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

ISN/Protocol 178-MA-3016

ClinicalTrials.gov Identifier: NCT02656173

Date of Protocol: 10 May 2016

Sponsor: Astellas Pharma Inc.

2-5-1, Nihonbashi-Honcho, Chuo-ku,

Tokyo 103-8411, Japan

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

Protocol for Phase 4 Study of Mirabegron for Overactive Bladder

ISN/Protocol 178-MA-3016

Version 4.0/ 10 May 2016

Sponsor: Astellas Pharma Inc. (API)

2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo

Prepared on May 10, 2016 (Version 4.0)

Investigator: Investigator information is on file at Astellas.

Table of Contents

I. SIGNATURES

AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This clinical study will be conducted in adherence to GCP, ICH Guidelines, and applicable laws and regulatory requirements, as well as this study protocol. As the evidence of the agreement, the Investigator and responsible person of the Sponsor inscribe in the bipartite agreement.

1. SPONSOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0

Responsible person:

Signature: [redacted] 10 May 2016
Date (DD MM YYYY)

Printed Name: [redacted]
Astellas Pharma Inc.

2. COORDINATING INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: [redacted] 17 May, 2016
Date (DD Mmm YYYY)

<*Insert name, department/affiliation, name of institution*>

Printed Name: [redacted]

Address: [redacted] ***Japan***

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: [redacted] 24 MAY 2016
Date (DD Mmm YYYY)

<*Insert name, department/affiliation, name of institution*>

Printed Name: [redacted]

Address: [redacted] ***KOREA***

3. INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0

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: _____

<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Contact Information for the Sponsor
Corporate Name: Astellas Pharma Inc.
Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo
Phone No.:
Fax:
Sponsor's personnel:

Contact numbers during non-business hours and for emergency:
Sponsor Personnel (Phone No);

Corporate Name: Astellas Pharma Singapore Pte. Ltd.
Location: 6 Temasek Boulevard #22-03/05 Suntec Tower Four, Singapore
Phone No.:
Fax:
Sponsor's personnel:
Contact numbers during non-business hours and for emergency:
Sponsor Personnel (Phone No);

Contact Information for the Contract Research Organization (CRO)
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Phone No.:
Fax:
CRO's personnel:
Contact numbers during non-business hours and for emergency:
CRO Contact (Phone No.):

Corporate name:
Location:

Phone No.:
Fax:
CRO's personnel:
Contact numbers during non-business hours and for emergency:
CRO Contact (Phone No.):

24h-Contact for Serious Adverse Events (SAEs) See Section 5.5.5	*Details will be added locally*
Medical Expert:	[redacted], Japan.

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
ANCOVA	Analysis of Covariance
API	Astellas Pharma, Inc.
AST	Aspartate aminotransferase (GOT)
AUC	Area under drug concentration-time curve
β-AR	Beta-adrenergic receptor
BPH	Benign prostatic hypertrophy
BOO	Bladder outlet obstruction
BPO	Benign prostatic obstruction
BUN	Blood urea nitrogen
CA	Competent Authority
cAMP	Cyclic adenosine monophosphate
CK	Creatinine kinase
Cmax	Maximum observed plasma concentration
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum vitae
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report form
ED	Erectile dysfunction
EDC	Electronic Data Capture
EDTA-2K	Ethylene diaminetetraacetic acid dipotassium salt dihydrate
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
γ-GTP	gamma-glutamyl transferase
HUS	hours of undisturbed sleep
ICF	Informed Consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFIS	Intraoperative Floppy Iris syndrome
INR	International normalized ratio
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International study number
LA-CRF	Liver Abnormality Case Report form
LUTS	Lower urinary tract symptoms
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measure
NASH	Non-alcoholic steatohepatitis

Abbreviations	Description of abbreviations
OAB	Overactive Bladder
OAB-q	Overactive Bladder questionnaire
OABSS	Overactive Bladder Symptom Score
OTC	Over-the-Counter
PD	Protocol deviation
PDE5	Phosphodiesterase 5
PI	Package Insert
PK	Pharmacokinetic(s)
PPS	Per Protocol Set
PR	Pulse rate
PSA	Prostate-specific antigen
PTNS	Percutaneous Tibial Nerve Stimulation
PTP	Press-through Package
PVR	Postvoid residual
Q	Quartile
Qmax	Maximum urine flow rate
QoL	Quality of Life
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SFL	Screening failure log
SGLT	Sodium-glucose transporter
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reactions
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TURP	Transurethral resection of prostate
UFM	Uroflowmetry
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
WBC	White blood cell
WHODDE	World Health Organization Drug Dictionary Enhanced

Definition of Key Study Terms

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

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	
Sponsor: Astellas Pharma Inc. (API)	**Protocol Number:** 178-MA-3016
Name of Study Drug: Mirabegron	**Phase of Development:** 4
Title of Study: A Phase 4, Double-Blind, Randomized, Placebo-controlled Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Male Subjects with OAB Symptoms, while taking the Alpha Blocker, Tamsulosin, for BPH	
Planned Study Period: December 2015 to August 2017	

Study Objective(s)**:**

Primary Objective:

To study the efficacy of mirabegron versus placebo in male patients with overactive bladder (OAB) symptoms while taking the alpha blocker, tamsulosin, for benign prostatic hypertrophy (BPH)

Secondary Objective:

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

Other Objectives:

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

The hypothesis being tested is that mirabegron is superior to placebo in the treatment of OAB symptoms.

Planned Total Number of Study Centers and Location(s):

Approximately 55 centers (Japan: ~50 centers; Korea: ~5 centers)

Study Population:

Men ≥40 years of age with OAB symptoms and taking the alpha blocker, tamsulosin, for BPH

Number of Subjects to be Enrolled/Randomized:

A total of 550 subjects (490 in Japan; 60 in Korea), with 275 subjects randomized (1:1) to each treatment group.

Study Design Overview

This is a randomized, double-blind, placebo-controlled, parallel group, multi-center study that will compare mirabegron with placebo in the treatment of OAB symptoms in men who are taking tamsulosin for BPH.

If a drug for the treatment of BPH (e.g., PDE5 inhibitor or alpha 1 blocker other than tamsulosin) is to be changed to tamsulosin to enroll a subject in this clinical study, the change to tamsulosin should be done only after ICF signature.

Treatment group	Screening period (single-blind)	Treatment period (double-blind)
Tamsulosin 0.2 mg / Mirabegron 50 mg	●+□	→ ●+■
Tamsulosin 0.2 mg / Placebo		→ ●+□

● : Tamsulosin 0.2mg Tablet
■ : Mirabegron 50mg Tablet
□ : Mirabegron 50mg Placebo Tablet

At Visit 1 (Screening), subjects will enter into a 4-week single-blind Screening period after enrollment and will receive mirabegron 50 mg placebo and tamsulosin 0.2 mg once daily after breakfast. Subjects who meet all entry criteria at the end of the tamsulosin Screening period will be randomized at Visit 2 (Baseline) to receive mirabegron 50 mg or matching placebo for 12 weeks, in addition to daily treatment with tamsulosin 0.2 mg.

During the treatment period, the subject will complete a 3-day micturition diary 3 days before Visit 2 (baseline), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/End of Treatment). As part of the questionnaire, subjects will complete the Overactive Bladder Symptom Score (OABSS) and International Prostate Symptom Score (IPSS) questionnaires at Visit 1 (Screening), Visit 2 (Baseline), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/End of Treatment); and at Visit 1 (Screening), Visit 2 (Baseline), and Visit 5 (Week 12/End of Treatment), subjects will complete the Overactive Bladder questionnaire (OAB-q). Post-void residual (PVR) urine volume will be assessed at Visit 1 (Screening), Visit 2 (Baseline), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12/End of Treatment). The total duration of study participation per subject is 16 weeks.

Inclusion/Exclusion Criteria:

Inclusion:

Inclusion Criteria assessed at Visit 1 (Screening):

1. Patient has given written informed consent before starting the study in accordance with the informed consent form approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of each study center
2. Male outpatient ≥40 years of age at the time of informed consent
3. Patient has been under treatment with tamsulosin 0.2mg for at least 4 weeks before the start of the Screening period
4. Patient with a history of an average of at least 2 episodes of urgency per 24 hours and an average of 8 or more micturitions per 24 hours during the last 3 days before the start of the Screening period (verified by interview).
5. Patient who has no wish to have children in the future *(Unique to Japan)*.
6. Male subjects and their female spouses/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control* (at least one of which must be a barrier method), starting at Screening, continuing throughout the study period, and for 28 days after the final study drug administration.
7. Subject must not donate sperm, starting at Screening, continuing throughout the study period, and for 28 days after the final study drug administration.
8. Patient is willing and able to complete the micturition diary and questionnaires correctly.
9. Subject agrees not to participate in another interventional study while receiving treatment in this study.

*Highly effective forms of birth control include:

- Consistent and correct usage of established oral contraception.
- Established intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository *(Unique to Korea: with spermicidal foam/gel/film/cream/suppository).*
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method).

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

10. Subject with an average of at least 2 episodes of urgency per 24 hours and an average of 8 or more micturitions per 24 hours based on a 3-day micturition dairy from the Screening period.
11. Subject continues to meet all inclusion criteria of Visit 1.

Waivers to the inclusion criteria will NOT be allowed.

Exclusion:

Exclusion Criteria assessed at Visit 1 (Screening):

1. Patient with suspected symptoms of OAB, with onset only transient (e.g., drug-induced, psychogenic).
2. Patient with PVR urine volume >100 mL or Q max <5 mL/sec.
3. Patient with prostate-specific antigen (PSA) ≥4 ng/mL.
4. Patient with neurogenic bladder (e.g., spinal-cord lesions or other damage that will clearly affect urination; multiple sclerosis; Parkinson's disease) or a history of surgery that caused damage to the pelvic plexus.
5. Patient with urethral stricture or bladder-neck stenosis.
6. Patient with diabetic neuropathy complications.
7. Patient who has undergone a surgical procedure (e.g., transurethral resection of prostate [TURP], laser therapy), previous pelvic radiation therapy, or hyperthermia therapy that may affect urinary tract function.
8. Patient with significant stress incontinence (i.e., patients presenting with symptoms of only stress urinary incontinence) or postsurgical prostate incontinence, as determined by the Investigator.
9. Patient with an indwelling catheter or practices intermittent self-catheterization.
10. Patient with 3 or more episodes of recurrent urinary tract infection (UTI) within the last 6 months.
11. Patient with a UTI; prostatitis; chronic inflammation, such as interstitial cystitis; urinary calculus (e.g. ureteral calculus, urethral calculus, bladder calculus); 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, full transverse colon, and proximal portion of the descending colon are in the abdomen).
12. Patient with a concurrent malignancy or history of any malignancy (within the past 5 years), except for non-metastatic basal-cell or squamous-cell carcinoma of the skin that has been treated successfully.
13. Patient with serious heart disease (e.g. myocardial infarction, cardiac failure, uncontrolled angina pectoris, serious arrhythmia, use of pacemaker), liver disease, kidney disease, immunological disease, lung disease.
14. Patient who has received intravesical injection within the last 12 months with botulinum toxin, resiniferatoxin, or capsaicin.
15. Patient who has received electrostimulation therapy for OAB (e.g., sacral nerve stimulation or Percutaneous Tibial Nerve Stimulation [PTNS]).
16. Patient who has received a bladder training program or pelvic floor exercises <28 days prior to the start of the Screening period.
17. Patient with postural hypotension or syncope, hypokalemia, or closed-angle glaucoma.
18. Patient with evidence of QT prolongation on electrocardiogram (ECG), defined as QTcF >450 msec.
19. Patient with severe uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg.
20. Patient with a clinically significant ECG abnormality, as determined by the Investigator.
21. Patient who has severe renal impairment, defined as an estimated glomerular filtration rate of <29 mL/min/1.73m^2; end-stage renal disease; or is undergoing dialysis.

22. Patient with aspartate transaminase (AST) or alanine transaminase (ALT) >2 times the upper limit of normal (ULN), or gamma-glutamyl transferase (γ-GT) >3 times the ULN.
23. Patient with moderate or severe hepatic impairment, defined as Child-Pugh Class B or C.
24. Patient with hypersensitivity to any of the components of mirabegron, other beta-adrenergic receptor (β-AR) agonists, or any of the inactive ingredients.
25. Patient with ongoing alcohol and/or drug abuse.
26. Patient with or a history of mood disorder, neurotic disorder, or schizophrenia.
27. Patient with dementia, cognitive dysfunction, or clinically significant cerebrovascular disorder
28. Patient who has been treated with an experimental device <84 days or received an investigational agent <84 days prior to the start of the Screening period.
29. Patient has used any prohibited concomitant medication (defined in Appendix 12.1) <28 days (but, <1 year for 5α-reductase inhibitors) before the start of the Screening period.
30. Patient with any clinically significant condition, which in the opinion of the Investigator, makes the subject unsuitable for study participation.
31. Patient who is involved in the conduct of the study as an employee of the Astellas group, a third party associated with the study, or the study site team.

Exclusion Criteria assessed at Visit 2 (Baseline):

32. Subject fulfills any exclusion criteria of Visit 1 at Visit 2.
33. Subject was noncompliant during the 4 week tamsulosin Screening period, defined as taking less than 80% or greater than 120% of prescribed dose of study medication.
34. Subject had an average total daily urine volume >3000 mL, as recorded in the 3-day micturition diary.
35. Subject is found to meet any of the exclusion criteria for enrollment at Visit 1 (Screening)

Waivers to the exclusion criteria will NOT be allowed.

Investigational Product(s)**:** Mirabegron 50 mg tablet

Dose(s): 50 mg once daily

Mode of Administration: Oral route, after breakfast

Comparative Drug(s): Placebo matched to mirabegron 50 mg tablet

Dose(s): Once daily

Mode of Administration: Oral route, after breakfast

Drug(s) for Screening Period: Mirabegron 50 mg matching placebo along with tamsulosin 0.2 mg
Dose(s): Mirabegron 50 mg placebo and tamsulosin 0.2 mg once daily
Mode of Administration: Oral route, after breakfast

Concomitant Medication Restrictions or Requirements:

The excluded concomitant meditations (defined in Appendix 12.1) can be allowed to use under the conditions below:

1. From the day following the dispensing of the study drug for the Screening period to the end of the Treatment period, none of the prohibited concomitant medications listed in Appendix 12.1 should be used. The following drugs, however, may be concomitantly used:
    - Eye drops
    - Transdermal formulations, excluding β-agonists and drugs for the treatment of urinary storage and voiding dysfunction
    - Nasal drops, excluding drugs for diabetes insipidus
    - Topical agents
    - Inhaled β-agonists used to relieve acute symptoms, such as bronchial asthma
    - Chinese herbal medicines used for the treatment of conditions other than urinary storage and voiding dysfunction
2. The following drugs may be used concomitantly for a short period of time (up to a total of 5 days during the interval from the day following a visit to the next visit), except during the micturition diary period:
    - Parasympathetic inhibitors/parasympatholytic drugs for peptic ulcer, etc.
    - Antihistamines, ephedrine hydrochloride, and methylephedrine hydrochloride for common cold, etc.
3. Transient concomitant use of parasympathetic inhibitors/parasympatholytic drugs will be allowed, if used in preparation for an examination, except during the micturition diary period.
4. Concomitant treatment with 5α-reductase inhibitors will be allowed (the dosage shall not be changed for study period), if the subject has been on treatment for a year or more.
5. Transient concomitant use of phosphodiesterase 5 (PDE5) inhibitor for treatment of erectile dysfunction (ED) will be allowed, except during the micturition diary period.
6. Nonpharmacological therapy for OAB, such as biofeedback therapy, bladder training, or pelvic-floor muscle exercise will be prohibited from 4 weeks before (<28 days) the start of the Screening period to the end of the Treatment period.

