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

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

ISN/Protocol 178-MA-2295

Version 2.0

22Mar2021

Sponsor:

Astellas Pharma China, Inc.

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SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 12 Sponsor Signature].

2. INVESTIGATOR'S SIGNATURE

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I have read all pages of this 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 International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my personnel have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: _____

Date (DD-MMM-YYYY)

Printed Name: _____ _____

Address of trial site: _____

_____

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

24-hour Contact for Serious Adverse Events See [Section 10.3.6 Reporting Procedures for Serious Adverse Events]	**Please fax or email the serious adverse events/special situations worksheet to:** Astellas Pharma Global Development Inc. Global Pharmacovigilance **Fax number: +1-888-396-3750** **Email: safety-us@astellas.com**
Medical Monitors	PPD

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Planned Study Period/Duration:
From approximately Q2/2020 to Q1/2023

Planned Total Number of Study Sites and Location(s):
Approximately 10-15 study sites in China

Study Objectives, Endpoints and Estimands:

Objectives and Endpoints:

The primary and secondary objectives and endpoints for this study are listed in the table below.

Objectives	Endpoints
Primary	
● To evaluate the efficacy of mirabegron 50 mg for the treatment of OAB in Chinese subjects	● Change from baseline to the end of 12-week treatment period in mean number of micturition/24 hours
Secondary	
● To evaluate the safety of mirabegron for the treatment of OAB in Chinese subjects	● Incidence and severity of AEs. ● Clinical laboratory tests (hematology, biochemistry and urinalysis) ● Vital signs (blood pressure and pulse) ● Routine 12-lead ECG ● Post Void Residual (PVR)
● To evaluate other efficacy variables of mirabegron 50 mg for the treatment of OAB	● Change from baseline to the end of 12-week treatment period in mean number of grade 3 or 4 (PPIUS) urgency episodes, incontinence episodes, urge incontinence episodes/24 hours and OABSS ● All efficacy variables change from baseline to weeks 4 and 8
● To explore mirabegron starting dose of 25 mg	● Change from baseline to weeks 4, 8, and 12 in mean number of micturition/24 hours, mean number of grade 3 or 4 (PPIUS) urgency episodes, incontinence episodes, urge incontinence episodes/24 hours and OABSS

AE: adverse event; NA: not applicable; OAB: overactive bladder; PPIUS: patient perception of intensity of urgency scale; OABSS: OAB Symptom Score.

Estimands

The estimand of most clinical importance for this study is defined by the following 4 attributes:

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

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

Study Population:

Male and female adult Chinese subjects (≥ 18 years of age) with overactive bladder (OAB; as defined according to the International Continence Society [ICS]).

Number of Subjects:

A total of 249 male and female Chinese subjects with OAB will be randomized into 2:1 ratio within 2 dose groups (50 mg of mirabegron and 25 mg of mirabegron).

Study Design Overview:

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

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

Treatment Groups and Duration:

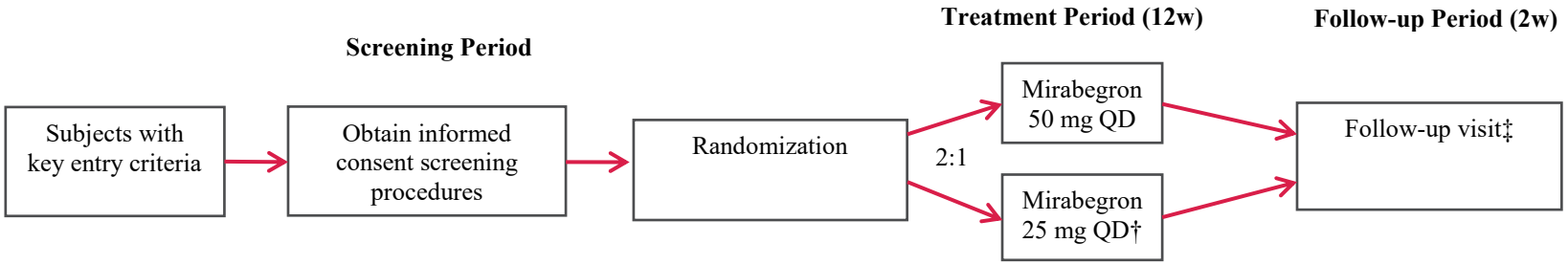
Arm/IP Name	Mirabegron (BETMIGA®)
Use	Test product
Dose	25 and 50 mg
Frequency/Duration	Once daily doses for 12 weeks
Route	Oral

IP: investigational product

The anticipated duration of the study for each subject, including screening and follow up, is approximately 16 weeks.

1.2 Study Schema

Figure 1 Study Schema



QD: once daily.

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

‡Telephone contact or site visit.

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

Assessments	Screening Period		Treatment Period			Follow up period
	Visit 1	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5 (EoT)[9]	Visit 6 (T/V[1]) or at Discontinuation of the Post treatment (End of Study)[11,12]
Week	-1 to -2	0	4	8	12	14
Visit Window (Days)	0	±2	±3	±3	±3	±3
Visit Number	1	2	3	4	5	6
Obtaining Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Medical History	X					
Demographics	X					
Physical Examination	X				X	
Randomization		X				
Dispense/Collect IP		X	X	X	X	
Administration of IP[2]		X	◄	———	►	
Issue Bladder e-diary	X[3]	X	X	X		
Retrieval of the Bladder e-diary		X	X	X	X	
OABSS[4]		X	X	X	X	
Vital Signs[5,9]	X	X	X	X	X	
Clinical Laboratory tests[6,9]	X				X	
Pregnancy Test[7]	X				X	
Routine 12-lead ECG[8,9]	X				X	
PVR[10]	X				X	
Previous and Concomitant Medication	X	X	X	X	X	X
AEs		X	X	X	X	X

AE: adverse event; CRF: case report form; ECG: electrocardiogram; eCRF: electronic case report form; e-diary: electronic diary; EoT: end of treatment; IP: investigational product; PVR: post void residual; OAB: overactive bladder; OABSS: OAB Symptom Score.

Footnotes continued on next page

1. T/V = Telephone contact or site visit.
2. Daily IP administration will start on day 1 (i.e., the day on visit 2/week 0 [baseline]). For 25 mg mirabegron group, a dose escalation to 50 mg is allowable on visit 3 and visit 4 by investigator's discretion.
3. For the screening visit (visit 1/week -1 to -2 [screening]), all subjects will start with the completion of a 3-day bladder e-diary which includes collection of micturition volume over 2 days.
4. The OABSS questionnaire will be completed on visit 2/week 0 (baseline), visit 3/week 4, visit 4/week 8 and visit 5/week 12 (EoT).
5. Blood pressure, pulse measurements and body temperature will be measured in single measurements. Subject to be in the sitting position (when possible, otherwise supine, but always in the same position for each procedure). Subject should have been calm and without distress for at least 5 minutes. Preferably, the right arm should be used to measure vital signs. Body temperature will be measured with an ear thermometer. These measurements will be used to assess eligibility.
6. Hematology, biochemistry and urinalysis (urinalysis dipstick) tests will be performed at visit 1/week -1 to -2 (screening) and visit 5/week 12 (EoT). Refer to Table 8 for the list of clinical laboratory tests.
7. Urine pregnancy tests will be performed only in female subjects of childbearing potential at visit 1/week -1 to -2 (screening) and visit 5/week 12 (EoT) except for cases in which the possibility of pregnancy was clearly ruled out by hysterectomy, bilateral oophorectomy or the passage of 2 or more years after last menstruation.
8. Routine 12-lead ECGs will be taken after the subject has been resting in the supine position for at least 5 minutes. Routine 12-lead ECGs will be taken as single measurements.
9. The following sequence will be in effect when more than 1 assessment is required at a time point: routine 12-lead ECG, vital signs, and sampling for clinical laboratories.
10. PVR volume will be assessed using ultrasonography at visit 1/week -1 to -2 (screening) and visit 5/week 12 (EoT).
11. Subjects who withdraw early from the study after having received IP should complete both the EoT and end of study visits.
12. The end of study visit (visit 6/week 14 [end of study]) should take place at least 14 days after the EoT visit (visit 5/week 12 [EoT]).

2 INTRODUCTION

The generic name of the investigational product (IP) is mirabegron sustained-release tablets (also called mirabegron oral controlled absorption system [OCAS] tablets internally) and the trade name is BETMIGA®.

Mirabegron is a selective agonist for human beta 3-adrenoceptor (beta 3-AR). It is an approved chemical entity and first-in-class compound with a distinct mechanism of action compared to the current standard of care (primarily antimuscarinics).

