A Phase 4 Open-label, Randomized, Single Oral Dose, Two-way Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Mirabegron in Healthy Chinese Subjects

ISN/Protocol 178-MA-2294

Version 1.3

Incorporating Nonsubstantial Amendment 3 [See Section 13]

17 Sep 2020

NCT04501640

Sponsor:

Astellas Pharma China, Inc.

No. 3 Jia 6 Road 10, Shenyang Economic and Technological Development Zone, Shenyang City, Liaoning Province, The People's Republic of China

Protocol History:
Version 1.0 Original [17 Feb 2020]
Version 1.1 Incorporating Nonsubstantial Amendment 1 [19 Mar 2020]
Version 1.2 Incorporating Nonsubstantial Amendment 2 [21 May 2020]

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SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 14 Sponsor's Signatures].

2. INVESTIGATOR'S SIGNATURE

A Phase 4 Open-label, Randomized, Single Oral Dose, Two-way Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Mirabegron in Healthy Chinese Subjects

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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 Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(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: ---------- ----------

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1 PROTOCOL SUMMARY

1.1 Synopsis

Date and Version of Protocol Synopsis:	17 Sep 2020 Version 1.3
Sponsor: Astellas Pharma China, Inc. (ACN)	**Protocol Number:** 178-MA-2294
Compound Name: Mirabegron	**Phase of Development:** Phase 4

Title of Study:
A Phase 4 Open-label, Randomized, Single Oral Dose, Two-way Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Mirabegron in Healthy Chinese Subjects

Planned Study Period:
3Q2020 to 1Q2021

Study Objectives and Endpoints:
The primary, secondary and exploratory objectives and endpoints for this study are listed in the table below.

Study Objectives and Endpoints

Objectives	**Endpoints**
Primary	
● To determine the effect of food on the pharmacokinetics of single oral doses of mirabegron in healthy Chinese male and female subjects	● Mirabegron plasma: AUC_{inf}, AUC_{last} and C_{max}
Secondary	
● To evaluate the safety and tolerability of single oral doses of mirabegron in healthy Chinese male and female subjects	● Nature, frequency and severity of AEs ● Clinical laboratory tests (biochemistry, hematology and urinalysis) ● Vital signs (blood pressure, body temperature and pulse) ● Routine 12-lead ECG
Exploratory	
● To evaluate the pharmacokinetics of single oral doses of mirabegron in healthy Chinese male and female subjects	● Mirabegron plasma: AUC_{inf}(%extrap), CL/F, $t_{½}$, t_{max}, t_{lag} and V_z/F

AE: adverse event; ECG: electrocardiogram

Planned Total Number of Study Sites and Location(s):
One study site in The People's Republic of China

Study Population:
Healthy Chinese male and female subjects (18 to 45 years of age, inclusive)

Number of Subjects to be Enrolled/Randomized:
A total of 24 Chinese male and female subjects will be randomized within 2 dose groups (25 and 50 mg mirabegron) of 12 subjects each.

Study Design Overview:

The study follows an open-label, randomized, 2-period, single oral dose crossover design at 2 dose levels in healthy Chinese male and female subjects. Each subject will participate in 2 periods separated by a washout of at least 10 days between investigational product (IP) administrations in each period.

Subjects will be randomized to 1 of 4 sequences according to the table below.

Sequences and Investigational Product Assignments

Dose (mg)	Sequence	n	Period 1	Period 2
25	**1**	6	Mirabegron (low-fat)	Mirabegron (fasted)
	2	6	Mirabegron (fasted)	Mirabegron (low-fat)
50	**1**	6	Mirabegron (low-fat)	Mirabegron (fasted)
	2	6	Mirabegron (fasted)	Mirabegron (low-fat)

The dose under fed conditions will be administered following a low-fat breakfast (total calories approximately 450 kcal, with approximately 70 kcal from fat).

Subjects will be screened for up to 21 days prior to IP administration on day 1 of period 1. Subjects who are eligible for study participation will be admitted to the clinical unit on day -1 of each period and will be confined until the last pharmacokinetic sample has been collected within each period. Subjects are to remain semirecumbent and avoid lying on either the left or right side for 4 hours postdose. Pharmacokinetic samples will be collected predose on day 1 of each period and at multiple time points following each dose.

The study will be completed with an end of study visit (ESV). The ESV will take place 5 to 9 days after the last pharmacokinetic sample is collected or at early discontinuation from the study.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

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

1. Institutional Review Board/Independent Ethics Committee-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 a healthy Chinese male or female subject between 18 to 45 years of age, inclusive at screening.
3. Subject has a body mass index range of 19.0 to 24.9 kg/m^2, inclusive and weighs at least 50 kg for male subjects and 45 kg for female subjects at screening.
4. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
   a. Not a woman of childbearing potential (WOCBP) (see [Appendix 12.3 Contraception Requirements])
   b. WOCBP who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent through at least 30 days after final IP administration
5. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 30 days after final IP administration.
6. 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.
7. Male subject with female partner(s) of childbearing potential (including breastfeeding partner[s]) must agree to use contraception (see [Appendix 12.3 Contraception Requirements]) throughout the study period and for 30 days after final IP administration.

8. Male subject must not donate sperm during the study period and for 30 days after final IP administration.
9. 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.
10. Subject agrees not to participate in another interventional study while participating in the present study, defined as 84 days prior screening until completion of the last study visit.

Exclusion Criteria:

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

1. Female subject who has been pregnant within 6 months prior to screening or breastfeeding within 3 months prior to screening.
2. Subject has a known or suspected hypersensitivity to mirabegron or any components of the formulation used.
3. Subject has had previous exposure with mirabegron.
4. Subject has any of the liver function tests (alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase and total bilirubin [TBL]) > 1.5 × upper limit of normal (ULN) on day -1 of period 1.
5. Subject has any clinically significant history of allergic conditions (including drug allergies, asthma, eczema or anaphylactic reactions, but excluding untreated, asymptomatic, seasonal allergies) prior to first IP administration.
6. Subject has any history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal and/or other major disease or malignancy, as judged by the investigator.
7. Subject has/had febrile illness or symptomatic, viral, bacterial (including upper respiratory infection) or fungal (noncutaneous) infection within 1 week prior to day -1 of period 1.
8. Subject has any of the following concerns with regard to tuberculosis:
   - History of active tuberculosis
   - Abnormalities detected in a chest X-ray on day -1 of period 1
   - Contact with infectious tuberculous patients
9. Subject has any clinically significant abnormality following the investigator's review of the physical examination, electrocardiogram (ECG) and protocol-defined clinical laboratory tests at screening or on day -1 of period 1.
10. Subject who deviated from the following range of vital signs or routine 12-lead ECG results at screening or on day -1 of period 1. If the mean blood pressure, pulse or corrected QT interval using Fridericia's formula (QTcF) exceeds the limits below, 1 additional triplicate can be taken. The final judgment should be based on the retest results.

Blood pressure	Systolic blood pressure: ≥ 90 mmHg, < 140 mmHg Diastolic blood pressure: ≥ 40 mmHg, < 90 mmHg
Pulse	≥ 45 bpm, ≤ 99 bpm
Body temperature	≥ 35.0°C, ≤ 37.5°C
Routine 12-lead ECG	Findings: Normal or clinically irrelevant abnormality QTcF: < 430 msec (for male subjects) < 450 msec (for female subjects)

11. Subject has used any prescribed or nonprescribed drugs (including vitamins, natural and herbal remedies, e.g., St. John's Wort and traditional Chinese medicine) in the 2 weeks prior to first IP administration, except for occasional use of paracetamol (up to 2 g/day), topical dermatological products, including corticosteroid products, hormonal contraceptives or hormone replacement therapy (HRT).