Duration of Treatment: Subjects will receive mirabegron 50 mg or matching placebo (along with tamsulosin 0.2 mg) once daily for 12 weeks after a 4-week Screening period on tamsulosin 0.2 mg + mirabegron 50 mg placebo. Subject participation will last approximately 16 weeks.

Endpoints for Evaluation:

Primary:

- Change from Baseline to End of Treatment in mean number of micturitions/24 hours, based on a 3-day micturition diary.

Secondary:

Change from Baseline to End of Treatment in:

- Mean number of urgency episodes/24 hours
- Mean number of urgency incontinence episodes/24 hours
- Mean number of incontinence episodes/24 hours
- Mean number of nocturia episodes
- Mean volume voided per micturition
- Total OABSS score
- Subscale score from OABSS score
- Total IPSS score
- Subscale score from IPSS score
- Symptom Bother and Total Health-Related Quality of Life scores, as assessed by the OAB-q questionnaire.

Exploratory:

Change from Baseline to End of Treatment in:

- Hours of undisturbed sleep (HUS)
- First nighttime voided volume
- Subscale scores from OAB-q
- Normalization rate of OABSS
- Normalization rate of micturition diary (number of episodes of micturition/urgency/urgency incontinence/incontinence/nocturia)

Safety Variables:

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

Statistical Methods:

Sample size justification:

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

For the Full Analysis set (FAS), 248 subjects per treatment group will provide 90% power to detect a 0.7 reduction in the mean number of micturitions/24 hours in the mirabegron group compared with the placebo group, at a two-sided alpha level of 0.05. A standard deviation (SD) of 2.4 is assumed.

Assumptions for the mean reduction and SD are based on data from previous studies (i.e., 178-CL-048, 178-CL-090 and 905-JC-001). If 90% of the randomized subjects are evaluable for efficacy, 550 subjects should be randomized, with 275 subjects randomized to each treatment group.

Efficacy:

The primary analysis set is the FAS, which will include all subjects who meet the following criteria:

- Those who took at least one dose of double-blind study medication after randomization
- Those who had a micturition measurement in the Baseline visit diary and at least one micturition measurement in the post- Baseline visit diary

Subjects who are included in the FAS and who meet all of the following criteria will be included in the Per Protocol Set (PPS):

- Those subjects who did not violate the inclusion or exclusion criteria
- Those subjects with no less than 80% drug compliance during the Screening and Treatment period
- Those subjects who took the study drug for at least 42 days during the Treatment period, from the day following dispensing. However, any subjects who discontinued the study for efficacy-related reasons, such as insufficient therapeutic effect, will be included in the PPS, even if the drug was taken for fewer than 42 days.
- Those subjects whose diary was completed for at least 2 of the 3 consecutive days for Visit 2 and the last visit during the Treatment period.
- Those subjects who did not receive any of the prohibited concomitant medications/therapies that could affect the evaluation of efficacy.

The End-of-Treatment assessment will be analyzed to account for subjects who prematurely discontinued from the study. The End-of-Treatment assessment is defined as the last post-Baseline visit assessment during the double-blind study period for which data for the primary efficacy variable is available.

Continuous variables will be summarized using descriptive statistics (i.e., mean, SD, minimum, median, Quartile 1 [Q1], Q3, and maximum). Categorical variables will be described using absolute and relative frequency.

The primary efficacy variable is the change from Baseline to End-of-Treatment in the mean number of micturitions/24 hours, based on the 3-day micturition diary. It will be analyzed using an Analysis of Covariance (ANCOVA), including treatment group and region as fixed factors and baseline as a covariate. Within the framework of the ANCOVA model, point estimates and two-sided 95% confidence intervals for the mean change from Baseline within each treatment group, as well as for the difference in mean change from Baseline between the mirabegron treatment group and placebo, will be calculated.

The primary endpoint and all secondary endpoints will be analyzed using the FAS, with the PPS used as a supportive analysis for the secondary endpoints.

Pharmacokinetics: Not applicable.

Pharmacodynamics: Not applicable.

Safety:
The safety analyses will be done on the Safety Analysis Set (SAF), which consists of subjects who received at least one dose of double-blind study medication. Treatment-emergent AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and will be summarized by treatment group. All laboratory data, including clinical chemistry, hematology, and urinalysis will be descriptively summarized for Baseline, Visits 3, 4, and 5, as well as the change from Baseline to each visit. Changes from Baseline in vital signs will be summarized by treatment group. In addition, PVR volume, as measured by ultrasonography and bladder scanning, will be summarized by change from Baseline.

Interim analyses: Not applicable.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Figure 1 Study Design Flow Chart

Study Schematic Diagram

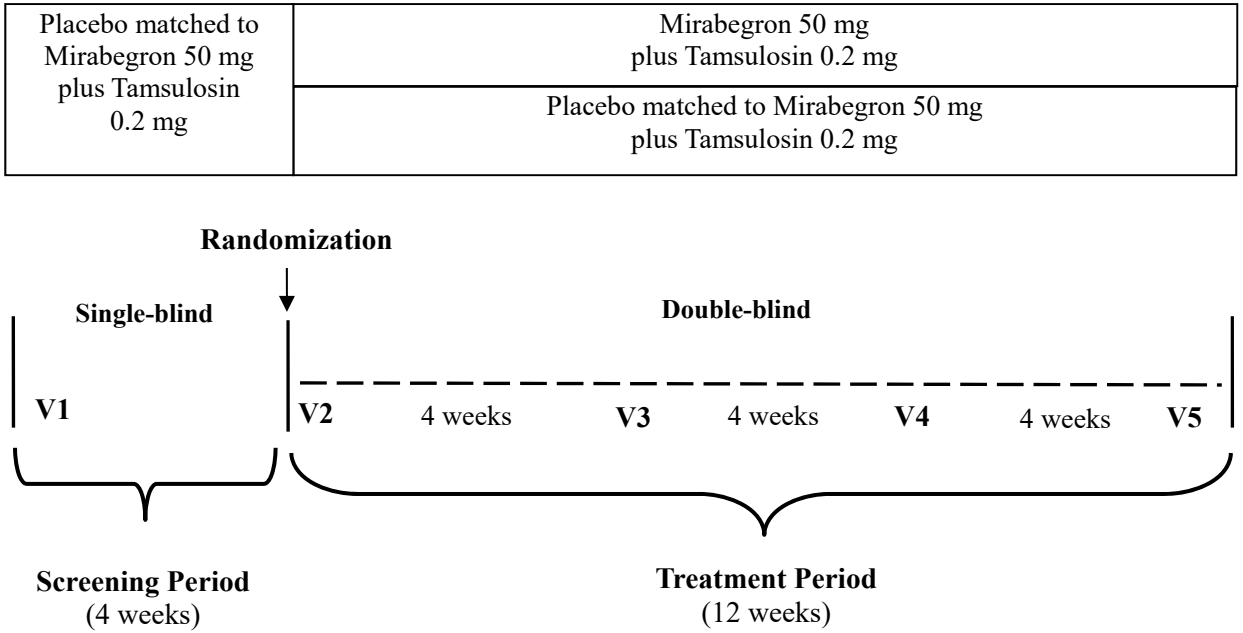


Table 1: Schedule of Assessments

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

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

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

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

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

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

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

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

f. Blood samples need not be under fasting conditions.

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

h. At the Tamsulosin Screening visit (Visit 1), all subjects will be provided a micturition diary that will be used to record the date and time of each of their micturitions, episodes of incontinence, urgency, and voiding volume. Voiding volumes will be collected at Visit 2 (Baseline) and Visit 5 (Week 12). Additionally, the diary will be used to record daily medication intake and self-measurement of blood pressure and pulse rate. Subjects will be instructed to begin completing the micturition diary 3 days prior to each in-office study visit, including Visit 2 (Baseline) and Visits 3 through 5 (Treatment Period), and to complete the diary for the full 3 days.

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

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

VI. ACCEPTABLE RANGE OF SCHEDULE OF ASSESSMENTS

Acceptable Time Ranges for Efficacy Assessments

A. Micturition Diary:

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

B. OABSS, IPSS and IPSS (QoL), OAB-q*

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

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

Acceptable Time Ranges for Safety Tests

Vital Signs

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

Hematology and Serum Chemistry

Time Point	Scheduled Day	Acceptable Time Range
Visit 1	-28	Day-35 to Day -21
Visit 2	1	-
Visit 5	85	Day 78 to Day 92
Final evaluation during Treatment period	Must be performed within 7 days after the last dose of study drug	

Urinalysis

Time Point	Scheduled Day	Acceptable Time Range
Visit 1	-28	Day -35 days to Day -21 days
Visit 2	1	-
Visit 5	85	Day 78 to Day 92
Final evaluation during Treatment period	Must be performed within 7 days after the last dose of study drug	

Residual Urine Volume

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

Uroflowmetry

Time Point	Scheduled Day	Acceptable Time Range
Visit 1	-28	Day-35 to Day -21
Visit 2	1	-
Visit 5	85	Day 78 to Day 92
Final evaluation during Treatment period	Must be performed within 7 days after the last dose of study drug	

Self-measurement of blood pressure and pulse rate by patients

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

1 INTRODUCTION

1.1 Background

Benign prostatic hyperplasia (BPH) is associated with lower urinary tract symptoms (LUTS) caused by benign enlargement of the prostate gland. The prevalence of LUTS is increasing with advancement of the aging society (especially, ≥50 years of age). These symptoms may be related to the obstructive effect of prostate enlargement, secondary effects on the bladder, or complications of BPH, and include symptoms associated with voiding, post-micturition, and bladder storage. The LUTS associated with BPH have been shown to be highly bothersome to patients, resulting in a negative impact on sleep, mental health, work productivity, and overall health-related quality of life (QoL)[1-4]. Therefore, a decrease in the level of bothersome symptoms may be a better indicator of patient satisfaction with BPH treatment in addition to the measures of symptom frequency.

Recommended first-line pharmacotherapy for LUTS associated with BPH is with an alpha1-adrenergic receptor antagonist (alpha1-blocker), which can alleviate both voiding symptoms and storage symptoms[5]. Tamsulosin is the most commonly used alpha1-blocker for this indication. However, LUTS in patients with both bladder outlet obstruction and detrusor overactivity may not sufficiently improve with alpha1-blocker monotherapy, and as a result, overactive bladder (OAB) symptoms may persist.

OAB is a symptom complex that is characterized by urinary urgency, with or without urinary incontinence, and is often associated with urinary frequency and nocturia[6]. The etiology of OAB is multifactorial, with urgency symptoms associated with overactivity of the detrusor muscle, which can be of neurogenic, myogenic, or idiopathic origin. Antimuscarinics (AMs) are the mainstay of pharmacological treatment of OAB, and represent the most commonly prescribed drugs for this condition, as there is substantial evidence of their efficacy.

A number of studies[7-13], have reported efficacy of AMs as add-on therapy to an alpha1-blocker for the treatment of residual OAB symptoms. The ASSIST (add-on therapy of solifenacin succinate for BPH with OAB symptoms treated by tamsulosin hydrochloride) study[7], which involved combined treatment with tamsulosin and solifenacin, is the only randomized, controlled, double-blind, placebo-controlled clinical trial of tamsulosin and an AM, and one of the most important studies in Japan that support the efficacy of add-on therapy for OAB. However, there are tolerability concerns with AMs, due to their actions on the salivary gland, intestine, and eye, resulting in side effects such as dry mouth, constipation, and blurred vision, all of which limits their chronic use. Also, combination therapy with an alpha1-blocker increases the risk of urinary retention, which occurs with an estimated incidence in men of 6.8 per 1000 person-years[14]. Urinary retention is painful, and significantly reduces QoL.

Mirabegron, discovered by Astellas Pharma Inc. (API) and approved in Japan in 2011 and Korea in 2014, is a highly selective β3-adrenergic receptor (β3-AR) agonist that offers a new treatment option for patients with OAB. Mirabegron has been demonstrated to improve OAB symptoms by stimulating β3-AR in the bladder smooth muscle, resulting in relaxation of the bladder and enhanced urine storage[15, 16]. In the Phase 3 studies for

mirabegron, the incidence of adverse events (AEs) among subjects receiving mirabegron was no greater than among subjects receiving placebo[17-21].

It is expected that mirabegron will be better tolerated than AMs, and therefore, add-on treatment with mirabegron may offer a safer alternative to the use of AMs for the treatment of OAB. There are two studies on the add-on therapy in Japan. The one is an open-label, randomized, controlled study that compared co-administration of mirabegron and tamsulosin to tamsulosin monotherapy[22]. The other is a nonrandomized, open-label study of mirabegron as add-on treatment to tamsulosin[23]. The add-on therapy of mirabegron to tamsulosin proved the effectiveness in the studies, otherwise, these were non-placebo and non-double-blind studies. Therefore, this study will be the first double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of mirabegron as add-on treatment to tamsulosin in subjects with BPH and residual OAB symptoms.

1.2 Non-clinical and Clinical Data

Nonclinical data:

1. β3-AR stimulatory effect:

   In an experiment using cells expressing human β3-AR, mirabegron induced a concentration-dependent increase of cyclic adenosine monophosphate (cAMP) levels in the cells. In cells expressing human β1-AR and β2-AR, mirabegron led to a minor increase of intracellular cAMP levels.

2. Bladder relaxing effect:

   In an experiment using isolated rat bladder, mirabegron induced an increase of cAMP levels in the tissues. In isolated rat and human bladders with carbachol-induced sustained contraction, mirabegron demonstrated a relaxing effect.

3. Effect on intravesical pressure:

   In anesthetized rats, mirabegron decreased the resting intravesical pressure.

4. Effects on bladder function:

   In conscious Cynomolgus monkeys, mirabegron led to an increased mean volume voided per micturition as well as decreased micturition frequency. In conscious rats with cerebral infarction, mirabegron led to an increased mean volume voided per micturition.

Please refer to the Package Insert (PI) for further information on nonclinical studies of mirabegron.

Clinical data:

Co-administration of mirabegron with tamsulosin:

In an open-label, randomized, controlled study that compared co-administration of mirabegron and tamsulosin to tamsulosin monotherapy in 94 subjects with OAB induced by benign prostatic obstruction (BPO), efficacy was assessed by changes from baseline in the Overactive Bladder Symptom Score (OABSS) and International Prostate Symptom

Score (IPSS). The efficacy results demonstrated a significant improvement in the combination therapy group compared to the tamsulosin monotherapy group in OABSS total score (-2.21 vs. - 0.87; p=0.012) and OABSS urgency score (-1.34 vs. -0.55; p=0.006). The changes from baseline in scores for OABSS daytime frequency, the IPSS storage symptom subscore, and the QoL Index after 8 weeks of treatment were all significantly greater in the combination treatment group than in the tamsulosin monotherapy group. Also, the change in post-void residual urine volume was significantly greater in the combination therapy group than in the tamsulosin monotherapy group. Urinary retention was observed in 1 subject in the combination therapy group. The authors concluded that mirabegron combined with tamsulosin was an effective and safe treatment for patients with BPO with OAB symptoms after tamsulosin monotherapy[22].

