A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Older Adult Subjects with Overactive Bladder (OAB)

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Sponsor: Astellas Pharma Global Development, Inc.

Medical Affairs, Americas

1 Astellas Way

Northbrook, IL 60062

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PILLAR

Protocol for Phase 4 Study of Mirabegron

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Incorporating Substantial Amendment 2

September 10, 2015

IND 69,416

Sponsor:

Astellas Pharma Global Development, Inc.

Medical Affairs, Americas

1 Astellas Way

Northbrook, IL 60062

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1. SPONSOR'S SIGNATURE

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Older Adult Subjects with Overactive Bladder (OAB)

ISN/Protocol 178-MA-1005 / Version 3.0

Incorporating Substantial Amendment 2 / September 10, 2015

Required signatures (e.g., protocol authors, Sponsor's reviewers and contributors, and Quality Assurance) are located in Attachment 2; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Older Adult Subjects with Overactive Bladder (OAB)

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Incorporating Substantial Amendment 2 / September 10, 2015

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

Principal Investigator:

Signature: .....

Date

Printed Name: .....

Address: .....

.....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	[redacted]
Clinical Research Contacts:	[redacted]
Study Physician:	[redacted]

III. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviation	Description of abbreviations
ADL	Activity of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANCOVA	Analysis of Covariance
ASMA	Astellas Scientific & Medical Affairs, Inc.
AST	Aspartate Aminotransferase (GOT)
AUC	Area under the plasma concentration – time curve
AUC_{inf}	Area under the plasma concentration – from time zero to infinity
AUC_{tau}	Area under the plasma concentration – from time zero to tau
AUST	Astellas U.S. Technologies, Inc.
β3-AR	Beta 3-adrenergic receptor
BOO	Bladder Outlet Obstruction
BP	Blood Pressure
Bpm	Beats per minute
CA	Competent Authority
cfu	Colony Forming Unit
CI	Confidence Intervals
CRCL	Creatinine Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CRO	Contract Research Organization
CTD	Clinical Trial Directive
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDC	Electronic Data Capture
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcomes
EU	Europe
FAS-I	Full Analysis Set – Incontinence
FDA	Food and Drug Administration
FWER	Family-wise error rate
GCP	Good Clinical Practice
GGT/γ-GT	γ-Glutamyl Transpeptidase (GGT)
GMP	Good Manufacturing Practice
HBPM	Home Based Blood Pressure Monitoring
HDPE	High-Density Polyethylene

Abbreviation	Description of abbreviations
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Study Number
kg	Kilogram
LA-CRF	Liver Abnormality – Case Report Form
LFT	Liver Function Tests
LOCF	Last Observation Carried Forward
LS	Least Square
LSO	Last Subject Out
LUTS	Lower Urinary Tract Symptoms
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MID	Minimally Important Difference
Min	Minutes
mL	Milliliter
mmHg	Millimeter of Mercury
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MUI	Mixed Urinary Incontinence
MVV	Mean Voided Volume
N/n	Number
NASH	Non-Alcoholic Steatohepatitis
NDA	New Drug Application
OAB	Overactive Bladder
OAB-q	Overactive Bladder – questionnaire
OAB-s	Overactive Bladder – satisfaction questionnaire
OCAS	Oral Controlled Absorption System
PBO	Placebo
PCS	Potential Clinically Significant
PHI	Personal Health Information
PPBC	Patient Perception of Bladder Condition
PPIUS	Patient Perception of Intensity of Urgency Scale
PPS	Per Protocol Set
PR	Pulse Rate
PRO	Patient Reported Outcomes
PTM	Placebo to Match
PTNS	Percutaneous Tibial Nerve Stimulation
PVR	Post-Void Residual Volume
QD	Once Daily
QoL	Quality of Life
QT	Time interval between QRS complex to end of T wave

Abbreviation	Description of abbreviations
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
sec	Second
SFL	Screen Failure Log
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal Elimination Half-Life
TBL	Total Bilirubin
TBS	Treatment Benefit Scale
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
TLF	Tables, Listings and Graphs
TS-VAS	Treatment Satisfaction Visual Analog Scale
UAB-LSA	University of Alabama Birmingham Life Space Assessment
ULN	Upper Limit of Normal
UPS	Urgency Perception Scale
US	United States
UUI	Urge Urinary Incontinence
UTI	Urinary Tract Infection
YM178	Mirabegron/Myrbetriq
VES	Vulnerable Elders Survey

List of Key Study Terms

Terms	Definition of terms
Adverse Event	An adverse event is as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment.
Baseline	The baseline value is defined as the last measurement before the first dose of double-blind study drug. For variables based on the micturition diary, the 3 days of the diary recorded prior to the randomization visit will be used to derive these variables at baseline.
Discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a trial by an enrolled subject.
End of study	The time of the last subject's last protocol-defined assessment.
Enrolled	A screened subject who has received the study medication.
Frequency	The complaint of voiding too often during the day.
Incontinence	Any involuntary leakage of urine.
Micturition	Any voluntary micturition (episodes of incontinence only are not included).
Mixed urinary incontinence	The complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.
Nocturia	Waking at night one or more times to void (i.e., any voiding associated with sleep disturbance between the time the subject goes to bed with the intention to sleep until the time the subject gets up in the morning with the intention to stay awake).
Overactive Bladder	Urgency, with or without urgency incontinence, usually with frequency and nocturia, which can be described as the OAB syndrome, urge syndrome or urgency-frequency syndrome.
Placebo Run-in failure	Enrolled subject who entered the placebo run-in period, but did not qualify to enter the double-blind treatment period, or decided not to participate anymore (withdrew consent) during the placebo run-in period.
Randomization	Action to allocate a subject to the treatment group or treatment cohort.
Screened	A subject who has signed informed consent and has performed the screening visit.
Screening failure	Screened subject who did not fulfill protocol inclusion and/or exclusion criteria, or decided not to participate anymore (withdrew consent) prior to starting the placebo run-in period. Subjects who are considered a screen failure cannot be re-screened into the study at a later date.
Serious Adverse Event	An adverse event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: results in death, is life threatening, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly, or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, or a medically important event.
Stress urinary incontinence	The complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.
Subject number	Number assigned to each subject by Interactive Response System after signature of informed consent and prior to any specific procedures.

Terms	Definition of terms
Treatment-emergent adverse event	An adverse event starting or worsening in the period from first double-blind medication intake until 30 days after last double-blind medication intake.
Urgency	A sudden and compelling desire to pass urine that is difficult to defer.
Urgency urinary incontinence	The complaint of involuntary leakage accompanied by or immediately proceeded by urgency.
Urinary incontinence	The complaint of any involuntary leakage of urine.

IV. SYNOPSIS

Title of Study	A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Older Adult Subjects with Overactive Bladder (OAB)
Planned Study Period	From 3Q2014 to 4Q2016
Study Objective(s)	*Primary Objective:* To assess the efficacy of mirabegron versus placebo (PBO) in the treatment of older adult subjects with OAB. *Secondary Objective:* To assess the safety and tolerability of mirabegron versus placebo (PBO) in the treatment of older adult subjects with OAB.
Planned Total Number of Study Centers and Location	Approximately 125 centers North America (possibly to include South America, Europe, Australia, and/or Asia Pacific)
Design and Methodology	This is a randomized, double-blind, placebo-controlled, parallel group, multi-center study. After Screening (Visit 1), subjects will enter into a 2-week placebo run-in period (Visit 2) prior to being randomized into the 12-week double-blind treatment period (Visit 3). Subjects will be asked to complete a 3-day training micturition diary during the placebo run-in period (Visit 2). If subjects meet all entry criteria at the end of the placebo run-in period, subjects will be randomized to 1 of 2 treatment groups (Mirabegron or PBO) for 12 weeks of treatment. Three days before Visits 4 (Week 4), 5 (Week 8), and 6 (Week 12), the subject will complete a 3-day micturition diary using the ePRO device. Post-void residual volume (PVR) will be assessed at Screening (Visit 1) and at Week 12/End of Treatment (Visit 6). Total study participation is approximately 20 weeks. During the study, subject enrollment will be monitored for the percent of subjects ≥ 75 years of age. If the proportion of subjects ≥ 75 years of age is < 30%, measures may be taken to enhance enrollment of sufficient number of subjects ≥ 75 years of age to ensure that the percentage of subjects ≥ 75 years is at least 30%. Subjects will be randomized to one of two treatment groups in a 1:1 ratio to either mirabegron or placebo (PBO). Randomization will be stratified by age < 75 years and ≥ 75 years. Those subjects randomized to mirabegron will start at 25 mg and may increase to 50 mg after 4 weeks or 8 weeks based on individual subject efficacy, tolerability and Investigator discretion. Those subjects randomized to PBO will start blinded product matched to the mirabegron 25 mg tablet and may also increase to 50 mg PBO after 4 or 8 weeks. Once a patient has increased dose, they will remain on that dose for the remainder of the study unless for safety reasons that require discontinuation of study drug.

Number of Subjects Planned	**Number of Subjects to be Enrolled / Randomized:** Approximately 1,150 subjects will be screened to achieve 800 randomized subjects. Subjects will be randomized 1:1 stratified by age (< 75 years, ≥ 75 years). 400 randomized to Mirabegron; 400 randomized to PBO
Selection Criteria	**Inclusion:** *Inclusion Criteria assessed at Visit 1 (Screening)*: 1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable). 2. Male or female subject greater than or equal to 65 years of age. 3. Subject is willing and able to complete the micturition diary and questionnaires correctly. 4. Subject has symptoms of wet OAB (urinary frequency and urgency with incontinence) for greater than or equal to 3 months prior to Screening. 5. Subject agrees not to participate in another interventional study from the time of screening until the final study visit. *Inclusion Criteria assessed after placebo run-in period at Visit 3 (Baseline):* 1. Subject continues to meet all inclusion criteria of Visit 1. 2. Subjects must experience at least one incontinence episode in the placebo run-in period based on the 3-day micturition diary. 3. Subject must experience at least 3 episodes of urgency (grade 3 or 4) based on the 3-day micturition diary. 4. Subject must experience an average of greater than or equal to 8 micturitions/day based on the 3-day micturition diary. Waivers to the inclusion criteria will NOT be allowed. **Exclusion:** *Exclusion Criteria assessed at Visit 1 (Screening)*: 1. Subject has ongoing symptoms suggestive of bladder outlet obstruction (BOO) or history of BOO that is not currently well controlled. 2. Subject has Post-Void Residual Volume (PVR) greater than 150 mL. 3. Subject has neurogenic bladder or neurological dysfunction or injury which could affect the lower urinary tract or nerve supply. 4. Subject has significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor as determined by the Investigator (for female subjects confirmed by a cough provocation test). Subjects with a history of stress incontinence that is currently treated (e.g., remote history of surgery for stress incontinence) may be included as long as they pass cough provocation test.

	5. Subject has an indwelling catheter or practices intermittent self-catheterization. 6. Subject has evidence of Urinary Tract Infection (UTI) Urine culture and sensitivity will be performed for positive leukocytes, or nitrites, or turbidity, or at the investigator's discretion, and will be confirmed with a culture greater than 100,000 cfu/mL If a subject has a UTI, at Screening (Visit 1) the subject can be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture). 7. Subject has a chronic inflammatory condition such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs (i.e., within the confines of the pelvis including the bladder and rectum in both sexes and the uterus, ovaries, and fallopian tubes in females; organs of the lower gastrointestinal tract are not necessarily considered pelvic organs as the distal ascending colon, the full transverse colon and proximal portion of the descending colon are in the abdomen). 8. Subject resides in a nursing home. 9. Subject is likely to enter a hospital or nursing home due to medical instability within the next 6 months in the opinion of the Investigator. 10. Subject has received intravesical injection in the past 12 months with botulinum toxin, resiniferatoxin, or capsaicin. 11. Subject has received electro-stimulation therapy for OAB (e.g., sacral nerve stimulation or PTNS). 12. Subject began or has changed a bladder training program or pelvic floor exercises less than 30 days prior to Screening. 13. Subject has moderate or severe hepatic impairment defined as Child-Pugh Class B or C. 14. Subject has severe renal impairment defined as estimated creatinine clearance less than 29 mL/min determined by Estimated Glomerular Filtration Rate (eGFR, Cockroft-Gault, or MDRD formulae). A subject with end stage renal disease or undergoing dialysis is also not a candidate for the study. 15. Subject has severe uncontrolled hypertension, which is defined as a sitting systolic blood pressure greater than or equal to 180 mmHg and/or diastolic blood pressure greater than or equal to 110 mmHg. 16. Subject has evidence of QT prolongation on ECG defined as QTc greater than 450 msec for males, QTc greater than 470 msec for females or a known history of QT prolongation. 17. Subject has a clinically significant ECG abnormality, as determined by the Investigator. 18. Subject has AST or ALT greater than 2x upper limit of normal (ULN), or γ-GT greater than 3x ULN and considered clinically significant by the Investigator.