12. Subject has a history of smoking > 10 cigarettes (or equivalent amount of tobacco) per day within 3 months prior to day -1 of period 1.
13. Subject has a history of consuming > 21 units for male subjects or > 14 units for female subjects of alcohol per week within 3 months prior to day -1 of period 1 (note: 1 unit = 10 g pure alcohol, 250 mL of beer [5%], 35 mL of spirits [35%] or 100 mL of wine [12%]) or the subject has a history of alcohol-dependency, drug-dependency, chemical-dependency, or alcohol or drug abuse within 2 years prior to screening or the subject tests positive for alcohol at screening or on day -1 of period 1.
14. Subject has used any drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and/or opiates) within 3 months prior to day -1 of period 1 or the subject tests positive for drugs of abuse (amphetamines, benzodiazepines, cannabinoids, cocaine and opiates) at screening or on day -1 of period 1.
15. Subject has used any inducer of metabolism (e.g., barbiturates and rifampin) in the 3 months prior to day -1 of period 1.
16. Subject has had significant blood loss, donated ≥ 400 mL of whole blood within 90 days, ≥ 200 mL of whole blood within 30 days or donated blood components within 14 days prior to day -1 of period 1 and/or received a transfusion of any blood or blood products within 60 days.
17. Subject has a positive serology test for hepatitis A virus antibodies (immunoglobulin M), hepatitis B core antibodies, hepatitis B surface antigen, hepatitis C virus antibodies, human immunodeficiency virus or syphilis at screening.
18. Subject is an employee of Astellas, the study-related contract research organizations or the clinical unit.
19. Subject is deemed unsuitable for participating in the study by the investigator or subinvestigator.

Investigational Product(s):

Name/Use:

BETMIGA® (mirabegron) sustained-release tablets in 25 and 50 mg (test product)

Dose(s):

Single dose of 25 mg mirabegron (1 × 25 mg tablet)

Single dose of 50 mg mirabegron (1 × 50 mg tablet)

Mode(s) of Administration:

Fasted Conditions: Following an overnight fast of at least 10 hours, subjects will receive a single dose of 25 or 50 mg mirabegron with 240 mL water. Subjects are to remain semirecumbent and avoid lying on either the left or right side for 4 hours postdose. No food or beverage will be allowed for at least 4 hours postdose. Water can be ingested as desired except for 1 hour predose and 1 hour postdose.

Fed Conditions: Following an overnight fast of at least 10 hours, subjects will start a low-fat breakfast. Subjects should eat the breakfast in 30 minutes or less. Subjects will receive a single dose of 25 or 50 mg mirabegron with 240 mL water 30 minutes after the start of the breakfast. Subjects are to remain semirecumbent and avoid lying on either the left or right side for 4 hours postdose. No food or beverage will be allowed for at least 4 hours postdose. Water can be ingested as desired except for 1 hour predose and 1 hour postdose. Except for the day 1 breakfast in each period, subjects will receive standardized meals scheduled at the same time during the stay at the clinical unit. The low-fat meal (total calories approximately 450 kcal, with approximately 70 kcal from fat) is cereal, low-fat milk, wheat bread, ham and ketchup.

Dose Modifications:

Not applicable.

Concomitant Treatment (Medication and Nonmedication Therapy) Restrictions or Requirements:

All medicinal products other than the IP(s), including prescribed or nonprescribed drugs (including vitamins, natural and herbal remedies, e.g., St. John's Wort and traditional Chinese medicine), used from first IP administration until the ESV (including washout between periods) will be considered concomitant medication.

Subjects will only be allowed to use the following concomitant medication, if needed, from first IP administration until the ESV (including washout between periods):

- Paracetamol (up to 2 g/day)
- Topical dermatological products, including corticosteroid products
- Hormonal contraceptives
- HRT

If a subject's health condition necessitates the use of any medication other than the permitted medications during the study, the investigator and medical monitor, or designee(s), will discuss the case and determine if the subject should be withdrawn from the study and/or excluded from analysis sets, depending on if, and how, the medication(s) used influence(s) the study outcome. The nonpermitted concomitant medication will be recorded as a protocol deviation.

All concomitant treatment (medication and nonmedication therapy) will be documented.

Duration of Dosing:

Two single periods separated by a washout of at least 10 days between IP administrations in each period

Dosing Discontinuation Criteria:

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

- Subject requests to stop dosing
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued dosing is not in the best interest of the subject
- Hepatic function parameters: ALT or AST > 3 × ULN and/or TBL > 2 × ULN
- Cardiac repolarization dysfunction: QTcF > 500 msec and/or if QTcF change from baseline > 60 msec at repeat measurements

Statistical Methods:

Sample Size Justification:

A total of 24 subjects (12 subjects per dose group) will be enrolled. Subjects who discontinue early from the study may be replaced at the discretion of the sponsor.

Based on data from Study 178-CL-091, a Chinese phase 1 study, the intrasubject coefficient of variation (CV) for pharmacokinetic parameters AUC_{inf}, AUC_{last} and C_{max} of the 50 mg mirabegron dose are estimated to be between 33% and 60%. Assuming the underlying variability is similar to 60% and an observed ratio between fasted and fed conditions of 100%, the 90% CI will lie within (60, 167) with > 80% probability.

Efficacy:

Not applicable.

Safety:

To characterize the safety profile, descriptive statistics will be presented for AEs, clinical laboratory tests (hematology and biochemistry) and vital signs (blood pressure, body temperature and pulse) by fasted/fed conditions for each dose group.

Pharmacokinetics:

To assess the effect of food on the pharmacokinetic of mirabegron, a mixed effects analysis of variance (ANOVA) model with fixed effects for food condition (fasted or fed) and period and subject as a random effect will be fitted on natural logarithm-transformed AUC_{inf}, AUC_{last} and C_{max}. Within the ANOVA, the least squares (LS) mean differences between fed and fasted, along with 90% CIs for the differences will be estimated for 25 and 50 mg mirabegron doses separately.

The LS means for AUC_{inf}, AUC_{last} and C_{max} will be back-transformed to produce the geometric LS means and presented with the number of subjects for each food condition. The geometric LS mean ratios and their corresponding 90% CIs for each pharmacokinetic parameter will be presented by back-transforming and expressed as percentages. The analysis will be repeated if all subjects did not complete both periods using an ANOVA with fixed effects for period, food condition and subject; this analysis will only include subjects with complete data in both periods.

Pharmacodynamics | Immunogenicity:

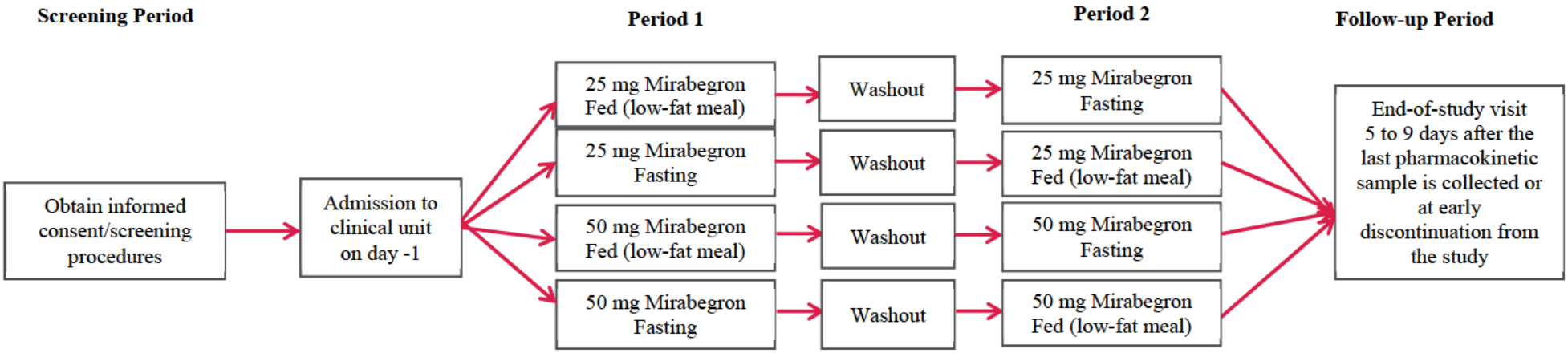
Not applicable.

Interim Analyses:

Not applicable.