In a nonrandomized, open-label study of mirabegron as add-on treatment to tamsulosin in 26 Japanese male subjects with OAB, efficacy was assessed by changes from baseline in OABSS, IPSS, free uroflowmetry (UFM), filling cystometry, and pressure-flow study (PFS). The results showed that mirabegron treatment significantly improved the OABSS (from 8.5 ± 2.3 to 4.7 ± 2.5; p <0.001), voided volume (from 135 ± 47 to 181 ± 102 mL; p = 0.01), maximum flow rate (from 10.7 ± 3.7 to 13.5 ±6.4 mL/sec; p<0.01), and average flow rate (from 5.5 ± 1.9 to 7.1 ±3.3 mL/sec; p<0.01). Also, maximum cystometric capacity significantly increased from 170 ±98 to 212 ±95 mL (p = 0.01). No subject discontinued mirabegron treatment due to an adverse event (AE). The authors concluded that the combined use of mirabegron and tamsulosin was a safe and effective treatment option for male patients with OAB, as it improved urine storage and voiding symptoms, urodynamic bladder storage, and urine flow rate, with no significant deleterious effect on bladder contractility[23].

1.3 Summary of Key Safety Information for Study Drugs

For detailed safety information on the study medications, please refer to the Package Inserts for mirabegron and tamsulosin.

1.4 Risk-Benefit Assessment

1.4.1 Foreseeable Risks with Mirabegron

1.4.1.1 Japanese Labeling

The following information on adverse reactions is from the Japanese labeling for Betanis®Tablets 25 mg and 50 mg (August 2015, 8th version):

Adverse Reactions

Adverse reactions to this product including abnormal laboratory values were reported in 313 (25.9%) of 1,207 patients with OAB in the safety evaluation in Japan. Major adverse reactions included 45 cases (3.7%) of γ-GTP increased, 35 cases (2.9%) of constipation, 31 cases (2.6%) of CK (CPK) increased, 30 cases (2.5%) of ALP increased, 21 cases (1.7%) of dry mouth, 21 cases (1.7%) of ALT (GPT) increased, 19 cases (1.6%) of AST (GOT) increased, 17 cases (1.4%) of protein urine present and 15 cases (1.2%) of white blood cell count decreased (At the time of approval: July 2011).

(1) Clinically significant adverse reactions

Urinary retention (incidence unknown): Since urinary retention may occur, patients should be monitored carefully. If any symptom is observed, this product should be discontinued and appropriate measures should be taken.

(2) Other Adverse Drug Reactions

System Organ Class	Preferred Term Incidence ≥1%, <5%	Preferred Term Incidence <1%	Preferred Term Incidence unknown
Blood and lymphatic system disorders	White blood cell count decreased	Platelet count increased White blood cell count increased Platelet count decreased	
Cardiac disorders		Bundle branch block right Palpitations Supraventricular extrasystoles Tachycardia Ventricular extrasystoles Blood pressure increased Heart rate increased	
Ear and labyrinth disorders		Vertigo	
Eye disorders			Vision blurred
Gastrointestinal disorders	Constipation Dry mouth	Abdominal discomfort Abdominal distension Diarrhoea Duodenal ulcer Gastritis Stomatitis	Nausea Vomiting Abdominal pain Abdominal pain upper Abdominal pain lower
General disorders and administration site conditions		Malaise Oedema Thirst	Chest discomfort Chest pain
Hepatobiliary disorders	AST (GOT) increased ALT (GPT) increased γ-GTP increased ALP increased	Bilirubin increased	
Infections		Cystitis Urinary sediment abnormal	
Metabolism and nutrition disorders	CK (CPK) increased	CK (CPK) decreased Blood glucose increased Blood glucose decreased Cholesterol increased, Uric acid increased	Decreased appetite
Nervous system disorders		Dizziness Headache	Tremor Hypoaesthesia Somnolence
Renal and urinary disorders	Protein urine present	Glucose urine present Creatinine increased BUN increased BUN decreased Residual urine	
Skin and subcutaneous tissue disorders		Rash Urticaria	Pruritus

System Organ Class	Preferred Term Incidence ≥1%, <5%	Preferred Term Incidence <1%	Preferred Term Incidence unknown
Vascular disorders		Hypertension	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CPK = creatine phosphokinase; GTP = glutamyl transpeptidase

1.4.1.2 Korean Labeling

The following information on adverse reactions is from the Korean labeling for Betmiga (mirabegron) prolonged-release 25 mg and 50 mg tablets (April 2015):

Adverse reactions

(1) Adverse reactions reported in foreign clinical trials

The safety of mirabegron was evaluated in 8433 subjects with OAB, of which 5648 received at least 1 dose of mirabegron in the Phase 2/3 program, and 622 subjects received mirabegron for at least 1 year. In the three 12-week Phase 3 double-blind, placebo-controlled studies, 88% of the subjects completed treatment with mirabegron and 4% discontinued from the study due to AEs. Most adverse drug reactions were mild-to-moderate in severity.

The most common adverse reactions reported in subjects treated with mirabegron 50 mg were urinary tract infections (UTI; 2.9%) and tachycardia (1.2%). Tachycardia led to discontinuation in 0.1% of subjects receiving mirabegron 50 mg. No cases of UTI in patients receiving mirabegron 50 mg led to discontinuation from the study. Serious adverse reactions included atrial fibrillation (0.2%).

The adverse reactions observed during the long-term (1-year) active-controlled (muscarinic antagonist) study were similar in nature and severity to those observed in the three 12-week placebo-controlled studies.

Adverse Reactions Observed in Subjects Treated with Mirabegron in Three Phase 3, Double-Blind, Placebo-Controlled Studies

MedDRA System Organ Class	Common ARs (1/100≤ , <1/10)	Uncommon ARs (1/1,000≤ , <1/100)	Rare ARs (1/10,000≤ , <1/1,000)
Infections and infestations	Urinary tract infection	Vaginal infection	
Eye disorders			Eyelid oedema
Cardiac disorders	Tachycardia	Palpitation Atrial fibrillation Blood pressure increased	
Gastrointestinal disorders		Dyspepsia Gastritis	Lip oedema
Skin and subcutaneous tissue disorders		Urticaria Rash Macular rash Papular rash Pruritus	Leukocytoclastic vasculitis Purpura
Musculoskeletal and connective tissue disorders		Joint swelling	
Urinary and reproductive system disorders		Vulvovaginal pruritus Cystitis	
Metabolism and nutrition system disorders		GGT increased AST increased ALT increased	

ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; MedDRA = Medical Dictionary for Regulatory Activities

In clinical trials conducted in Asia, the safety of mirabegron was evaluated in 1103 patients with OAB in Phase 3, double-blind placebo- and active-controlled studies. The most common (≥2.0%) treatment-emergent adverse reactions reported in Asian patients treated with mirabegron 50 mg for 12 weeks was dry mouth (4.1%). The incidence of dry mouth was similar in the placebo group (4.4%), but higher in the active control group (8.1%), which was consistent with the pharmacological effects of antimuscarinics.

Global post-marketing experience with mirabegron includes spontaneous reports of urinary retention and nausea, although the frequency and causality of these reported adverse reactions cannot be reliably determined.

In a Phase 3, 12-week, multicenter, randomized, double-blind, placebo- and active-controlled parallel-group study, the most common treatment-emergent adverse reaction (≥2% in any treatment group) was dry mouth, reported in 15/366 (4.1%) subjects receiving mirabegron, 16/366 (4.4%) subjects receiving placebo, and 30/371 (8.1%) of subjects receiving the antimuscarinic, tolterodine.

1.4.1.3 Clinically significant adverse drug reactions with mirabegron treatment

Identified risks with mirabegron treatment include increased heart rate and tachycardia as well as hypersensitivity reactions. Potential risks include QT prolongation, increased

blood pressure, UTI, urinary retention, fetal disorders after exposure during pregnancy, and events induced by increased exposure to CYP2D6 substrates. The risks of QT prolongation, increased heart rate, or increased blood pressure are greater with increasing exposure at supratherapeutic doses, and can be mitigated with optimal dose selection. The maximum therapeutic dose of mirabegron, based on the overall benefit-risk is 50 mg once daily. In patients with severe renal impairment or moderate hepatic impairment, the dose of mirabegron is 25 mg once daily. Further dose adjustments for renal impairment, hepatic impairment and concomitant use of strong CYP3A4 inhibitors may be required.

Overall, mirabegron at the therapeutic oral doses of 25 mg and 50 mg once daily is considered to be a safe and effective for the treatment of adult patients with OAB. The benefits of treatment exceed the risk associated with the use of the product. Mirabegron was approved in Japan in 2011, and to date has been approved in more than 50 countries, including the United States and European Union.

1.4.2 Foreseeable Risks with Tamsulosin

1.4.2.1 Japanese Labeling

The following information on adverse reactions is from the Japanese labeling for Harnal® D (tamsulosin hydrochloride) 0.1 mg and 0.2 mg tablets (January 2013, 9th version):

Adverse Reactions

Adverse reactions, including abnormalities in clinical laboratory findings, were observed in 104 (2.2%) of 4,724 subjects in clinical trials prior to approval and in drug-use surveys for HARNAL Capsules. The major adverse reactions associated with tamsulosin use were dizziness and stomach discomfort.

Clinically Significant Adverse Reactions

Syncope/unconsciousness (incidence unknown): Since transient unconsciousness may appear with a decrease in blood pressure, patients should be carefully observed. If any abnormal findings are observed during treatment, administration should be discontinued and appropriate measures should be taken.

Hepatic function disorder or jaundice (incidence unknown for each): Since increases of AST (GOT), ALT (GPT), or jaundice may appear, patients should be carefully observed. If any abnormal findings are observed during treatment, appropriate measures, such as drug discontinuation, should be taken.

Other Adverse Reactions

System Organ Class	Incidence		
	≥0.1% , <5%	**<0.1%**	**Unknown**
Psychoneurologic	Dizziness Swaying feeling	Dizziness on standing up Headache Sleepiness	Bad mood Numbness
Cardiovascular		Blood pressure decreased Orthostatic hypotension Tachycardia Palpitations	Arrhythmia
Hypersensitivity*		Itching Rash	Urticaria Erythema multiforme
Gastrointestinal	Stomach discomfort	Queasy Vomiting Thirst Constipation Stomach heaviness Gastralgia Anorexia Diarrhea Dysphagia	
Others		Nasal congestion Oedema Urinary incontinence Burning sensation of pharynx General malaise	Dysgeusia Gynecomastia Priapism Ejaculation disorder Intraoperative floppy iris syndrome Vision blurred Visual impairment Hot flush Feeling hot Burning sensation

* If hypersensitivity reactions are observed, treatment should be discontinued.

1.4.2.2 Korean Labeling

The following information on adverse reactions is from the Korean labeling for Harnal®D (tamsulosin hydrochloride) 0.2 mg tablets (June 2015):

Adverse Reactions

Syncope/unconsciousness (incidence unknown): Since transient unconsciousness etc. may appear with the decrease of blood pressure, patient should be carefully observed. If such reactions are observed during treatment, administration should be discontinued and appropriate measures should be taken.

Nervous system: Dizziness, giddiness, dizziness on standing up, headache, somnolence, nervousness, insomnia, libido, bad mood (incidence unknown), and numbness (incidence unknown) decreased may occasionally appear.

Cardiovascular system: Tachycardia, blood pressure dropped, orthostatic hypotension, palpitation, and arrhythmia may occasionally appear.

Hypersensitivity: Rash, itching, and urticarial may occasionally appear. If such reactions are observed during treatment, administration should be discontinued.

Digestive system: Nausea, vomiting, stomach discomfort, stomach heaviness, stomach ache, appetite decreased, dipsosis, obstipation, diarrhea, tooth disorder, and dysphagia may occasionally appear.

Hepatic dysfunction or jaundice (Incidence unknown for each): Since increases of AST, ALT, or jaundice may appear, patient should be carefully observed. If such reactions are observed during treatment, appropriate measures, such as drug discontinuation, should be taken.

Others: Dysphagia, burning sensation of pharynx, generalized fatigue, nasal obstruction, epistaxis, edema, urinary incontinence, dysgeusia, gynaecomastia, priapism, infection, asthenia, back pain, chest pain, rhinitis, pharyngitis, cough increased, sinusitis, abnormal ejaculation, amblyopia, Intraoperative Floppy Iris Syndrome (IFIS), vision blurred, visual impairment, erythema multiforme, and dermatitis exfoliative may occasionally appear.

The following ARs have been identified in post-marketing surveillance reports in the United States: allergic-type reactions, such as skin rash; pruritus; angioedema of tongue, lips, and face and urticaria have been reported with positive rechallenge in some cases. Priapism has been rarely reported. Infrequent reports of palpitations, hypotension, skin desquamation, constipation, and vomiting have been received during the post-marketing period. During cataract and glaucoma surgery, a variant of small-pupil syndrome known as IFIS has been reported in association with alpha1 blocker therapy. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: 1) the seriousness of the reaction; 2) the frequency of reporting; or 3) the strength of causal connection to the drug.

As elderly patients are more likely to experience renal dysfunction, they should be started on a lower dose of tamsulosin (0.1 mg) and be carefully monitored. If no abnormalities are detected, the dose can be increased to 0.2 mg.

1.4.3 Potential Risks with Combined Treatment

Alpha-adrenergic receptor antagonists, like tamsulosin, are associated with cardiovascular side effects, such as orthostatic hypotension, syncope, tachycardia, and palpitations. An open-label, randomized, two-arm, two-sequence, crossover Phase 1 study in 48 healthy men aged 44 to 72 years of age evaluated the potential pharmacokinetic (PK) and cardiovascular interactions with concomitant tamsulosin and mirabegron treatment[24].

The effect of steady-state mirabegron 100mg/day on single-dose 0.4mg/day tamsulosin was evaluated in 1 treatment arm, and the effect of steady-state tamsulosin on single-dose mirabegron was evaluated in the second treatment arm. The PK results showed that with combined treatment, the maximum observed plasma concentration (C_{max}) and area under the drug concentration-time curve (AUC) for tamsulosin increased ~60%, and mirabegron exposure decreased by ~16%.

With respect to cardiovascular safety, the combined treatment resulted in no statistically significant changes in pulse rate (PR) or systolic blood pressure (SBP), compared to monotherapy, up to 12 hours after dosing. Although mean diastolic blood pressure (DBP) was significantly lower with combination treatment, the effect was small and not associated with orthostatic symptoms or an increase in positive orthostatic stress tests. Furthermore, orthostatic events were balanced across the treatment groups.

Thus, the results of this study showed that with co-administration, the increase in tamsulosin exposure and decrease in mirabegron exposure were not associated with clinically relevant pharmacodynamic interactions between the two drugs.

1.4.4 Potential Benefits

Although OAB is not a life-threatening disease, it has profound psychological and social influences on patients, their families, and their caregivers, and may lead to a decline in quality of life.

Mirabegron is a highly selective β3-AR agonist that activates β3-ARs in the detrusor muscle of the bladder, resulting in muscle relaxation and an increase in bladder capacity, thereby improving OAB symptoms of urinary urgency, frequency, and urge urinary incontinence. Mirabegron has a more favorable safety profile than antimuscarinic agents, which are often associated with dry mouth, constipation, and blurred vision.

Tamsulosin is an alpha adrenergic blocker indicated for the treatment of BOO associated with BPH. Its mechanism of action is inhibition of alpha1 ARs in the urethra and prostate.

Mirabegron should be an effective add-on treatment to mitigate OAB symptoms that persist in patients treated with tamsulosin for BPH-associated BOO.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

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

2.2 Study Design and Dose Rationale

2.2.1 Study Design

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

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

At the conclusion of the 4-week tamsulosin Screening period, subjects will complete a 3-day micturition diary just prior to Visit 2 (Baseline). Subjects who meet entry criteria at the end of the tamsulosin Screening period will be randomized (at Visit 2) to receive

either mirabegron 50 mg or matching placebo for 12 weeks of double-blind treatment, while continuing their treatment with tamsulosin 0.2 mg daily. Randomization will be in a 1:1 ratio, with 275 subjects randomized to each treatment group. The key efficacy assessments are as follows:

- Subjects will complete a 3-day micturition diary 3 days before Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12).
- Subjects will complete the Overactive Bladder Symptom Score (OABSS) and International Prostate Symptom Score (IPSS) at Visit 1 (Screening), Visit 2 (Baseline), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12).
- Subjects will complete the Overactive Bladder questionnaire (OAB-q) at Visit 1 (Screening), Visit 2 (Baseline), and Visit 5 (Week 12).