	19. Subject has a hypersensitivity to any components of mirabegron, other β-AR agonists, or any of the inactive ingredients. 20. Subject has any clinically significant condition, which in the opinion of the Investigator makes the subject unsuitable for study participation. 21. Subject has been treated with an experimental device within 28 days or received an investigational agent within 28 days or 5 half-lives, whichever is longer, prior to Screening. 22. Subject has a concurrent malignancy or history of any malignancy (within the past 5 years), except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully. 23. Subject with current history of alcohol and/or drug abuse. 24. Subject is using prohibited medications which cannot be stopped safely during the period defined in Appendix 1. 25. Subject has stopped, started or changed the dose of a restricted medication (defined in Appendix 1) within the last 30 days prior to Screening. 26. Subject is involved in the conduct of the study as an employee of the Astellas group, third party associated with the study, or the study site team. 27. Subject has previously received mirabegron. *Exclusion Criteria assessed after placebo run-in period at Visit 3 (Baseline)*: 1. Subject fulfills any exclusion criteria of Visit 1 (subject does not need to repeat screening assessments [PVR, cough provocation test, chemistry/hematology/urinalysis]). 2. Subject was non-compliant during 2-week placebo run-in period, defined as taking less than 80% or greater than 120% of study medication. 3. Subject has any systolic blood pressure measurement > 180 mmHg or diastolic blood pressure measurement > 110 in the 3-day diary or during the baseline visit. Waivers to the exclusion criteria will NOT be allowed.
Discontinuation Criteria	Subjects will be discontinued if they meet any of the following criteria: • ALT or AST > 3x ULN and total bilirubin > 2x ULN • ALT or AST > 8x ULN on one occasion • ALT or AST > 5x ULN for more than 2 weeks • ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%) Subjects may also be discontinued for: • Medically important adverse event(s) • Protocol violation (e.g., subject took prohibited medication that in the Investigator's opinion, after discussion with the Astellas Study Physician, may negatively impact the subject's safety or

	demonstrated lack of cooperation in following protocol-specified procedures/instructions) • Withdrawal of consent • Investigator and/or Sponsor feels it is in the subject's best interest
Test Drug Dose: **Mode of Administration:** **Duration of Treatment:**	Mirabegron 25 mg QD with option to titrate to Mirabegron 50 mg QD at 4 or 8 weeks post baseline Oral QD for 12 weeks
Reference Therapy Dose: **Mode of Administration:** **Duration of Treatment:**	Placebo matched to mirabegron 25 mg with option to titrate to Placebo matched to mirabegron 50 mg at 4 or 8 weeks post baseline Oral QD for 12 weeks
Drugs for Run-In Period: **Mode of Administration:** **Duration of Treatment:**	Placebo Oral QD for 2 weeks
Concomitant Medication	*Prohibited Medications (Appendix 1, part A)* Medications prohibited between Screening (Visit 1) and Week 12/End of Treatment (Visit 6) include anticholinergics, antispasmodics, and CYP2D6 substrates with narrow therapeutic index (see Appendix 1, Part A). These medications must have been discontinued at least 30 days prior to Screening (Visit 1). Current or previous use of mirabegron at any time is prohibited. *Restricted medications (Appendix 1, part B)* Medications restricted between Screening (Visit 1) and Week 12/End of Treatment (Visit 6) include loop diuretics, alpha blockers and 5-Alpha reductase inhibitors. All medications in Part B of Appendix 1 are permitted provided the subject has been taking this medication on a long-term basis, i.e. has not stopped, started or changed dose within the 30 days prior to Screening (Visit 1), no new drug of the same class has been added to the regimen within the 30 days prior to Screening (Visit 1), and the subject remains on the medication at the same dose during the course of the study. *Restricted Non-Drug Therapy* Subjects participating in any behavioral modification therapy (i.e. pelvic floor exercises, Kegel exercises, biofeedback, timed voiding, etc.) or other non-drug therapy must have started the therapy at least 30 days prior to Screening (Visit 1) and must continue the same schedule through Week 12/End of

	Treatment (Visit 6).
Duration of Treatment	Subjects will be randomized to 1 of 2 treatment groups in a 1:1 randomization (Mirabegron or Placebo) for a maximum of 12 weeks. Subject participation will last approximately 20 weeks.
Primary Endpoints	The co-primary efficacy endpoints are: • Change from baseline to the end of treatment in mean number of micturitions/24 hour based on a 3-day micturition diary. • Change from baseline to end of treatment in mean number of incontinence episodes/24 hour based on a 3-day micturition diary.
Secondary Endpoints	Secondary endpoints: • Change from baseline to the end of treatment in mean volume voided per micturition. • Change from baseline to the end of treatment in symptom bother and total health related quality of life scores as assessed by OAB-q questionnaire. • Change from baseline to the end of treatment in Patient Perception of Bladder Condition (PPBC).
Other Endpoints	Other efficacy variables are the change from Baseline (Week 0) to End of Treatment (Week 12) in: • Mean number of urgency episodes (grade 3 and/or 4)/24 hour • Mean number of urgency incontinence episodes/24 hour • Mean level of urgency • Mean number of nocturia episodes/24 hour • Subscale score from OAB-q scores • TS-VAS 1. University of Alabama, Birmingham - Life Space Assessment (UAB-LSA) 2. Responder analysis as defined by >= 50% reduction from baseline in mean number of incontinence episodes/24 hours or zero incontinence episodes post-baseline.
Safety Variables	Safety variables include: • Adverse events (AE)s • Vital signs: sitting systolic and diastolic blood pressure and pulse rate (home based measurements and office measurements) • Laboratory parameters (serum chemistry, hematology, and urinalysis) • Change from baseline to end of treatment in Montreal Cognitive Assessment (MoCA) score

Statistical Methods

Sample Size Justification:

The co-primary endpoints for this study are change from baseline to end of treatment in the mean number of micturitions per 24 hours based on the 3-day micturition diary and change from baseline to end of treatment in mean number of incontinence episodes per 24 hours based on the 3-day micturition diary.

The sample size calculation first of all evaluates the number of subjects needed to test the change from baseline to end of treatment in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary and then assesses whether this same sample size is adequate to test the change from baseline to end of treatment in the mean number of micturitions per 24 hours based on the 3-day micturition diary. The overall power is then calculated for the study based on these co-primary endpoints.

The sample size calculation for the change from baseline in the final visit mean number of incontinence episodes per 24 hours is based on nonparametric methods since the results from previous phase 2 and 3 studies indicated that the assumption of normality may not be valid. The results of these studies showed frequent ties for the number of episodes and therefore the sample size calculation is based on dividing this endpoint into 7 categories. The actual primary statistical analysis will not group the data. The categories are shown below together with the percentages occurring for placebo and mirabegron 50 mg as found in older adult subjects (≥65 years of age) from North American sites in studies 178-CL-047 and 178-CL-074.

Table 1 - Categories for Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours, for North America, ≥65 years

Mean Change Incontinence Category	Placebo N =185	Mirabegron 50 mg N=187
≤ -2.67	15.68%	16.04%
[-2.67, -2.00)	7.03%	9.09%
[-2.00, -1.33)	12.43%	22.46%
[-1.33, -0.67)	13.51%	9.63%
[-0.67, -0.34)	12.43%	11.76%
[-0.34, 0.33)	17.84%	20.86%
≥ 0.33	21.08%	10.16%

Based on Table 1, the probability that a subject on mirabegron will respond better than a subject on placebo is 56.3% (nQuery 7.0). Based on a Wilcoxon (Mann-Whitney) rank-sum test that P(X<Y) = 0.5 (continuous outcome), 340 incontinent subjects per treatment group will yield 82% power with a 2-sided test at a significance level of 0.05.

The pivotal study showed a 0.796 mean (SD=2.7) reduction for mirabegron 50 mg compared to PBO in the mean number of micturition per 24 hours in North American subjects who were 65 years or older. A sample size of 340 subjects per treatment group will yield 97% power to detect a reduction of .796 in mean number of micturitions per 24 hours using a two-sided t-test at a significance level of 0.05 assuming a SD of 2.7 (nQuery 7.0).

Assuming 'Change from baseline in mean number of micturitions per day' and 'Change from baseline in mean number of incontinence episodes per

	day' are independent the overall power would therefore be 80%. The historical data show at least 15% of the randomized subjects will drop out during the double-blind period. Consequently an additional 60 subjects per treatment group need be enrolled. This brings the total required incontinent subjects per treatment group to 400. Based on the historical data a 20% failure rate is predicted due to lack of incontinence and another 10% failure due to a combination of drop out and placebo response during the placebo run-in period. Therefore, a 30% screen failure rate is expected. In order to randomize 800 subjects with incontinence, it is expected that 1,150 subjects will need to be screened. **Efficacy:** All analyses will be performed comparing two treatment groups: Mirabegron (regardless of dose) versus PBO. **Analysis on Co-Primary Endpoints** The primary analysis set for efficacy analyses will be the Full Analysis Set – Incontinence (FAS-I) which comprises randomized subjects who took at least one dose of randomized study drug, have a micturition measurement at baseline, have at least one incontinence episode at baseline, and have at least one post-baseline micturition measurement (measurement includes micturition and incontinence episodes). Change from baseline to end of treatment in mean number of micturitions per 24 hours will be analyzed using a stratified Analysis of Covariance (ANCOVA) model. The response variable will be the mean change in number of micturitions episodes per 24 hours from baseline to the end of treatment with treatment group and gender as fixed factors and baseline mean number of micturitions episodes per 24 hours as the covariate in the model. Age group (<75 years, ≥75 years) will be included as the stratification factor. As part of the ANCOVA results, LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided. Differences in LS means between mirabegron and placebo will be derived together with 95% CIs and p-values. In order to test for statistical differences in Change from baseline to end of treatment in mean number of incontinence episodes per 24 hours between mirabegron and placebo, a stratified rank Analysis of Covariance (ANCOVA) will be used. The response variable is the standardized ranks of change from baseline to end of treatment value in mean number of incontinence episodes per 24 hours. Treatment group and gender will be added as fixed factors in the model while the standardized ranks of mean number of incontinence episodes per 24 hours at baseline will be included as a covariate. Age group (<75 years, ≥75 years) will be included as the stratification factor. Responder analyses will be performed using a logistic regression model including the same factors as the ANCOVA model. Odds ratios that compare treatment effect between mirabegron and placebo will be reported with 95% CIs.

	Analysis on Secondary Endpoints The change from baseline to end of treatment for other secondary endpoints (excluding mean voided volume [MVV]) will be analyzed using a similar ANCOVA model as described above for mean number of micturitions per 24 hours. The change from baseline to end of treatment in MVV will be analyzed using the Stratified Rank ANCOVA and ANCOVA model as described above for mean number of incontinence episodes. **Safety:** Safety analyses will be performed on the Safety Analysis Set (SAF) defined as all subjects who receive at least one dose of double-blind medication. Number and percentage of treatment-emergent adverse events reported during the double-blind period will be summarized by system organ class, preferred term, seriousness, severity, and relationship to treatment, overall and by treatment group. Statistical differences in change from baseline to end of treatment in cognitive assessment will be tested using a paired sample Wilcoxon test. Changes from baseline for PVR and laboratory assessments (biochemistry and hematology) will be summarized in tables by treatment group and visit. Vital sign data will be analyzed separately based on the 3-day diary and the site assessment at each clinic visit. Change from baseline in vital sign variables will be analyzed using the same ANCOVA model as described for the analysis of change from baseline in mean number of micturitions per 24 hours. No p-values will be a calculated. ECGs will be performed at Screening (Visit 1), the placebo run-in period (Visit 2), Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6). **Interim Analysis:** N/A