1.2 Study Schema

Figure 1 Study Schema



1.3 Schedule of Assessments

Table 1 Schedule of Assessments

Assessments	Screening Period		Periods 1/2[1]			ESV	Withdrawal
Day(s)	-21 to -2	-1	1	2 to 4	5	12±2	
Residential Period		X	X	X	X		
Ambulant Visits	X					X	
Informed Consent	X						
Chest X-ray		X[2]					
Inclusion and Exclusion Criteria	X	X[2]					
Medical History	X	X[2]					
Body Weight and Height	X	X[3]					
Demographics	X						
Drugs of Abuse and Alcohol Tests	X	X					
Randomization[4]		X[2]					
IP Administration[5]			X				
Physical Examination	X	X[2]	X		X	X	X
Vital Signs (Blood Pressure, Body Temperature and Pulse)[6]	X	X	predose†, 2, 8, 24, 48, 72 and 96 hours postdose			X	X
Clinical Laboratory Tests (Serology, Hematology, Biochemistry and Urinalysis)[7]	X	X†			X	X	X
12-lead ECG[8]	X	X†				X	X
Blood Sampling for Mirabegron Pharmacokinetics			predose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 24, 36, 48, 72 and 96 hour(s) postdose				
Serum Pregnancy Test (Female Subjects Only)[9]	X	X					
FSH Test (Postmenopausal Female Subjects Only)	X						
Adverse Event Assessment	X						
Previous/Concomitant Treatment (Medication and Nonmedication Therapy)	X						

Footnotes appear on the next page

ECG: electrocardiogram; ESV: end-of-study visit; FSH: follicle-stimulating hormone; IP: investigational product; X: to be conducted

† Baseline

1. Periods will be separated by a washout of at least 10 days between IP administrations in each period. There is no washout after period 2.
2. Period 1 only.
3. Body weight only.
4. Subjects will be randomized to 1 of 4 sequences.
5. *Fasted Conditions*: Following an overnight fast of at least 10 hours, subjects will receive a single dose of 25 or 50 mg mirabegron with 240 mL water. Subjects are to remain semirecumbent and avoid lying on either the left or right side for 4 hours postdose. No food or beverage will be allowed for at least 4 hours postdose. Water can be ingested as desired except for 1 hour predose and 1 hour postdose.
   Fed Conditions: Following an overnight fast of at least 10 hours, subjects will start a low-fat breakfast. Subjects should eat the breakfast in 30 minutes or less. Subjects will receive a single dose of 25 or 50 mg mirabegron with 240 mL water 30 minutes after the start of the breakfast. Subjects are to remain semirecumbent and avoid lying on either the left or right side for 4 hours postdose. No food or beverage will be allowed for at least 4 hours postdose. Water can be ingested as desired except for 1 hour predose and 1 hour postdose. Except for the day 1 breakfast in each period, subjects will receive standardized meals scheduled at the same time during the stay at the clinical unit. The low-fat meal (total calories approximately 450 kcal, with approximately 70 kcal from fat) is cereal, low-fat milk, wheat bread, ham and ketchup.
6. Measurements will be taken after the subject has been resting in the supine position for at least 5 minutes. Blood pressure and pulse measurements will be taken in triplicate at screening and on day -1 of each period and at all other time points as single measurements. Body temperature measurements will be taken as single measurements.
7. Blood collection for serology tests (screening only), hematology and biochemistry; urine collection for urinalysis.
8. Routine 12-lead ECGs will be taken after the subjects has been resting in the supine position for at least 5 minutes. Routine 12-lead ECG will be taken in triplicate at screening and on day -1 of each period and at all other time points as single measurements.
9. Not for postmenopausal female subjects.

2 INTRODUCTION

The generic name of the investigational product (IP) is mirabegron sustained-release tablets (also called mirabegron oral controlled absorption system tablets internally) and the trade name is BETMIGA® [Betmiga Package Insert, Aug 2019].

Mirabegron is a selective agonist for human beta 3-adrenoceptor. It is a new 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 is renewed.

2.1 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 definition [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 in Canada, Germany, Italy, Sweden and the UK (the European Prospective Investigation into Cancer and Nutrition study) [Osman & Chapple, 2013; Irwin et al, 2006; Abrams et al, 2002]. In the US (the National Overactive Bladder Evaluation study) reported an overall OAB prevalence of 16.5%. The figure increased by age, with a similar distribution between the 2 sexes.

In Asia, a questionnaire-based survey conducted in adult women in China, Hong Kong, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, South Korea, Taiwan and Thailand reported an 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 adult male patients [Moorthy et al, 2004]. An internet-based self-administered survey was conducted among men and women ≥ 40 years of age in China, Taiwan and South Korea, reporting an OAB prevalence of 20.8% (19.5% in men and 22.1% in women), increasing significantly with age (10.8% in those 40 to 44 years of age to 27.9% in those > 60 years of age ($p = 0.001$)) [Chuang & Liu, 2019].

OAB patients experience significantly greater symptom bother, worse health-related quality of life (HRQoL), higher rates of depression and decreased enjoyment of sexual activity [Chen & Li, 2016; Osman & Chapple, 2013; Coyne et al, 2008; Stewart et al, 2003]. In addition, the economic costs 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 and represent the most commonly prescribed drugs. Meta-analyses of several randomized controlled studies 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, which may occur due to the side-effects or the lack of perceived efficacy [Andersson, 2013]. A systematic literature review indicated high rates of discontinuation from 12-week randomized controlled studies, 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 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 randomized controlled studies 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].

2.1.1 Nonclinical and Clinical Data

Mirabegron is a selective beta 3-adrenoceptor agonist showing selective agonistic activity and high affinity for human beta 3- as compared with beta 1- and beta 2-adrenoceptors.

The primary pharmacology studies show bladder relaxation with mirabegron during the filling phase and inhibition of the frequency of nonvoiding activity, without impairing voiding efficiency.

The nonclinical data provide proof of principle that mirabegron enhances urine storage function by stimulating beta 3-adrenoceptors in the bladder, without affecting voiding contractions.

The mirabegron clinical pharmacology program in the Chinese population consisted of 2 studies in 48 volunteers. The results in the Chinese population showed that the exposure of mirabegron was largely similar among different ethnic groups (Chinese, Japanese and Western subjects), considering a large intersubject variability of plasma concentration of mirabegron.

The efficacy of mirabegron in the treatment of symptoms of OAB is well demonstrated with the following data.

Study 178-CL-090 assessed the efficacy and safety of mirabegron in Asian patients (total 1126 patients, including 344 Chinese). Mirabegron 50 mg per day for 12 weeks demonstrated superior efficacy to placebo in the change from baseline in the mean number of micturitions per 24 hours and the secondary efficacy variables (change from baseline to last visit in mean volume voided per micturition, mean number of urgency episodes per 24 hours, mean number of incontinence episodes per 24 hours and mean number of urge incontinence episodes per 24 hours). The efficacy trend in Asian and Chinese patient was same. The clinical study showed mirabegron was safe and well-tolerated. No clinically relevant concerns were identified.

The efficacy of mirabegron has also been demonstrated across 6 phase 2b and 3, 12-week global studies, evaluating doses of 25, 50 or 100 mg mirabegron orally once daily in a total of 4285 patients in the full analysis set (FAS) population and 2815 patients in the FAS-incontinence population. Mirabegron consistently demonstrated superiority compared with placebo in reducing both coprimary endpoints of the mean number of incontinence episodes per 24 hours and the mean number of micturitions per 24 hours.

The long-term effect of mirabegron was established by a 1-year study, Study 178-CL-049. Improvement in incontinence episodes, micturitions and mean volume voided per micturition was observed for mirabegron 50 and 100 mg once daily; results were similar to tolterodine. Improvement was also established in subjective endpoints as well as responder analyses indicating that the patients had clinically meaningful benefit from treatment.

Mirabegron at the proposed therapeutic dose is well-tolerated in the OAB population studied, inclusive of patients with multiple comorbidities and concomitant medications. The data from the clinical program are generalizable to the population of patients intended for the use of mirabegron in the treatment of OAB.

Adverse events (AEs) of interest have been thoroughly evaluated, generally do not represent product-related safety concerns, and where appropriate, can be addressed in labeling and other routine pharmacovigilance.

Preclinical and clinical safety data, including AEs of interest, support the safety of mirabegron under labeled condition in the treatment of patients with OAB.

The effect of food on the pharmacokinetics of mirabegron has been evaluated in healthy subjects in the US and Japan [Studies 178-CL-041 and 178-CL-078]. Both low-fat and high-fat meals decreased the peak and systemic exposures to mirabegron (50 or 100 mg dose) when compared with fasting conditions, however, the magnitude of the food effect was greater for the low-fat than the high-fat meal. Following a low-fat meal, C_{max} was reduced by approximately 64% to 75% and AUC_{inf} was reduced by approximately 47% to 51% relative to the fasted state. Following a high-fat meal, C_{max} was reduced by approximately 39% to 53% and AUC_{inf} was reduced by approximately 17% to 29% relative to the fasted state. No clear difference was observed between male and female subjects.

Refer to the [Investigator's Brochure] for detailed information.

