

12.2 Appendix 2: Liver Safety Monitoring and Assessment

If laboratory testing for a subject enrolled in study and receiving study drug reveals an increase in serum aminotransferases (AT) to >3X ULN, bilirubin > 2 × ULN, at least all four of the usual serum hepatic measures (ALT, AST, ALP, and TBL) must be repeated. Testing should be repeated within 48-72 hours of notification of the test results. Alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the Investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3× ULN	or	> 2× ULN
Severe*	> 3× ULN	and	> 2× ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8× ULN
- ALT or AST > 5× ULN for more than 2 weeks
- ALT or AST > 3× ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The Investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a Serious Adverse Event (SAE). The Sponsor should be contacted and informed of all subjects for

whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the Investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The Investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - acute viral hepatitis (A, B, C, D, E or other infectious agents)
    - ultrasound or other imaging to assess biliary tract disease
    - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The Investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5) (If INR testing is applicable/evaluated)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.3 Appendix 3: Common Serious Adverse Events

For this protocol, there is no list of common serious adverse events that the Sponsor considers to be associated with the disease state being studied for which a single occurrence will be excluded from IND safety reporting. All SAEs should be reported.

12.4 Appendix 4: Investigator Criteria for Hypertension

Investigator Criteria for Determining TEAE of Hypertension

During each office visit a systolic and diastolic blood pressure will be measured. The Investigator responsibility for reporting the TEAE of hypertension will be based on office visit measurements and not on diary review.

For post-baseline assessments, the Investigator will use the following criteria, as defined in the protocol, to determine if a subject is considered hypertensive:

An AE of hypertension will be recorded if one of the following criteria is met on 2 consecutive 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 subjects who were normotensive (average systolic blood pressure < 140 mmHg and average diastolic blood pressure < 90 mmHg [WHO-ISH, 2013]) 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 subjects 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.

In addition, the Investigator can record an AE based on clinical assessment.

12.5 Appendix 5: Investigator Criteria for Tachycardia

Investigator Criteria for Determining TEAE of Tachycardia

During each office visit pulse rate will be measured. The Investigator responsibility for reporting the TEAE of tachycardia will be based on office visit measurements and not on diary review. Tachycardia is defined as a resting heart frequency > 100 beats per minute (bpm) measured as pulse rate. If pulse rate is > 100 bpm at the office visit, the Investigator is to record an AE of tachycardia. However, if the Investigator's clinical assessment was that this did not constitute an AE of tachycardia, then an AE will as not be recorded.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 4

I. The purpose of this amendment is:

Substantial Changes
1. Updated Reference Safety Information (RSI)
DESCRIPTION OF CHANGE:
Revised RSI from the US Package Insert, Canadian Monograph, and SmPC to the Company Core Data Sheet for mirabegron.
RATIONALE:
Astellas Pharmacovigilance (PV) refers to the Company Core Data Sheet for mirabegron as the physical reference for RSI. There is no change in the risk to patients or what safety information is reported with this update to the protocol. This update provides consistency of RSI with PV and the protocol.

II. Amendment Summary of Changes:

Substantial Changes:

1. Updated Reference Safety Information (RSI)
Page 58, 5.5.5 Reporting of Serious Adverse Events (SAEs)
WAS:
The reference safety information for mirabegron to be used for this study is the US Package Insert for the US, EU SmPC for EU countries and the Canadian Monograph for Canada. The reference safety information is equal in each document.
IS AMENDED TO:
The reference safety information for mirabegron to be used for this study is the **Company Core Data Sheet (CCDS) for mirabegron, Section 4.8 Undesirable effects.**~~US Package Insert for the US, EU SmPC for EU countries and the Canadian Monograph for Canada. The reference safety information is equal in each document.~~

1. Updated Reference Safety Information (RSI)
Page 77, 11 References
ADDED:
Company Core Data Sheet for mirabegron.

14 SPONSOR'S SIGNATURES

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 Prostate Hyperplasia (BPH)

ISN/Protocol 178-MA-1008 / Version 5.2 / 22 January 2018

1.1. PROTOCOL AUTHORS:

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1.2. PROTOCOL APPROVED BY:

Protocol Approval Committee

Signature: _____ Date _____

[redacted]

(GPF 4.1)