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Figure 1 Flow Chart

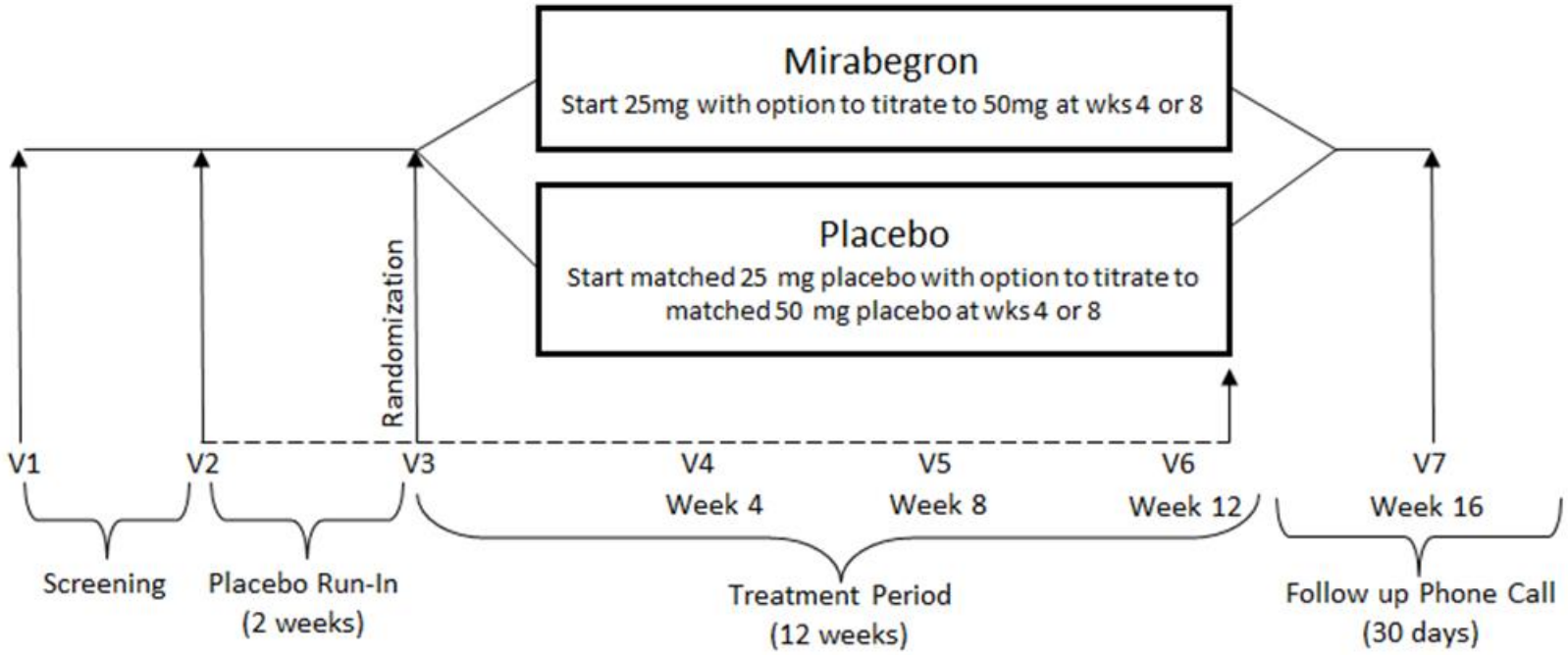

Table 1 Schedule of Assessments

	Screening	Placebo Run-In	Treatment Period				Follow-up Phone Call
Visit	1	2	3	4	5	6	7
Day	-28	-14	1	28	56	84	112
Week	-4	-2	0/Baseline	4	8	12/EOT	16
Visit Windows (Days) [a]	+/- 10	+/- 3	+/- 3	+/- 7	+/- 7	+/- 7	+/- 3
Informed Consent/HIPAA	X						
Inclusion/Exclusion Criteria	X		X				
Medical History and OAB History	X						
Demographics	X						
Enter 2-week Placebo Run-in [b]		X					
Randomization [c]			X				
Physical Exam (including height [d] and weight)	X					X	
Vital Signs – in office (includes pulse and blood pressure)	X	X	X	X	X	X	
Cough Provocation test (Females only)	X						
Serum chemistry, hematology & urinalysis [e]	X					X	
[redacted]	[redacted]						
12-Lead ECG	X	X	X	X	X	X	
Ultrasound or Bladder Scan (PVR)	X					X	
Medication History and OAB Medication History	X		X				
Clinical Assessment for Dose Increase				X	X		
Concomitant Medications Assessment	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X
Dispense Study Drug		X	X	X	X		
Drug Accountability			X	X	X	X	
Instruct Subject on 3-day Micturition Diary [g]		X	X	X	X	X	
Complete 3-day Micturition Diary including vital sign measurements and PPIUS [h,i]			X [h]	X [h]	X [h]	X [h]	
OAB-q			X	X	X	X	
Patient Perception of Bladder Condition Scores (PPBC)			X	X	X	X	
TS-VAS			X	X	X	X	
Montreal Cognitive Assessment Test (MoCA)			X			X	
Univ Alabama Birmingham Life Space Assessment (UAB -LSA)			X	X	X	X	

Table continues on next page

	Screening	Placebo Run-In	Treatment Period				Follow-up Phone Call
Visit	1	2	3	4	5	6	7
Day	-28	-14	1	28	56	84	112
Week	-4	-2	0/Baseline	4	8	12/EOT	16
Visit Windows (Days) [a]	+/- 10	+/- 3	+/- 3	+/- 7	+/- 7	+/- 7	+/- 3
Barthel ADL Assessment			X			X	
Vulnerable Elders Survey 13 (VES-13)			X			X	
Review Subject Diary [j]			X	X	X	X	

a. Visits 1 and 2 are negatively scheduled from the Baseline (Visit 3) date. A subject has a combined timeframe of up to 38 days to complete both Visits 1 and 2; however, Baseline (Visit 3) must occur at least 18 days but no more than 38 days after Visit 1 (Screening) and at least 11 days but no more than 17 days after Visit 2 (Placebo Run-In). After Visit 2 (Placebo Run-In), visit windows/study days will be calculated based on the Visit 3 (Baseline) visit date. Study procedures (e.g. bladder scan) for a particular visit do not need to be completed on the visit date if this is not feasible for the subject, as long as, study procedures are performed per protocol within the applicable visit window. Any procedure not done or performed outside the applicable visit window will be noted as a protocol deviation.

b. Subjects must take at least 11 days, but no more than 17 days of placebo run-in medication.

c. Randomization is to occur after confirming all eligibility criteria and after performing all other visit procedures at Visit 3.

d. Height will only be assessed at the Screening Visit.

e. Urine culture and sensitivity will be performed for positive leukocytes, or nitrites, or turbidity, or at the discretion of the PI. If a subject has a UTI, the subject can be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).

f. [redacted]

g. At Visit 2 (Placebo Run-In), all subjects will be provided with an ePRO device (electronic diary) that will be used to record the date and time of each of their micturitions, incontinence, urgency episodes, measure of urine volume voided, and sleep interruption (micturition diary). Additionally, the diary will be used to record medication intake and home measurements of am and pm pulse rate and systolic and diastolic blood pressure. Training on device use must be done at Visit 2 (Placebo Run-In) and as necessary throughout the study. Subjects will be instructed to begin completing the electronic micturition diary 3 days prior to each in-office study visit including Visits 3-6 (Treatment Period) and complete the diary for the full 3 days.

h. Subjects will complete the electronic diary 3 days prior to the study visit and complete the diary for the full 3 days leading up to the visit.

i. During this activity, the subject will not come to the clinic for a visit. Site staff will contact the subject 3 days prior to the scheduled Visit to remind the subject they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable). The subject will need to complete the 3-day electronic diary at home the full 3 days leading up to Visits 3, 4, 5 & 6.

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

1 INTRODUCTION

1.1 Background

Overactive bladder (OAB) is a frequent condition affecting older adults. It is estimated that more than half the elderly population experience voiding dysfunction, which may be attributed to idiopathic, neurologic, or cognitive impairment [Nassau et al, 2014]. The frequency and urgency associated with OAB are often highly debilitating. In addition, OAB-related urinary incontinence (UUI, MUI) has been associated with other deleterious health related outcomes in community dwelling seniors, including falls and fractures, urinary tract infections, skin infections, depression, and chronic constipation [Wagg et al, 2014; Wagg et al, 2013; Kashyup et al, 2014]. Antimuscarinic anticholinergics in immediate-release and sustained-release formulations have been demonstrated to be efficacious in controlling urgency and incontinence episodes in older adults. However, their anticholinergic properties have been shown in several studies to be especially concerning for the older adult patients. As a result of the combination of age-related changes in blood-brain barrier permeability and comorbidity-related changes in cerebrovascular status, impaired cognitive function has been associated with increasing anticholinergic drug burden [Boustani et al, 2008; Cai et al, 2013; Fox et al, 2011].

Older patients are known to experience more AEs than younger patients and the AEs they experience with oral antimuscarinic treatment may be more pronounced [Wagg et al, 2010; Allman et al, 2006]. Of particular concern are the potentially adverse effects of antimuscarinic medications caused by age-related changes in central cholinergic transmitter systems [Kay et al, 2005]. Indeed, immediate and extended-release formulations of oxybutynin have been associated with cognitive impairment in older people who are cognitively intact although trospium chloride, as well as other newer antimuscarinics, have been reported to have no adverse effects on cognition in the cognitively-intact older adult patients and those with mild cognitive impairment [Wagg et al, 2013; Boustani et al, 2008; Cai et al, 2013; Fox et al, 2011; American Geriatrics Society, 2012; Kay et al, 2006; Holick 2008].

For example, a recent 12-week, double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of fesoterodine in 794 patients aged 65 years and older with OAB symptoms for 3 months or longer [Wagg et al, 2013]. The trial also included patient reported outcome assessments [including OAB-q, Treatment Benefit Scale (TBS), PPBC, Urgency Perception Scale (UPS), and OAB-s] and a Mini-Mental State Examination (MMSE) at baseline and 12 weeks. Although results of this study showed a statistically significant improvement over placebo in urgency episodes, no change in MMSE score was reported [Wagg et al, 2013]. There are very few data on the effects of the newer antimuscarinic medications using more sensitive measures of cognitive function (see for example Kay et al, 2006), and no data regarding their effects in combination with other anticholinergic medications. Therefore, the American Geriatrics Society has cited oral antimuscarinics as “potentially inappropriate medications and classes to avoid in older adults” [American Geriatrics Society 2012].

Recently the first in class β_3 adrenergic agonist mirabegron was approved in the US, Canada and many other countries around the world. The mirabegron phase 3 program has demonstrated it to be a safe and efficacious option for the drug treatment of symptoms of OAB with or without incontinence. Mirabegron works through a different mechanism of action to that of antimuscarinics by stimulating the β3-AR in the detrusor muscle leading to bladder relaxation and increased inter-void interval. Mirabegron also has a distinct tolerability profile from that of antimuscarinics. The incidence of dry mouth and constipation, two of the most common and bothersome side effects with antimuscarinics, often a reason for discontinuation, were similar between placebo and mirabegron 50 mg [Herschorn et al, 2013].

There exists an unmet need within the community dwelling senior population for non-pharmacologic and pharmacologic interventions that can simultaneously demonstrate control of OAB symptoms and positively impact direct and indirect measures of Activities of Daily Living (ADL), such as life-space assessment, while at the same time not adding to the risk of cognitive impairment. Life-space measures used within community dwelling older adult patients suggest that life-space can assess mobility-enhancing interventions as well as the effect of biomedical, psychological, socioeconomic, environmental, and social support factors on mobility [Allman et al, 2006; Abe et al, 2009; Shimada et al, 2010; Stewart et al, 2009]. Multiple studies have demonstrated both beneficial and neutral effects on social engagement with successful treatment of urinary incontinence among civilian and Veteran's Administration long term care older adult populations [Moga et al, 2013; Ouslander et al, 1982].

Pivotal studies with mirabegron included a significant number of older patients. In the three large, placebo-controlled, randomized, 12-week phase 3 trials with mirabegron, 36–39% of patients were ≥ 65 years of age and 7–12% were ≥ 75 years of age. In a pre-specified subanalysis of these studies based on patient age, mirabegron 25 mg and 50 mg once-daily reduced the mean number of incontinence episodes and micturitions per 24 hours from baseline to final visit in these two groups of older OAB patients with no loss of efficacy with age [Wagg et al, 2014]. Patient Reported Outcome (PRO) measures have also been reported for the older adult population. In an analysis to evaluate the magnitude of PRO improvement stratified by age in patients enrolled in mirabegron phase 3 clinical trials, statistically significant improvements were observed in patients ≥ 65 years of age for treatment satisfaction (TS-VAS), PPBC and OAB-q (all $p<0.001$). Older patients generally perceived mirabegron 50 mg to be more efficacious than placebo in treating symptoms of OAB. Compared to the < 75 year old cohort, patients ≥ 75 years of age reported higher numerical improvement vs placebo across all PRO measures, including the OAB-q.