2.1.2 Summary of Key Safety Information for Investigational Product(s)

Preclinical and clinical safety data, including 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 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 (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, Appendix 1].

2.2 Study Rationale

This phase 4 study will be an open-label, randomized, 2-period, single oral dose crossover design at 2 dose levels in healthy Chinese male and female subjects. It is intended to determine the effect of food on the pharmacokinetics of 25 and 50 mg mirabegron tablets, and to evaluate the pharmacokinetics, safety and tolerability of single oral doses of 25 and 50 mg mirabegron under fasted and fed (low-fat meal) conditions.

2.3 Risk Benefit Assessment

Subjects participating in this study will not benefit from administration of mirabegron. In contrast, subjects might experience AEs related to mirabegron or procedural complications (e.g., blood draws, slight skin irritation from the adhesive on the ECG electrodes). AEs are described in [Section 2.1.1 Nonclinical and Clinical Data], the package insert [Betmiga Package Insert, Aug 2019] and interview form of mirabegron. Unknown AEs that have not been reported in the past may occur in this study.

Overall, the risk associated with the participation of healthy subjects in this study is considered acceptable.

3 STUDY OBJECTIVE(S) AND ENDPOINT(S)

The primary, secondary and exploratory objectives and endpoints for this study are listed in [Table 2].

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the effect of food on the pharmacokinetics of single oral doses of mirabegron in healthy Chinese male and female subjects	• Mirabegron plasma: AUC_{inf}, AUC_{last} and C_{max}
Secondary	
• To evaluate the safety and tolerability of single oral doses of mirabegron in healthy Chinese male and female subjects	• Nature, frequency and severity of AEs • Clinical laboratory tests (biochemistry, hematology and urinalysis) • Vital signs (blood pressure, body temperature and pulse) • Routine 12-lead ECG
Exploratory	
• To evaluate the pharmacokinetics of single oral doses of mirabegron in healthy Chinese male and female subjects	• Mirabegron plasma: AUC_{inf} (%extrap), CL/F, $t_{½}$, t_{max}, t_{lag} and V_z/F

AE: adverse event; ECG: electrocardiogram

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Study Design

The study follows an open-label, randomized, 2-period, single oral dose crossover design at 2 dose levels in healthy Chinese male and female subjects. Each subject will participate in 2 periods separated by a washout of at least 10 days between IP administrations in each period.

Subjects will be randomized to 1 of 4 sequences according to [Table 3].

Table 3 Sequences and Investigational Product Assignments

Dose (mg)	Sequence	n	Period 1	Period 2
25	**1**	6	Mirabegron (low-fat)	Mirabegron (fasted)
	2	6	Mirabegron (fasted)	Mirabegron (low-fat)
50	**1**	6	Mirabegron (low-fat)	Mirabegron (fasted)
	2	6	Mirabegron (fasted)	Mirabegron (low-fat)

The dose under fed conditions will be administered following a low-fat breakfast (total calories approximately 450 kcal, with approximately 70 kcal from fat).

Subjects will be screened for up to 21 days prior to IP administration on day 1 of period 1. Subjects who are eligible for study participation will be admitted to the clinical unit on day -1 of each period and will be confined until the last pharmacokinetic sample has been drawn within each period. Subjects are to remain semirecumbent and avoid lying on either the left or right side for 4 hours postdose. Pharmacokinetic samples will be collected predose on day 1 of each period and at multiple time points following each dose (see the Schedule of Assessments [Table 1]).

The study will be completed with an end-of-study visit (ESV). The ESV will take place 5 to 9 days after the last pharmacokinetic sample is collected or at early discontinuation from the study.

4.2 Dose Rationale

Mirabegron 50 mg is commercially available worldwide; however, the recommended starting dose in the US is 25 mg. In accordance with the Centre for Drug Evaluation's request to continue the study on the posology of Chinese patients, including the initial dose and taking the drug before and after a meal, and submit the study results when the Imported Drug License is renewed, both 25 and 50 mg doses of mirabegron will be investigated.

4.3 End of Study Definition

The study start is defined as the date the first subject signs informed consent. 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 healthy Chinese male and female subjects (18 to 45 years of age, inclusive). 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 a healthy Chinese male or female subject between 18 to 45 years of age, inclusive at screening.
3. Subject has a body mass index (BMI) range of 19.0 to 24.9 kg/m^2, inclusive and weighs at least 50 kg for male subjects and 45 kg for female subjects at screening.
4. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
   a. Not a woman of childbearing potential (WOCBP) (see [Appendix 12.3 Contraception Requirements])
   b. WOCBP who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent through at least 30 days after final IP administration.
5. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 30 days after final IP administration.
6. 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.
7. Male subject with female partner(s) of childbearing potential (including breastfeeding partner[s]) must agree to use contraception (see [Appendix 12.3 Contraception Requirements]) throughout the study period and for 30 days after final IP administration.
8. Male subject must not donate sperm during the study period and for 30 days after final IP administration.
9. 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.
10. Subject agrees not to participate in another interventional study while participating in the present study, defined as 84 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:

1. Female subject who has been pregnant within 6 months prior to screening or breastfeeding within 3 months prior to screening.
2. Subject has a known or suspected hypersensitivity to mirabegron or any components of the formulation used.
3. Subject has had previous exposure with mirabegron.
4. Subject has any of the liver function tests (alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase and total bilirubin [TBL]) ≥ 1.5 × upper limit of normal (ULN) on day -1 of period 1.
5. Subject has any clinically significant history of allergic conditions (including drug allergies, asthma, eczema or anaphylactic reactions, but excluding untreated, asymptomatic, seasonal allergies) prior to first IP administration.
6. Subject has any history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal and/or other major disease or malignancy, as judged by the investigator.
7. Subject has/had febrile illness or symptomatic, viral, bacterial (including upper respiratory infection) or fungal (noncutaneous) infection within 1 week prior to day -1 of period 1.
8. Subject has any of the following concerns with regard to tuberculosis:
   - History of active tuberculosis
   - Abnormalities detected in a chest X-ray on day -1 of period 1
   - Contact with infectious tuberculous patients
9. Subject has any clinically significant abnormality following the investigator's review of the physical examination, electrocardiogram (ECG) and protocol-defined clinical laboratory tests at screening or on day -1 of period 1.
10. Subject who deviated from the following range of vital signs or routine 12-lead ECG results at screening or on day -1 of period 1. If the mean blood pressure, pulse or corrected QT interval using Fridericia's formula (QTcF) exceeds the limits below, 1 additional triplicate can be taken. The final judgment should be based on the retest results.

Blood pressure	Systolic blood pressure (SBP): ≥ 90 mmHg, < 140 mmHg Diastolic blood pressure (DBP): ≥ 40 mmHg, < 90 mmHg
Pulse	≥ 45 bpm, ≤ 99 bpm
Body temperature	≥ 35.0°C, ≤ 37.5°C
Routine 12-lead ECG	Findings: Normal or clinically irrelevant abnormality QTcF: < 430 msec (for male subjects) < 450 msec (for female subjects)

11. Subject has used any prescribed or nonprescribed drugs (including vitamins, natural and herbal remedies, e.g., St. John's Wort and traditional Chinese medicine) in the 2 weeks prior to first IP administration, except for occasional use of paracetamol (up to 2 g/day), topical dermatological products, including corticosteroid products, hormonal contraceptives or hormone replacement therapy (HRT).
12. Subject has a history of smoking > 10 cigarettes (or equivalent amount of tobacco) per day within 3 months prior to day -1 of period 1.
13. Subject has a history of consuming > 21 units for male subjects or > 14 units for female subjects of alcohol per week within 3 months prior to day -1 of period 1 (note: 1 unit = 10 g pure alcohol, 250 mL of beer [5%], 35 mL of spirits [35%] or 100 mL of wine [12%]) or the subject has a history of alcohol-dependency, drug-dependency, chemical-dependency, or alcohol or drug abuse within 2 years prior to screening or the subject positive for alcohol at screening or on day -1 of period 1.
14. Subject has used any drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and/or opiates) within 3 months prior to day -1 of period 1 or the subject tests positive for drugs of abuse (amphetamines, benzodiazepines, cannabinoids, cocaine and opiates) at screening or on day -1 of period 1.
15. Subject has used any inducer of metabolism (e.g., barbiturates and rifampin) in the 3 months prior to day -1 of period 1.
16. Subject has had significant blood loss, donated ≥ 400 mL of whole blood within 90 days, ≥ 200 mL of whole blood within 30 days or donated blood components within 14 days prior to day -1 of period 1 and/or received a transfusion of any blood or blood products within 60 days.
17. 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, human immunodeficiency virus (HIV) or syphilis at screening.
18. Subject is an employee of Astellas, the study-related contract research organizations (CROs) or the clinical unit.
19. Subject is deemed unsuitable for participating in the study by the investigator or subinvestigator.