Safety and tolerability of mirabegron administered concomitantly with tamsulosin will be assessed by the incidence and severity of treatment-emergent adverse events (TEAEs), laboratory parameters (i.e., serum chemistry, hematology, and urinalysis), vital signs measurements (i.e., sitting systolic and diastolic blood pressure and pulse rate), post-void residual (PVR) urine volume, and maximum urine flow rate (Qmax).

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

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

2.2.2 Dose Rationale

As this study is being conducted in adult men with OAB, it will employ the approved dose and dosing regimens prescribed in the respective Package Inserts for each drug:

- The dose of mirabegron is 50 mg once daily by the oral route.
- The dose of tamsulosin is 0.2 mg once daily by the oral route.

The 4-week Screening period will be sufficient for evaluation of baseline symptoms with tamsulosin monotherapy.

The 12-week double-blind Treatment period for mirabegron versus placebo will allow sufficient time to assess the treatment effect, as well as safety and tolerability of mirabegron administered concomitantly with tamsulosin.

2.3 Endpoints

2.3.1 Primary Endpoint

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

2.3.2 Secondary Endpoints

The secondary endpoints include the change from Baseline to End of Treatment in:

- Mean number of urgency episodes/24 hours
- Mean number of urgency incontinence episodes/24 hours
- Mean number of incontinence episodes/24 hours
- Mean number of nocturia episodes

- Mean volume voided per micturition
- Total OABSS score
- Subscale score from OABSS score
- Total IPSS score
- Subscale score from IPSS score
- Symptom Bother and Total Health-Related Quality of Life scores, as assessed by OAB-q questionnaire.

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

Subjects will complete the OABSS and IPSS/IPSS (QoL) assessments at Visit 1, Visit 2, Visit 3, Visit 4, and Visit 5.

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

2.3.3 Exploratory Endpoints

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

- Hours of undisturbed sleep (HUS)
- First nighttime voided volume
- Subscale scores from OAB-q scores
- Normalization rate of OABSS
- Normalization rate of micturition diary (number of episodes of micturition/urgency/urgency incontinence/incontinence/nocturia)

2.3.4 Safety Endpoints

- Incidence and severity of TEAEs
- Vital signs: sitting systolic and diastolic blood pressure and pulse rate (home based self-measurements and office measurements)
- Laboratory parameters (serum chemistry, hematology, and urinalysis)
- PVR urine volume
- Qmax

3 STUDY POPULATION

3.1 Selection of Study Population

Patients with OAB will be eligible for enrollment in the study, based on the following inclusion and exclusion criteria.

3.2 Inclusion Criteria

A patient is eligible for enrollment in the study if all of the following apply:

Inclusion Criteria assessed at Visit 1 (Screening):

1) Patient has given written informed consent before starting the study in accordance with the informed consent form approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of each study center

2) Male outpatient ≥40 years of age at the time of informed consent
3) Patient has been under treatment with tamsulosin 0.2mg for at least 4 weeks before the start of the Screening period
4) Patient with a history of an average of at least 2 episodes of urgency per 24 hours and an average of 8 or more micturitions per 24 hours during the last 3 days before the start of the Screening period (the conditions are checked by interview).
5) Patient who has no wish to have children in the future (*Unique to Japan*).
6) Male subjects and their female spouses/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control* (at least one of which must be a barrier method) starting at Screening, continuing throughout the study period, and for 28 days after the final study drug administration.
7) Subject must not donate sperm, starting at Screening, continuing throughout the study period, and for 28 days after the final study drug administration.
8) Patient is willing and able to complete the micturition diary and questionnaires correctly.
9) Subject agrees not to participate in another interventional study while receiving treatment in this study.

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

1) Subject with an average of at least 2 episodes of urgency per 24 hours and an average of 8 or more micturitions per 24 hours, based on the 3-day micturition diary from the Screening period.
2) Subject continues to meet all inclusion criteria of Visit 1.

Waivers to the inclusion criteria will NOT be allowed.

*Highly effective forms of birth control include:
- Consistent and correct usage of established oral contraception.
- Established intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository *(Unique to Korea: with spermicidal foam/gel/film/cream/suppository).*
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method)

3.3 Exclusion Criteria

Exclusion Criteria assessed at Visit 1 (Screening):

1. Patient with suspected symptoms of OAB, with onset only transient (e.g., drug-induced, psychogenic).
2. Patient with PVR urine volume >100 mL or Qmax <5 ml/sec.
3. Patient with prostate-specific antigen (PSA) ≥4 ng/mL.

4. Patient with neurogenic bladder (e.g., spinal cord lesions or other damages that will clearly affect urination; multiple sclerosis; Parkinson's disease) or a history of surgery that caused damage to the pelvic plexus.
5. Patient with urethral stricture or bladder-neck stenosis.
6. Patient with diabetic neuropathy complications.
7. Patient who has undergone a surgical procedure (e.g., transurethral resection of prostate [TURP], laser therapy), previous pelvic radiation therapy, or hyperthermia therapy that may affect urinary tract functions.
8. Patient with significant stress incontinence (i.e., patients presenting with only symptoms of stress urinary incontinence) or postsurgical prostate incontinence, as determined by the Investigator.
9. Patient with an indwelling catheter or practices intermittent self-catheterization.
10. Patient with 3 or more episodes of recurrent urinary tract infection (UTI) within the last 6 months.
11. Patient with a UTI; prostatitis; chronic inflammation, such as interstitial cystitis; urinary calculus (e.g., ureteral calculus, urethral calculus, bladder calculus); 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).
12. Patient with a concurrent malignancy or history of any malignancy (within the past 5 years), except for nonmetastatic basal-cell or squamous-cell carcinoma of the skin that has been treated successfully.
13. Patient with serious heart disease (e.g., myocardial infarction, cardiac failure, uncontrolled angina pectoris, serious arrhythmia, use of pacemaker), liver disease, kidney disease, immunological disease, lung disease.
14. Patient who has received intravesical injection within the last 12 months with botulinum toxin, resiniferatoxin, or capsaicin.
15. Patient who has received electrostimulation therapy for OAB (e.g., sacral nerve stimulation or Percutaneous Tibial Nerve Stimulation [PTNS]).
16. Patient who has received a bladder training program or pelvic floor exercises <28 days prior to the start of the Screening period.
17. Patient with postural hypotension or syncope, hypokalemia, or closed-angle glaucoma.
18. Patient with evidence of QT prolongation on electrocardiogram (ECG), defined as QTcF >450 msec.
19. Patient with severe uncontrolled hypertension, defined as a sitting SBP >180 mmHg and/or DBP >110 mmHg.

20. Patient with a clinically significant ECG abnormality, as determined by the Investigator.
21. Patient with severe renal impairment, defined as estimated glomerular filtration rate <29 mL/min/1.73m^2; end-stage renal disease; or is undergoing dialysis.
22. Patient with AST or ALT >2 times the upper limit of normal (ULN), or gamma-glutamyl transferase (γ-GT) >3 times the ULN.
23. Patient with moderate or severe hepatic impairment, defined as Child-Pugh Class B or C.
24. Patient with hypersensitivity to any components of mirabegron, other β-AR agonists, or any of the inactive ingredients.
25. Patient with ongoing alcohol and/or drug abuse.
26. Patient with or a history of mood disorder, neurotic disorder, or schizophrenia.
27. Patient with dementia, cognitive dysfunction, or clinically significant cerebrovascular disorder.
28. Patient has been treated with an experimental device <84 days or received an investigational agent <84 days prior to the start of the Screening period.
29. Patient has used any prohibited concomitant medication (defined in Appendix 12.1) <28 days (but, <1 year for 5α-reductase inhibitors) before the start of the Screening period.
30. Patient with any clinically significant condition, which in the opinion of the Investigator, makes the subject unsuitable for study participation.
31. Patient who is involved in the conduct of the study as an employee of the Astellas group, a third party associated with the study, or the study site team.

Exclusion Criteria assessed at Visit 2 (Baseline):

32. Subject fulfills any exclusion criteria of Visit 1 at Visit 2.
33. Subject was noncompliant during the 4 week tamsulosin Screening period, defined as taking less than 80% or greater than 120% of the prescribed dose of study medication.
34. Subject had an average total daily urine volume >3000 mL, as recorded in the 3-day micturition diary.
35. Subject is found to meet any of the exclusion criteria for enrollment at Visit 1 (Screening)

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

During the 4 week, single-blind Screening period, all subjects will receive tamsulosin 0.2 mg along with mirabegron matching placebo once daily after breakfast.

During the 12 week, double-blind Treatment period, subjects will receive their randomized treatment (mirabegron 50 mg or matching placebo) along with tamsulosin 0.2 mg once daily after breakfast.

4.1 Identification of Investigational Product(s)

Study drugs to be administered during the single-blind Screening period:

- Mirabegron 50 mg matching placebo tablet

and

- Tamsulosin 0.2 mg tablet

Study drugs to be administered during the double-blind Treatment period:

- Mirabegron 50 mg tablet

or

- Mirabegron 50 mg matching placebo tablet

and

- Tamsulosin 0.2 mg tablet

4.1.1 Test Drug(s)

Mirabegron 50 mg, tamsulosin 0.2 mg, and placebo are tablets, to be administered by the oral route.

Mirabegron 50 mg tablet:

Nonproprietary name	Mirabegron
Chemical name	2-(2-Amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide
Molecular formula and molecular weight	$C_{21}H_{24}N_4O_2S$ Molecular weight: 396.51
Content and dosage form	Mirabegron 50 mg tablet for the Treatment period: Each tablet contains 50 mg of mirabegron.
Size	Major axis, approx. 12.1 mm; minor axis, approx. 6.1 mm; thickness, approx. 5.2 mm
Lot number	Information described in Pharmacy Manual (written procedures for handling of study drugs)
Storage conditions	Room temperature
Manufacturer	Astellas Pharma Inc.

Tamsulosin 0.2 mg tablet:

Nonproprietary name	Tamsulosin
Chemical name	5-{(2R)-2-[2-(2-ethoxyphenoxy)ethylamino]propy}-2-methoxybenzenesulfonamide monohydrochloride
Molecular formula and molecular weight	$C_{20}H_{28}N_2O_5S \cdot HCl$ Molecular weight: 444.97
Content and dosage form	Tamsulosin 0.2 mg tablet for the Screening period and double-blind treatment period: Each round, white tablet contains 0.2 mg of tamsulosin hydrochloride.
Size	8.5mm in diameter; 4.2 mm thickness
Lot number	Information described in Pharmacy Manual (written procedures for handling of study drugs)
Storage conditions	Room temperature
Manufacturer	Astellas Pharma Inc.

4.1.2 Comparative Drug(s)

The placebo for mirabegron 50 mg will be supplied as a matching tablet, visually indistinguishable from the active drug.

Mirabegron 50 mg Placebo:

Content and dosage form	Mirabegron 50 mg placebo tablet for the Screening period and double-blind treatment period.
Size	Major axis, approx. 12.1 mm; minor axis, approx. 6.1 mm; thickness, approx. 5.2 mm
Lot number	Information described in Pharmacy Manual (written procedures for handling of study drugs)
Storage conditions	Room temperature
Manufacturer	Astellas Pharma Inc.

4.1.3 Drug(s) for Screening Period

A daily dose of tamsulosin 0.2 mg along with mirabegron 50 mg matching placebo will be administered to all subjects during the 4-week Screening period. Both study drugs are in tablet form to be administered orally.

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at API or the Sponsor's designee in accordance with API or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, Internation Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

Each carton will bear a label conforming to regulatory guidelines, GMP, and local laws and regulations, and which identifies the contents as an investigational drug.

4.2.1 Packaging

Mirabegron 50 mg tablets/matching placebo: 10 mirabegron 50 mg tablets or matching placebo will be included in 1 Press-Through Package (PTP) sheet; 4 PTP sheets will be packed in a small box.

Tamsulosin 0.2 mg tablets: 14 tamsulosin 0.2 mg tablets will be included in 1 PTP sheet; 2 PTP sheets will be in an aluminum pouch, which will be packed in a small box.

4.2.2 Labeling

The study drug labeling will be in the same language as the translated protocol.

4.3 Study Drug Handling

Current GCP guidelines require the Head of the study site to ensure that the study drug deliveries from the Sponsor are received by a responsible person (e.g., pharmacist) and that the following measures take place *(Unique to Japan)*:

Current GCP guidelines require the Investigator to ensure that the study drug deliveries from the Sponsor are received by a responsible person (e.g., pharmacist) and that the following measures take place *(Unique to Korea)*:

- The deliveries are recorded
- The study drug is handled and stored safely and properly
- The study drug is dispensed to study subjects in accordance with the protocol
- Any unused study drugs (including those returned from study subjects) are returned to the Sponsor

Either the Head of the study site *(Unique to Japan)*, the investigator *(Unique to Korea)* or the study drug storage manager is accountable for the study drugs as follows:

- The study drugs will be stored and accounted for according to the Sponsor's written procedures for handling the study drugs.
- Records of receipt of the study drugs, the inventory at the study site, the use by each subject, and the return to the Sponsor or alternative disposal of unused study drugs will be prepared and retained. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study drugs and subjects.
- Records will be prepared and retained that document that the subjects were adequately provided the doses specified in the protocol, and that all the study drugs supplied from the Sponsor are reconciled.

4.4 Blinding

4.4.1 Blinding Method

Subjects will be randomized to receive mirabegron 50 mg or matching placebo in a double-blind fashion such that neither the Investigator, the Sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. The randomization number will be assigned to each subject, based on information obtained from the Interactive Response Technology (IRT).

The mirabegron 50 mg tablet and the placebo tablet, as well as the packaging for each treatment, are visually indistinguishable.

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

The active mirabegron 50 mg tablet and the matching placebo tablet, as well as the packaging, are visually indistinguishable. Both tablets are ~12.1 mm long, ~6.1 mm wide, and 5.2 mm in thickness.

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

The randomization list and study medication blind will be maintained by the IRT system.

4.4.4 Breaking the Treatment Code for Emergency

The treatment assignment may be unblinded for a study subject who experiences a serious adverse event (SAE), and for whom, knowledge of the study treatment is required for appropriate management/treatment of the SAE.

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.

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the Investigator or other persons designated as Sub-investigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

Unblinding of the study medication should only be considered for subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the investigational staff must be reported immediately to the Sponsor and must include an explanation of why the study medication was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study medication.

4.5 Assignment and Allocation

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

Randomization will be performed via IRT. Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment for each subject. Specific procedures for randomization through the IRT are described in the study procedures manual.

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

Screening Period:

During the 4-week Screening period, all subjects will receive 1 tamsulosin 0.2 mg tablet along with 1 mirabegron 50 mg matching placebo tablet once daily after breakfast.

Treatment Period:

During the 12-week Treatment period, all subjects will receive their randomized treatment (1 mirabegron 50 mg tablet or 1 matching placebo tablet) along with 1 tamsulosin 0.2 mg tablet, to be taken once daily after breakfast.

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

No dose increases or decreases are allowed in this study, as the study subjects are to receive the approved doses for mirabegron and tamsulosin, as stated in the respective Package Inserts.

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

5.1.3.1 Prior Treatment

All prior medications and non-medication therapies for BPH and OAB received by a study subject within 4 weeks prior to Visit 1 (Screening) will be recorded on the electronic Case Report Form (eCRF), as described below. Any prior treatment with tamsulosin will be recorded, regardless of the time frame in which it was taken.