With regard to safety, the three most common TEAEs in patients ≥ 65 years of age receiving mirabegron 50 mg were the same as in the overall population: hypertension, nasopharyngitis and UTI (9.9%, 4.1%, and 3.1%, respectively). In the ≥ 65 year old subgroup, the incidence of the most common TEAEs was similar for both doses of mirabegron and placebo over 12 weeks, except for hypertension, UTI and dizziness which occurred with a higher incidence

in the mirabegron 25 mg group than the placebo or mirabegron 50 mg groups. In patients randomized to mirabegron 50 mg in the ≥ 75 year old subgroup, headache, dry mouth and pain in extremity (each 2.6%) were more common than UTI (1.9%). In a 1-year mirabegron study, hypertension and UTI were still the most common TEAEs with mirabegron 50 mg in older subjects [Wagg et al, 2014].

While the mechanism of action of mirabegron does not suggest an effect on the brain, specific studies of cognitive function have not been conducted. When studied in animal models (rat, monkey), mirabegron was extensively distributed in organs and other tissues after oral and IV administration, except the brain [Astellas. Data on file. 2012]. The same characteristics of tissue distribution are expected in humans; however, no human studies have been conducted to determine if mirabegron penetrates the blood brain barrier [Astellas. Data on file. 2012]. The effect of mirabegron on cognitive function was also not assessed in the three large phase 3 pivotal trials. However, there were no adverse events reported of memory impairment or cognitive disorder in the mirabegron 25 mg and 50 mg treatment groups (n = 586 and 1,889, respectively). Although no cognitive function assessment tools were utilized during these studies, the lack of any adverse events reported in the cognitive function domain supports the safety profile for mirabegron in older adult patients with OAB [Adapted from Astellas. Myrbetriq. Integrated Summary of Safety (ISS) Final. Data on File].

There is evidence that vitamin D plays a role in the pathophysiology of OAB. Calcium is involved in bladder function through its role in detrusor smooth muscle contraction. In a study of women with OAB, a deficiency in dietary vitamin D was found to lead to a higher incidence of OAB symptoms [Dallosso et al, 2004]. Another study found that treatment of women with a vitamin D analog improved symptoms of OAB [Digesu et al, 2012]. Although the elderly are at high risk of having vitamin D deficiency, there are currently no data evaluating the vitamin D status of patients with OAB related to efficacy on OAB oral therapy [Holick 2008].

In conclusion, this will be the first mirabegron OAB study to specifically evaluate the efficacy and safety of mirabegron in an older population of patients with OAB. This study will also be the first to explore the effect of mirabegron on cognitive function in older adult patients. Oral antimuscarinic agents have historically been the preferred treatment option for OAB; however, these agents can be suboptimal in their effect and lead to burdensome adverse events, as seen in previous studies in older patients. This study is designed to demonstrate the reduction in frequency of incontinence episodes and micturitions in older adults (> 65 years) and support that mirabegron is a suitable option for the treatment of OAB in older patients with multiple comorbidities, not adversely affecting cognitive function in patients with impaired mental status, and increasing quality of life. [redacted]

1.2 Non-clinical and Clinical Data

Detailed information on the non-clinical studies conducted with mirabegron can be found in the approved product labeling. Summaries of findings from non-clinical and clinical studies with mirabegron which may have relevance for the current study are listed below.

1.2.1 Summary of Non-clinical Safety Data with Mirabegron

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

Increases in heart rate have been observed following mirabegron administration to rats, dogs, and monkeys. Decreases in blood pressure were observed in dogs but not in rats or monkeys. Assessment of the potential for mirabegron to delay cardiac repolarization demonstrated that mirabegron and its most abundant human metabolites were free from effects on cardiac repolarization in isolated dog Purkinge fibers and guinea pig papillary muscles. Furthermore, in isolated perfused dog ventricular tissue neither mirabegron nor its metabolites induced electrophysiological changes. Mirabegron and its five most abundant human metabolites did not significantly alter the IKr (hERG), IKs (hKvLOT1/mink), Ito (hKv4.3/KChip2.2), Ina (hNAV1.5), or Ica (hCav 1.2) conductance in in vitro studies at relevant concentrations (>100-fold human C_{max} at a 100 mg dose.

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

1.2.2 Summary of the Pharmacokinetics of Mirabegron

After oral administration of mirabegron in healthy volunteers, peak mirabegron plasma concentrations were attained between 3 to 5 hours. The absolute bioavailability increases from 29% at a dose of mirabegron 25 mg to 45% at a dose of mirabegron 150 mg under fasted conditions in healthy volunteers. Mean C_{max} and AUC_{inf} increased more than dose proportionality over the recommended dose range. Steady state concentrations were achieved within 7 days of once daily dosing with mirabegron. The C_{max} and AUC_{tau} of

mirabegron and its metabolites following multiple oral doses in older adult subjects (≥ 65 years) were similar to those in younger subjects (18 to 45 years). The C_{max} and AUC_{tau} of mirabegron were approximately 40 – 60% higher in females than in males. The mean terminal $t_{1/2}$ is comparable in both sexes. Evaluation of special populations in the phase 1 studies demonstrated that volunteers with severe renal impairment (CRCL 15 to 29 mL/min or eGFR 15 to 29 mL/min per 1.73m^2) or moderate hepatic impairment (Child-Pugh Class B) had an approximately 2-fold increase in exposure to mirabegron relative to normal healthy volunteers.

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

1.2.3 Summary of Clinical Data with Mirabegron

The clinical development program consists of 43 completed clinical studies to date over approximately 10 years and is comprised of 10,552 subjects (1,812 volunteers and 9,878 patients) including patients with OAB, type 2 diabetes mellitus, and lower urinary tract symptoms (LUTS)/bladder outlet obstruction (BOO). A total of 30 phase 1 studies and 13 phase 2 and 3 studies (10 in patients with OAB, 1 in patients with LUTS/BOO and 2 in patients with type 2 diabetes mellitus) have been conducted globally.

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

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

In the U.S. Package Insert, mirabegron has warnings and precautions for increases in blood pressure, urinary retention in patients with bladder outlet obstruction, and in patients taking drugs metabolized by CYP2D6.

In the Canadian Monograph, mirabegron has contraindications for patients with severe uncontrolled hypertension, patients who are pregnant, and patients who are hypersensitive to mirabegron or to any ingredient in the formulation or component of the container. Mirabegron has warnings and precautions for neoplasm, Stevens-Johnson syndrome, increases in serum

ALT/AST, QTc prolongation, increases in blood pressure and heart rate, urinary retention, and in patients taking drugs metabolized by CYP2D6. The monograph does not recommend use of mirabegron in patients with severe hepatic impairment, end stage renal disease, pregnant and nursing women, and pediatric patients (< 18 years of age).

For further information, please refer to the full prescribing information for mirabegron [Mirabegron US Package Insert, 2012 and Myrbetriq Canadian Monograph, March 2013].

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Summary of Key Safety Information for Mirabegron

Mirabegron was first approved in Japan on 1 July 2011, and was launched to market on 16 September 2011 under the trade name Betanis®. On 28 June 2012, mirabegron received approval in the United States (trade name: Myrbetriq®). The approved indication is the treatment of OAB with symptoms of urinary incontinence, urgency, and urinary frequency. On 20 December 2012, mirabegron received marketing approval in the EU under the trade name Betmiga®. On 6 March 2013, mirabegron received approval in Canada (trade name: Myrbetriq®). On 1 October 2013, mirabegron received approval in Australia (trade name: Betmiga®). Additional regulatory approvals have been obtained in countries including Hong Kong, Korea, Turkmenistan, and Argentina.

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

Important potential risks include QT prolongation with supratherapeutic doses or in high-risk populations, increased heart rate, increased blood pressure, non-immediate cutaneous hypersensitivity reactions and exposure in utero. The potential risks of QT prolongation, increased heart rate or increased blood pressure are greater with increasing exposure. The expected adverse drug reactions for mirabegron are presented in Table 2. The approved therapeutic dose of mirabegron in the United States and Canada is 25 mg once daily which may be increased to 50 mg once daily based on individual patient efficacy and tolerability [Mirabegron US Package Insert, 2012 and Myrbetriq Canadian Monograph, March 2013]. The favorable benefit risk profile of mirabegron is not expected to change over time.

A mean change of approximately 1 bpm for pulse rate was observed in OAB patients who received mirabegron 50 mg. This magnitude of change was similar for both 12-week and long-term studies, for men and women and in the mirabegron and tolterodine treatment groups. In patients with OAB, categorical increases in pulse rate were noted more frequently with mirabegron and tolterodine than with placebo, with similar changes observed for mirabegron 50 mg and tolterodine. Pulse increases were more pronounced in young subjects in comparison to older adults (age 55 years and greater) subjects. Changes in pulse were reversible upon discontinuation of treatment.

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

Table 2 Adverse Events Exceeding the Placebo Rate and Reported by Greater Than or Equal to 1% of Mirabegron-Treated OAB Patients in the 12-Week Phase 3 Studies

	Placebo (%)	Mirabegron 25 mg (%)	Mirabegron 50 mg (%)
Number of Patients	**1380**	**432**	**1375**
Hypertension *	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

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

Detailed information on the clinical safety profile of mirabegron can be found in the full prescribing information [Mirabegron US Package Insert, 2012 and Myrbetriq Canadian Monograph, March 2013].

According to Section 8.5 of the current mirabegron US Package Insert, there is no dose adjustment necessary for older adult patients. The pharmacokinetics of mirabegron is not significantly influenced by age. The C_{max} and AUC of mirabegron following multiple oral doses in older adult volunteers (≥ 65 years) were similar to those in younger volunteers (18 to 45 years). Of 5,648 patients who received mirabegron in the phase 2 and 3 studies, 2,029 (35.9%) were 65 years of age or older, and 557 (9.9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies [Mirabegron US Package Insert, 2012].

1.4 Risk-Benefit Assessment

Mirabegron is a new medication with a distinct mechanism of action (beta 3-AR agonist) compared with the current standard of care, primarily antimuscarinics, for the treatment of

symptoms of OAB. The clinical efficacy of mirabegron 25 mg and mirabegron 50 mg was established in the phase 3 clinical program. The effect of mirabegron has been shown to be superior to placebo.

Results from subjective endpoints provide evidence that the patients not only obtained objective evidence of improvement, but also clinically meaningful benefits from mirabegron in the treatment of their disease. The long-term study has demonstrated persistence of effect over a 1-year treatment period. The favorable benefit risk profile of mirabegron is not expected to change over time. The approved therapeutic dose of mirabegron in the United States is 25 mg once daily which may be increased to 50 mg once daily based on individual patient efficacy and tolerability [Mirabegron US Package Insert, 2012 and Myrbetriq Canadian Monograph, March 2013].

Pertinent details for cardiovascular and neoplastic events, as defined in a separate charter, will be collected to ensure complete details are fully available to characterize these events for Adjudication Committee review.

Overall, the data support the acceptable safety of mirabegron in the treatment of OAB at the approved therapeutic doses.

2 STUDY OBJECTIVE(S), DESIGN AND VARIABLES

2.1 Study Objectives

The primary objective is to assess the efficacy of mirabegron versus placebo (PBO) in the treatment of older adult subjects with OAB.

The secondary objective is to assess the safety and tolerability of mirabegron versus placebo (PBO) in the treatment of older adult subjects with OAB.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

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

After Screening (Visit 1), subjects will enter into a 2-week placebo run-in period (Visit 2) prior to being randomized into the 12-week double-blind treatment period (Visit 3). Subjects will be asked to complete a 3-day training micturition diary during the placebo run-in period (Visit 2). If subjects meet all entry criteria at the end of the placebo run-in period, subjects will be randomized to 1 of 2 treatment groups (Mirabegron or PBO) for 12 weeks of treatment. Three days before Visits 4 (Week 4), 5 (Week 8), and 6 (Week 12), the subject will complete a 3-day micturition diary using the ePRO device. Post-void residual volume (PVR) will be assessed at Screening (Visit 1) and at Week 12/End of Treatment (Visit 6). Total study participation is approximately 20 weeks.

During the study, subject enrollment will be monitored for the percent of subjects ≥ 75 years of age. If the proportion of subjects ≥ 75 years of age is < 30%, measures may be taken to enhance enrollment of subjects ≥ 75 years of age.

Subjects will be randomized to one of two treatment groups in a 1:1 ratio to either mirabegron or placebo (PBO). Randomization will be stratified by age < 75 years and ≥ 75 years. Those subjects randomized to mirabegron will start at 25 mg and may increase to 50 mg after 4 weeks or 8 weeks based on individual subject efficacy, tolerability and Investigator discretion. Those subjects randomized to PBO will start blinded product matched to the mirabegron 25 mg tablet and may also increase to 50 mg PBO after 4 or 8 weeks. Once a patient has increased dose, they will remain on that dose for the remainder of the study unless for safety reasons that require discontinuation of study drug.