5.3 Restrictions During the Study

5.3.1 Exercise

Subjects will refrain from strenuous exercise from 48 hours prior to first admission to the clinical unit up to and including the ESV.

Subjects are encouraged to walk and stretch while in the clinical unit to avoid AEs associated with the sedentary environment.

5.3.2 Smoking

Subjects are not allowed to smoke or use tobacco-containing products and nicotine or nicotine-containing products (e.g., electronic vapes) from screening up to and including the ESV.

5.3.3 Dietary and Fluid Restrictions

To avoid false-positive results of the drugs of abuse test, no food or drinks containing poppy seeds (e.g., specialty breads and muffins) will be allowed from 48 hours prior to first admission to the clinical unit up to and including the ESV.

Subjects will not be allowed to consume food and drinks, which may interact with circulatory, gastrointestinal, liver or renal function from at least 24 hours for alcohol or xanthine-containing products (including caffeine) and 72 hours for grapefruit/Seville orange or grapefruit/Seville orange-containing products prior to first admission to the clinical unit up to and including the ESV.

Subjects will be served normal balanced caloric drinks and meals at consistent times during their stay in the clinical unit. Total daily caloric intake will preferably not exceed normal daily limits (2600 kcal/male and female subjects). On day 1 of each period, when IP administration is under fed conditions, a low-fat breakfast (total calories approximately 450 kcal, with approximately 70 kcal from fat) applies. Dietary and fluid restrictions apply to dosing conditions as specified in [Section 6.1 Investigational Product(s) Administered]. The menu and nutritional information, including the caloric and content breakdown (carbohydrates, proteins and fat), will be documented in the clinical study file and will be described in the clinical study report.

Standardized and identical, lunch and dinner will be served at fixed time points on day 1 of each period. On other days the subjects will receive standard meals.

5.4 Screen Failures

A screen failure is defined as a potential subject who signed the informed consent form (ICF) but did not meet 1 or more criteria required for participation in the study and was not randomized.

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 4 Investigational Product(s)

Name	**BETMIGA® (Mirabegron)**
Use	Test product
Dosage Formulation	Sustained-release tablet
Physical Description	25 mg: oval, brown, film-coated tablet 50 mg: oval, yellow, film-coated tablet
Dose Strength	25 and 50 mg
Packaging and Labeling	10 tablets per carton
Route of Administration	Oral
Administration Instruction	Mirabegron will be administered as single oral doses under fed or fasted conditions on day 1 of each period. Fasted Conditions: Following an overnight fast of at least 10 hours, subjects will receive a single dose of 25 or 50 mg mirabegron with 240 mL water. Subjects are to remain semirecumbent and avoid lying on either the left or right side for 4 hours postdose. No food or beverage will be allowed for at least 4 hours postdose. Water can be ingested as desired except for 1 hour predose and 1 hour postdose. Fed Conditions: Following an overnight fast of at least 10 hours, subjects will start a low-fat breakfast. Subjects should eat the breakfast in 30 minutes or less. Subjects will receive a single dose of 25 or 50 mg mirabegron with 240 mL water 30 minutes after the start of the breakfast. Subjects are to remain semirecumbent and avoid lying on either the left or right side for 4 hours postdose. No food or beverage will be allowed for at least 4 hours postdose. Water can be ingested as desired except for 1 hour predose and 1 hour postdose. Except for the day 1 breakfast in each period, subjects will receive standardized meals scheduled at the same time during the stay at the clinical unit. The low-fat meal (total calories approximately 450 kcal, with approximately 70 kcal from fat) is cereal, low fat milk, wheat bread, ham and ketchup.
IMP or Non-IMP	IMP
Sourcing	Provided centrally by sponsor

IMP: investigational medicinal product

Refer to the product label and package insert [Betmiga Package Insert, Aug 2019] for detailed information regarding handling and storage of the IP.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All IP used in this study will be commercial products. Each carton will bear a label conforming to regulatory guidelines, Good Manufacturing Practice (GMP) and local laws and regulations that identifies the contents as investigational drug.

Refer to the product label and package insert [Betmiga Package Insert, Aug 2019] for detailed information regarding packaging and labeling of the IP.

6.2.2 Handling, Storage and Accountability

1. 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.
2. Only subjects enrolled in the study may receive IP and only authorized study site personnel may supply or administer IP. Only IP with appropriate expiry/retest dating may be dispensed.
3. 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.
4. 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).

Refer to the package insert [Betmiga Package Insert, Aug 2019] for detailed information regarding handling and storage of the IP.

6.3 Randomization and Blinding

6.3.1 Blinding Method

Not applicable.

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 1:1:1:1 ratio to a dosing sequence according to the randomization schedule. All subjects who meet the eligibility criteria will be randomized.

Prior to dosing on day 1 of period 1, subjects will be assigned a randomization number in accordance with the randomization code generated by the sponsor's designee.

Once a randomization number has been allocated to a subject, it will not be assigned to another subject. If a subject withdraws prematurely from the study and is replaced under the direction of the sponsor, then a replacement randomization number will be assigned. A replacement randomization code will be generated such that replacement subjects are assigned to the same dosing sequence as the discontinued subject.

6.4 Investigational Product(s) Compliance

Dosing will take place in the clinical unit. The administration of IP will be supervised to ensure study compliance. After IP administration, a check of the subject's mouth and hands will be performed. The exact day and time of IP administration will be documented.

6.5 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

6.5.1 Previous Treatment (Medication and Nonmedication Therapy)

All medicinal products, including prescribed or nonprescribed drugs, used prior to first IP administration will be considered previous medication.

The subjects must abstain from use of any prescribed or nonprescribed drugs (including vitamins, natural and herbal remedies, e.g., St. John's Wort and traditional Chinese medicine) in the 2 weeks prior to first IP administration, except for:

- Paracetamol (up to 2 g/day)
- Topical dermatological products, including corticosteroid products
- Hormonal contraceptives
- HRT

At the screening, subjects will be questioned regarding the medicinal products that they have been taking over the past 3 months. All medication taken within 4 weeks prior to first admission to the clinical unit will be documented.

6.5.2 Concomitant Treatment (Medication and Nonmedication Therapy)

All medicinal products other than the IP(s), including prescribed or nonprescribed drugs (including vitamins, natural and herbal remedies, e.g., St. John's Wort and traditional Chinese medicine), used from first IP administration until the ESV (including washout between periods) will be considered concomitant medication.

Subjects will only be allowed to use the following concomitant medication, if needed, from first IP administration until the ESV (including washout between periods):

- Paracetamol (up to 2 g/day)
- Topical dermatological products, including corticosteroid products
- Hormonal contraceptives
- HRT

If a subject's health condition necessitates the use of any medication other than the permitted medications during the study, the investigator and medical monitor, or designee(s), will discuss the case and determine if the subject should be withdrawn from the study and/or excluded from analysis sets, depending on if, and how, the medication(s) used influence(s) the study outcome. The nonpermitted concomitant medication will be recorded as a protocol deviation (see [Section 9.9 Major Protocol Deviations]).

All concomitant treatment (medication and nonmedication therapy) will be documented within the source.

6.6 Dose Modification

Not applicable.

6.7 Criteria for Continuation of Dosing

Not applicable.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Efficacy Assessments

Not applicable.

7.2 Safety Assessments

7.2.1 Adverse Events

See [Section 7.3 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

7.2.2 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 [Appendix 12.7 Laboratory Assessments].

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

Drugs of abuse and alcohol tests will be performed according to the clinical site's preferred method. Drugs of abuse and alcohol tests will be performed as indicated in the Schedule of Assessments [Table 1].

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

A blood sample will be collected for follicle-stimulating hormone (FSH) tests (postmenopausal female subjects only) 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]).

7.2.3 Vital Signs

Blood pressure (SBP and DBP), body temperature and pulse measurements will be taken as indicated in the Schedule of Assessments [Table 1]. Measurements will be taken after the subject has been resting in the supine position for at least 5 minutes. Blood pressure and pulse measurements will be taken in triplicate with approximately 2-minute intervals at screening and on day -1 of each period (the mean will be used). At all other time points and for body temperature, single measurements will be taken.