Previous treatment	Investigation period	Data to be entered on the eCRF
Previous medication (For BPH and OAB)	From 4 weeks before Visit 1 (Screening) to Visit 1	Drug name, daily dose, route of administration, administration period, reason for use, time of administration
Previous therapy (For BPH and OAB)		Therapy name, treatment period, reason for use, time of treatment

5.1.3.2 Concomitant Treatment

Drug classes and specific medications that are prohibited during the study are provided in Appendix 12.1 List of Excluded Concomitant Medications.

All concomitant medications and non-medication therapies received by a subject from Baseline to the end of the Treatment period will be entered on the eCRF, as described below:

Concomitant treatment	Investigation period	Data to be entered on the eCRF
Concomitant medication (all drugs)	From Visit 1 to the end of the Treatment period	Drug name, route of administration, administration period, reason for use
Concomitant therapy (all non-medication therapies)		Therapy name, treatment period, reason for use

The excluded concomitant meditations (defined in Appendix 12.1) can be allowed to use under the conditions below:

1) From the day following the dispensing of the study drug for the Screening period to the end of the Treatment period, none of the prohibited concomitant medications listed in Appendix 12.1 should be concomitantly used. However, the following drugs may be concomitantly used:
   - Eye drops
   - Transdermal formulations, excluding β-agonists and drugs for the treatment of urinary storage and voiding dysfunction
   - Nasal drops, excluding drugs for diabetes insipidus
   - Topical agents
   - Inhaled β-agonists used to relieve acute symptoms such as bronchial asthma
   - Chinese herbal medicines used for the treatment of conditions other than urinary storage and voiding dysfunction
2) The following drugs may be used concomitantly for a short period of time (i.e., up to a total of 5 days during the interval from the day following a visit to the next visit), except during the micturition diary period:
   - Parasympathetic inhibitors/parasympatholytic drugs for peptic ulcer, etc.
   - Antihistamines, ephedrine hydrochloride, and methylephedrine hydrochloride for common cold, etc.
3) Transient concomitant use of parasympathetic inhibitors/parasympatholytic drugs will be allowed, if used in preparation for an examination, except during the micturition diary period.
4) Concomitant use of 5α-reductase inhibitors will be allowed (the dosage shall not be changed for study period), if the subject has been on treatment for a year or more.
5) Transient concomitant use of PDE5 inhibitor for ED treatment will be allowed, except during the micturition diary period.
6) Nonpharmacological therapy for OAB, such as biofeedback therapy, bladder training, or pelvic floor muscle exercise will be prohibited from 4 weeks (<28 days) before the start of the Screening period to the end of the Treatment period.

5.1.4 Treatment Compliance

The Investigator or designee will confirm treatment compliance of each study subject throughout the study period. At each visit, treatment compliance will be evaluated based on the information provided by the subject (i.e., amount of prescribed drugs, returned unused drugs, lost drugs, etc.) and recorded in the medical record or other source documents, with the amounts of prescribed, returned, and lost drugs entered into the eCRF. Consistency with drug accountability logs will be checked, as required.

If treatment compliance is found to be poor as the result of the evaluation, the reason for poor compliance will be investigated, and the subject will be given instructions to improve compliance.

Treatment compliance should be monitored closely, and any deviation in compliance should be reported to the Sponsor.

5.1.5 Restrictions During the Study

(1) Medication

When prescribing the study medication, the Investigator or Sub-investigator will explain to the subjects how to take the study medication, with emphasis on the following:

- The subject should take the study medication with water, once daily after breakfast.
- The subject should start taking the prescribed study medication on the day following dispensing of the study drug(s).
- The subject should return any unused study medication at the next visit, and report their compliance to the Investigator or Sub-investigator.
- If the subject has discontinued taking the study medication at his/her own discretion, he/she must visit the study site at the earliest possible time to undergo examination by the Investigator or Sub-investigator.

(2) Micturition diary

The Investigator or Sub-investigator will provide each subject with a micturition diary, after entering into the diary the date of the next scheduled visit, the dates on which the diary should be completed, and the subject number. When providing the micturition diary to the subject, the Investigator or Sub-investigator will explain to the subject how to complete the micturition diary, with emphasis on the following:

- As a rule, the subject will complete the micturition diary during the 3 days immediately before each of the scheduled visits (i.e., at Visits 2, 3, 4, and 5/End of Treatment. Each diary day starts at 06:00 and ends at 05:59 on the following day.
- For the 3 days of recording in the micturition diary, the subject will record their awakening and bedtime hours; time of each micturition; number of micturition episodes, urgency episodes, urinary incontinence episodes, voided volume, sitting blood pressure (SBP and DBP) and pulse rate with the times of measurements. In addition, the subject will record the time of medication. Voided volume will be recorded at Visits2, and 5 only.
- Sitting blood pressure and pulse rate will be measured twice consecutively on awakening and before bedtime. The second measured value will be recorded in the patient diary. When measurements on awakening are not possible, these should be taken before taking medication for the day as far as possible.
- The subject should bring their completed micturition diary to the next visit.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

At Visit 1, the following subject background data will be obtained and entered into the eCRF: the subject's date of birth, sex, race, ethnicity, height, body weight, information on

the target disease, medical history, previous treatment, disease duration of BPH, prostate volume, ECG (QTcF), and PSA.

Please refer to Section 5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease for information on the target disease, and Section 5.2.2 Medical History for past and concurrent diseases, and Section 5.1.3 Previous and Concomitant Treatment.

5.2.2 Medical History

Both past and concurrent diseases will be recorded at Visit 1. Past diseases are defined as diseases that resolved by the day of dispensing of the study drug. For recent past diseases that resolved within 1 year prior to Visit 1, the diagnosis, time of onset, and time of resolution will be entered into the eCRF. As a rule, no entries should be made on the eCRF for non-urological temporary diseases (e.g., common cold), or otorhinolaryngological, dental, dermatological, or ocular diseases. The duration of the disease should be indicated in months or years.

Concurrent diseases are defined as diseases that have not resolved as of the day of dispensing of the study drug during the Screening period. For all concurrent diseases, the diagnosis and time of onset are to be entered into the eCRF.

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

At Visit 1, the following information on OAB and BPH will be confirmed, with the information entered into the eCRF:

- Diagnosis: OAB, BPH
- Time of onset (i.e., time when symptoms were apparent)
- Type of urinary incontinence (e.g., urge or mixed)

5.3 Efficacy Assessments

5.3.1 Micturition Diary

The micturition diary will be used to record the date and time of each micturition, incontinence episodes, urgency episodes, and voiding volume. Voiding volume will be recorded at Visits 2, and 5 only. The diary will also be used to record daily medication intake. The diary must be completed for at least 2 days in order to be included in the efficacy assessment for that visit.

5.3.2 Overactive Bladder Symptom Score (OABSS)

The OABSS is a 4-item questionnaire that assesses urinary frequency (Appendix 12.4). The subject is to fill out the questionnaire at *each* study visit.

5.3.3 Overactive Bladder Questionnaire (OAB-q)

The OAB-q is a 33-item questionnaire that assesses Symptom Bother and the effect of the symptoms on the subject's life (Appendix 12.4). The subject is to fill out the questionnaire at Visit 1, Visit 2, and Visit 5.

5.3.4 International Prostate Symptom Score (IPSS and IPSS [QoL])

The IPSS and IPSS (QoL) includes an 8-item questionnaire that assesses urinary frequency and incomplete voiding along with a QoL assessment (Appendix 12.4). The subject is to fill out the questionnaire at *each* study visit.

5.4 Safety Assessment

5.4.1 Vital Signs

Office-measured sitting BP and PR (at rest):

At all visits, sitting BP and pulse rate will be measured at the study site and entered into the eCRF. The values obtained at Visit 1 and Visit 2 will be used for eligibility determination by the Investigator or Sub-investigator.

Self-measured sitting blood pressure and pulse rate (at rest):

Subjects will measure sitting blood pressure and pulse rate using an automatic sphygmomanometer for 3 days immediately before each of the scheduled visits [at Visit 2, 3, 4 and 5(or End of Treatment)], and record the measured values with the times of measurements in the patient diary. For details, refer to Section 5.1.5 “Restrictions During the Study” Part (2).

5.4.2 Adverse Events

See **Section 5.5 Adverse Events and Other Safety Aspects** for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See **Appendix 12.2 Liver Safety Monitoring and Assessment** for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function tests (LFTs; AST, ALT, bilirubin) or is suspected to be due to hepatic dysfunction.

Any subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

(1) Test parameters

Table 2 shows the listing of laboratory tests to be performed during the study. Refer to “V. FLOW CHART AND SCHEDULE OF ASSESSMENTS” for the test schedule by visit.

The sampling and measurement for biochemistry, hematology and Coagulation tests will be performed centrally at [redacted] ([redacted], Japan) and [redacted] ([redacted], Korea) under coordination with the study site, investigator, and sub-investigators. In principle, urinalysis will be performed at the study site.

Table 2 Laboratory Tests to be Performed During the Study

Laboratory Test	Visit(s)	Analytes	Collection Tube
Serum Chemistry	Visit 1	PSA	Blood collection tube for serum separation (4 mL)
	Visit 1, Visit 2, and Visit 5 (or discontinuation)	AST (GOT) ALT (GPT) γ-GTP ALP CK Creatinine Total bilirubin BUN Uric acid Total protein Total cholesterol Albumin Sodium Potassium Chloride	Blood collection tube for serum separation (4 mL)
Hematology	Visit 1, Visit 2, and Visit 5 (or discontinuation)	RBC count WBC count Hemoglobin Hematocrit Platelet count	Blood collection tube containing EDTA-2K (2 mL)
Coagulation	Visit 1	Prothrombin	Blood collection tube containing Sodium citrate 3.2% (3 mL)
Urinalysis	Visit 1, Visit 2, and Visit 5 (or discontinuation)	Glucose (qualitative) Protein (qualitative)	Dipstick
		Sediment	Urine collection tube

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatinine kinase; EDTA-2K = ethylenediaminetetraacetic acid dipotassium salt dihydrate; γ-GTP = gamma glutamyl transpeptidase; RBC = red blood cell; WBC = white blood cell

(2) Measurement results

[redacted] ([redacted], Japan) will send the central laboratory test results by mail to the Investigator or Sub-investigator. The Investigator or Sub-investigator will determine the eligibility of each subject, based on the laboratory values at Visit 1. If any test parameters specified in the exclusion criteria (i.e., AST, ALT, GGT, creatinine, PSA) cannot be measured in the sample collected at Visit 1, they will be re-measured to evaluate the test values by Visit 2.

For parameters locally measured at the study site, results will be entered into the eCRF. Urinary sediment (normal or abnormal) will be determined according to the normal ranges used by the study center, and results will be entered into the eCRF.

The clinical significance of out-of-range laboratory findings is to be determined and documented by the Investigator/Sub-investigator.

5.4.4 Measurement of Residual Urine Volume

Residual urine volume will be measured at all visits and recorded in the eCRF. The measurement of residual urine volume will be performed using either ultrasonography or bladder scan; however, the same measurement method must be used for a given subject throughout the study period.

5.4.5 Measurement of Uroflowmetry

Uroflowmetry (UFM) will be performed at Visits 1, 2 and 5/End of Treatment, and the results will be entered on the eCRF. To ensure that an adequate volume of urine can be voided for the test, subjects will be instructed to drink approximately 180 mL of water approximately 1.5 hours before the test. Subjects will also be instructed to void as usual (i.e., without abdominal pressure).

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

The Investigator or Sub-investigator will submit a copy of the uroflowmetrogram to the Sponsor.

- Average flow rate: volume voided per micturition (voided volume) divided by time for the micturition (flow time)[*1]
- Maximum flow rate (Qmax)[*2]
- Volume voided per micturition[*3]

[*1] The time over which measurable flow actually occurs (i.e., not including the time for interruption of micturition)

[*2] If a value exceeding 3 times the average flow rate is noted, the urinary flow pattern will be reviewed. If a spike or other patterns suggestive of abdominal pressure is seen, such abnormally high value(s) will be excluded when determining the maximum flow rate.

[*3] If the voided volume is too small, re-testing will be considered.

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 eCRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical examination) 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.

5.5.1.1 Treatment-Emergent Adverse Events (TEAEs)

For the purposes of analysis of the safety data following the completion of the study, a TEAE is defined as follows:

- An AE with onset during the double-blind Treatment period
- An AE with onset during the Screening period, with worsening severity during the double-blind Treatment period

Thus, AEs with onset during the Screening period that either resolved during that period or continued into the double-blind Treatment period with the same or lesser severity will NOT be counted as TEAEs.

5.5.2 Definition of Serious Adverse Events

An AE 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 AE 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 AE 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.

Safety events of interest in case 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 situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and on the SAE worksheet/report.

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 (See Appendix 12.3).

If a female partner of a study subject becomes pregnant during the study, the pregnancy is to be reported as an SAE (See Section 5.5.7 Procedure in Case of Pregnancy).

5.5.3 Criteria for Causal Relationship to the Study Drug

The Investigator or Sub-investigator will assess the causal relationship between each AE and the study drugs (mirabegron and tamsulosin) to record the results in the eCRF.

Adverse events that fall under either "Possible," "Probable," or "Not Assessable" should be defined as "AEs 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 a laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide plausible explanations of causality.
Possible	A clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the study 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 a laboratory test abnormality, with a reasonable time sequence to administration of the study drug, and 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).
Not assessable	A report suggesting an adverse reaction, but which cannot be judged as information is insufficient or contradictory, and cannot be supplemented or verified.

5.5.4 Criteria for Defining the Severity of an Adverse Event

The Investigator will use the following definitions to rate the severity of each AE:

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

The severity will also be determined by reference to the grading specified in the "Standards for Classification of Serious Adverse Drug Reactions," PAB/SD Notification No. 80, dated 29 Jun 1992 (Appendix 12.5. Classification of Seriousness of Adverse Drug Reaction). *(Unique to Japan)*

5.5.5 Reporting of Serious Adverse Events

In the case of an SAE, the investigator or sub-investigator must report to the head of the study site and must contact the Sponsor/delegated Contract Research Organization (CRO) by telephone or fax immediately (within 24 hours of becoming aware of the event).

The Investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor/delegated CRO by fax immediately (within 24 hours of awareness) and to the Head of the hospital. If the faxing of the SAE Worksheet is not possible or is not possible within 24 hours, the Sponsor/delegate should be informed by phone.

For contact details, see Section II Contact Details of Key Sponsor's Personnel.

Please fax SAE Worksheet to:

CRO:

[redacted]

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 AE progresses to an ″SAE″, or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Even if the subject does not return to normal or baseline level, the follow-up can be considered unnecessary or finished when the following procedures have been taken:

1. **Unnecessary**: for AEs unrelated to the study drug, the Investigator/Sub-investigator judges that further follow-up is no longer necessary and the Sponsor judges that the reason is acceptable.
2. **Finished**: based on the clinical course during the follow-up period, the Investigator/Sub-investigator judges that further follow-up is not necessary and the rationale for this judgment is recorded in follow-up report or other relevant documents. The Sponsor judges the rationale is acceptable in consideration of safety of the subject.

Please refer to **Appendix 12.2 Liver Safety Monitoring and Assessment** for detailed instructions on Drug Induced Liver Injury.

5.5.7 Procedure in Case of Pregnancy

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

Information should be obtained by the Investigator on the estimated date of conception, estimated delivery date, and pregnancy outcome.