2.2.2 Dose Rationale

Mirabegron 25 mg, which may be increased to 50 mg based on individual efficacy and tolerability, is the approved dose in the treatment of overactive bladder in the United States and Canada [Mirabegron US Package Insert, 2012 and Myrbetriq Canadian Monograph, March 2013]. The dosing regimen of mirabegron 25 mg increased to mirabegron 50 mg after 4 weeks of treatment is intended to reflect a pragmatic and clinically plausible regimen. The treatment effect size at Week 4 in the phase 3a program approaches the maximum treatment response for incontinence and micturition.

The study design employs an optional dose increase from 25 mg mirabegron to 50 mg mirabegron at either Week 4 (Visit 4) or Week 8 (Visit 5) based on the individual subject efficacy, tolerability, and Investigator discretion. Once a patient has increased dose, they will remain on that dose for the remainder of the study unless for safety reasons that require discontinuation of study drug.

2.3 Variables

2.3.1 Primary Variable

The co-primary efficacy endpoints are:

- Change from baseline to the end of treatment in mean number of micturitions/24 hour based on a 3-day micturition diary.
- Change from baseline to end of treatment in mean number of incontinence episodes/24 hour based on a 3-day micturition diary.

2.3.2 Secondary Variables

Secondary endpoints are:

- Change from baseline to the end of treatment in mean volume voided per micturition.
- Change from baseline to the end of treatment in symptom bother and total health related quality of life scores as assessed by OAB-q questionnaire.
- Change from baseline to the end of treatment in Patient Perception of Bladder Condition (PPBC).

2.3.3 Other Variables

Other efficacy variables are the change from Baseline (Week 0) to End of Treatment (Week 12) in:

- Mean number of urgency episodes (grade 3 and/or 4)/24 hour
- Mean number of urgency incontinence episodes/24 hour
- Mean level of urgency
- Mean number of nocturia episodes/24 hour
- Subscale score from OAB-q scores
- TS-VAS
- University of Alabama, Birmingham - Life Space Assessment (UAB-LSA)
- Responder analysis as defined by >= 50% reduction from baseline in mean number of incontinence episodes/24 hours from baseline or zero incontinence episodes post-baseline.

3 STUDY POPULATION

3.1 Selection of Study Population

This study will enroll male and female subjects greater than or equal to 65 years old who have symptoms of OAB. Eight hundred subjects will be randomized (1:1) to either mirabegron or placebo, stratified by age (< 75 years, ≥ 75 years).

3.2 Inclusion Criteria

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

Inclusion Criteria assessed at Visit 1 (Screening):

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Male or female subject greater than or equal to 65 years of age.
3. Subject is willing and able to complete the micturition diary and questionnaires correctly.
4. Subject has symptoms of OAB (urinary frequency and urgency with incontinence) for greater than or equal to 3 months prior to Screening.
5. Subject agrees not to participate in another interventional study from the time of screening until the final study visit.

Inclusion Criteria assessed after placebo run-in period at Visit 3 (Baseline):

1. Subject continues to meet all criteria of Visit 1.
2. Subjects must experience at least one incontinence episode based on the 3-day micturition diary.
3. Subject must experience at least 3 episodes of urgency (grade 3 or 4) based on the 3-day micturition diary.

4. Subject must experience an average of greater than or equal to 8 micturitions/day based on the 3-day micturition diary.

Waivers to the inclusion criteria will NOT be allowed.

3.3 Exclusion Criteria

Exclusion Criteria assessed at Visit 1 (Screening):

1. Subject has ongoing symptoms suggestive of bladder outlet obstruction (BOO) or history of BOO that is not currently well controlled.
2. Subject has Post-Void Residual Volume (PVR) greater than 150 mL.
3. Subject has neurogenic bladder or neurological dysfunction or injury which could affect the lower urinary tract or nerve supply.
4. Subject has significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor as determined by the Investigator (for female subjects confirmed by a cough provocation test). Subjects with a history of stress incontinence that is currently treated (e.g., remote history of surgery for stress incontinence) may be included as long as they pass cough provocation test.
5. Subject has an indwelling catheter or practices intermittent self-catheterization.
6. Subject has evidence of Urinary Tract Infection (UTI). Urine cultures and sensitivity will be performed for positive leukocytes, or nitrites, or turbidity, or at the investigator's discretion, and will be confirmed with a culture greater than 100,000 cfu/mL. If a subject has a UTI, at Screening (Visit 1) the subject can be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).
7. Subject has a chronic inflammatory condition such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs (i.e., within the confines of the pelvis including the bladder and rectum in both sexes and the uterus, ovaries and fallopian tubes in females; organs of the lower gastrointestinal tract are not necessarily considered pelvic organs as the distal ascending colon, the full transverse colon and proximal portion of the descending colon are in the abdomen).
8. Subject resides in a nursing home.
9. Subject is likely to enter a hospital or nursing home due to a medical instability within the next 6 months in the opinion of the Investigator.
10. Subject has received intravesical injection in the past 12 months with botulinum toxin, resiniferatoxin, or capsaicin.
11. Subject has received electro-stimulation therapy for OAB (e.g., sacral nerve stimulation or PTNS).
12. Subject began or has changed a bladder training program or pelvic floor exercises less than 30 days prior to Screening.
13. Subject has moderate or severe hepatic impairment defined as Child-Pugh Class B or C.
14. Subject has severe renal impairment defined as estimated creatinine clearance less than 29 mL/min determined by Estimated Glomerular Filtration Rate (eGFR, Cockroft-Gault, or MDRD formulae). A subject with end stage renal disease or undergoing dialysis is also not a candidate for the study.

15. Subject has severe uncontrolled hypertension, which is defined as a sitting systolic blood pressure greater than or equal to 180 mmHg and/or diastolic blood pressure greater than or equal to 110 mmHg.
16. Subject has evidence of QT prolongation on ECG defined as QTc greater than 450 msec for males, QTc greater than 470 msec for females or a known history of QT prolongation.
17. Subject has a clinically significant ECG abnormality, as determined by the Investigator.
18. Subject has AST or ALT greater than 2x upper limit of normal (ULN), or γ-GT greater than 3x ULN and considered clinically significant by the Investigator.
19. Subject has a hypersensitivity to any components of mirabegron, other β-AR agonists, or any of the inactive ingredients.
20. Subject has any clinically significant condition, which in the opinion of the Investigator makes the subject unsuitable for study participation.
21. Subject has been treated with an experimental device within 28 days or received an investigational agent within 28 days or 5 half-lives, whichever is longer, prior to Screening.
22. Subject has a concurrent malignancy or history of any malignancy (within the past 5 years), except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully.
23. Subjects with current history of alcohol and/or drug abuse.
24. Subject is using prohibited medications which cannot be stopped safely during the period defined in Appendix 1.
25. Subject has stopped, started or changed the dose of a restricted medication (defined in Appendix 1) within the last 30 days prior to Screening.
26. Subject is involved in the conduct of the study as an employee of the Astellas group, third party associated with the study, or the study site team.
27. Subject has previously received mirabegron.

Exclusion Criteria assessed after placebo run-in period at Visit 3 (Baseline):

1. Subject fulfills any exclusion criteria of Visit 1 (subject does not need to repeat screening assessments [PVR, cough provocation test, chemistry/hematology/urinalysis]).
2. Subject was non-compliant during 2-week placebo run-in period, defined as taking less than 80% and greater than 120% of study medication.
3. Subject has any systolic blood pressure measurement ≥ 180 mmHg or diastolic blood pressure measurement ≥ 110 in the 3-day diary or during the baseline visit.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENTS

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug

Mirabegron will be supplied as 25 mg and 50 mg OCAS (Oral Controlled Absorption System) modified release tablets.

Mirabegron OCAS tablets contain the following excipients: [redacted]

The mirabegron OCAS tablets are packaged in 30 cc round wide mouth white HDPE bottles sealed with white child resistant polypropylene caps. Each bottle contains 30 tablets and must be stored at room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

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

4.1.2 Placebo

The placebo to match (PTM) mirabegron OCAS tablets contain [redacted]

The mirabegron PTM tablets are packaged in a 30 cc round wide mouth white HDPE bottles sealed with white child resistant polypropylene caps. Each bottle contains 30 tablets. The HDPE bottles must be stored at room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person(s) at Astellas U.S. Technologies, Inc. (AUST) in accordance with AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the Investigator to ensure that study drug deliveries from the Sponsor are received by a responsible person designated by the Investigator (e.g. pharmacist, study coordinator), and

- that such deliveries are recorded
- that study drug is handled and stored safely and properly
- that study drug is only dispensed to study subjects in accordance with the protocol
- that any unused study drug is returned to the Sponsor or standard procedures for the alternative disposition of unused study drug are followed and authorized by Astellas.

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

- The Investigator agrees not to supply study drugs to any persons except the subjects in this study.
- The Investigator/pharmacist will keep the study drugs in a locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the Investigator to dispense these test drugs.
- A study drug inventory will be maintained by the Investigator/pharmacist. The inventory will include details of material received, a clear record of when they were dispensed and to which subject, and when and how much was returned by each subject.
- At the conclusion or termination of this study, the Investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

4.4 Blinding

4.4.1 Blinding Method

This is a randomized, double-blind, parallel group study. Subjects will be assigned to a treatment group in the order which they meet the criteria for randomization. After the completion of the 2-week placebo run-in period, subjects will be randomized to either 25 mg mirabegron or placebo for 12 weeks of treatment. Subjects will receive their allocated treatment according to a computer-generated randomization schedule prepared by the Sponsor or designee prior to the start of the study. The subject, Investigator and Sponsor will not be aware of the treatment regimen.

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

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

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

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

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

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

4.4.4 Breaking the Treatment Code for Emergency

Breaking the treatment code, or unblinding of an individual subject's treatment assignment, may be done only for reasons relating to subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. As noted in Section 4.4.3, the reason to break the blind must be discussed with the Astellas Study Physician prior to unblinding.

After receiving authorization for unblinding from the Sponsor, the Investigator will utilize the interactive response technology (IRT) system to unblind. Unblinding through the interactive system may only be done by the designated individuals at the site.

If it becomes necessary to break the code during the study, the date, time and reason will be recorded in the subject's Electronic Case Report Forms (eCRF).

4.4.5 Breaking the Treatment Code by the Sponsor

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

4.5 Assignment and Allocation

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

Subjects who meet all the inclusion and none of the exclusion criteria will enter a 2-week placebo run-in period (Visit 2). At Visit 3 (Baseline), subjects will be randomly assigned to receive 25 mg mirabegron or placebo using a 1:1 randomization schedule.

To obtain the randomized treatment, the Investigator or designee will utilize a web or phone-based IRT, available seven days a week and 24 hours a day. After submitting certain information about the eligible subject, the randomized drug assignment will be provided by the IRT. Study drug assignment will remain blinded to all staff. Study drug will be packaged in bottles. Each study drug bottle will be preprinted with a Medication ID number. The Medication ID number assigned to the subject will be noted in the electronic case report form (eCRF) for study drug.

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

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drugs and Other Medications

5.1.1 Dose/Dose Regimen and Administration Period

Subjects will be randomized to one of two treatment groups in a 1:1 ratio to either mirabegron or placebo (PBO). Randomization will be stratified by age < 75 years and ≥ 75 years. Those subjects randomized to mirabegron will start at 25 mg and may increase to 50 mg after 4 weeks or 8 weeks based on based on individual subject efficacy, tolerability and Investigator discretion. Those subjects randomized to PBO will start blinded product matched to the mirabegron 25 mg tablet and may also increase to 50 mg PBO after 4 or 8 weeks. Once a patient has increased dose, they will remain on that dose for the remainder of the study unless for safety reasons that require discontinuation of study drug.

5.1.2 Previous and Concomitant Medication (Drugs and Therapies)

5.1.2.1 Previous Medication (Drugs and Therapies)

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

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

5.1.2.2 Concomitant Medication (Drugs and Therapies)

Concomitant medications will be captured from Screening (Visit 1) through the Follow-up Phone Call (Visit 7/Week 16).

Prohibited Medications

Medications prohibited between Screening (Visit 1) and Week 12/End of Treatment (Visit 6) include anticholinergics, antispasmodics, and CYP2D6 substrates with narrow therapeutic index (see Appendix 1, Part A). These medications must have been discontinued at least 30 days prior to Screening (Visit 1). Current or previous use of mirabegron at any time is prohibited. This list is not inclusive of all possible prohibited medications. In case of doubt, the Investigator must contact the local study monitor.