7.2.4 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]).

7.2.5 Electrocardiogram

7.2.5.1 Routine 12-lead 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 in triplicate at screening and on day -1 of each period with approximately 1-minute intervals and all 3 ECGs will be completed within 5 minutes. At all other time points, single measurements will be taken.

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.

7.2.6 Order of Assessments

When time points for procedures overlap, blood sampling for pharmacokinetics will be collected at the nominal time point. Blood and urine sampling for clinical laboratory tests, routine 12-lead ECG and vital signs are to be collected before or after the nominal blood

sampling for pharmacokinetics. Vital signs are recommended to be collected before venipuncture or, if necessary, after venipuncture from the opposite arm.

The allowed collection windows for procedures are shown in [Table 5].

Table 5 Order of Assessments

Assessment	Time Point	Window
Blood Sampling for Pharmacokinetics	Predose	-90 to 0 minutes
	0 to < 4 hours	± 2 minutes
	4 to < 12 hours	± 5 minutes
	12 to < 48 hours	± 15 minutes
	48 hours and thereafter	± 30 minutes
Vital Signs	Predose	-60 to 0 minutes
	0 to < 12 hours	± 15 minutes
	> 12 hours	± 30 minutes

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that met the definition of an AE or SAE.

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

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received IP. AE collection begins after the signing of the ICF and will be collected until the ESV or when the subject is determined to be a screen failure.

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The methods of recording, evaluating and assessing seriousness, causality and severity of AEs and SAEs are described in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting]. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

An AE with a change in severity is recorded as a new AE.

7.3.3 Follow-up of Adverse Events

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

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 Reporting of Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential, so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

In the case of an SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

Procedures for reporting SAEs to the sponsor are described in [Section 12.4.5 Reporting Procedures for Serious Adverse Events].

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

Not applicable.

7.3.6 Adverse Events of Special Interest

AEs of special interest are AEs that the sponsor may wish to carefully monitor. These AEs may be serious or nonserious and should be collected on the eCRF and the SAE worksheet and reported within 24 hours as described in [Section 12.4.5 Reporting Procedure for Serious Adverse Events]. These AEs are not considered SAEs unless they meet the definition of an SAE. AEs of special interest in this study will include:

- Increased heart rate and tachycardia
- Increased blood pressure
- Hypersensitivity reactions

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 collected in the eCRF, as protocol deviations per [Section 10.3 Major Protocol Deviations] or may require special reporting, as described below. These special situations are not considered AEs, but are required 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 12.4.5 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.

The special situations are:

- Pregnancy
- 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 [Appendix 12.4.6 Reporting Procedures for Special Situations].

7.3.8 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.

7.3.9 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.

7.3.10 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 dosing, 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.

7.4 Pharmacokinetics

7.4.1 Analysis of Mirabegron in Plasma

Blood samples will be collected for pharmacokinetic analysis of mirabegron as indicated in the Schedule of Assessments [Table 1].

The actual date and time of pharmacokinetic blood sample collection will be captured in the source. Blood sample collection, handling and storage will be described in the laboratory manual. Plasma samples will be analyzed using a validated method.

7.5 Pharmacodynamics | Immunogenicity

Not applicable.

7.6 Electronic Clinical Outcome Assessment

Not applicable.

7.7 Other Assessments

Not applicable.

7.8 Total Amount of Blood

The approximate total blood volume taken per subject will be as follows:

Table 6 Blood Volume

Sample Type	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Clinical Laboratory Tests	6	7.0 (12.0)†	47.0
Pregnancy Test (Female Subjects Only)	3	3.0	9.0
FSH Test (Postmenopausal Female Subjects Only)	1	3.0	3.0
Mirabegron Pharmacokinetics	34	4.0	136.0
Total			183.0 for males 192.0 for females 186.0 for postmenopausal females

FSH: follicle-stimulating hormone

† 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 400 mL.

8 DISCONTINUATION

8.1 Discontinuation of Individual Subject(s) From Study Dosing

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

The subject is free to withdraw from the study dosing 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 dosing 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 dosing must be documented in the subject's medical records.

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

- Subject requests to stop dosing
- Any clinical AE, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued dosing is not in the best interest of the subject
- Hepatic function parameters: ALT or AST > 3 × ULN and/or TBL > 2 × ULN; for additional information on hepatic parameter abnormalities, refer to [Appendix 12.5 Liver Safety Monitoring and Assessment]
- Cardiac repolarization dysfunction: QTcF > 500 msec and/or if QTcF change from baseline > 60 msec at repeat measurements

8.2 Discontinuation of Individual Subject(s) From Study

All subjects who discontinue study dosing 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.

8.2.1 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 and record outstanding data.

8.3 Discontinuation of the Study Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

8.4 Discontinuation of the Study

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

9 STATISTICAL METHODOLOGY

In general, all 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 nonmissing observation prior to first administration of IP, unless otherwise specified.

9.1 Sample Size

A total of 24 subjects (12 subjects per dose group) will be enrolled. Subjects who discontinue early from the study may be replaced at the discretion of the sponsor.

Based on data from Study 178-CL-091, a Chinese phase 1 study, the intrasubject coefficient of variation (CV) for pharmacokinetic parameters AUC_{inf}, AUC_{last} and C_{max} of the 50 mg mirabegron dose are estimated to be between 33% and 60%. Assuming the underlying variability is similar to 60% and an observed ratio between fasted and fed conditions of 100%, the 90% CI will lie within (60, 167) with > 80% probability.

9.2 Analysis Sets

For each sequence, the number and percentage of subjects will be characterized for all randomized subjects and by each analysis set.

9.2.1 Safety Analysis Set

The safety analysis set (SAF) consists of all subjects who receive at least 1 dose of IP.

The SAF will be used for all summaries and analyses of the safety data.

9.2.2 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) consists of all subjects who receive at least 1 dose of IP for which concentration data are available to facilitate derivation of at least 1 primary pharmacokinetic parameter. Inclusion of subjects in the PKAS with missing data or major protocol deviations will be considered by the pharmacokineticist on a case-by-case basis.

The PKAS will be used for all summaries and analyses of the pharmacokinetic data.

9.3 Demographics and Baseline Characteristics

9.3.1 Demographics

Demographics and baseline characteristics (age, sex, race, body weight, height and BMI) will be summarized by dose group, sequence and overall for all randomized subjects.

9.3.2 Subject Disposition

The number and percentage of subjects who completed and discontinued dosing and reasons for dosing discontinuation will be presented for all randomized subjects and for subjects in the SAF by dose group, sequence and overall. Similar tables for investigational period disposition and follow-up disposition will also be presented for all randomized subjects by dose group, sequence and overall. All disposition details and dates of first and last evaluations for each subject will be listed.

9.3.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

Previous and concomitant treatment (medication and nonmedication therapy) will be listed.

9.3.4 Medical History

Medical history for each subject will be listed.

9.3.5 Investigational Product Exposure

The number and percentage of subjects exposed to IP will be summarized by dose group and sequence under fed and fasted conditions.

IP exposure data will be listed.

9.4 Analysis of Efficacy

Not applicable.

9.5 Analysis of Safety

9.5.1 Adverse Events

AEs will be coded using MedDRA. An AE with onset at any time from first dosing until last scheduled procedure will be classified as a TEAE for inclusion in the summary tabulations. An IP-related TEAE is defined as any TEAE with a causal relationship assessed as "yes" by the investigator, or records where the relationship is missing.

An overview and separate summaries of the number and percentage of subjects with TEAEs, drug-related TEAEs, TEAEs leading to withdrawal of dosing, IP-related TEAEs leading to withdrawal of dosing and TEAEs excluding SAEs that equal or exceed a threshold of 5% in any dose group under fed and fasted conditions will be presented by SOC, preferred term, by fed and fasted conditions for each dose group. Also included in the overview are the number and percentage of subjects with serious TEAEs, IP-related serious TEAEs, TEAEs leading to death and IP-related TEAEs leading to death.

AE data will be listed.

9.5.2 Laboratory Assessments

For quantitative clinical laboratory measurements (hematology and biochemistry), descriptive statistics will be used to summarize results and change from baseline by fed and fasted conditions and visit for each dose group.

Laboratory data will be listed.