5.5.8 Emergency Procedures and Management of Overdose

Mirabegron

In a Japanese Phase 1 clinical study, mirabegron was administered to healthy adult males at doses of up to 400 mg/day. In the 400 mg/day group, there were 3 cases of 'heart rate increased', 1 case of palpitations, and 1 case of 'ALT increased' reported as adverse drug reactions. Only supportive treatment is available for overdose of mirabegron. If a subject has inadvertently taken an overdose of mirabegron, the Investigator or Sub-investigator will provide emergency treatment and general maintenance therapy, as required according to the symptoms, and will perform appropriate examinations, such as vital sign measurements and 12-lead ECG.

Tamsulosin

Overdosage of tamsulosin may cause a decrease in blood pressure. Should an overdose occur, restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used, and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin hydrochloride is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit.

5.5.9 Supply of New Information Affecting the Conduct of the Study

When new information becomes available that is necessary for proper conduct of the study, the Sponsor will inform all investigators involved in the study, as well as regulatory authorities. The investigators should inform the IRB/IEC of such information.

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 68-10 Paragraph 1 of the Pharmaceutical Affairs Law, the Sponsor should inform all the investigators involved in the clinical study, the Head of the study site, and the Regulatory Authorities of such information. The Head of the study site who receives such information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The Investigator will supply the new information to the subjects, in compliance with Section 8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information. *(Unique to Japan)*
2. In addition to the above item (1), when the Head of the study site receives the revisions of the Package Insert, protocol, or written information, information on the

matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB should be sent to the IRB. *(Unique to Japan)*

5.5.10 Deviations from the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects *(Unique to Japan)*

The Investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the Investigator does not follow the protocol in order to avoid urgent risks for subjects, the Investigator should take the following actions:

1. Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the Sponsor and the Head of the study site. Keep a copy of the notice.
2. Consult with the Sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the Head of the study site as well as written approval from the Sponsor.

5.6 Test Drug Concentration

Not applicable to this study.

5.7 Other Measurements, Assessments or Methods

Not applicable to this study.

5.8 Total Amount of Blood Drawn

Table 3 shows the specifics of blood sample collection, including the category/type of test, time points for blood collection, and the volume of blood samples. The total volume of blood to be drawn from each subject is 25 mL.

Table 3 Blood Sample Collection During the Study

Test	Time Point	Volume of Blood per Collection	Scheduled Number of Collections	Total Volume	Total Volume of Blood Per Subject
Serum Chemistry	Visit 1 Visit 2 Visit 5	4 mL	3	12 mL	25 mL
Hematology	Visit 1 Visit 2 Visit 5	2 mL	3	6 mL	
Coagulation	Visit 1	3 mL	1	3 mL	
Serum PSA	Visit 1	4 mL	1	4 mL	

PSA = prostate-specific antigen

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

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

The subject is free to withdraw from study treatment and/or the 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 and has an ongoing AE 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 is no longer clinically significant.

Treatment Discontinuation Criteria for Individual Subjects:

- Due to an AE
    - When continuation in the study is judged to be difficult due to development of an AE or SAE
    - When continuation in the study is judged to be difficult due to aggravation of a concurrent disease requiring a change in treatment from the protocol
- Lack of efficacy
- Withdrawn consent
- Lost to follow-up
- Deviation from the inclusion or exclusion criteria during the Screening period
- Protocol deviations
    - When a subject is found not to have met the inclusion criteria at enrollment, or to have met the exclusion criteria after enrollment and therefore, was determined to be ineligible for the study
    - Any other serious violation of the protocol
- Other
    - When the Investigator judges that the subject must be withdrawn from the study, for any reason.

For those subjects who are withdrawn from the study after study drug administration, the examinations and evaluations scheduled for the final visit of the treatment period will be performed at the time of discontinuation, as much as possible (See Section V, Figure 1 Study Design Flow Chart and Table **1** Schedule of Assessments). If the subject is discontinued due to an AE, appropriate treatment will be provided, as necessary.

The Investigator will record the date and reason for the subject discontinuation and enter in the eCRF.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor and the Head of the study site.

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 API. 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 breaking the treatment code. Any changes from the planned analyses in the SAP will be described and justified in the Clinical Study Report.

7.1 Sample Size

The sample size for this study was based on 248 subjects per treatment group (using the Full Analysis Set [FAS]) to provide 90% power to detect a 0.7 reduction in the mean number of micturitions/24 hours in the mirabegron group compared to the placebo group, at a two-sided alpha level of 0.05. A standard deviation (SD) of 2.4 is assumed. Assumptions for the mean reduction and SD are based on data from previous studies (178-CL-048, 178-CL-090 and 905-JC-001; Table 4-6). If 90% of the randomized subjects are evaluable for efficacy, 550 subjects should be randomized, with 275 subjects randomized to each treatment group.

Table 4 178-CL-048[17] Change from Baseline in the Mean Number of Micturitions at the Final Assessment

	Placebo (n = 368)	Mirabegron 50 mg (n = 369)
Baseline	11.29 ± 2.748	11.15 ± 2.650
Final assessment	10.44 ± 2.777	9.48 ± 2.528
Change	−0.86 ± 2.354	−1.67 ± 2.212

*Mean ± SD

Table 5 178-CL-090[21] Change from Baseline to Last Visit in Mean Number of Micturitions Per 24-hour

	Placebo				Mirabegron 50mg			
	N	mean	SE	95% CI	N	mean	SE	95% CI
Overall	323	-1.48	0.178	(-1.83, -1.13)	338	-2.04	0.174	(-2.38, -1.70)
China	[redacted]							
India								
Korea								
Taiwan								

* Adjusted change from baseline results are generated from the ANCOVA model with treatment group as a fixed factor and baseline as a covariate.

Table 6 905-JC-001[7] Changes in average 24-hour frequency of urination

	Tamsulosin 0.2mg + Placebo (n = 209)	Tamsulosin 0.2mg + Vesicare 5.0mg (n = 208)
Adjusted mean (95% confidence interval)	-0.22 (-0.51, 0.06)	-1.06 (-1.34, -0.77)

*Analysis of covariance was performed with the treatment group as a factor and baseline average 24-hour frequency of urgency as a covariate, and multiplicity was adjusted by a closed testing procedure to start with comparison of the Ha0.2mg+Vc5.0mg group.

7.2 Analysis Set

The analysis will be performed using the following analysis populations, based on ICH guidelines E3 and E9. The final handling of the analysis sets will be decided with the decisions based on the opinions and advice of medical experts prior to breaking of the randomization code.

7.2.1 Full Analysis Set

The primary analysis dataset is the FAS, which will consist of all subjects who are randomized and receive at least 1 dose of double-blind study drug and have a Baseline micturition measurement and at least 1 post-Baseline micturition measurement.

All secondary efficacy analyses will be performed on the FAS.

7.2.2 Per Protocol Set

Subjects from the FAS who meet all of the following criteria will be included in the Per Protocol Set (PPS):

1. Those subjects who did not violate the inclusion criteria.
2. Those subjects who did not violate the exclusion criteria.
3. Those subjects with drug compliance during the Screening period and Treatment period of not less than 80%.
4. Those subjects who took the study drug during the Treatment period for 42 days or longer from the day following dispensing. However, subjects who discontinued the study for efficacy-related reasons, such as insufficient therapeutic effect, will be included in the PPS, even if the drug was taken for less than 42 days.
5. Subjects with diary entries for at least 2 of the 3 consecutive days at Visit 2 and the last visit during the Treatment period.
6. Subjects who did not receive any of the prohibited concomitant medications/therapies that may affect the evaluation of efficacy.

7.2.3 Safety Analysis Set

The analysis of safety data will be performed on the Safety Analysis Set (SAF), which will include all subjects who received at least 1 dose of double-blind study medication.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for the FAS, PPS, and SAF. Descriptive statistics will include: number of subjects; mean,

SD, minimum, Q1, median, Q3 and maximum for continuous endpoints; and frequency and percentage for categorical endpoints.

7.4 Analysis of Efficacy

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

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint, change from Baseline to End of Treatment in the mean number of micturitions per 24 hours, will be analyzed using an Analysis of Covariance (ANCOVA), including treatment group and region as fixed factors and baseline as a covariate. Within the framework of the ANCOVA model, point estimates and two-sided 95% confidence intervals for the mean change from Baseline both within and between treatment groups will be calculated. The two-sided significance level will be set at 5%.

The hypotheses for the treatment group comparisons are as follows:

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

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

The primary and secondary efficacy analyses will be conducted using the FAS, which includes all subjects who receive at least 1 dose of double-blind study medication *and* have both a Baseline and post-Baseline micturition assessment.

For those subjects who discontinue the study prematurely, the End-of-Treatment assessment will be analyzed. The End-of-Treatment assessment is defined as the last post-Baseline assessment during the double-blind study period for which primary efficacy data are available.

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

7.4.1.2 Secondary Analysis

The primary efficacy endpoint, change from Baseline to End of Treatment in the mean number of micturition episodes per 24 hours, will be analyzed using a Mixed Model Repeated Measure (MMRM) for the secondary analysis. Further details on the MMRM analyses will be provided in the Statistical Analysis Plan (SAP).

7.4.1.3 Subgroup Analysis

Subgroup analyses will include analyses by geographic region and by urgency incontinence at Baseline. Further details on subgroup analyses will be provided in the SAP.

7.4.2 Analysis of Secondary Endpoints

The secondary endpoints include the change from Baseline to End of Treatment in:

- Mean number of urgency episodes/24 hours
- Mean number of urgency incontinence episodes/24 hours
- Mean number of incontinence episodes/24 hours
- Mean number of nocturnal episodes
- Mean volume voided per micturition
- Total OABSS score
- Subscale score from OABSS score
- Total IPSS score
- Subscale score from IPSS score
- Symptom Bother and total Health-Related QoL scores, as assessed by the OAB-q questionnaire.

The secondary endpoints will be analyzed using the FAS, with the PPS as a supportive analysis. For the changes in mean number of incontinence and urge incontinence episodes, the analysis will be based on those subjects who have at least 1 incontinence episode at Baseline.

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

The secondary efficacy endpoints, except for the changes in mean number of incontinence and urge incontinence episodes, will be analyzed using an Analysis of Covariance (ANCOVA), including treatment group and region as fixed factors and baseline as a covariate. Within the framework of the ANCOVA model, point estimates and two-sided 95% confidence intervals for the mean change from Baseline both within and between treatment groups will be calculated. The two-sided significance level will be set at 5%.

The changes in mean number of incontinence and urge incontinence episodes will be analyzed using a Stratified Rank Analysis of Covariance (RANCOVA). Details on the RANCOVA analyses will be provided in the Statistical Analysis Plan (SAP).

7.4.3 Analysis of Exploratory Endpoints

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

- Hours of undisturbed sleep (HUS)
- First nighttime voided volume
- Subscale scores from OAB-q
- Normalization rate of OABSS
- Normalization rate of micturition diary (number of episodes of micturition/urgency/urgency incontinence/incontinence/nocturia

The exploratory endpoints will be analyzed using the FAS.

Based on the following definitions of normalization, the percentage of subjects normalized were of the subjects who were not normalized at Baseline:

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

- Urgency episodes: mean number per 24 hours of zero
- Urgency incontinence episodes: mean number per 24 hours of zero
- Incontinence episodes: mean number per 24 hours of zero
- Nocturia episodes: mean number per 24 hours of zero

Details on the analyses will be provided in the Statistical Analysis Plan (SAP).

7.5 Analysis of Safety

The safety analysis will be performed on the SAF.

7.5.1 Adverse Events

Adverse events will be recorded at each visit. The incidence and severity (mild, moderate, or severe) of TEAEs will be tabulated.

Adverse events will be coded using the MedDRA dictionary.

Adverse events reported during the double-blind Treatment period will be analyzed as follows:

- The number and percentage of subjects with AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by System Organ Class (SOC), Preferred Term (PT), and treatment group. The treatment groups will be compared using Fisher's Exact test, with a two-sided 95% confidence interval and 5% significance level. The number and percentage of AEs, by severity, will also be summarized. All AEs will be displayed in a listing, by subject.

Adverse events reported during the Screening period will be analyzed as follows:

- The number and percentage of subjects with AEs and the number and percentage of subjects with SAEs will be summarized by SOC and PT. A two-sided 95% confidence interval will be presented. The number and percentage of subjects with AEs by severity will also be summarized.

7.5.2 Laboratory Assessments

Laboratory tests, including serum chemistry, hematology, and urinalysis, will be performed at Visit 1 (Screening), prior to dosing on Visit 2 (Baseline), and at Visit 5 (Week 12/End of Treatment).

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Shifts in laboratory test values relative to the normal range from Baseline to each time point during the Treatment period will also be tabulated. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

Vital signs, including SBP, DBP, and PR will be measured at each visit.

Descriptive statistics will be used to summarize vital sign measurements and changes from Baseline by treatment group and time point. Vital signs data will be displayed in listings, by subject.

7.5.4 Residual Urine Volume

For residual urine volume, descriptive statistics will be used to summarize the measurement values and changes from Baseline, by treatment group and time point. Residual urine volume data will be provided in a listing, by subject.

7.5.5 Qmax

For Qmax, descriptive statistics will be used to summarize the measurements and changes from Baseline, by time point and treatment group. Qmax data will be provided in a listing, by subject.

7.6 Analysis of Pharmacokinetics

Not applicable to this study.

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

No formal interim analysis is planned.

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

7.8.1 Missing Data

The final handling of missing data will be decided by the time of database lock, and will be based on the opinion and advice of a medical expert. If multiple observed values have been obtained within the same visit window for 1 subject, the value closer to the scheduled date will be used for analysis. If the number of days deviated from the scheduled date is equal between these values, the value obtained on the later date will be used for the analysis.

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

and the following day is defined as Day 2.

As a general rule, missing efficacy data will not be imputed. Exceptions to this are the start and stop dates of AEs and concomitant medications.

Listings of AEs and concomitant medications will show the actual partial dates; imputed dates will not be shown. The SAP will define the visit windows to be used for analyses by visit.

7.8.2 Outliers

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

7.8.3 Visit Windows

As indicated in Section 7.8.2, the final handling of outliers will be decided by the time of database lock, and will be based on the opinion and advice of a medical expert. However, the policy described below will be followed as a general rule:

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

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

Micturition Diary:

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

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

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

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

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

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

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

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

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

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

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

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

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

Electronic Case Report Form (eCRF)

The Investigator, Sub-investigator, or collaborator will promptly enter individual subject data into the computer using the Electronic Data Capture (EDC) system in accordance with the protocol instructions for each visit (including laboratory findings if necessary). For a subject who discontinues the study after informed consent, but prior to the dispensing of the study drug for the Screening period, minimum necessary demographic information (subject number, sex, date of birth, and date of obtaining consent) and the reason for discontinuation will be entered into the SFL using the EDC system.

The Investigator must ensure that all data on the eCRF (including SFL) are submitted to the Sponsor, the responses to queries are accurate and complete, and the entries are verifiable against the source documents. In addition, the source documents must be properly retained at the study site.

The Monitor will verify the data on the eCRF against the source documents to confirm that they are consistent. If any correction of data is found, the Monitor will confirm that the data correction is appropriately recorded.

OABSS, OAB-q, IPSS with IPSS QoL, and Micturition Diary

At each visit, the Investigator or Sub-investigator will review the OABSS, OAB-q, IPSS with IPSS QoL, and micturition diary recorded by the subjects. If there is any unclear

entry, the Investigator, Sub-investigator or their designee will inquire of the subject for the entry and request the subject to make necessary additions or corrections. If the Investigator or Sub-investigator makes any additions or corrections, he/she will place the date of correction, and signature or seal to the added or corrected portions. Finally, the Investigator or Sub-investigator will review all entries, place the date of review, and signature or seal on the OABSS, OAB-q, IPSS with IPSS QoL, and micturition diary and then will submit copies of these documents to the Sponsor.