Restricted Medications

Medications restricted between Screening (Visit 1) and Week 12/End of Treatment (Visit 6) include loop diuretics, alpha blockers and 5-Alpha reductase inhibitors. All medications in Part B of Appendix 1 are permitted provided the subject has been taking this medication on a long-term basis, i.e., has not stopped, or started or changed dose within the 30 days prior to Screening (Visit 1), no new drug of the same class has been added to the regimen within the

30 days prior to Screening (Visit 1), and the subject remains on the medication at the same dose during the course of the study.

Restricted Non-Drug Therapy

Subjects participating in any behavioral modification therapy (i.e., pelvic floor exercises, Kegel exercises, biofeedback, timed voiding, etc.) or other non-drug therapy must have started the therapy at least 30 days prior to Screening (Visit 1) and must continue the same schedule through Week 12/End of Treatment (Visit 6).

5.1.3 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug at each monthly visit after baseline. When study drug is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be documented.

If compliance is less than 80% or more than 120%, the Investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects who are less than 80% or more than 120% compliant with the dosage regimen for any two consecutive visit periods during the study should be withdrawn from the study.

5.1.4 Emergency Procedures and Management of Overdose

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, adverse events reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 bpm (3 of 6 subjects). Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers. Treatment for overdosage must be symptomatic and supportive. In the event of overdosage, pulse rate, blood pressure and ECG monitoring is recommended.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

The subject's date of birth, sex, race, ethnicity, height, and weight will be recorded at Screening (Visit 1).

5.2.2 Medical History

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

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

A detailed OAB history for each subject will be obtained at Screening (Visit 1).

5.3 Efficacy

5.3.1 Patient Diary - Micturition and Incontinence

During the study, subjects will be requested to complete a 'Subject diary' which will be implemented on an electronic handheld device. This diary will collect data on micturition and incontinence. The information from the diaries will be used to evaluate the efficacy of treatment. Therefore, subjects will receive full instructions and training on how to complete the diary at Visit 2 (Placebo Run-In) and will be counseled on the importance of completing the diaries prior to the next visit. The training diary will be reviewed with the subject by the Investigator or designee to ensure accuracy and completion. The diaries and questionnaires will be reviewed during each visit after Visit 2 (Placebo Run-In) by the Investigator or designee to ensure accuracy of completion.

Diaries will be completed 3 consecutive days prior to each visit: Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6). During this activity, the subject will not come to the clinic for a visit. Site staff will contact the subject 3 days prior to the scheduled Visit to remind the subject they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable).

A diary day starts at midnight and ends at midnight the following day. Time to bed with intention to sleep, time to awake with intention of staying awake, type of episode (urination/incontinence), time of episode, urgency severity (see Section 5.3.4), measure of urine volume voided, and sleep interruption will be recorded by the subject in the micturition diary.

At Visit 3, diary data, including the frequency of micturition (urination episodes) urgency episodes (grade 3 and 4) and incontinence episodes per 24 hours, will be reviewed to confirm inclusion criteria.

Micturitions will be counted as only urination episodes and not episodes of incontinence.

In addition to the micturition information, the electronic diary will also collect time of medication intake.

5.3.2 Barthel Index of Activities of Daily Living

The Barthel Index consists of 10 items that measure a person's daily functioning; specifically the activities of daily living and mobility.

The Barthel Index will be completed at Baseline (Visit 3) and Week 12/End of Treatment (Visit 6).

5.3.3 Vulnerable Elders Survey

The Vulnerable Elders Survey (VES-13) is a simple function-based tool for screening community-dwelling populations to identify older persons at risk for health deterioration.

The VES considers age, self-related health, limitation in physical function, and functional disabilities.

The Vulnerable Elders Survey will be completed at Baseline (Visit 3) and Week 12/End of Treatment (Visit 6).

5.3.4 Patient Perception of Intensity of Urgency Scale

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

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

0 – No urgency, I felt no need to empty my bladder, but did so for other reasons.

1 – Mild urgency, I could postpone voiding as long as necessary, without fear of wetting myself.

2 – Moderate urgency, I could postpone voiding for a short while, without fear of wetting myself.

3 – Severe urgency, I could not postpone voiding, but had to rush to the toilet in order not to wet myself.

4 – Urge incontinence, I leaked before arriving at the toilet.

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

OAB has significant effects on health-related quality of life (QoL) of the afflicted subjects. This has been quantified in various empirical studies [Wall et al, 1993]. QoL is determined by socio-demographic, clinical, psychological and social factors. This underlines the importance of assessing the perceptions of subjects themselves when evaluating the effects of medical or pharmacological treatment. This is done in QoL research, also in the OAB field [Palmtag 2004]. In this study, the Overactive Bladder-questionnaire (OAB-q), the Patient Perception of Bladder Condition (PPBC), TS-VAS, and University of Alabama – Birmingham Life Space Assessment (UAB-LSA) will be utilized.

5.3.5.1 Overactive Bladder-questionnaire

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

The OAB-q will be assessed at Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6).

5.3.5.2 Patient Perception of Bladder Condition

The Patient Perception of Bladder Condition (PPBC) is a validated, global assessment tool using a 6-point Likert scale that asks subjects to rate their subjective impression of their current bladder condition [Coyne et al, 2006]. The PPBC questionnaire will be assessed at Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6).

5.3.5.3 Treatment Satisfaction – Visual Analog Scale

The Treatment Satisfaction – Visual Analog Scale (TS-VAS) is a visual analog scale that asks subjects to rate their satisfaction with the treatment by placing a vertical mark on a line that runs from 0 (No, not at all) to 10 (Yes, completely). The TS-VAS will be assessed at Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6).

5.3.5.4 University of Alabama, Birmingham Life Space Assessment

The University of Alabama, Birmingham (UAB) Study of Aging Life-Space Assessment (LSA) measures mobility in terms of the spatial extent of a person's life. The purpose of the Life-Space Assessment is to determine a person's usual pattern of mobility during the month preceding the assessment. Life-space is defined based upon the distance a person routinely travels to perform activities over this time frame. The UAB-LSA includes determining how far and how often the person leaves his or her place of residence and the degree of independence the person has.

Each level of life-space represents a distance further from the room where one sleeps.

0 = Mobility limited to the room where one sleeps

1 = Mobility limited to within one's dwelling

2 = Mobility limited to the space just proximal to one's personal living space (for instance, a porch, patio, or yard just outside the home or hallway outside of an apartment)

3 = Mobility limited to one's neighborhood

4 = Mobility limited to one's town

5 = Mobility outside one's town

The UAB-LSA will be assessed at Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6).

5.4 Safety Assessment

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

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

5.4.1 Vital Signs

Vital signs, including pulse rate and blood pressure, will be measured at all in-office visits according to Table 1, Schedule of Assessments.

The patient should be seated comfortably for at least 5 minutes with the back supported, feet on the floor, arm supported in a horizontal position, and the blood pressure cuff at heart level for each blood pressure measurement. The Investigator will use the same device and cuff size throughout the study. The same arm should be used throughout the study.

An AE of hypertension will be recorded if one of the following criteria is met on 2 or more consecutive visits:

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

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

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

5.4.2 Patient Diary - Subject Measurement Vital Signs

During Visit 2 (Placebo Run-In), the Investigator should instruct the subject on how to perform and document in the electronic diary the self-measurement of BP and PR. The subject will have an opportunity to familiarize him/herself with the self-measurement of BP and PR and recording of the data.

Diaries for vital signs (measured at home) will be completed in both am and pm for 3 consecutive days prior to each visit: Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6).

Validated devices for measuring BP and PR will be provided to subjects along with detailed operating instructions. The Investigator should measure the circumference of the upper arm in order to give the subject the device with the correct cuff type (Adult: 25-35 cm; Adult Plus: 33-40 cm arm circumference).

At home, according to the "The ABCD's of Blood Pressure Measurement" [American Heart Association, April 2012], the subject should rest for at least 5 minutes before taking the measurements. The subject should be quiet and relaxed, sitting in a chair with feet on the floor, legs should not be crossed, and arms should be bare and supported at heart level. The cuff should be put on according to the instructions of the Investigator. The subject should not move and should remain silent during the reading as moving and talking can affect the reading.

The subject should measure his/her BP and PR in triplicate during the 3 consecutive days prior to the next visit, on the arm chosen from the Screening measurements. Measurements should be taken after waking up in the morning and again in the evening. The subject should ensure that the morning measurements of vital signs are taken before breakfast and before study medication intake.

Three readings should be taken at every occasion, each about 2 minutes apart.

The subject should keep adequate records of the readings. Date, time, systolic and diastolic BP, and PR should be documented in the electronic diary. The subject should take care to have a 30 minute rest after exercise or smoking or intake of caffeine or alcohol, prior to taking a measurement.

An AE of tachycardia should be reported if the mean am or pm PR in the resting state from subject reported measurements at home over the last 3 diary days is >100 bpm.

5.4.3 Montreal Cognitive Assessment

Montreal Cognitive Assessment (MoCA) will be assessed at Baseline (Visit 3) and Week 12/End of Treatment (Visit 6).

The MoCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points [Nasreddine et al, 2005].

5.4.4 Adverse Events

AE collection will begin from the time of informed consent and continue through the Follow-up Phone Call (Visit 7/Week 16). See **Section 5.5 Adverse Events and Other Safety Aspects** for information regarding adverse event collection and data handling.

5.4.4.1 Adverse Events of Possible Hepatic Origin

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

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

5.4.5 Laboratory Assessments

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

Table 3 Laboratory Assessments

Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Hematology	CBC Hemoglobin Hematocrit
Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Chemistry	Sodium Potassium Calcium Chloride Glucose Creatinine Alkaline phosphatase AST ALT GGT Total bilirubin Total protein Albumin INR
Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Urinalysis	Protein Glucose pH Blood Urine Culture*
[redacted]	[redacted]	[redacted]

* Urine culture and sensitivity will be performed for positive leukocytes, or nitrites, or turbidity, or at the discretion of the PI.

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

5.4.6 Physical Examination

The subject will have a physical examination performed at Screening (Visit 1) and Week 12/End of Treatment (Visit 6). This includes examination of main body systems. Date

of physical examination and any clinically relevant adverse changes will be recorded as an AE in the eCRF (see Section 5.5.1).

5.4.7 Electrocardiogram (ECG)

A 12-lead ECG will be recorded at Screening (Visit 1), the Placebo Run-In (Visit 2), Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6). ECGs will be taken with the subject in the sitting or supine position. The patient's sitting or supine position for the ECG should be consistent throughout the course of the study.

All tracings will be read locally by the Investigator to ensure patient safety and care management. Any abnormalities must be evaluated in clinical context (based on subject's medical history and concomitant medication) and the Investigator must determine if it is clinically significant. Clinically significant abnormalities must be reported as an AE.

5.4.8 Post-Void Residual Volume

Post-Void Residual (PVR) volume will be assessed by ultrasonography or bladder scan at Screening (Visit 1) and Week 12/End of Treatment (Visit 6).

5.4.9 Cough Provocation Test

The cough provocation test will be performed for female subjects at Screening (Visit 1). Female subjects will be asked to come to the clinic with a comfortably full bladder. With the subject in the supine position, the volume of urine in the bladder is measured by ultrasound. The bladder volume must exceed 100 mL for the assessment of stress incontinence. Subsequently the subject will be asked to cough vigorously in the standing position. An immediate loss of urine will confirm a clinical diagnosis of stress incontinence [Wall et al, 1993].

5.4.10 Follow-up Phone Calls to Patient

Subjects will be contacted 4 weeks after End of Treatment (Visit 6/Week 12) by telephone for a Follow-up Phone Call (Visit 7/Week 16) to assess concomitant medication and any adverse events that may have occurred following the end of treatment.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

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

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

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

Due to the study objective(s), design, and variables identified in Section 2 of the protocol and during the conduct of the study from the time of informed consent until the final study visit, lack of efficacy with the study medication intended to treat overactive bladder will not be submitted to a Health Authority as an expedited adverse event report.

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death,
- Is life threatening (an adverse event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death),
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly, or birth defect,
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious),
- Other medically important events.

Medical and scientific judgment must 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, must also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion).

All of the events of interest noted above should be recorded in the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and the SAE worksheet.

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

5.5.3 Criteria for Causal Relationship to the Study Drug

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

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

5.5.4 Criteria for Defining the Severity of an Adverse Event

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

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

5.5.5 Reporting of Serious Adverse Events (SAEs)

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

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

within 24 hours, the local drug safety contact should be informed by phone. Please fax the SAE Worksheet to:

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

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

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

The following minimum information is required:

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

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

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

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

5.5.6 Follow-up to Adverse Events

All adverse events occurring during the study are to be followed until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

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

5.5.7 Monitoring of Common Serious Adverse Events (SAEs)

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

5.5.8 Procedure in Case of Pregnancy

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

5.5.9 Emergency Procedures and Management of Overdose

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

5.5.10 Supply of New Information Affecting the Conduct of the Study

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

5.6 Test Drug Concentration

Not applicable.