Mirabegron is indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

In the mirabegron approval letter, China National Medical Products Administration (NMPA) requested further investigation into the usage (before/after meal) and dosage (including initiation dose) of mirabegron in Chinese patients and data should be submitted when the Imported Drug License (IDL) is renewed.

2.1 Study Rationale

In mirabegron approval letter, the NMPA has asked further data on the use of mirabegron in Chinese patients. The data ought to comprise mirabegron usage with two different starting doses available in China, 25mg and 50mg, as a prerequisite submission for the upcoming mirabegron IDL renewal.

This study will be an open-label, randomized, prospective, interventional post-authorized, oral dose once daily during 12-week period in male and female Chinese subjects with OAB. It is intended to determine the efficacy and safety of mirabegron with starting doses 50 mg and 25 mg for the treatment of OAB in Chinese subjects.

2.2 Background

OAB is a syndrome characterized by symptoms of urinary urgency with or without urge incontinence, often accompanied by frequency and nocturia in the absence of pathologic or metabolic factors that would explain these symptoms, according to the 2002 International Continence Society (ICS) definition [Neurourology and Urodynamics, 2019; Abrams et al, 2002, Charlson et al, 1987].

Several publications have studied the prevalence of OAB in developed countries. An overall OAB prevalence of 11.8% was observed in a population-based, cross-sectional survey of adults ≥ 18 years of age in Canada, Germany, Italy, Sweden and the UK (the European Prospective Investigation into Cancer and Nutrition [EPIC] study). The prevalent rates of OAB were similar in men and women (10.8% versus 12.8%, respectively) and increased in individuals with age of > 40 years (13.1% in men and 14.6% in women, respectively) [Osman & Chapple, 2013; Irwin et al, 2006; Abrams et al, 2002]. A population-based survey of adults ≥ 18 years of age in the US (the National Overactive Bladder Evaluation [NOBLE]

study) reported an overall OAB prevalence of 16.5% with a similar distribution between the 2 sexes (16.0% in men and 16.9% in women).

The knowledge of the epidemiology of OAB is limited in Asia. A questionnaire-based survey conducted in randomly selected women 18 to ≥ 70 years of age, who were treated at the outpatient clinics for nonurologic or nongynecologic problems under the supervision of medically trained personnel in 11 Asian countries (China, Hong Kong, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, South Korea, Taiwan and Thailand), reported an overall OAB prevalence of 53.1%, with only 21.1% wanting treatment [Lapitan & Chye, 2001]. In the same 11 Asian countries, a prevalence of 29.9% was reported in a self-administered questionnaire survey completed by a randomly chosen sample of male patients (18 to ≥ 70 years of age) visiting clinics other than urology clinics [Moorthy et al, 2004]. An internet-based self-administered survey conducted among men and women at least 40 years of age in China, Taiwan and South Korea reported an OAB prevalence of 20.8% (19.5% in men and 22.1% in women) and increased significantly with age, from 10.8% in those 40 to 44 years of age to 27.9% in those > 60 years of age ($p = 0.001$) [Chuang et al, 2019]. An overall OAB prevalence of 26.5% in adults 30 years of age and older (18.0% in men and 28.7% in women) was reported in another population-based, cross-sectional questionnaire survey conducted in South China [Chen and Li, 2016].

Many studies have shown significantly greater symptom bother, worse health-related quality of life (HRQoL), higher rates of depression and decreased enjoyment of sexual activity in OAB patients [Chen & Li, 2016; Osman & Chapple, 2013; Coyne et al, 2008; Stewart et al, 2003]. In addition, the economic burden of OAB is substantial.

The management of OAB is multimodal, including lifestyle modifications, behavioral therapies and pharmacological therapeutic strategies. Antimuscarinics, which exert their effect through the blockade of postjunctional muscarinic receptors, are currently the mainstay of pharmacological treatment of OAB and they represent the most commonly prescribed drugs. Meta-analyses of several randomized controlled trials (RCTs) have shown that antimuscarinics (including propiverine, fesoterodine, tolterodine, oxybutynin, solifenacin, trospium and darifenacin) are efficacious, safe and well-tolerated therapies that improve HRQoL [Chapple et al, 2008; Novara et al, 2008]. However, the lack of persistence with antimuscarinics is a well-known challenge in OAB treatment, which may occur due to the side-effects such as dry mouth, conspiration, blurred vision and urinary retention or the lack of perceived efficacy [Andersson, 2013]. A systematic literature review indicated high rates of discontinuation from 12-week RCTs, ranging from 4% to 31% in treatment groups and 5% to 20% in placebo groups, respectively. Findings from medical claims data also suggested that over half of the patients never refilled their initial prescription and that adherence levels were low, with mean/median medication possession ratio (MPR) values ranging from 0.30 to 0.83 [Sexton et al, 2011].

Mirabegron, a first in class beta-3-adrenergic receptor agonist, has been approved for OAB treatment in the US, Europe, Canada, Japan, Australia, Hong Kong, Korea, China and Taiwan. A review of 6 RCTs of mirabegron concluded that mirabegron had clinically

significant efficacy and tolerability in treating OAB symptoms. The tolerability profile of mirabegron provided the potential for improving patient adherence with OAB treatment, as dry mouth was often the reason for antimuscarinics treatment discontinuation [Chapple et al, 2014].

2.3 Risk/Benefit Assessment

2.3.1 Risk Assessment

Preclinical and clinical safety data, including adverse events (AEs) of interest, support the safety of 50 mg mirabegron in the treatment of patients with OAB.

The global OAB 12-week phase 2/3 studies (178-CL-046, 178-CL-047 and 178-CL-074) included 4414 patients treated with mirabegron, 2142 patients treated with placebo and 958 patients treated with tolterodine.

One or more serious adverse events (SAEs) were reported by 1.7% of mirabegron patients, 1.8% of placebo patients and 1.7% of tolterodine patients, with no apparent mirabegron dose response. The most common SAEs in the total mirabegron group were atrial fibrillation (mirabegron: 0.1%; placebo: < 0.1%; tolterodine: 0%), chest pain (mirabegron: 0.1%; placebo: 0.1%; tolterodine: 0%) and pneumonia (mirabegron: 0.1%; placebo: < 0.1%; tolterodine: 0%). The most common treatment-emergent adverse events (TEAEs) (by preferred term) reported in the total mirabegron group were nasopharyngitis (mirabegron: 6.7%; placebo: 6.6%; tolterodine: 5.9%), hypertension (mirabegron: 5.0%; placebo: 5.0%; tolterodine: 4.5%) and blood glucose increased (mirabegron: 4.7%; placebo: 5.4%; tolterodine: 7.6%).

Study 178-CL-090 included 366 patients treated with mirabegron, 371 patients treated with tolterodine and 366 patients treated with placebo. One or more SAEs were reported by 1.4% of mirabegron patients, 1.6% of tolterodine patients and 1.9% of placebo patients. All SAEs were unique to a single patient in each treatment group. All SAEs were considered by the investigator to be not related to the IP except for headache and vomiting, which occurred in 1 patient in the tolterodine sustained release 4 mg group.

In the 1-year long term study, Study 178-CL-049, 1632 patients treated with mirabegron and 812 patients treated with tolterodine were included. The most common SAEs in the total mirabegron group were osteoarthritis (mirabegron: 0.2%; tolterodine: 0.1%) and cerebrovascular accident (mirabegron: 0.2%; tolterodine: 0.1%). The most common TEAEs (by preferred term) reported in the total mirabegron group were hypertension (mirabegron: 9.5%; tolterodine: 9.6%), urinary tract infection (UTI) (mirabegron: 5.7%; tolterodine: 6.4%) and nasopharyngitis (mirabegron: 4.1%; tolterodine: 3.1%).

AEs of interest have been thoroughly evaluated in all completed studies and do not represent product-related safety concerns. Potential risks included QT prolongation with supratherapeutic doses or in high-risk populations, increased heart rate with supratherapeutic doses, increased blood pressure with supratherapeutic doses, nonimmediate cutaneous hypersensitivity reactions and exposure in utero. The potential risks of QT prolongation,

increased heart rate or increased blood pressure are greater with increasing exposure at supratherapeutic doses and can be mitigated with optimal dose selection.

Detailed reference safety information (RSI) can be found in the Investigator's Brochure.

2.3.2 Benefit Assessment

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.

Medical evaluations/assessments associated with study procedures include; completion of electronic diary (e-diary), clinical laboratory tests, vital signs, physical examination, electrocardiogram (ECG), post void residual (PVR) volume assessments, and OAB Symptom Score (OABSS).

2.3.3 Overall Risk-Benefit Conclusion

Subjects participating in this study might benefit from administration of mirabegron. In addition, subjects might experience AEs related to mirabegron or procedural complications (e.g., blood draws, slight skin irritation from the adhesive on the ECG electrodes).