The Investigator or Sub-investigator will enter the data from the micturition diary and questionnaire into the computer using the EDC system as follows with the data from the eCRF.

Laboratory Data

Laboratory tests will be performed at a central laboratory. Laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the 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
- Source medical records and attached records (Investigator will submit copies of UFM chart to Sponsor, while retaining the originals)
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- OABSS, OAB-q, IPSS and IPSS (QoL), and micturition diary (the Investigator will review all entries, date the review, apply a signature/seal to the documents, and submit copies of the documents to the Sponsor, while retaining the originals.)
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts
- Dispensing and return of study drug details
- Reason for premature discontinuation
- Randomization number

The eCRF will serve as the source data for the following information, unless there are any records in the medical chart:

- Route of administration of a prior or concomitant medication and reason for and time of use

- Reason for and time of prior or concomitant therapy
- Details of ECG charts, images, etc., if used for diagnosis or evaluation at enrollment
- Details of AEs (outcome, severity, seriousness, treatment, other measures taken, and causal relationship to the study drug), date of the final observation, date and reason for discontinuation

Other comments in the eCRF (or comments in the CRF for follow-up when a follow-up of adverse events is conducted)

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 Data Science department of the Sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by the Data Management department. The eCRF retrieval and correction process will be referenced in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and the World Health Organization Drug Dictionary Enhanced (WHODDE) drug dictionary.

8.1.6 Protocol Deviations (*Unique to Korea*)

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 study 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 were 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 that 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 Authority 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.

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 the 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)

Prior to concluding the study contract, the IRB/IEC of the respective study site will review and approve the protocol and several documents used to obtain a patient's consent in order to secure the patient's human rights, safety, and well-being.

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/her 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/her 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 and place a personal seal. A copy of the signed/sealed 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

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

All individuals and organizations involved in the study must pay very careful attention to protect subjects' privacy with appropriate measures, for example, by prohibiting the use of any private information that may identify a subject (e.g., name or address). These details shall be processed in accordance with the applicable local and regional laws.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

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 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.

After agreement between Investigator(s) and Sponsor, the manuscript can be submitted for publication.

8.3.2 Documents and Records Related to the Clinical Study

The Sponsor will provide the Investigator and/or institution with the following:

- Study protocol (and amendments, where applicable)
- PI (and amendments, where applicable)
- CRFs and SAE Worksheet
- Study medication, with all necessary documentation
- Study contract

In order to start the study, the Investigator and/or study site is required to provide the following documentation to the Sponsor:

- Signed Investigator's Statement in this protocol and CRF
- Current Curricula Vitae (CV) of all investigators
- List of sub-investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Instruction and decision of the head of the study site
- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

At the end of the study, the Sponsor is responsible for the collection of:

- Unused CRFs and other study documentation,
- Unused study drug

The Investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation.

The records to be retained at the study sites are the ones listed as essential documents in GCP. These records shall be retained by the Head of the study site or the record keeper designated by the Head until notice issued by the Sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the Sponsor or regulatory authorities.

The Head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site concerned until the date defined in 1 or 2 below, whichever comes later.

1. Approval date of marketing of the test drug (if development of the drug is stopped, until three years after the decision to discontinue development is notified)
2. Until 3 years after discontinuation or termination of the study.

The following are the major documents to be retained at the study site.

1. Source documents (clinical data, documents, and records for preparing the CRF), hospital records, medical records, test records, memoranda, micturition diary or check lists for evaluation, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the Sponsor, records of clinical coordinators, and records related to the clinical study selected from those verified in other departments or hospitals.
2. Contracts, written informed consent forms, written information, and other documents or their copies prepared by the study personnel. A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), CVs of investigators, list of sub-investigators, list of signatures and print of seals (copy), and case report forms (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds one year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained. An agreed-upon protocol (including revisions), IB (including revisions), operational procedures for the investigator, materials and information supplied by the Sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation), and the review result report of the IRB (including continuous deliberation), etc.
4. Records of control for study drugs and other duties related to the clinical study. Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs, and the prescriptions for concomitant medications

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 and/or revisions. Depending on the nature of the amendment, either approval or notification of the IRB and Competent Authority may be required. The changes will become effective only after the approval of the Sponsor, the Investigator, and the IRB (if applicable), followed by the approval of the Head of the study site.

8.3.4 Insurance of Subjects and Others

If a subject suffers any study-related injury, the Sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the Sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs a injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The Sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the Sponsor. Both parties should work together towards compensation settlement.
3. The Sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The Sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.3.5 Signatory Investigator for Clinical Study Report

The Medical Expert and/or 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 signatory will be the Medical Expert and/or the representative for the Coordinating Investigator(s) or the Principal Investigator(s), and Vice President, Clinical Development Administration.

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, eCRFs, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC)

Not applicable.

10.2 Other Study Organization

Not applicable.

10.3 Registration of Subjects

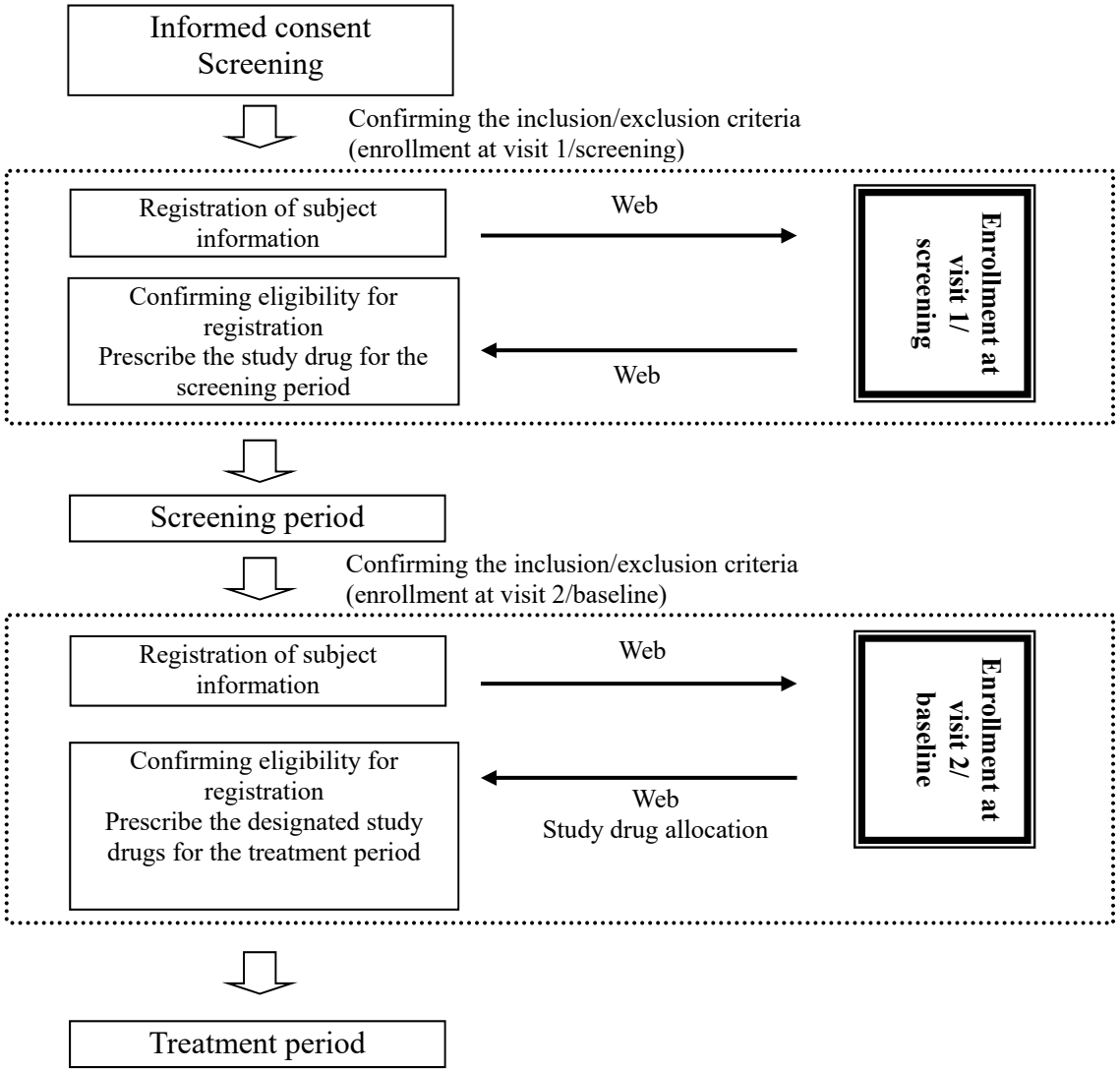
The Investigator or Sub-investigator will obtain written informed consent from each screened patient after investigating his/her background.

After confirming that the subject meets all the inclusion criteria and none of the exclusion criteria, the Investigator or Sub-investigator will enter necessary information on the registration screen of the web registration system. On receiving registration information, the Registration Center will confirm whether the subject meets all the inclusion criteria and none of the exclusion criteria. The study drugs will be allocated to eligible subjects after enrollment at Visit 2/Baseline. The Registration Center will notify the study site of registration results and allocated drugs via the web registration system.

The Investigator or Sub-investigator will confirm that the subject is eligible for enrollment at Visit 1/Screening and prescribe the study medication (tamsulosin 0.2 mg tablet + mirabegron 50 mg placebo tablet) for the Screening period at enrollment. Prior to Visit 2/Baseline, subjects will be randomized to receive mirabegron 50 mg or matching placebo along with tamsulosin 0.2 mg for the Treatment period.

If the subject is determined to be ineligible for enrollment at Visit 1/Screening or Visit 2/Baseline, the subject will be discontinued from the study.

Flow of Subject Registration:



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12 APPENDICES

12.1 List of Excluded Concomitant Medications

<table>
<tr><td colspan="2">Therapeutic agents for urinary incontinence/pollakiuria:</td></tr>
<tr><td>Anticholinergics
Oxybutynin
Flavoxate
Fesoterodine
Propiverine
Imidafenacin
Solifenacin
Tolterodine
etc.</td><td>β_2-agonist
Clenbuterol
etc.

β_3-agonist
Mirabegron
etc.

PDE5 inhibitor</td></tr>
<tr><td colspan="2">Agents that have anticholinergic effects:</td></tr>
<tr><td>Antidepressants
Imipramine
Amitriptyline
etc.

Antihistamines
Diphenylpyraline
Cyproheptadine
etc.

Anti-vertigenous drugs
Difenidol
etc.</td><td>Antiparkinsonian drugs
Piroheptine
Mazaticol
etc.

Parasympathetic inhibitors/parasympatholytic drugs (including narcotic drugs)
Tiquizium
Piperidolate
etc.

Gastrointestinal drugs
Mepenzolate
Pipethanate
etc.</td></tr>
<tr><td colspan="2">Other drugs:</td></tr>
<tr><td>Sympathomimetic drugs
Amezinium
etc.

α-agonists
Methoxamine
Midodrine
etc.

α- and β-agonists
Etilefrine
Methylephedrine
etc.

β-agonists
Isoproterenol
Methoxyphenamine
etc.</td><td>α-blockers
Doxazosin
Bunazosin
etc.

α- and β-blockers
Amosulalol
Labetalol
etc.

β-blockers
Penbutolol
Bopindolol
etc.

Cholinesterase inhibitors
Donepezil
Ambenonium
etc.</td></tr>
</table>

Other drugs (cont'd):	
Cholinergics Acetylcholine Bethanechol etc. Therapeutic agents for prostatic hypertrophy Allylestrenol Oxendolone Tadalafil etc. Chinese herbal medicines for urinary storage and voiding dysfunction Therapeutic agents for diabetes insipidus Desmopressin Vasopressin etc. MAO inhibitors Selegiline etc. 5α-reductase inhibitors Dutasteride Finasteride etc. Class Ia antiarrhythmics Procainamide Disopyramide etc. Class III antiarrhythmics Amiodarone Sotalol etc. SGLT(sodium-glucose transporter) 2 inhibitor Ipragliflozin Dapagliflozin etc. OTC drugs for urinary storage and voiding dysfunction	Loop diuretics Furosemide Bumetanide etc. Narcotics Opium Opium ipecac etc. CYP2D6 substrates Flecainide Propafenone etc. Phenothiazine antipsychotics Perphenazine Chlorpromazine etc. Strong CYP3A4 inhibitors Clarithromycin Erythromycin Atazanavir Indinavir etc. Other drugs Cyclosporine Tacrolimus Pimozide Digoxin

The above excluded concomitant meditations however, can be allowed to use under the conditions below:

1. From the day following dispensing of the study drug for the Screening period to the end of the Treatment period, none of the prohibited concomitant medications listed in Appendix 12.1 should be concomitantly used. However, the following drugs may be concomitantly used:
   - Eye drops
   - Transdermal formulations, excluding β-agonists and drugs for the treatment of

urinary storage and voiding dysfunction
- Nasal drops, excluding drugs for diabetes insipidus
- Topical agents
- Inhaled β-agonists used to relieve acute symptoms such as bronchial asthma
- Chinese herbal medicines used for the treatment of conditions other than urinary storage and voiding dysfunction

2. The following drugs may be used concomitantly for a short period of time (up to a total of 5 days during the interval from the day following a visit to the next visit), except during the micturition diary period:
   - Parasympathetic inhibitors/parasympatholytic drugs for peptic ulcer, etc.
   - Antihistamines, ephedrine hydrochloride, and methylephedrine hydrochloride for common cold, etc.
3. Transient concomitant use of parasympathetic inhibitors/parasympatholytic drugs will be allowed, if used in preparation for an examination, except during the micturition diary period.
4. Concomitant treatment with 5α-reductase inhibitors will be allowed (the dosage shall not be changed for study period), if the subject has been on treatment for a year or more.
5. Transient concomitant use of PDE5 inhibitor for ED treatment will be allowed except during the micturition diary period.
6. Nonpharmacological therapy for OAB, such as biofeedback therapy, bladder training, or pelvic floor muscle exercise will be prohibited from 4 weeks (<28 days) before the start of the screening period to the end of the treatment period.

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to >3 × ULN, or bilirubin >2 × ULN, should undergo detailed testing for liver enzymes (including ALT, AST, ALP, and total bilirubin). Testing should be repeated within 48 to 72 hours of notification of the test results. For studies for which a central laboratory is used, 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 according to the following criteria:

	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 with any of the following criteria:

- 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 International Normalized Ratio [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) that has been developed globally and can be activated for any study. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 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 an 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 eCRF. 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 eCRF. 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 LFTs, 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%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant)." The two "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by transaminase elevations greater than 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"); 2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's

syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2006 15(4):241-3.]