5.7 Other Measurements, Assessments, or Methods

Not applicable.

5.8 Total Amount of Blood

Blood samples will be taken for the purposes of hematology and biochemistry analysis at Screening (Visit 1) and Week 12/End of Treatment (Visit 6). It is anticipated the total amount of blood taken will not exceed 20 mL.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

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

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

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

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

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

Subjects may also be discontinued for:

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

6.2 Discontinuation of the Site

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

6.3 Discontinuation of the Study

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

7 STATISTICAL METHODOLOGY

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

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

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

The End of Treatment (EOT) visit is defined as the last post-baseline visit at the end of the double-blind treatment period for which data is available. The EOT visit value for diary variables is the average or number of the diary measurements for Week 12, as applicable. If no Week 12 diary data measurements are available, then the last available earlier post-baseline average or number of the dairy measurements within a designated visit window will be used.

All statistical comparisons will be made using a two-sided test at $\alpha = 0.05$ significance level and confidence intervals will be reported with a coverage consistent with this significance level. Efficacy and safety variables will be summarized using descriptive statistics. Continuous variables will be summarized using mean, standard deviation (SD) or standard error (SE), minimum, median, maximum unless specified otherwise. Categorical variables will be described using absolute and relative frequency.

7.1 Sample Size

Sample Size Justification:

The co-primary endpoints for this study are change from baseline to end of treatment in the mean number of micturitions per 24 hours based on the 3-day micturition diary and change from baseline to end of treatment in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary.

The sample size calculation first of all evaluates the number of subjects needed to test the change from baseline to end of treatment in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary and then assesses whether this same sample size is adequate to test the change from baseline to end of treatment in the mean number of micturitions per 24 hours based on the 3-day micturition diary. The overall power is then calculated for the study based on these co-primary endpoints.

The sample size calculation for the change from baseline in the final visit mean number of incontinence episodes per 24 hours is based on nonparametric methods since the results from previous phase 2 and 3 studies indicated that the assumption of normality may not be valid. The results of these studies showed frequent ties for the number of episodes and therefore the sample size calculation is based on dividing this endpoint into 7 categories. The actual primary statistical analysis will not group the data. The categories are shown below together with the percentages occurring for placebo and mirabegron 50 mg as found in older adult

subjects (≥ 65 years of age) from North American sites in studies 178-CL-047 and 178-CL-074.

Table 4 Categories for Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours, for North America, ≥ 65 years

Mean Change Incontinence Category	Placebo N =185	Mirabegron 50 mg N=187
≤ -2.67	15.68%	16.04%
[-2.67, -2.00)	7.03%	9.09%
[-2.00, -1.33)	12.43%	22.46%
[-1.33, -0.67)	13.51%	9.63%
[-0.67, -0.34)	12.43%	11.76%
[-0.34, 0.33)	17.84%	20.86%
≥ 0.33	21.08%	10.16%

Based on the table above, the probability that a subject on mirabegron will respond better than a subject on placebo is 56.3% (nQuery 7.0). Based on a Wilcoxon (Mann-Whitney) rank-sum test that P(X<Y) = 0.5 (continuous outcome), 340 incontinent subjects per treatment group will yield 82% power with a 2-sided test at a significance level of 0.05.

The pivotal study showed a 0.796 mean (SD=2.7) reduction for mirabegron 50 mg compared to PBO in the mean number of micturition per 24 hours in North American subjects who were 65 years or older. A sample size of 340 subjects per treatment group will yield 97% power to detect a reduction of .796 in mean number of micturitions per 24 hours using a two-sided t-test at a significance level of 0.05 assuming a SD of 2.7 (nQuery 7.0).

Assuming 'Change from baseline in mean number of micturitions per day' and 'Change from baseline in mean number of incontinence episodes per day' are independent the overall power would therefore be 80%.

The historical data show at least 15% of the randomized subjects will drop out during the double-blind period. Consequently an additional 60 subjects per treatment group need be enrolled. This brings the total required incontinent subjects per treatment group to 400.

Based on the historical data a 20% failure rate is predicted due to lack of incontinence and another 10% failure due to a combination of drop out and placebo response during the run in period. Therefore a 30% screen failure rate is expected.

In order to randomize 800 subjects with incontinence it is expected that 1,150 subjects will need to be screened.

7.2 Analysis Set

7.2.1 Full Analysis Set - Incontinence (FAS-I)

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

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

The FAS-I will be used for the summary of all baseline characteristics, including demographics, disease state data, prior medications, prior medical history and a statistical analysis of efficacy endpoints and QoL instruments.

7.2.2 Per Protocol Set (PPS)

The PPS will include all subjects who meet the following criteria:

- Subjects in the FAS-I set,
- Completed the study without major deviations of the protocol.

These criteria will be used to capture relevant non-adherence to the protocol and will be defined in the SAP. The PPS will be a secondary analysis set for efficacy. Selected demographic and baseline characteristics may also be summarized for the PPS.

7.2.3 Safety Analysis Set (SAF)

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

7.3 Demographics and Other Baseline Characteristics

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

7.4 Analysis of Efficacy

A step-down gatekeeping procedure will be performed to control the type I error rate at the 0.05 significance level for the multiple endpoints of the co-primary efficacy variables of change from baseline to end of treatment in mean number of micturitions per 24 hours and mean number of incontinence episodes per 24 hours and the key secondary efficacy variable of change from baseline to end of treatment in mean volume voided per micturition. The hypotheses will be tested in the following order: mean number of micturitions per 24 hours, mean number of incontinence episodes per 24 hours and mean volume voided per micturition.

7.4.1 Analysis of Primary Variable

7.4.1.1 Primary Analysis

The primary analysis set for efficacy analyses will be the Full Analysis Set - Incontinence (FAS-I). The co-primary efficacy variables are Change from baseline to end of treatment in mean number of micturitions per 24 hours based on a 3-day micturition diary and Change from baseline to end of treatment in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary.

Mean number of micturitions per 24 hours

The hypothesis being tested for the mean number of micturitions per 24 hours can be stated as;

H_0: Mean change from baseline in number of micturitions per 24 hours at end of treatment is the same for placebo and mirabegron.

H_1: Mean change from baseline in number of micturitions per 24 hours at end of treatment is different for placebo and mirabegron.

Change from baseline to end of treatment in mean number of micturitions per 24 hours will be tested using a stratified Analysis of Covariance (ANCOVA) model. The response variable will be the mean change in number of micturitions episodes per 24 hours from baseline to the end of the study with treatment group and gender as fixed factors and baseline mean number of micturitions episodes per 24 hours as the covariate in the model. Age group (<75, ≥75) will be included as the stratification factor. As part of the ANCOVA results, LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided. Differences in LS means between mirabegron and placebo will be derived together with 95% CIs and p-values.

Mean number of incontinence episodes per 24 hours

The hypothesis being tested for the mean number of incontinence episodes per 24 hours can be stated as;

H_0: Mean change from baseline in number of incontinence episodes per 24 hours at end of treatment is the same for placebo and mirabegron.

H_1: Mean change from baseline in number of incontinence episodes per 24 hours at end of treatment is different for placebo and mirabegron.

In order to test for statistical differences in Change from baseline to end of treatment in mean number of incontinence episodes per 24 hours between mirabegron and placebo, a stratified rank Analysis of Covariance (ANCOVA) will be used. The response variable is the standardized ranks of change from baseline to end of treatment value in mean number of incontinence episodes per 24 hours. Treatment group and gender will be added as fixed factors in the model while the standardized ranks of mean number of incontinence episodes per 24 hours at baseline will be included as a covariate. Age group (<75, ≥75) will be included as the stratification factor. LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided using an ANCOVA model with the same dependent and independent variables but not using the rank scale for the mean number of incontinence episodes data.

7.4.1.2 Secondary Analysis

Residual plots will be produced to check the assumptions of the underlying statistical models for mean number of micturitions per 24 hours. If the fit of the models is questionable, the

dependent variable may be logarithmically transformed in order to improve the fit or a non-parametric analysis could be applied as a secondary analysis.

An additional test will be applied to test the probability of a subject on mirabegron responding better than a subject on placebo. A Wilcoxon-Mann-Whitney Ordered Category test will be used to achieve this. The categories for responses will be the same as the categories in the sample size section above.

The analysis of the primary variables will be performed for Visits 3, 4 and 5. The statistical tests applied will be the same as the test applied to the ones described in Section 7.4.1.1

All analysis may be repeated for the PPS which is considered secondary. Additional sensitivity analysis may be performed to assess the robustness of the primary analysis findings. Details will be included in the SAP.

Responder Analysis for Incontinence Episodes and Improvement in Patient Perception of Bladder Condition

Two responder analyses based on incontinence episodes will be performed using a logistic regression model including the same factors as the ANCOVA model. Odds ratios that compare treatment effect between mirabegron and placebo will be reported with 95% CIs. The two responder definitions are as follows:

- Zero Incontinence Episodes: A responder is defined as a subject with 0 incontinence episodes post-baseline.
- Reduction in Incontinence Episodes: A responder is defined as a subject with ≥ 50% decrease from baseline in mean number of incontinence episodes per 24 hours.

Sub-group Analysis

Sub-group analysis of the co-primary endpoints will be conducted using ANCOVA models with an interaction term. The interaction term will be the treatment arm and the subgroup. The sub-groups to be considered for the analysis will include;

- Age group
- Race
- Gender

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

7.4.2 Analysis of Secondary Variables

The key secondary efficacy variable will be the change from baseline to end of treatment in mean volume voided per micturition. The other secondary variables are:

- Change from baseline to end of treatment in symptom bother and total health related quality of life scores as assessed by OAB-q questionnaire, and

- Change from baseline to end of treatment in Patient Perception of Bladder Condition (PPBC).

Change from baseline to end of treatment in mean volume voided

Change from baseline to end of treatment in mean volume voided will be tested using a stratified Analysis of Covariance (ANCOVA) model. The response variable will be the mean change in mean volume voided from baseline to the end of the study with treatment group and gender as fixed factors and baseline mean volume voided as the covariate in the model. Age group (<75, ≥75) will be included as the stratification factor. As part of the ANCOVA results, LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided. Differences in LS means between mirabegron and placebo will be derived together with 95% CIs and p-values.

Sensitivity analysis

As a sensitivity analysis, a non-parametric test will be applied in investigating MVV. Differences in change from baseline to end of treatment in mean volume voided per micturition between mirabegron and placebo will be analyzed using a stratified rank ANCOVA model. The response variable will be the standardized ranks of the change from baseline to end of treatment in mean volume voided per micturition. Treatment group and gender will be fixed factors in the model while the standardized ranks of the baseline mean volume voided per micturition will be included as covariate. Age group (<75, ≥75) will be included as the stratification factor.

Change from baseline in symptom bother and total health related quality of life scores as assessed by OAB-q questionnaire.

Differences in change from baseline of symptom bother and total health related quality of life scores as assessed by OAB-q between mirabegron and placebo will be analyzed using a stratified ANCOVA model. The response variable will be the change from baseline in symptom bother and total health related quality of life scores. Treatment group and gender will be fixed factors in the model while the baseline symptom bother and total health related quality of life scores will be included as covariate. Age group (<75, ≥75) will be included as the stratification factor. As part of the ANCOVA results, LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided.

Change from Baseline in Patient Perception of Bladder Condition (PPBC)

Differences in change from baseline of PPBC between mirabegron and placebo will be analyzed using a stratified ANCOVA model. The response variable will be the change from baseline in PPBC. Treatment group and gender will be fixed factors in the model while the baseline symptom bother and total health related quality of life scores will be included as covariate. Age group (<75, ≥75) will be included as the stratification factor. As part of the ANCOVA results, LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided.

Responder Analysis for OAB-q and PPBC

A responder analysis will be performed for OAB-q at Week 12 or LOCF using a logistic regression model. This will be based on the change in percentage OAB-q from baseline. The definition of the categories of the response variable is based on the results of the OAB-q study by Coyne *et al*, 2007. The responder groups will be defined as follows:

A responder is a subject with a minimally important difference (MID) ≥ 10% change in OAB-q while a non-responder will be a subject with a MID < 10% change in OAB-q.

Two responder analyses will be performed for PPBC at Week 12 or LOCF using a logistic regression. Two logistic regression models will be fitted with binary response variables that are based on change from baseline in PPBC. The response variables will be categorized as follows;

- Improvement: ≥ 1 point improvement from baseline to post-baseline for PPBC
- Major improvement: ≥ 2 point improvement from baseline to post-baseline for PPBC

Logistic regression for the responder analysis will include treatment group, gender and baseline measurements as the explanatory variables.