Overall, the risk associated with the participation of OAB patients in this study is considered acceptable.

3 OBJECTIVES, ENDPOINTS AND ESTIMANDS

Objectives and Endpoints:

The primary and secondary objectives and endpoints for this study are listed in the table below.

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
● To evaluate the efficacy of mirabegron 50 mg for the treatment of OAB in Chinese subjects	● Change from baseline to the end of 12-week treatment period in mean number of micturition/24 hours
Secondary	
● To evaluate the safety of mirabegron for the treatment of OAB in Chinese subjects	● Incidence and severity of AEs. ● Clinical laboratory tests (hematology, biochemistry and urinalysis) ● Vital signs (blood pressure and pulse) ● Routine 12-lead ECG

Objectives	Endpoints
	● Post Void Residual (PVR)
● To evaluate other efficacy variables of mirabegron 50 mg for the treatment of OAB	● Change from baseline to the end of 12-week treatment period in mean number of grade 3 or 4 (PPIUS) urgency episodes, incontinence episodes, urge incontinence episodes/24 hours and OABSS ● All efficacy variables change from baseline to weeks 4 and 8
● To explore mirabegron starting dose of 25 mg	● Change from baseline to weeks 4, 8, and 12 in mean number of micturition/24 hours, mean number of grade 3 or 4 (PPIUS) urgency episodes, incontinence episodes, urge incontinence episodes/24 hours and OABSS

AE: adverse event; NA: Not applicable; OAB: overactive bladder; PPIUS: patient perception of intensity of urgency scale; OABSS: OAB Symptom Score.

Estimands

The estimand of most clinical importance for this study is defined by the following 4 attributes:

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

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

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Overall Study Design

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

Planned total number of study sites include approximately 10-15 study sites across China.

This study is designed to support the IDL renewal and mirabegron safety surveillance in China. Subjects fulfilling the screening inclusion/exclusion criteria will be randomized in 2:1 ratio to 50 mg mirabegron and 25 mg mirabegron using a computer-generated randomization to reduce selection bias.

Treatments will be administered once daily orally recommended at the same time after meal during a 12-week, open-label treatment period. Study visits will take place at weeks 4, 8 and 12. For 25 mg mirabegron group, a dose escalation to 50 mg is permitted on visit 3 and visit 4 according to investigators' discretion.

4.2 Scientific Rationale for Study Design

An open-label design will be applied considering the primary objective is to assess the efficacy of mirabegron in Chinese population, measured with the mean number of micturition/24 hours. Subjects will be randomized to treatment to reduce selection bias. The ratio of 2:1 was determined based on the optimal dose of 50 mg rather than 25 mg. A follow-up of 12-week was chosen as previously documented in several Phase III clinical studies.

4.3 Dose Rationale

In mirabegron approval letter, NMPA has asked further investigation on the usage and dosage of (including the initiation dose) mirabegron in Chinese subjects and data should be submitted upon IDL renewal.

In accordance with Decree No. 81 of the Ministry of Health Provisions for Adverse Drug Reaction Reporting and Monitoring (July 2011) and draft guidance issues in 2013, drug manufacturers shall conduct regular safety surveillance for produced drugs and perform intensive monitoring over drugs during the new drug observation period as well as drugs imported for the first time within 5 years. Mirabegron sustained release tablets 50 mg and 25 mg are applicable for implementing the intensive monitoring.

In accordance with the NMPA’s request, to continue the study on the posology of Chinese subjects, including the initial dose and taking drug after the meal and submit the study results upon renewal, both 25 and 50 mg doses of mirabegron will be investigated.

Mirabegron label in China recommended the use of 25mg in liver and renal impairment patients. However there is a risk that there will be absent or too few subjects in 25mg arm to make meaningful conclusions should the label is followed. Therefore the study recruits the same inclusion criteria to be randomized in both arms.

The 50mg group serves as the primary efficacy and safety assessment whilst the 25mg group is an exploratory starting dose observation in Chinese subjects. The investigators in 25mg group may want to assess in the next follow-ups if a dose escalation to 50mg is required at their own discretion. The study does not allow dose reduction from 50mg to 25mg as the former is considered a safe and effective recommended dose.

4.4 End of Study Definition

The end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Assessments [Table 1] for the last subject in the study.

5 STUDY POPULATION

The study population will consist of Chinese male and female subjects with OAB (≥ 18 years of age). Eligible subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

All screening assessments must be completed and reviewed to confirm the potential subject meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

5.1 Inclusion Criteria

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

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult (≥ 18 years of age) according to local regulation at the time of signing the informed consent form (ICF).
3. Subject should exhibit symptoms of OAB for at least 12 weeks before initiation of the screening period.
4. Subject should have an average of ≥ 8 micturitions/24 hours.
5. Subject should have an average of ≥ 1 episode of grade 3 or 4 (PPIUS) urgency or urgency incontinence/24 hours, during a 3-day micturition diary period.
6. Female subject is not pregnant (see [Section 10.2 Appendix 2: Contraception Requirements]) and at least one of the following conditions apply:
   a. Not a woman of childbearing potential (WOCBP) (see [Section 10.2 Appendix 2: Contraception Requirements])
   b. WOCBP who agrees to follow the contraceptive guidance (see [Section 10.2 Appendix 2: Contraception Requirements]) from the time of informed consent through at least 30 days after final IP administration.
7. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 30 days after final IP administration.
8. Female subject must not donate ova starting at first dose of IP and throughout the study period and for 30 days after final IP administration.
9. Male subject with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception (see [Section 10.2 Appendix 2 Contraception Requirements]) throughout the treatment period and 30 days after final IP administration.
10. Male subject must not donate sperm during the treatment period and for 30 days after final IP administration.

11. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 30 days after final IP administration.
12. Subject agrees not to participate in another interventional study while participating in the present study, defined as 28 days prior screening until completion of the last study visit.

5.2 Exclusion Criteria

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

Exclusion at Visit 1/Week -1 to -2 (Screening)

1. Subject has stress urinary incontinence as a predominant symptom.
2. Subject has an average total daily urine volume > 3000 mL (as recorded in a 3-day voiding diary period).
3. Subject has indwelling catheter or practices intermittent self-catheterization.
4. Subject has neurogenic detrusor overactivity or indicated pathology other than OAB.
5. Subject has monosymptomatic enuresis.
6. Subject has PVR volume of ≥ 100 mL or a clinically significant lower urinary tract obstructive disease, except if successfully treated.
7. Subject has anatomical anomalies (surgically treated or untreated) that affect lower urinary tract function.
8. Subject with hematuria on dipstick test. In the case of hematuria on dipstick test in a female during menstruation, the test can be repeated before randomization (after the end of menstruation).
9. Subject has lower urinary tract stones or clinically significant kidney stones requiring treatment.
10. Subject has interstitial cystitis.
11. Subject has suffered from chronic UTI or has had more than 3 UTIs in the 2 months prior to visit 1/week -1 to -2 (screening).
12. Subject has uncontrolled hypertension (sitting systolic blood pressure [SBP] ≥ 180 mmHg or diastolic blood pressure [DBP] ≥ 110 mmHg).
13. Subject has pulse rate ≥ 110 beats per minute (bpm) or < 50 bpm.
14. Subject has corrected QT interval by Fredericia (QTcF) > 440 msec on screening ECG or a risk of QT prolongation (e.g., hypokalemia, long QT syndrome [LQTS] or family history of LQTS or exercise-induced syncope).
15. Subject's aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is ≥ 2 × upper limit of normal (ULN) or total bilirubin (TBL) is ≥ 1.5 × ULN according to age and sex (subjects with Gilbert's syndrome are excepted from the bilirubin threshold).
16. Subject has moderate or severe renal impairment.
17. Subject has a symptomatic (symptoms can include pain, fever, hematuria, new onset foul-smelling urine) UTI. Note: if the UTI is treated successfully (clinical recovery: confirmed by dipstick test and repeated dipstick test after 14 days [both should be negative]), the subject can be rescreened.