9.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects by fed and fasted conditions and time point for each dose group.

Vital signs data will be listed.

9.5.4 Electrocardiogram

9.5.4.1 Routine 12-lead Electrocardiogram

Routine 12-lead ECG data and interpretations will be listed.

9.6 Analysis of Pharmacokinetics

Descriptive statistics will include n, mean, SD, CV, geometric mean, geometric CV, median, minimum and maximum. For the pharmacokinetic parameters t_{max} and t_{lag}, only n, median, minimum and maximum will be calculated.

9.6.1 Plasma Concentrations

Plasma concentrations under both fasted and fed conditions will be listed and summarized using descriptive statistics by scheduled time point for each dose group. Standard graphics including mean plasma concentration-time profiles, overlay (spaghetti) plots and individual subject plasma concentration-time profiles will be produced.

9.6.2 Estimation of Pharmacokinetic Parameters

Noncompartmental analysis will be used for the calculation of plasma pharmacokinetic parameters using Phoenix® (Certara LP, 100 Overlook Center, Suite 101, Princeton, NJ 08540, US).

Plasma pharmacokinetic parameters under both fasted and fed conditions will be listed and summarized using descriptive statistics for each dose group.

9.6.3 Statistical Analysis of Pharmacokinetic Parameters

To assess the effect of food on the pharmacokinetic of mirabegron, a mixed effects analysis of variance (ANOVA) model with fixed effects for food condition (fed or fasted) and period and subject as a random effect will be fitted on natural logarithm-transformed AUC_{inf}, AUC_{last} and C_{max}. Within the ANOVA, the least squares (LS) mean differences between fed and fasted, along with 90% CIs for the differences will be estimated for 25 and 50 mg mirabegron doses separately.

The LS means for AUC_{inf}, AUC_{last} and C_{max} will be back-transformed to produce the geometric LS means and presented with the number of subjects for each food condition. The geometric LS mean ratios and their corresponding 90% CIs for each pharmacokinetic parameter will be presented by back-transforming and expressed as percentages. The analysis will be repeated if all subjects did not complete both periods using an ANOVA with fixed effects for period, food condition and subject; this analysis will only include subjects with complete data in both periods.

9.7 Analysis of Pharmacodynamics | Immunogenicity

Not applicable.

9.8 Other Analyses

Not applicable.

9.9 Major Protocol Deviations

Major protocol deviations as defined in [Section 10.3 Major Protocol Deviations] will be listed.

9.10 Interim Analysis (and Early Discontinuation of the Study)

Not applicable.

9.11 Additional Conventions

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medications if they are missing on day of first IP administration. The imputed dates will be used to assess if the AEs or concomitant medications are treatment emergent or concomitant, respectively. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

10 OPERATIONAL CONSIDERATIONS

10.1 Data Collection

The investigator or site designee will enter data collected using an electronic data capture system. In the interest of collecting data in the most efficient manner, the investigator or designee should record data (including clinical laboratory values, if applicable) in the eCRF within 10 working days after the subject's visit. The data will be entered after HGRAC data filing approval if required by site.

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

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

Clinical laboratory tests and ECG are performed at a local laboratory.

10.2 Demographics and Baseline Characteristics

10.2.1 Demographics

Demographics and baseline characteristics will be collected as indicated in the Schedules of Assessments [Table 1]. This will include age, sex, race, body weight, height and BMI.

10.2.2 Medical History

A complete medical history will be collected as indicated in the Schedules of Assessments [Table 1].

10.3 Major Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. All deviations from the protocol are to be recorded. A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and well-being of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to subjects.

A major protocol deviation is one that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a subject. Major protocol deviations will have additional reporting requirements.

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

The major protocol deviation criteria that will be summarized at the end of the study are as follows:

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

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

PD3 - Received incorrect dose

PD4 - Received excluded concomitant treatment

The investigator will also assure that deviations meeting IRB/IEC and appropriate regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and appropriate regulatory authorities will be provided to the sponsor and maintained within the trial master file.

10.4 Study organization

10.4.1 Independent Data Monitoring Committee | Data and Safety Monitoring Board | Monitoring Committee | Adjudication Committee | Other Evaluation Committee(s)

Not applicable.

10.4.2 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 Ethical, Regulatory and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

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

12.1.2 Institutional Review Board/Independent Ethics Committee/Competent Authorities

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

Any substantial amendments to the protocol will require competent authority and IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to 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 study site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU Regulation No. 536/2014 for studies (if applicable), and all other applicable local regulations

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or nonsubstantial amendments. Depending on the nature of the amendment, either IRB/IEC or competent authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, investigator, IRB/IEC and appropriate regulatory authorities.

Amendments to this protocol must be signed by the sponsor and investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

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

12.1.4 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.

12.1.5 Informed Consent of Subjects

12.1.5.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF will be reviewed, signed and dated by the subject, the person who administered the ICF and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. If the subject signs 2 original ICFs, 1 of the original ICFs will be given to the subject and the other original ICF will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that the ICF was signed prior to any study-related procedures and that the subject received a signed copy of the ICF.

The signed ICFs will be retained by the investigator and made available (for review only) to the study monitor, auditor and appropriate regulatory authorities and other applicable individuals upon request.

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

1. The investigator or his/her representative will immediately inform the subject 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.
2. 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.

12.1.6 Source Documents

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.

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.

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.

12.1.7 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data, case report forms [CRFs] and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subject's medical records and/or study progress notes.

12.1.8 Subject Confidentiality and Privacy

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 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.

12.1.9 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 drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this 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.

12.1.10 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final clinical study report 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 hard-lock.

12.2 Procedure for Study Quality Control

12.2.1 Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP and the study data reported by the investigator/subinvestigator are accurate, complete and verifiable with the source. The sponsor is responsible for assigning the study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO, as well as inspections from the IRB/IEC and appropriate regulatory authorities. In these instances, they must provide all study-related records including source documents when they are requested by the sponsor monitors and auditors, the CRO, the IRB/IEC or appropriate regulatory authorities. The confidentiality of the subject's identity shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2.3 Data Management

Data management will be coordinated by the Data Science department or designee of the sponsor in accordance with the standard operating procedures (SOPs) for data management. All study-specific processes and definitions will be documented by data management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and the WHO Drug Dictionary, respectively. Data management is accountable for eCOA.

12.2.4 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 7 Quality Tolerance Limit

QTL #: Name and Parameter	Definition	Parameter Justification
QTL1: Pharmacokinetic sample collection compliance	% of pharmacokinetics samples that are not collected or collected outside the allowed collection window	A high percentage of pharmacokinetic samples missed or collected outside of the collection window can have an impact on the assessment of the pharmacokinetic parameters
QTL2: Time of meal intake and IP administration compliance	% of meal intake and IP administration that are conducted outside the allowed time window	A high percentage of food intake and IP administration conducted outside of the designated time window can have an impact on the evaluation of the food effect

IP: investigational product; QTL: quality tolerance limit

Additional information regarding the QTL and limit justification, as well as associated activities can be found in STL-3458 QTL monitoring plan.

QTL Management Activities:

- For control of risks associated with QTL1: Pharmacokinetic sample collection compliance, refer to the Schedule of Assessments [Table 1] and [Section 7.2.6 Order of Assessments]
- For control of risks associated with QTL2: Time of meal intake and IP administration compliance, refer to the Schedule of Assessments [Table 1]

The allowed collection window for pharmacokinetic blood samples is shown in [Table 8].

Table 8 Acceptable Collection Window for Pharmacokinetic Blood Samples

Nominal Time	Acceptable Window (half-life < 48 hours)
Predose	-90 to 0 minutes
0 to < 4 hours	± 2 minutes
4 to < 12 hours	± 5 minutes
12 to < 48 hours	± 15 minutes
48 hours and thereafter	± 30 minutes

12.3 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 1 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 1 FSH measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Females on HRT and whose menopausal status is in doubt will be required to use 1 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 1 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 dosing 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.

12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

12.4.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered an IP, and which does not necessarily have to have a causal relationship with this IP. 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 IP whether or not considered related to the IP.

12.4.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, biochemistry or urinalysis) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), 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.