Reference

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

12.3 Events Always Considered to be Serious

If any of the following AEs occurs during the study, they will be considered SAEs and are to be reported as described in Section 5.5.5 Reporting of Serious Adverse Events:

- Acute liver failure
- Renal failure acute
- Acute respiratory failure
- Agranulocytosis
- Anaphylaxis
- Any malignancy
- Aplastic anemia
- Confirmed or suspected transmission of an infectious agent via product
- Congenital anomalies
- Hepatic necrosis
- Malignant hypertension
- Pulmonary hypertension
- Convulsion
- Torsades de pointes
- Toxic epidermal necrolysis
- Ventricular fibrillation
- Hemolytic anemia
- Bone marrow failure
- Myocardial infarction
- Cardiac arrest
- Deafness
- Blindness
- Pancreatitis acute
- Acute graft versus host disease
- Septic shock
- Sepsis
- Rhabdomyolysis
- Respiratory failure
- Stevens-Johnson syndrome

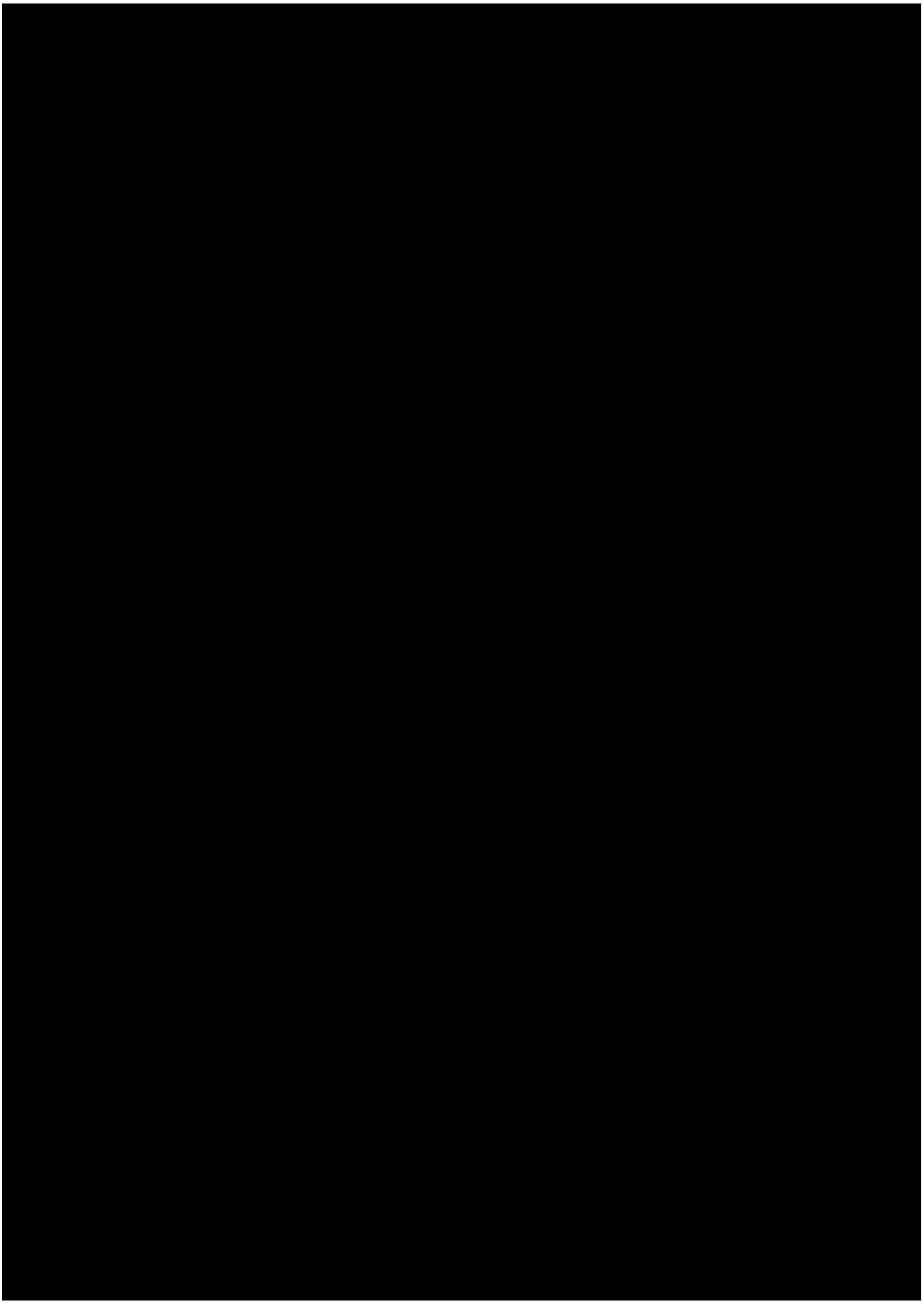
12.4 OABSS, OAB-q, IPSS and IPSS (QoL)

Overactive Bladder Symptom Score (OABSS):

[redacted]

Overactive Bladder Questionnaire (OAB-q):

[redacted]



International Prostate Symptom Score (IPSS):

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

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

(GPF 4.1)

		Ver. 3.0	Ver. 4.0	Reason for amendment
1	**SIGNATURES** **1.SPONSOR'S SIGNATURE**	ISN/Protocol 178-MA-3016, Version 3.0 Printed Name: [redacted]	ISN/Protocol 178-MA-3016, Version 4.0 Printed Name: [redacted]	Change of organization
2	**CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL**	Corporate Name: Astellas Pharma Singapore Pte. Ltd. Location: 6 Temasek Boulevard #22-**04**/05 Suntec Tower Four, Singapore Phone No.: [redacted] Fax: [redacted] Sponsor's personnel: [redacted] Contact numbers during non-business hours and for emergency: Sponsor Personnel (Phone No) [redacted]	Corporate Name: Astellas Pharma Singapore Pte. Ltd. Location: 6 Temasek Boulevard #22-**03**/05 Suntec Tower Four, Singapore Phone No.: [redacted] Fax: [redacted] Sponsor's personnel: [redacted] Contact numbers during non-business hours and for emergency: Sponsor Personnel (Phone No): [redacted]	Change of organization
3	**SYNOPSIS** **Inclusion:**	Highly effective forms of birth control include: • Consistent and correct... • Established intrauterine device (IUD)... • Barrier methods of contraception: condom... • Calendar-based contraceptive methods (Knaus-Ogino or rhythm method). **(Unique to Japan)**	Highly effective forms of birth control include: • Consistent and correct... • Established intrauterine device (IUD)... • Barrier methods of contraception: condom... • Calendar-based contraceptive methods (Knaus-Ogino or rhythm method).	Confirmed it is also acceptable in Korea
4	**SYNOPSIS** **Exclusion:**	22. Patient with aspartate transaminase (AST) or alanine transaminase (ALT) >2 times the upper limit of normal (ULN), or gamma-glutamyl transferase (γ-GT) >3 times the ULN **and considered clinically significant by the Investigator**.	22. Patient with aspartate transaminase (AST) or alanine transaminase (ALT) >2 times the upper limit of normal (ULN), or gamma-glutamyl transferase (γ-GT) >3 times the ULN.	Correction of intention er roneous
5	**3.2 Inclusion Criteria**	*Highly effective forms of birth control include: • Consistent and correct... • Established intrauterine device (IUD)... • Barrier methods of contraception: condom... • Calendar-based contraceptive methods (Knaus-Ogino or rhythm method). **(Unique to Japan)**	*Highly effective forms of birth control include: • Consistent and correct... • Established intrauterine device (IUD)... • Barrier methods of contraception: condom... • Calendar-based contraceptive methods (Knaus-Ogino or rhythm method).	Confirmed it is also acceptable in Korea

		Ver. 3.0	Ver. 4.0	Reason for amendment
6	**3.3 Exclusion Criteria**	22. Patient with aspartate transaminase (AST) or alanine transaminase (ALT) >2 times the upper limit of normal (ULN), or gamma-glutamyl transferase (γ-GT) >3 times the ULN **and considered clinically significant by the Investigator**.	22. Patient with aspartate transaminase (AST) or alanine transaminase (ALT) >2 times the upper limit of normal (ULN), or gamma-glutamyl transferase (γ-GT) >3 times the ULN.	Correction of intention er roneous
7	**5.3.1 Micturition Diary**	The micturition diary will be used to record the date and time of each micturition, incontinence episodes, urgency episodes, and voiding volume. Voiding volume will be recorded at Visits **1,** 2, and 5 only. The diary will also be used to record daily medication intake....	The micturition diary will be used to record the date and time of each micturition, incontinence episodes, urgency episodes, and voiding volume. Voiding volume will be recorded at Visits 2, and 5 only. The diary will also be used to record daily medication intake....	Correction of description erroneous
	5.5.4 Criteria for Defining the Severity of an Adverse Event	The severity will also be determined by reference to the grading specified in the "Standards for Classification of Serious Adverse Drug Reactions," PAB/SD Notification No. 80, dated 29 Jun 1992 (Appendix 12.**4**. Classification of Seriousness of Adverse Drug Reaction). (Unique to Japan)	The severity will also be determined by reference to the grading specified in the "Standards for Classification of Serious Adverse Drug Reactions," PAB/SD Notification No. 80, dated 29 Jun 1992 (Appendix 12.**5**. Classification of Seriousness of Adverse Drug Reaction). (Unique to Japan)	Correction of description erroneous
8	**5.5.9 Supply of New Information Affecting the Conduct of the Study**	1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Enforcement Regulations of the **Pharmaceutical Affairs Law**, in compliance with Article **80-2** Paragraph **6** of the Pharmaceutical Affairs Law, the Sponsor should inform all the investigators involved in the clinical study, the Head of the study site,....	1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Enforcement Regulations of the **Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics**, in compliance with Article **68-10** Paragraph **1** of the Pharmaceutical Affairs Law, the Sponsor should inform all the investigators involved in the clinical study, the Head of the study site,...	Correction of description erroneous
9	**7.2 Analysis Set**	The analysis will be performed using the following analysis populations, based on ICH guidelines E3 and E9. The final handling of the analysis sets will be decided **at the Blind Data Review Meeting,** with the decisions based on the opinions and advice of medical experts prior to breaking of the randomization code.	The analysis will be performed using the following analysis populations, based on ICH guidelines E3 and E9. The final handling of the analysis sets will be decided with the decisions based on the opinions and advice of medical experts prior to breaking of the randomization code.	Correction of description erroneous

Protocol Addendum

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

Protocol for Phase 4 Study of Mirabegron for Overactive Bladder

Section	Ver 4.0	Ver 4 Addendum	Reason for amendment
5.5.5 Reporting of Serious Adverse Events	Please fax SAE Worksheet to: CRO: [redacted]	Please fax or e-mail SAE Worksheet to: CRO: **Unique to Japan:** [redacted] **Unique to Korea:** [redacted]	To add additional number and mailbox

SPONSOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0 Addendum

Responsible person:

Signature: [redacted] 31 May 2016

Printed Name: [redacted] Date (DD MM YYYY)

[redacted] Astellas Pharma Inc.

COORDINATING INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0 Addendum

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: [redacted] 3 June, 2016

<*Insert name, department/affiliation, name of institution*> Date (DD Mmm YYYY)

Printed Name: [redacted]

[redacted]

Address: [redacted] ***Japan***

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: [redacted] 07 JUN 2016

<*Insert name, department/affiliation, name of institution*> Date (DD Mmm YYYY)

Printed Name: [redacted]

[redacted]

Address: ***KOREA***

INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0 Addendum

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: ----------

<*Insert name and qualifications of the Investigator*> Date (DD Mmm YYYY)

Printed Name: ----------

Address: ----------

Protocol Addendum 2

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

Protocol for Phase 4 Study of Mirabegron for Overactive Bladder

Section	Ver 4.0	Ver 4 Addendum 2	Reason for amendment
I. SIGNATURES 1.SPONSOR'S SIGNATURE	Printed Name: [redacted] Astellas Pharma Inc.	Printed Name: [redacted] Astellas Pharma Inc.	Change of organization
II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL	Corporate Name: Astellas Pharma Singapore Pte. Ltd. Location: 6 Temasek Boulevard #**22**-03/05 Suntec Tower Four, Singapore Phone No.: +65-6500-9419 Fax: +65-6836-5350 Sponsor's personnel: [redacted] Contact numbers during non-business hours and for emergency: Sponsor Personnel (Phone No); [redacted]	Corporate Name: Astellas Pharma Singapore Pte. Ltd. Location: 6 Temasek Boulevard #**26**-03/05 Suntec Tower Four, Singapore Phone No.: +65-6500-9419 Fax: +65-6836-5350 Sponsor's personnel: [redacted] Contact numbers during non-business hours and for emergency: Sponsor Personnel (Phone No); [redacted]	Relocation of office
II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL	Corporate name: [redacted]	Corporate name [redacted]	Change of personel
Section 8.3.5	Signatory Investigator for Clinical Study Report The Medical Expert and/or 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 signatory will be the Medical Expert and/or the representative for the Coordinating Investigator(s) or the Principal Investigator(s), and Vice President, **Clinical Development Administration.**	Signatory Investigator for Clinical Study Report The Medical Expert and/or 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 signatory will be the Medical Expert and/or the representative for the Coordinating Investigator(s) or the Principal Investigator(s), and Vice President, **Medical Science**.	Change of organization

SPONSOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0 Addendum 2

Responsible person:

Signature: [redacted] 11/04/2017

Printed Name: [redacted] Date (DD MM YYYY)

[redacted] Astellas Pharma Inc.

COORDINATING INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0 Addendum 2

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: [redacted] 16/Apr/2017

<Insert name, department/affiliation, name of institution> Date (DD Mmm YYYY)

Printed Name: [redacted]

Address: [redacted] ***Japan***

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: [redacted] 20 APR 2017

<Insert name, department/affiliation, name of institution> Date (DD Mmm YYYY)

Printed Name: [redacted]

Address: [redacted] ***KOREA***

INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 178-MA-3016, Version 4.0 Addendum 2

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: _____

<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

2017年 4月 3日

別紙 1

[redacted]

その他の試験実施組織

1. 試験依頼者

   アステラス製薬株式会社

   〒103-8411　東京都中央区日本橋本町二丁目 5 番 1 号

   TEL：03-3244-3000（代表）

2. 試験依頼責任者

   アステラス製薬株式会社

   [redacted]

   〒103-8411　東京都中央区日本橋本町二丁目 5 番 1 号

   [redacted]

3. 医学専門家

   [redacted]

   役割：試験依頼者に対して試験全般［試験実施計画書作成，重篤な有害事象，症例の取り扱い，試験総括報告書作成等］に関する医学的アドバイスを行う。

4. 試験調整医師

   [redacted]

   [redacted]

   役割：医学専門家の意見をもとに，試験依頼者によって作成された試験実施計画書の内容について，試験実施側の立場で意見を述べることを主な業務とする。

5. 試験責任医師

   別紙 2 参照

6. 割付表作成責任者

[redacted]

役割：二重盲検試験において第三者の立場として試験に参画し，キーコードの作成・保管，緊急キーコードの作成等を行う。

7. 緊急キーコード管理責任者

[redacted]

役割：緊急キーコードを保管し，試験依頼者からの要請に基づいて緊急用キーコードの開封を行う。

8. 症例登録センター

[redacted]

役割：症例登録システムの構築及び保守・管理を行う。

9. 医薬品開発業務受託機関（CRO）

[redacted]

業務内容：実施医療機関に対して，試験依頼者との間で定められた手順書に従いモニタリング全般を実施する。

10. 臨床検査業務受託機関

[redacted]

業務内容：日本施設の臨床検査の検体回収，結果の報告を行う。

[redacted]

業務内容：韓国施設の臨床検査の検体回収，結果の報告を行う。

11. 臨床検査測定施設

[redacted]

業務内容：日本施設の臨床検査の測定を行う。

[redacted]

業務内容：韓国施設の臨床検査の測定を行う。

12. 試験薬の保管・配送機関

[redacted]

役割：日本施設の試験薬の保管・配送を行う。

[redacted]

役割：韓国施設の試験薬の保管・配送を行う。

13. データマネジメント担当者

[redacted]

[redacted]

14. 統計解析担当者

[redacted]

15. 監査担当者

アステラス製薬株式会社 [redacted]

[redacted]

16. 試験依頼事務局及びモニタリング担当者

アステラス製薬株式会社

[redacted]

2017年4月3日

試験依頼者：API

[redacted]

ISN/Protocol <178-MA-3016>
対応する試験実施計画書：第4.0版
作成日：2017年4月3日

別紙2

試験実施施設，試験責任医師一覧

施設番号	施設名	診療科名	責任医師名	所在地
001	[redacted]			
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003				
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施設番号	施設名	診療科名	責任医師名	所在地
030	[redacted]			
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