18. Subject has a history or presence of any malignancy (previous or current diagnosis of bladder or prostate cancer).
19. Subject uses any drugs that are sensitive cytochrome P450 2D6 (CYP2D6) substrates with a narrow therapeutic index or sensitive P-glycoprotein (P-gp) substrates after the start of washout.
20. Subject is using or has used prohibited prior and/or concomitant medication(s) [Section 10.5 Appendix 5 List of Excluded Concomitant Medications]. In case α1-AR antagonists, 5α-reductase inhibitors (5-ARIs) and Phosphodiesterase type 5 inhibitors (PED-Is) are used for Benign Prostatic Hyperplasia(BPH), Subject can be included in the study.
21. Subject has known or suspected hypersensitivity to mirabegron or any components of the formulations used.
22. Subjects previously treated for OAB including medication and nondrug treatment. If the treatment stopped for 2 weeks or more prior to the screening visit, Subjects can be included in the study.
23. Subject has participated in another clinical study (and/or subject has received any investigational therapy within 30 days (or 5 half-lives of the drug, or the limit set by national law, whichever is longer) prior to visit 1/week -1 to -2 (screening).
24. Subject has constipation as defined by the Rome IV criteria that cannot be successfully treated prior to study entry.
25. Female subject who has been pregnant within 6 months prior to screening or breastfeeding within 3 months prior to screening.
26. Subject has a positive serology test for hepatitis A virus (HAV) antibodies (immunoglobulin M [IgM]), hepatitis B core (HBc) antibodies, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibodies, antibodies to human immunodeficiency virus (HIV) or syphilis at screening.
27. Subject is an employee of Astellas, the study-related contract research organizations (CROs) or the clinical unit.
28. Subject has any condition, which in the opinion of the investigator, makes the subject unsuitable for study participation.

<u>Additional Exclusion at Visit 2/Week 0 (Baseline)</u>

29. Subject has stress urinary incontinence as a predominant symptom.
30. Subject has an average total daily urine volume > 3000 mL (as recorded in a 3-day voiding diary period).
31. Subject has monosymptomatic enuresis confirmed by the bladder e-diary.
32. Subject suffers from a symptomatic (symptoms can include pain, fever, hematuria, new onset foul-smelling urine) UTI. Note: if a symptomatic UTI is present, all visit 2/week 0 (baseline) assessments must be postponed until the UTI is successfully treated (clinical recovery: confirmed by dipstick test and repeated dipstick test after 14 days [both should be negative]). The postponed visit 2/week 0 (baseline) should be within 14 days of the intended visit 2/week 0 (baseline).

33. Subject with hematuria on dipstick test. In the case of hematuria on dipstick test in a female during menstruation, the test can be repeated before randomization (after the end of menstruation).
34. Subject has uncontrolled hypertension (sitting SBP ≥ 180 mmHg or DBP ≥ 110 mmHg).
35. Any reason, in the opinion of the investigator, that makes the subject unsuitable for study participation.

5.3 Lifestyle Considerations

Restrictions for foods and drinks are not applicable. On visit days dosing should occur in the clinic and breakfast should be eaten at the clinic within 1 hour before dosing.

Concomitant medications such as α1-AR antagonists, medication for diabetes insipidus (desmopressin, vasopressin), antidepressants (Selective Serotonin Reuptake Inhibitors [SSRIs] or tricyclic antidepressants), 5α-reductase inhibitors, capsaicin or resiniferatoxin injections into bladder, botulinum toxin injections to bladder muscles, strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors, antimuscarinics medications for OAB, and those metabolized by CYP2D6 should be restricted during the study except α1-AR antagonists, 5α-reductase inhibitors (5-ARIs) and Phosphodiesterase type 5 inhibitors (PED-Is) use for Benign Prostatic Hyperplasia(BPH)

5.4 Screen Failures

A screen failure is defined as a potential subject who signed the ICF but did not meet one or more criteria required for participation in the study and was not enrolled.

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the electronic case report form (eCRF).

5.4.1 Rescreening

Rescreening is allowed only in situations in which a subject underwent the screening procedures and due to logistical circumstances, the allocated time window for these tests has expired and the subject is documented as a screen failure. In order to rescreen, a new ICF must be signed and a new subject screening number assigned. Rescreening is only allowed once for an individual subject.

6 INVESTIGATIONAL PRODUCT(S)

6.1 Investigational Product(s) Administered

Table 3 Investigational Product(s)

Name	Mirabegron (BETMIGA®)
Use	Test product
Dosage Form	Sustained-release tablet
Physical Description	25 mg: oval, brown, film-coated tablet 50 mg: oval, yellow, film-coated tablet
Unit Dose Strength	25 and 50 mg

Packaging and Labeling	10 tablets per PTP sheet, 1 sheet per carton
Route of Administration	Oral
Administration	IMP will be administered orally, once daily in the morning around the same time of day and around time of food intake (i.e., within 1 hour after breakfast). Tablets will be administered with a sip of water (tablet should be taken as a whole and should not be chewed, divided or crushed).
IMP or Non-IMP	IMP
Sourcing	Provided locally by study site

IMP: investigational medicinal product; PTP: Press Through Package.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All IP used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at Astellas Pharma China, Inc. (ACN) or sponsor's designee in accordance with ACN or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Refer to the product label and package insert for detailed information regarding packaging and labeling of the IP.

6.2.2 Handling, Storage and Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
- Only subjects consented in the study may receive IP and only authorized study site personnel may supply or administer IP. Only IP with appropriate expiry/retest date may be dispensed.
- All IP must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions and access must be limited to the investigator and authorized study site personnel.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records).
- After final reconciliation is confirmed, further guidance and instructions on final disposition of used and unused IP will be provided.

The site must return all IP (including unused or returned by subject) to the sponsor or designee at the end of study or upon expiration. If due to institutional policy or local law, unused, expired or returned IP cannot be returned to the sponsor or designee the IP may be destroyed according to local law.

6.3 Randomization and Blinding

6.3.1 Blinding Method

This section is not applicable as this is an open-label study.

6.3.2 Assignment and Allocation

6.3.2.1 Subject Number

Subjects will be assigned a subject number at study entry (i.e., signing the ICF). The subject numbers will be sequential and rising.

The subject number will comprise of a 5 digit clinical unit number and 5 digit screening number.

6.3.2.2 Randomization Number

Subjects will be randomized in a 2:1 ratio to 50 mg mirabegron and 25 mg mirabegron using a computer-generated randomization Interactive Web Response System (IWRS). All consented subjects who meet the eligibility criteria will be randomized through IWRS. This service is set up prior to the study to allow the sites real-time allocation of the treatment to the next eligible subject based on the specifications and algorithm provided in the Randomization Specification Document.

At visit 2/week 0 (baseline), subjects will be assigned a randomization number in accordance with the randomization code generated by the sponsor’s designee.

6.3.2.3 Subject Replacement

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

6.4 Investigational Product Compliance

Subject compliance with IP will be assessed at each visit. Compliance will be assessed by counting returned tablets. Deviations from the prescribed dose regimen will be recorded.

If compliance is less than 80%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance.

6.5 Dose Modification

For 25 mg mirabegron group, a dose escalation to 50 mg is permitted on visit 3 and visit 4, according to investigators' discretion.

6.6 Continued Access to Investigational Product After the End of the Study

Mirabegron has been approved and commercially available in China.

6.7 Treatment of Overdose

Mirabegron administered at single doses up to 400 mg or at multiple doses up to 300 mg daily for 10 days cause overdose. Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure and ECG monitoring are recommended.

6.8 Concomitant Therapy

Subjects are not allowed to use ongoing treatment with any of the following prohibited medications after the start of the washout:

Any medication, other than the IP, used for the treatment of OAB

- Any drugs that are sensitive CYP3A inhibitors, CYP2D6 substrates with a narrow therapeutic index or sensitive P-gp substrates.
- Intradetrusor botulinum toxin injections; except if given > 9 months prior screening and symptoms reappeared comparable to those before botulinum toxin injections.
- Drugs such as α1-AR antagonists, medication for diabetes insipidus (desmopressin, vasopressin), antidepressants ([SSRIs] or tricyclic antidepressants), 5α-reductase inhibitors, capsaicin or resiniferatoxin injections into bladder.
- Nonmedication therapies like chiropractic, physical therapy will also be collected on the nonmedication therapy eCRF.

Subjects are allowed to continue ongoing treatment of α1-AR antagonists, 5α-reductase inhibitors (5-ARIs) and Phosphodiesterase type 5 inhibitors (PED-Is) in case of use for Benign Prostatic Hyperplasia (BPH).

Please refer to [Section 10.5 Appendix 5 List of Excluded Concomitant Medications] for drug classes or specific medications that are prohibited during participation in the study.

7 STUDY PROCEDURES AND ASSESSMENTS

- Study procedures and their timing are summarized in the Schedule of Assessments [Table 1]. Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct. Prospective protocol waivers or exemptions are not allowed.
- Any change, divergence or departure from the study design or procedures identified in the protocol is considered a protocol deviation. All deviations from the protocol are to be recorded.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the subject's routine clinical management (e.g., imaging, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments [Table 1].

7.1 Efficacy Assessments

7.1.1 Bladder e-Diary

The bladder diary is part of the subject's e-diary which is used to collect micturition frequency, incontinence episodes as well as volume measurements. After a successful visit 1 /week -1 to -2 [screening]), all subjects will start with the completion of a 3-day bladder e-diary recording micturition frequency and incontinence episodes as well as collection of micturition volume over 2 days. The bladder e-diary should be completed over 3 consecutive days, at minimum 3 days, but not more than 7 days, prior to visit 2/week 0 (baseline).