12.4.1.2 Potential Cases of Drug-induced Liver Injury

Refer to [Appendix 12.5 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 [Appendix 12.5 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 [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

12.4.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, the event:

- Results in death
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death; it does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect

- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE)
- Other medically important events (defined in paragraph below)

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

12.4.3 Criteria for Causal Relationship to Investigational Product

A medically qualified investigator is obligated to assess the relationship between IP and each occurrence of each (S)AE. This investigator will use medical judgment as well as the RSI (see [Investigator's Brochure, Appendix 1]) to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

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 been caused by the suspect drug? 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 laboratory investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pre-, during and post-dosing)
- 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
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible temporal relationship between exposure to the IP and (S)AE onset and/or resolution will be provided. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?

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 assesses causality for every event before the initial transmission of the SAE data to the sponsor. 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.

12.4.4 Criteria for Defining the Severity of an Adverse Event

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

- Mild (Grade 1): No disruption of normal daily activities
- Moderate (Grade 2): Affect normal daily activities
- Severe (Grade 3): Inability to perform daily activities

12.4.5 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 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.

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

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

Astellas Pharma Global Development Inc.
Global Pharmacovigilance
Fax number: +44-800-471-5263
Email: safety-us@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 on 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., suspected unexpected serious adverse reaction [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 (NMPA) where required. Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the study site.

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

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.

12.4.6 Reporting Procedures for Special Situations

12.4.6.1 Pregnancy

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 [Appendix 12.4.5 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 sponsor according to the timelines in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] using the SAE worksheet as a special situation.

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 [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the SAE worksheet.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes 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)

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.

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

If a medication error (defined as an unintended failure in the dosing 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 what is stated in the protocol) is suspected, refer to [Section 10.3 Major Protocol Deviations]. 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 [Appendix 12.4.5

Reporting Procedures for Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use".

In the event of suspected overdose, refer to the approved package insert, summary of product characteristics or local product information supplied by the manufacturer for the IP.

12.4.6.3 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 [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the misuse or abuse of the IP.

12.4.6.4 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 situation worksheet.

12.4.6.5 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 [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the suspected drug-drug interaction.

12.5 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. Any subject enrolled in a study with active drug therapy and reveals an increase of serum aminotransferases (ATs) to > 3 × ULN or TBL > 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. 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 9 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 a maximum of 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 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%)

† 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 Dosing 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 dosing. The investigator may determine that it is not in the subject's best interest to continue study dosing. Discontinuation of study dosing should be considered if:

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

† 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 dosing 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 TBL (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, 1 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; pre-existing or acute liver disease; or another drug capable of causing the observed injury

References

Temple R. Hy's Law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15(4):241-3.

12.6 List of Excluded Concomitant Medications

Not applicable.

12.7 Laboratory Assessments

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

Table 10 Clinical Laboratory Tests

Panel/Assessments	Matrix	Parameters to be Analyzed
Hematology	Blood	Hemoglobin Hematocrit Erythrocytes Leukocytes Differential leukocytes Platelets
Biochemistry	Plasma/serum	Sodium Potassium Calcium Chloride Magnesium Inorganic Phosphorus Glucose Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma-glutamyl transferase Total bilirubin Total cholesterol Triglycerides Blood urea Creatinine Creatine kinase Lactate dehydrogenase Total protein Uric acid Albumin FSH (postmenopausal female subjects only)
Urinalysis (Dipstick)	Urine	Protein Glucose pH Occult blood Leukocytes Urobilinogen Bilirubin Ketones Nitrite
Urinalysis (Microscopy)	Urine	Erythrocytes Leukocytes

Table continued on next page

Panel/Assessments	Matrix	Parameters to be Analyzed
Serology	Plasma/serum	HAV antibodies (IgM) HBsAg HBc antibodies HCV antibodies HIV antibodies Treponema pallidum antibodies
Drugs of Abuse and Alcohol Test	Urine	Amphetamines Benzodiazepines Cannabinoids Cocaine Opiates
	Breath test/blood/urine	Alcohol
Pregnancy Test	Serum	Human chorionic gonadotropin (female subjects only)

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

12.8 List of Abbreviations and Definition of Key Study Terms

List of Abbreviations

Abbreviations	Description of abbreviations
ACN	Astellas Pharma China, Inc.
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AT	aminotransferases
AUC_{inf}	area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{inf} (%extrap)	area under the concentration-time curve from the time of dosing extrapolated to time infinity as a percentage of total area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from the time of dosing to the last measurable concentration
BMI	body mass index
CL/F	apparent total systemic clearance after extravascular dosing
C_{max}	maximum concentration
CRF	case report form
CRO	contract research organization
CV	coefficient of variation
DBP	diastolic blood pressure
DPD	Data Protection Directive
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EEA	European Economic Area
ESV	end-of-study visit
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
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

Abbreviations	Description of abbreviations
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
LA-CRF	liver abnormality case report form
LS	least square(s)
NMPA	National Medical Products Administration
OAB	overactive bladder
PKAS	pharmacokinetic analysis set
QA	quality assurance
QC	quality control
QTcF	corrected QT interval using Fridericia's formula
QTL	quality tolerance limit
RSI	reference safety information
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set
SBP	systolic blood pressure
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
t_{lag}	time prior to the time corresponding to the first measurable (nonzero) concentration
t_{max}	time of maximum concentration
ULN	upper limit of normal
USM	urgent safety measure
V_z/F	apparent volume of distribution during the terminal elimination phase after extravascular dosing
WOCBP	woman of childbearing potential

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Assessments of subjects as they enter a study before they receive any IP.
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.
Intervention	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.
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 1 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.

13 ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 3

I. The purpose of this amendment is:

Nonsubstantial Changes
1. Change the planned study period
DESCRIPTION OF CHANGE:
Change the planned study period.
RATIONALE:
This update is being made in order to take the COVID-19 impact in consideration.
2. Change the blood collection volume for PK analysis
DESCRIPTION OF CHANGE:
Change the blood collection volume for PK analysis.
RATIONALE:
The blood sample volume for mirabegron pharmacokinetics is changed due to the change of blood collection tube. The blood collection tube is changed because the tube which was planned to be used is not available in China.
3. Add data entry requirement
DESCRIPTION OF CHANGE:
Add data entry requirement into eCRF according to local regulation and site requirement.
RATIONALE:
This update is being made in order to take the local regulation and site requirement in consideration.

II. Amendment summary of changes:

1 Protocol Summary *1.1 Synopsis*
WAS:
Planned Study Period: 3Q2020 to 4Q2020

IS AMENDED TO:

Planned Study Period:
3Q2020 to ~~4Q2020~~**1Q2021**

7 Study Procedures and Assessments
7.8 Total Amount of Blood

WAS:

Table 11 Blood Volume

Sample Type	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Clinical Laboratory Tests	6	7.0 (12.0)†	47.0
Pregnancy Test (Female Subjects Only)	3	3.0	9.0
FSH Test (Postmenopausal Female Subjects Only)	1	3.0	3.0
Mirabegron Pharmacokinetics	34	5.0	170.0
Total			217.0 for males 226.0 for females 220.0 for postmenopausal females

FSH: follicle-stimulating hormone

† Includes serology test at screening.

IS AMENDED TO:

Table 12 Blood Volume

Sample Type	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Clinical Laboratory Tests	6	7.0 (12.0)†	47.0
Pregnancy Test (Female Subjects Only)	3	3.0	9.0
FSH Test (Postmenopausal Female Subjects Only)	1	3.0	3.0
Mirabegron Pharmacokinetics	34	~~5~~**4**.0	~~170~~**136**.0
Total			~~217~~**183**.0 for males ~~226~~**192**.0 for females ~~220~~**186**.0 for postmenopausal females

FSH: follicle-stimulating hormone

† Includes serology test at screening.

10 Operational Considerations *10.1 Data Collection*
WAS:
In the interest of collecting data in the most efficient manner, the investigator or designee should record data (including clinical laboratory values, if applicable) in the eCRF within 10 working days after the subject's visit.
IS AMENDED TO:
In the interest of collecting data in the most efficient manner, the investigator or designee should record data (including clinical laboratory values, if applicable) in the eCRF within 10 working days after the subject's visit. **The data will be entered after HGRAC data filing approval if required by site.**

III. Nonsubstantial amendment rationale:

Rationale for nonsubstantial designation
All revisions made to the protocol are administrative in nature and do not impact the safety or scientific value of the clinical study.

14 SPONSOR'S SIGNATURES

Astellas Signatories

(Electronic signatures are attached at the end of the document.)

PPD	Medical Affairs
PPD	Clinical Pharmacology and Exploratory Development
PPD	Data Science