Upon successful completion of the 3-day bladder e-diary, subject should return for visit 2/week 0 as soon as possible, and no more than 7 days after the start of the diary completion. The completed e-diary data should be reviewed by the investigator, discussed and confirmed with the subject at the start of visit 2/week 0. Upon confirmation of eligibility criteria, the subject shall proceed to randomization. If the investigator is under the impression that the subject is not able to perform all the required assessments and to complete all required forms with credible data, this subject should not be considered for randomization.

After successful randomization, subsequent bladder e-diaries will be completed by the subject over 3 consecutive days in the week prior to visit 3/week 4, visit 4/week 8 and visit 5/week 12. Completion of the 3-day bladder diaries should start at minimum, 3 days (but not more than 7 days) prior to the indicated visit.

7.2 Safety Assessments

Study procedures and their timing are summarized in the Schedule of Assessments [Table 1]. Protocol waivers or exemptions are not allowed.

7.2.1 Laboratory Assessments

Clinical laboratory tests will be performed at a local laboratory.

Blood samples will be collected via a peripherally placed intravenous cannula or by direct venipuncture in a suitable forearm vein.

Blood samples for hematology and biochemistry and urine samples for urinalysis will be collected as indicated in the Schedule of Assessments [Table 1]. The clinical laboratory tests to be performed in the study are listed in [Section 10.6 Appendix 6 Laboratory Assessments].

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

Urine pregnancy tests (female subjects only) will be performed according to the clinical site's preferred method. Pregnancy tests will be performed as indicated in the Schedule of Assessments [Table 1].

If any of the clinical laboratory tests results be outside the normal range at any scheduled time point during the study, the investigator may decide to repeat the test(s) on new samples. The clinical relevance of the abnormal results will be documented. Clinically relevant changes will be recorded as AEs (see [Section 7.3 Adverse Events and Other Safety Aspects]).

7.2.2 Vital Signs

Blood pressure (SBP and DBP), pulse measurements, and body temperature will be taken as indicated in the Schedule of Assessments [Table 1]. Single measurements of blood pressure and pulse will be measured in the sitting position (when possible, otherwise supine, but always in the same position). Subject should have been calm and without distress for at least 5 minutes. Preferably, the right arm should be used to measure vital signs. Body temperature will be measured with an ear thermometer. These measurements will be used to assess eligibility.

7.2.3 Physical Examination

Physical examination will be performed as indicated in the Schedule of Assessments [Table 1] and whenever there is a medical indication.

The investigator should perform physical examinations in accordance with routine procedures. Any abnormal finding observed at screening must be assessed and documented as not clinically significant if a subject is to be enrolled in the study. After IP administration, new clinically significant findings or a worsening of an ongoing clinically significant abnormal condition will be recorded as an AE (see [Section 7.3 Adverse Events and Other Safety Aspects]).

7.2.4 Electrocardiogram

Routine 12-lead ECGs will be taken as indicated in the Schedule of Assessments [Table 1]. Routine 12-lead ECGs will be taken after the subject has been resting in the supine position for at least 5 minutes. Routine 12-lead ECGs will be taken as single measurements.

The investigator will review, sign and date the ECG after recording to ensure subject safety. The time of the ECG, the interval measurements, as well as an overall conclusion, will be documented. This overall conclusion will be recorded as normal, abnormal not clinically significant, or abnormal clinically significant. If the overall conclusion is abnormal, the details must be recorded.

Per time point, the ECG will be stored electronically and reviewed in a timely manner by the investigator. The electronic data file with all generated ECG variables and electronic files with the digitized tracings will be transferred to the sponsor at the end of the study.

7.2.5 Post Void Residual Volume Assessments

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

7.2.6 Overactive Bladder Symptom Score

The OABSS, an assessment tool which has been found to be reliable and valid and highly responsive to treatment related fluctuations in OAB will be performed at visit 2/week 0 (baseline), visit 3/week 4, visit 4/week 8 and visit 5/week 12 (EoT) [Urology; 2006]. Repeating the test after treatment interval is an effective way to assess the efficacy of a mirabegron treatment on OAB symptoms. The OABSS questionnaire is designed to quantify OAB symptoms experienced in the previous week as a single score, and contains questions that address 4 symptoms of overactive bladder:

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

The OABSS has a maximum score of 15 with more weight assigned to urgency and urgency incontinence than on frequency, (see [Section 10.7 Appendix 7 Overactive Bladder Symptom Score questionnaire]).

Questionnaires to be completed by the subject in the local language and provided via the e-diary. Results will be directly entered in the e-diary by the subject.

7.2.7 Order of Assessments

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

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Sections 10.3.1 Definition of Adverse Events and 10.3.2 Definition of Serious Adverse Events], respectively.

AEs will be reported by the subject.

The investigator and any qualified designees are responsible for detecting, documenting and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study IP, or that caused the subject to discontinue the IP and/or study [Section 10.3 Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in [Section 10.3 Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

7.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until 30 days after the final IP administration or when the subject is determined to be a screen failure and reported in the eCRF.

All AEs will be collected from the signing of the ICF until 30 days after the final IP administration or when the subject is determined to be a screen failure and reported in the eCRF.

If the severity of an SAE/AE changes, the event should be relisted in the eCRF with the new severity and new onset date.

If the severity decreases, the SAE/AE should be relisted in the eCRF with the new severity and new onset date. The exception is ongoing pre-dose events that continue post-dose and improve post-dose. Such events should not be re-listed.

If the severity of an SAE reduces, the details of the AE should be provided on the SAE worksheet for the medical assessor to be able to assess the course of the event.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in [Section 10.3 Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting]. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study IP or study participation, the investigator must promptly notify the sponsor.

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

7.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AEs of special interest (AESI) (as defined in [Section 7.3.6 Adverse Events of Special Interest]) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in [Section 8.3 Lost to Follow-up]). Further information on follow-up procedures is provided in [Section 10.3 Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

If after the protocol-defined AE collection period (see [Section 7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information]), an AE progresses to an SAE, or the investigator learns of any (S)AE (serious adverse event or adverse event) including death, where he/she considers there is reasonable possibility it is related to the IP or study participation, the investigator must promptly notify the sponsor.

7.3.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE within 24 hours is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study IP under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study IP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Under this protocol, the following event(s) will not be considered as an (S)AE:

Disease progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as (S)AEs. These data will be captured as efficacy assessment data as outlined in [Section 7.1 Efficacy Assessments]. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the IP and the event, it should be reported as an (S)AE. All deaths up to 30 days after the final administration of IP must be reported as an SAE, even if attributed to disease progression.

7.3.6 Adverse Events of Special Interest

AEs (serious or nonserious) of special interest are to be collected via the SAE worksheet and reported within 24 hours as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events].

AESI are AEs the sponsor may wish to carefully monitor. These AEs may be serious or non-serious and should be reported on the eCRF and the SAE worksheet. These AEs are not considered SAEs unless they meet the definition of an SAE. AESI in this study will include:

- Increased heart rate and tachycardia
- Increased blood pressure
- Hypersensitivity reactions
- Urinary retention
- QT prolongation

7.3.7 Special Situations

Certain special situations observed in association with the IP, such as incorrect administration (e.g., wrong dose of IP or background therapy) are reported as protocol deviations and/or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in the eCRF. If the AE meets the definition of an SAE, the SAE is to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on the special situation worksheet or pregnancy reporting form.

The special situations are:

- Pregnancy
- Lactation
- Medication error, overdose and off-label use
- Misuse/abuse
- Occupational exposure
- Suspected drug-drug interaction

Instructions and procedures for reporting special situations are provided in [Section 10.3.7 Reporting Procedures for Special Situations].

7.4 Pharmacokinetics

Not applicable.

7.5 Pharmacodynamics

Not applicable.

7.6 Electronic Clinical Outcome Assessment

For this study, it has been decided that there are justifiable scientific reasons (i.e., recall bias) to limit subject reported changes to changes reported by the subject to the site within 1 business day of its entry, as changes outside of this window could potentially impact the data integrity of the study. The data under this rule should be: all subject, primary and secondary endpoints data. However, the site/investigator can remove/inactivate any data that they determine to be in error at any time with recording the reason for the removal/inactivation. The inactivated data will be accessed and reviewed by study monitors. Subject bladder diaries, questionnaires and other data completed by the subject will be entered on an electronic device (e-diary). The information on the electronic device will be automatically uploaded to a central website. The investigator or site designee should review the diaries and questionnaire data on the website for correct completion before each planned visit of the subject (on site visit for all except end of study which can be either site visit or telephone contact) and discuss the results or retrain the subject if applicable. In case clinically relevant adverse changes are noticed during review of the e-diary, these will be recorded as an AE [Section 10.3 Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

The bladder e-diary, questionnaire results and other data collected in the e-diary will be transferred electronically to sponsor or designee at predefined intervals during the study. The vendor will provide sponsor or designee with a complete and clean copy of the data.

For this study the following information will be collected and entered by the subject in the e-diary (see [Section 7.2.6 Overactive Bladder Symptom Score for detailed information per visit):

- Bladder e-diary
- OABSS

The investigator must guide the subject to ensure that on the evening before and during the 2-day period of micturition volume collection, the subject's fluid intake should be regulated (as per investigator guidance) to an appropriate level considering, e.g., age, sex and subject's condition into account. The intake must remain as consistent as possible on these volume collecting days prior to visit 2/week 0 (baseline).

7.7 Other Assessments

Not applicable.

7.8 Total Amount of Blood

The total amount of blood for each subject will vary depending on the course of their disease, duration on treatment and local laboratory requirements. At any time during the study, if any laboratory abnormalities are found for a subject, additional blood may be drawn for safety monitoring.

Table 4 Blood Volume

Sample Type	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Clinical Laboratory Tests	2	8-10 (+5†)	25
Total			**25**

†Includes serology test at screening.

Additional blood may be drawn for safety reasons. The maximum amount of blood drawn during the study will not exceed 50 mL.

8 SUBJECT DISCONTINUATION

Refer to [Section 10.1.9 Study and Site Start and Closure] regarding discontinuation of study sites or of the study as a whole.

8.1 Discontinuation of Individual Subject(s) from Study Treatment

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

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

The reason for discontinuation from study treatment must be documented in the subject's medical records.

A subject must discontinue study treatment for any of the following reasons:

- Subject requests to stop treatment
- Any clinical AEs, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject
- If signs or symptoms of hypersensitivity to mirabegron are observed (e.g., anaphylactic reaction, erythema multiforme or exfoliative dermatitis)
- 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 international normalized ratio (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%)

If a subject discontinues treatment prematurely, the subject will be encouraged to complete all scheduled visits to record all available information.

8.2 Discontinuation of Individual Subject(s) from Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in Schedule of Assessments [Table 1]. The only exception to this is when the subject specifically withdraws

consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

8.3 Lost to Follow-up

Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments, record outstanding data and retrieve IP. These contact attempts should be documented in the subject's medical record.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The hypothesis for comparisons is given as follows:

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

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

9.2 Sample Size Determination

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

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF.
Randomized	All subjects who are randomized. Subjects will be analyzed according to the study treatment to which they are randomized.
Full Analysis Set	The FAS will consist of all subjects who are randomized and receive at least 1 dose of IP and have at least 1 post baseline measurement for mean number of micturitions per 24 hours. The FAS will be analyzed by treatment arm as randomized (i.e., treatment arm based on randomization assignment). This will be the primary analysis set for efficacy analyses.
Safety Analysis Set	The SAF will consist of all subjects who took at least 1 dose of IP. The safety set will be analyzed by treatment arm as treated (i.e., based on the treatment the subject actually received rather than the treatment to which the subject was randomized).

FAS: Full Analysis Set; ICF: informed consent form; IP: investigational product; SAF: Safety Analysis Set.

9.4 Statistical Analyses

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. Changes from the planned analyses in the final SAP that impact the statistical analyses will be justified in the clinical study report (CSR).

9.4.1 General Considerations

In general, data will be summarized with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints, unless otherwise specified. Percentages by categories will be based on the number of subjects with no missing data (i.e., will add up to 100%).

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

9.4.2 Analysis of Efficacy

Efficacy analysis will be conducted on the full analysis set (FAS). The interpretation of results from statistical tests will be based on the FAS.

9.4.2.1 Analysis of Primary Endpoint

9.4.2.1.1 Primary Analysis

The primary efficacy endpoint change from baseline in mean micturitions per 24 hours will be analyzed using a Mixed Models Repeated Measures (MMRM). The MMRM model will include visit (the repeated term), treatment group (25 mg or 50 mg), pooled site, sex, and the interaction term between treatment and visit as fixed effects and baseline measurement (mean number of micturitions per 24 hours) as covariate. If necessary, pooled centers will be generated and documented prior to database lock. If the inclusion of pooled centers creates modeling problems, then dropping that factor will be considered. Subject will be identified as subject in the repeated statement. By treatment least squares (LS) means (± standard error

[SE]) along with 2-sided 95% CIs will be presented for changes at weeks 4, 8 and 12 (the primary endpoint). Consistent with the estimand described in section 3, data from subjects who switch from 25 to 50 mg mirabegron will be summarized only after switching, not included in MMRM model. Data from those subjects prior to switching would still be included in the MMRM model.

9.4.2.2 Sensitivity Analysis

Any additional sensitivity analyses, if applicable, will be described in the SAP.

9.4.2.2.1 Subgroup Analysis

The same analysis (MMRM) as for the primary endpoint will be applied to change from baseline for the following subgroups:

- Prior OAB treatment

9.4.2.3 Analysis of Secondary Endpoints

The same analysis (MMRM, with corresponding baseline measurement for the endpoint as the covariate) as for the primary endpoint will be applied to change from baseline (weeks 4, 8 and 12) for:

- Mean number of grade 3 or 4 (PPIUS) urgency episodes per 24 hours
- Mean number of daytime incontinence episodes per 24 hours
- Mean number of nighttime incontinence episodes per 24 hours
- Mean number of urge incontinence episodes per 24 hours
- OABSS, the sum score of four symptoms (daytime frequency, nighttime frequency, urgency, and urgency incontinence)

9.4.2.4 Analysis of Exploratory Endpoints

Not applicable.

9.4.3 Analysis of Safety

Safety analysis will be conducted on the safety analysis set (SAF). Safety endpoints will be summarized using descriptive statistics.

9.4.3.1 Adverse Events

AEs will be coded using MedDRA. A TEAE is defined as an AE observed after starting administration of the IP and 30 days after the final administration of IP. An IP-related TEAE is defined as any TEAE with a causal relationship assessed as “yes” by the investigator.

The number and percentage of subjects with TEAEs, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to leading to withdrawal of treatment and drug-related TEAEs leading to leading to withdrawal of treatment as well as TEAEs of special interest [Section 7.3.6 Adverse Events of Special Interest] will be summarized by SOC, preferred term and treatment group. The number and percentage of TEAEs by severity will also be summarized. The worst severity will be summarized if the same AE is recorded more than once for a subject.

AE data will be listed.

9.4.3.2 Laboratory Assessments

For quantitative clinical laboratory measurements (hematology, biochemistry and urinalysis), descriptive statistics will be used to summarize results and change from baseline by treatment group and visit.

Shifts relative to normal ranges from baseline to each visit during the treatment period in clinical laboratory tests will be tabulated.

Laboratory data will be listed.

The laboratory parameters that will be assessed during the conduct of the study are listed in [Section 10.6 Appendix 6 Laboratory Assessments].

9.4.3.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects in the SAF by treatment group and visit.

Vital signs data will be listed.

9.4.3.4 Physical Examination

Abnormal findings/conditions identified during the physical examinations will be listed as part of the medical history for the screening visit, or as AEs at later visits.

9.4.3.5 Routine 12-lead Electrocardiogram

The routine 12-lead ECG results will be summarized by treatment group and visit.

9.4.3.6 Post Void Residual Volume

The PVR volume data and change from baseline data will be summarized by treatment group and visit.

9.4.4 Analysis of Pharmacokinetics

Not applicable.

9.4.5 Analysis of Pharmacodynamics | Immunogenicity

Not applicable.

9.4.6 Other Analyses

Additional data driven exploratory analyses may be performed as appropriate.

9.5 Interim Analysis

There is no planned interim analysis but a data cut with summaries and the planned primary analysis for the end of the study may be generated at a specific timepoint during the study for regulatory reporting purposes. No decisions regarding conduct of the study (i.e., stopping) will be based on these results.

9.6 Additional Conventions

If the start and stop dates of AEs and concomitant medications are incomplete, imputed dates will be used to determine whether an AE is/is not treatment emergent or to allocate a concomitant medication to the study period it was taken.

See the SAP for details of the definition for analysis windows to be used for analyses by visit/timepoint.

Study sites that do not enroll sufficient subjects to allow estimation of a study site effect will be pooled for analyses by study site (pooled site). The pooling decisions will be made and documented prior to study hardlock.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Ethical, Regulatory and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent of Subjects

10.1.3.1 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject.

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

- The investigator or his/her representative will immediately inform the subject verbally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participating in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
- The investigator must update the subject's 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 reconsent subjects with the updated ICF even if relevant information was provided verbally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF 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 reconsent process.

10.1.4 Data Protection

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the investigator 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 study without justifiable reasons.

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

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

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then the sponsor shall serve as the controller of such data, as defined by the European Union (EU) Data Protection Directive (DPD), and investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If the sponsor is not based in the EEA, the sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the DPD.

10.1.5 Committee(s) Structure

An independent Data and Safety Monitoring Board (DSMB) can be implemented to act in an advisory capacity to the sponsor to monitor subject safety and data quality once it is required.

A separate charter will describe the responsibilities, remit and timing of DSMB meetings.

10.1.6 Dissemination of Clinical Study Data

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final CSR that forms part of a marketing authorization application, be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator(s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for the coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

10.1.7 Data Quality Assurance

- All subject data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically in an external data file (e.g., local laboratory data). The investigator is responsible for verifying that data entries on the eCRF are accurate and correct by physically or electronically signing the eCRF.

- Guidance on completion of CRFs will be provided in a separate eCRF Completion Guideline.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator according to ICH or applicable local regulatory requirements, whichever is longer, after study completion. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

1. Source data must be available at the study site to document the existence of the 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.
2. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
3. The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, electronic clinical outcome assessment (eCOA) and/or drug accountability.
4. Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information, if applicable). All printed records must be kept in the subject file and be available for archiving.

5. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

The study start date is the date the first subject signs the ICF for the study.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study test product development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
- Total number of subjects included earlier than expected

If the study is prematurely terminated or suspended, the sponsor or designee shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10 Arrangement for Use of Information and Publication of the Study

Information concerning the test product, patent applications, processes, unpublished scientific data, the Investigator’s Brochure 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 study in connection with the development of the product 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 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 study agreement.

10.1.11 Quality Assurance

The sponsor is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

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

To support quality around subject safety and reliability of study results, quality tolerance limits (QTLs) are defined and monitored. QTLs represent the acceptable variation of study data, taking into consideration the current state of medical and statistical knowledge about the variables to be analyzed, as well as the statistical design of the study. It is a level, point, or value associated with a parameter that should trigger an evaluation if a deviation is detected to determine if there is a possible systematic issue (i.e., a trend has occurred). The QTLs defined for this study are provided below.

Table 5 Quality Tolerance Limits

QTL #: Name and Parameter	Definition	Parameter Justification
QTL1: Eligibility: % randomized subjects not meeting key criteria.	% of randomized subjects who do not meet critical inclusion/ exclusion criteria, measured through protocol deviations, which lead to per-protocol population exclusion.	A high percentage of eligibility violations can have a negative impact on interpretation of the endpoint data and overall study data validity, particularly the inclusion criteria that rely upon ongoing, consistent compliance from subjects for self-administered pain assessments and electronic subject-reported outcome data collection.
QTL2: Protocol Compliance: > 5% of subjects with major protocol deviations.	% of subjects with protocol deviations, as measured via ongoing study monitoring, that leads to a lack of reliability around pharmacokinetic and AE/tolerability data.	Assurance and impact on safety and overall data reliability.

AE: adverse event; QTL: quality tolerance limit.

QTL Management Activities:

For control of risks associated with QTLs refer to Study Monitoring Plan.

10.2 Appendix 2: Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the Schedule of Assessments [Table 1]. Pregnancy test results must confirm that the subject is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

Females in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal with one of the following (i.e., permanently sterile):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal

A postmenopausal state is defined as at least 12 months after last menstrual bleeding without an alternative medical cause.

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than one follicle-stimulating hormone (FSH) measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

Documentation of any of these categories can come from the study site personnel's review of the female subject's medical records, medical examination or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

Female subjects of childbearing potential are eligible for participation in the study if they agree to use one of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 30 days after the final IP administration [a].

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Other combined (estrogen- and progesterone-containing) methods
  - Vaginal ring
  - Injectable
  - Implantable
  - Intrauterine hormone-releasing system or intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner
  A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the test product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. It is not necessary to use any other method of contraception when complete abstinence is elected.

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE SUBJECTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL.

Male subjects with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 30 days after final drug administration.[a]

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator
- Use a condom
- Female partners of male subjects who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

10.3.1 Definition of Adverse Events

AE Definition:

An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study IP whether or not considered related to the study IP.

"Adverse event" means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study IP. This includes events related to the comparator and events related to the (study) procedures.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study IP administration even though it may have been present before the start of the study

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease, does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

10.3.1.2 Potential Cases of Drug-induced Liver Injury

Refer to [Section 10.4 Appendix 4: Liver Safety Monitoring and Assessment] for detailed instructions on drug induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Section 10.4 Appendix 4: Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 10.3.6 Reporting Procedures for Serious Adverse Events].

10.3.2 Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE 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 medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, 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.

If an event is not an AE per definition in [Section 10.3.1 Definition of Adverse Events], then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

10.3.3 Assessment of Causality

- The investigator is obligated to assess the relationship between study IP and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IP administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Following a review of the relevant data, the causal relationship between the IP and each (S)AE will be assessed by answering "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the IP?"

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a "reasonable possibility" that an (S)AE may have been caused by the IP (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the subject been administered IP?
- Plausibility (i.e., could the event have been caused by the suspect IP? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and study data, etc.)
- Dechallenge/dose reduction/rechallenge:
  - Dechallenge: did the (S)AE resolve or improve after only stopping the dose of the suspect drug without any treatment?
  - Dose reduction: did the (S)AE resolve or improve after reducing the dose of the suspect drug?
  - Rechallenge: did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results: a specific lab investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of IP exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc., and strength of the alternative explanation
- Temporal relationship between exposure to the IP and (S)AE onset and/or resolution. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible will be provided.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. While it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the sponsor, the initial report should be submitted without delay (i.e., within 24 hours of awareness). With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of "no" is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new

information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

10.3.4 Assessment of Severity

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

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

10.3.5 Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.6 Reporting Procedures for Serious Adverse Events

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit the reports as required by local regulation, containing all necessary information, to the competent authority.

The SAE worksheet must be signed by a medically qualified investigator (as identified on delegation of authority log). Signature confirms accuracy and completeness of the SAE data, as well as the investigator causality assessment including the explanation for the causality assessment.

For contact details, see [Contact Details of Sponsor's Key Personnel]. Fax or email the SAE/special situations/product defect worksheet to:

Astellas Pharma Global Development Inc.
Global Pharmacovigilance
Fax number: +1-888-396-3750
Email: safety-us@astellas.com (copy ACN_PV@astellas.com)

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or their designee [Contact Details of Sponsor's Key Personnel].

Follow-up information for the event should be sent promptly (as soon as available but no longer than within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/special situation worksheet and in the eCRF.

The following minimum information is **required**:

- International study number/study number
- Subject number, sex and age
- Date of report
- Description of the SAE (event and seriousness criteria)
- Causal relationship to the IP (including reason)
- Drug provided (if any)

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., SUSAR reporting) according to current local/regional regulatory requirements. The sponsor or sponsor's designee will submit expedited safety reports to competent authorities and concerned ethics committee per current local regulations and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the study site. In the US, FDA expedited Investigational New Drug (IND) reporting guidelines will be followed.

The sponsor will notify all investigators responsible for ongoing clinical studies with the test product of all SUSARs, which require submission per local requirements IRB/IEC.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the rights, safety or well-being of the subject.

10.3.7 Reporting Procedures for Special Situations

10.3.7.1 Contraceptive Guidance and Collection of Pregnancy Information

If a female subject becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] using the SAE worksheet as a special situation and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing and report the information to the sponsor according to the timelines in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] using the special situation worksheet or pregnancy form.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data, etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female subject as an AE in the eCRF or SAE per [Section 10.3.6 Reporting Procedures for Serious Adverse Events]. Subject pregnancy outcomes listed below are to be reported as SAEs:

- Spontaneous abortion/miscarriage, abortion and missed abortion
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the IP
- If an infant dies more than 1 month after the birth, it is to be reported if a relationship between the death and intrauterine exposure to the IP is judged as *"*possible*"* by the investigator
- Congenital anomaly (including anomaly in miscarried fetus)
- Benign hydatidiform mole
- Blighted ovum

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination or other means as appropriate. (S)AEs experienced by the newborn/infant should be reported via the pregnancy reporting form. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

10.3.7.2 Medication Error, Overdose and "Off-label Use"

If a medication error (defined as an unintended failure in the treatment process that leads to, or has the potential to lead to, harm to the subject), overdose or "off-label use" (i.e., use outside of the target disease defined in the protocol) is suspected, refer to [Section 6.7 Treatment of Overdose]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use."

10.3.7.3 Misuse/Abuse

Definition of misuse: situations where the IP is/are intentionally and inappropriately used not in accordance with the intended use as defined in the protocol.

Definition of abuse: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

If misuse or abuse of the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with details of the misuse or abuse of the IP.

10.3.7.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the IP of study site personnel while preparing it for administration to the subject) to the IP occurs, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the special situation are to be reported on the special situations worksheet.

10.3.7.5 Suspected Drug-drug Interaction

If a drug-drug interaction associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with details of the suspected drug-drug interaction.

10.3.8 Supply of New Information Affecting the Conduct of the Study

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

The investigator will also inform the subjects, who will be required to sign an updated ICF in order to continue in the study.

10.3.9 Urgent Safety Measures

An urgent safety measure (USM) is an intervention that is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant competent authorities, IRB/IEC, where applicable, in order to protect subjects from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

10.3.10 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the study physician (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be a USM, the sponsor will take appropriate action to ensure the safety and welfare of the subjects. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

10.4 Appendix 4: Liver Safety Monitoring and Assessment

The purpose of this appendix is to provide guidance for the monitoring of drug-induced liver injury during the course of the study. It should be noted that this section does not specify the end-of-study analyses of liver enzymes. The end-of-study liver enzymes analyses will be described in the SAP. Any subject enrolled in a 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 at least alkaline phosphatase [ALP], ALT, AST and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a local laboratory is used, alerts will be generated by the local laboratory regarding moderate and severe liver abnormality to inform the investigator and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN is as shown below.

Table 6 Moderate and Severe Liver Abnormalities

	ALT or AST		TBL
Moderate	> 3 × ULN	or	> 2 × ULN
Severe	> 3 × ULN	and†	> 2 × ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal

†Samples taken simultaneously or within maximum 24 hours.

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

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

†Samples taken simultaneously or within a maximum of 24 hours.

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 clinical laboratory tests. The study site personnel are to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests should be repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the IP has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to IP 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 are to be recorded as “AEs” within the eCRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects and may be associated with

fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.

- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications are to be entered in 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 clinical laboratory tests, including INR and 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 Treatment Discontinuation

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of study 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 > 5 × ULN and† (TBL > 2 × ULN in subjects with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

†Samples taken simultaneously or within a maximum of 24 hours.

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, study treatment 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 2 "requirements" for Hy's Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in AT elevations > 3 × ULN ("2 × ULN elevations are too common in treated and untreated subjects to be discriminating").

2. Cases of increased total bilirubin (at least 2 × ULN) with concurrent AT elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

FDA Guidance for Industry titled, "Drug-induced Liver Injury: Premarketing Clinical Evaluation" issued by the FDA on July 2009:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among subjects showing such AT elevations, often with ATs much greater than 3 × ULN, one or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

10.5 Appendix 5: List of Excluded Concomitant Medications

Any medication used for the management of OAB (including tricyclic antidepressants, 1st generation H1-antagonists and α1-AR antagonists) and any drugs that are sensitive CYP2D6 substrates with a narrow therapeutic index and sensitive P-gp substrates. Use of these medications is not permitted during the study phase. This list is not exhaustive. In case of doubt, the investigator should contact the local study monitor.

Subjects are allowed to continue ongoing treatment of α1-AR antagonists, 5α-reductase inhibitors (5-ARIs) and Phosphodiesterase type 5 inhibitors (PED-Is) in case of use for Benign Prostatic Hyperplasia (BPH).

Anticholinergics/antimuscarinics	Tricyclic/heterocyclic antidepressants	1st generation H1-antagonists†
Darifenacin	Alimemazine/Trimipramine	Tripelennamine
Dicyclomine/Dicycloverine	Amitriptyline	Dimenhydrinate
Fesoterodine	Amoxapine	Clemastine
Flavoxate	Clomipramine	Bromazine
Isopropamide	Desipramine	Orphenadrine
Oxybutynin	Dosulepin/Dothiepin	Doxylamine
Oxyphencyclimine	Doxepine	Carbinoxamine
Propantheline	Imipramine	Diphenhydramine
Propiverine	Lofepramine	Cyclizine
Tolterodine	Maprotiline	Chlorcyclizine
Trospium	Mianserin	Hydroxyzine
Solifenacin	Mirtazapine	Meclizine
	Nortriptyline	
	Protriptyline	
α1-AR antagonists	**CYP2D6 with narrow therapeutic index**	**Sensitive P-gp substrates**
Tamsulosin	Thioridazine	Digoxin
Alfuzosin	Flecainide	Dabigatran
Doxazosin	Propafenone	
Terazosin	Imipramine	
Silodosin	Desipramine	
Strong CYP3A4 inhibitors	**Other**	
Itraconazole	Mirabegron (except for study drug)	
Ketoconazole	Botulinum toxin	
Ritonavir	Opioids	
Clarthromycin		

P-gp: P-glycoprotein

†Incidental use for motion sickness is accepted.

10.6 Appendix 6: Clinical Laboratory Assessments

Laboratory tests will be performed according to the Schedule of Assessments [Table 1] and sent to a local laboratory for analysis.

Table 7 Clinical Laboratory Tests

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

HAV: hepatitis A virus; HBc: hepatitis B core; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IgM: immunoglobulin M

10.7 Appendix 7: Overactive Bladder Symptom Score Questionnaire

OABSS questionnaire (Please circle the score that best applies to your urinary condition during the past week in response to each question).

Question	Score	Frequency

How many times do you typically urinate from waking in the morning until sleeping at night	0	7 or less
	1	8 to 14
	2	15 or more
How many times do you typically wake up to urinate from sleeping at night until waking in the morning?	0	0
	1	1
	2	2
	3	3 or more
How often do you have a sudden desire to urinate, which is difficult to control?	0	Not at all
	1	Less than once a week
	2	Once a week or more
	3	About once a day
	4	2 to 4 times a day
	5	5 times a day or more
How often do you accidentally urinate because you can't control the sudden desire to urinate?	0	Not at all
	1	Less than once a week
	2	Once a week or more
	3	About once a day
	4	2 to 4 times a day
	5	5 times a day or more

10.8 List of Abbreviations and Definition of Key Study Terms

List of Abbreviations

Abbreviations	**Description of abbreviations**
ACN	Astellas Pharma China, Inc.
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adrenoceptor
AST	aspartate aminotransferase
AT	aminotransferases
BPH	Benign Prostatic Hyperplasia
CIOMS	Council for International Organizations of Medical Sciences
CSR	clinical study report
CYP3A	cytochrome P450, family 3, subfamily
CYP2D6	cytochrome P450 2D6
DBP	diastolic blood pressure
DPD	Data Protection Directive
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
e-diary	electronic diary
EEA	European Economic Area
EoT	end of treatment

Abbreviations	Description of abbreviations
EPIC	European Prospective Investigation into Cancer and Nutrition
EU	European Union
5-ARIs	5α-reductase inhibitors
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HAV	hepatitis A virus
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	International Continence Society
IDL	Imported Drug License
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LA-CRF	liver abnormality case report form
LS	least squares
LQTS	long QT syndrome
MMRM	Mixed Models Repeated Measures
MPR	medication possession ratio
NMPA	National Medical Products Administration
NOBLE	National Overactive Bladder Evaluation
OAB	overactive bladder
OABSS	OAB Symptom Score
OCAS	oral controlled absorption system
PED-Is	Phosphodiesterase type 5 inhibitors
P-gp	P-glycoprotein
PPIUS	Patient perception of intensity of urgency scale
PVR	post-void residual
QA	quality assurance
QC	quality control

Abbreviations	Description of abbreviations
QTcF	corrected QT interval by Fredericia
QTLs	quality tolerance limits
RCTs	randomized controlled trials
RSI	reference safety information
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SE	standard error
SOP	standard operating procedure
SSRIs	Selective Serotonin Reuptake Inhibitors
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TBL	total bilirubin
ULN	upper limit of normal
USM	urgent safety measure
UTI	urinary tract infection
WOCBP	woman of childbearing potential

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	The last non-missing observation prior to first administration of IP, unless otherwise specified.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a study. Note: once a subject has received the IP or placebo, the protocol applies to the subject.
Investigational Product	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test product or comparative drug (sometimes without randomization) is given to a subject and continues until the last assessment after completing administration of the test product or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. NOTE: unequal randomization is used to allocate subjects into groups at a differential rate; for example, 3 subjects may be assigned to a treatment group for every 1 assigned to the control group.
Screen failure	Potential subject who signed the ICF, but did not meet one or more criteria required for participation in the study and was not randomized.
Screening	A process of active consideration of potential subjects for randomization in a study.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent form until just before the test product or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first study site initiation date to the last study site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

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12 SPONSOR SIGNATURE

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Signature: _____ _____

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