7.4.3 Analysis of Other Variables

The analysis of change from baseline scores for the following additional efficacy endpoints will be analyzed in the same way as described for the mean number of micturitions, i.e., using a stratified ANCOVA including treatment (placebo and mirabegron) and genders a fixed factor and baseline as a covariate. Age group will be used as the stratification variable.

- Change from baseline in mean number of urgency episodes (grade 3 and/or 4)/24 hour
- Change from baseline in mean number of urgency incontinence episodes/24 hour
- Change from baseline in mean level of urgency
- Change from baseline in mean number of nocturia episodes/24 hour
- Change from baseline in subscale score from OAB-q scores
- Change from baseline in TS-VAS
- Change from baseline in University of Alabama, Birmingham - Life Space Assessment (UAB-LSA)

Responder analysis as defined by >= 50% reduction from baseline in mean number of incontinence episodes/24 hours from baseline or zero incontinence episodes post-baseline.

7.4.4 Exploratory Analysis

[redacted]

7.5 Analysis of Safety

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

this study with the exception of the change from baseline in Montreal Cognitive Assessment Test (MoCA) and for vital signs analysis.

Differences in change from baseline of MoCA scores between mirabegron and placebo will be analyzed using a stratified ANCOVA model. The response variable will be the change from baseline in MoCA scores. Treatment group and gender will be fixed factors in the model while the baseline symptom bother and total health related quality of life scores will be included as covariate. Age group (<75, ≥75) will be included as the stratification factor. As part of the ANCOVA results, LS means and two-sided 95% CIs for mean changes from baseline within each treatment group will be provided.

Vital Signs will be summarized by treatment group and by Home Based Blood Pressure Monitoring (HBPM) versus office based using descriptive statistics for baseline value, specified post-baseline time point values (Week 4, Week 8, Week 12/EOT), and change from baseline to each specified post-baseline time points. Office based and morning and evening blood pressure will be reported separately. For HBPM the first reading from each time period will be discarded and the subsequent two readings for each time period will be averaged over the 3-day diary. HBPM and office based monitoring will be reported separately (See Appendix 4).

7.5.1 Adverse Events

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

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

7.5.2 Laboratory Assessments

Laboratory variables (biochemistry, hematology, and urinalysis) will be descriptively summarized for Screening and Week 12/End of Treatment and change from Screening to End of Treatment will be summarized by treatment group.

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

Laboratory abnormalities will be evaluated based on the Potential Clinically Significant (PCS) laboratory criteria. For each laboratory PCS criterion, the number and percent of subjects who have a laboratory value meeting the PCS criteria during the double-blind

treatment period will be summarized by treatment group. The directions of changes (high or low) in PCS will be indicated in the tables.

7.5.3 Vital Signs

Pulse rate, systolic blood pressure, and diastolic blood pressure will be summarized by treatment group using descriptive statistics (mean, standard deviation, minimum, maximum and median) for baseline value, specified post-baseline time point values (Week 4, Week 8, and Week 12/EOT), and change from baseline to each specified post-baseline time points. The average change from baseline to end of treatment for each vital sign variable will be analyzed using the ANCOVA model with treatment group and gender as fixed factors and baseline vital sign value as covariate. Vital sign data will be analyzed separately based on the 3-day diary and the site assessment at each clinic visit. Change from baseline in vital sign variables will be analyzed using the same ANCOVA model as described for the analysis of change from baseline in mean number of micturitions per 24 hours. No p-values will be calculated.

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

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

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

7.5.4 Physical Examination

Physical examination will be listed by treatment group.

7.5.5 Electrocardiograms (ECG)

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

7.6 Analysis of Pharmacokinetics

Not applicable.

7.7 Analysis of Pharmacodynamics

Not applicable.

7.8 Protocol Deviations and Other Analysis

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

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

- PD1- Entered into the study even though the subject did not satisfy entry criteria
- PD2- Developed withdrawal criteria during the study and was not withdrawn
- PD3- Received wrong treatment or incorrect dose
- PD4- Received excluded concomitant treatment

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

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

No formal interim analysis is planned.

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

For efficacy variables and vital sign data, analysis at End of Treatment will take into account subjects who withdraw before Week 12 and therefore do not have measurements available for that visit. The End of Treatment analysis is a LOCF (last observation carried forward) approach.

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

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

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

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

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

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

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

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

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

8.1.2 Specification of Source Documents

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

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

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

8.1.3 Clinical Study Monitoring

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

8.1.4 Direct Access to Source Data/Documents

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

8.1.5 Data Management

Data management will be coordinated by the CRO appointed by the Sponsor in accordance with the CRO's standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. Coding of medical terms will be performed using MedDRA.

8.1.6 Protocol Deviations

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

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

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

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

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

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

The Investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

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

8.1.7 End of Study

The end of study in all participating countries is defined as the last subject's last visit.

8.2 Ethics and Protection of Subject Confidentiality

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

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent (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 IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

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

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

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

8.2.2 Ethical Conduct of the Study

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

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior

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

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

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

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

8.2.4 Subject Confidentiality

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

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

8.3 Administrative Matters

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

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains

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

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

8.3.2 Documents and Records Related to the Clinical Study

The Investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The Sponsor will notify the site/Investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The Investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

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

8.3.3 Protocol Amendment and/or Revision

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

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

If there are changes to the 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.

8.3.4 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which 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 Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating Investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

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

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

10 STUDY ORGANIZATION

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

Not applicable.

10.2 Other Study Organization

10.2.1 Cardiovascular Adjudication Committee

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

10.2.2 Neoplasm Adjudication Committee

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

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12 APPENDICES

12.1 Appendix 1: List of Prohibited and Restricted Concomitant Medications

Part A – Prohibited Medications

Use of these medications in any formulation is not permitted between Screening (Visit 1) and Week 12/End of Treatment (Visit 6). This list is not exhaustive. In case of doubt, the Investigator must contact the local study monitor. These medications must have been discontinued at least 30 days prior to Screening (Visit 1). Current or previous use of mirabegron at any time is prohibited.

Anticholinergics/Antispasmodics		
Atropine	Baclofen	Biperiden
Bentropine/Benzatropine	Clomipramine	Cyclobenzaprine
Darifenacin	Dicyclomine/Dicycloverine	Emepronium
Glycopyrronium/Glycopyrrolate	Fesoterodine	Flavoxate
Glycopyrolate	Hyoscine	Hyoscyamine
Ipratropium	Isopropamide	Meclozine
Orphenadrine	Otilonium	Oxybutynin
Oxyphencyclimine	Procyclidine	Propantheline
Propiverine	Scopolamine/(Butyl)hyoscine	Solifenacin
Tiotropium	Tolterodine	Trospium
CYP2D6 Substrates with Narrow Therapeutic Index		
Aripiprazole (neuroleptic)	Desipramine (TCA)	Donepezil (Acetylcholinesterase inhibitor)
Thioridazine (anti-psychotic)	Flecainide (anti-arrhythmic)	Propafenone (anti-arrhythmic)
Imipramine (TCA)	Tramadol (analgesic)	Venlafaxin (SNRI)
OAB Medications		
Mirabegron	Other medication if used to treat OAB	
Medications to Treat Dementia		
Donepezil	Rivastigmine	Galantamine
Memantine	Other medication if used to treat dementia	

Part B - Medications Permitted With Restrictions

Medications restricted between Screening (Visit 1) and Week 12/End of Treatment (Visit 6) include loop diuretics, alpha blockers and 5-Alpha reductase inhibitors. All medications in Part B of Appendix 1 are permitted provided the subject has been taking this medication on a long-term basis, i.e., has not stopped, or started or changed dose within the 30 days prior to Screening (Visit 1), no new drug of the same class has been added to the regimen within the 30 days prior to Screening (Visit 1), and the subject remains on the medication at the same dose during the course of the study.

Loop Diuretics		
Furosemide	Bumetanide	Piretanide
Alpha Blockers		
Alfuzosin	Doxazosin	Prazosin
Phenoxybenzamine	Phentolamine	Tamsulosin
Terazosin		
5-alpha Reductase Inhibitors		
Dutasteride	Finasteride	

12.2 Appendix 2: Liver Safety Monitoring and Assessment

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

Definition of Liver Abnormalities

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

	ALT or AST		Total Bilirubin
Moderate	> 3 x ULN	or	> 2 x ULN
Marked (Hy's Law)	> 3 x ULN	and	> 2 x ULN

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

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

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

Follow-up Procedures

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

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

Marked hepatic liver function abnormalities, in the absence of another etiology, may be considered an important medical event and reported as a Serious Adverse Event (SAE). The Astellas Study Physician must be contacted and informed of all subjects for whom marked hepatic liver function abnormalities possibly attributable to study drug are observed.

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

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

Study Discontinuation

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

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

Reference

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

12.3 Appendix 3: Most Common Serious Adverse Events

The following is a list of serious adverse events that the Sponsor considers to be associated with the disease state being studied. The list does NOT change your reporting obligations or prevent the need to report an adverse event meeting the definition of an SAE as detailed in Section 5.5.2 Definition of Serious Adverse Events (SAEs). The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events". You are required to follow the requirements detailed in Section 5.5.5 Reporting of Serious Adverse Events (SAEs).

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicate they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

Most Common SAEs for Mirabegron:

Serious adverse events reported by at least 2 patients and exceeding active control included cerebrovascular accident (0.4%) and osteoarthritis (0.2%). Serum ALT/AST increased from baseline by greater than 10-fold in 2 patients (0.3%) taking Mirabegron 50 mg, and these markers subsequently returned to baseline while both patients continued Mirabegron. In one study, serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with Mirabegron 50 mg, Mirabegron 100 mg and active control once daily, respectively. Neoplasms reported by 2 patients treated with Mirabegron 100 mg included breast cancer, lung neoplasm malignant and prostate cancer.

12.4 Appendix 4: Investigator Criteria for Hypertension

Investigator Criteria for Determining TEAE of Hypertension

During each office visit a systolic and diastolic blood pressure will be measured and Home Based Blood Pressure Monitoring results will be reviewed.

Home-Based Blood Pressure Monitoring is to consist of three readings approximately 2 minutes apart with the at home blood pressure device. The average for each vital sign parameter using the last 2 of the 3 readings from each measurement will be calculated programmatically as follows:

Average of self-measurement device (AVGSM) = (measurement 2 + measurement 3)/2

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

An AE of hypertension will be recorded if one of the following criteria is met on 2 consecutive visits:

1. If the average systolic blood pressure is ≥ 140 mmHg AND/OR the average diastolic blood pressure is ≥ 90 mmHg at two consecutive visits after Baseline (Visit 3) in subjects who were normotensive (average systolic blood pressure < 140 mmHg and average diastolic blood pressure < 90 mmHg [WHO-ISH, 2003]) at Baseline (Visit 3).

2. If the average systolic blood pressure is increased >20mmHg AND/OR the average diastolic blood pressure is increased > 10 mmHg at two consecutive visits as compared to Baseline (Visit 3) in subjects with hypertension at Baseline (Visit 3).

3. If treatment with antihypertensive drugs is initiated for treatment of hypertension or if the dose of prior antihypertensive drugs is increased due to an increase in blood pressure.

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

12.5 Appendix 5: Investigator Criteria for Tachycardia

Investigator Criteria for Determing TEAE of Tachycardia

Tachycardia is defined as a rest heart frequency > 100 beats per minute (bpm) measured as pulse rate. Based on pulse rate measurements taken by the subject with the self-measurement device and recorded in the 3-day diary, if the mean am and/or pm pulse rate in the resting state was > 100 bpm over the prior 3 days, the Investigator is to record an AE of tachycardia. However, if the Investigator's clinical assessment was that this did not constitute an AE of tachycardia, then an AE will not be recorded.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 2

I. The purpose of this amendment is:

Substantial Change
1. Addition of home based vital sign measurements.
DESCRIPTION OF CHANGE:
The addition of home based vital signs (sitting systolic and diastolic blood pressure and pulse rate) will be measured in the am and pm and recorded into the 3-day diary.
RATIONALE:
The addition of home based vital sign measurement provides additional safety data to be collected regarding effects of mirabegron and hypertension.

Non-Substantial Changes
1. Updated Sponsor Name
DESCRIPTION OF CHANGE:
The sponsor affiliation of Astellas Scientific & Medical Affairs (ASMA) was updated to Astellas Pharma Global Development, Inc. (APGD), Medical Affairs, Americas.
RATIONALE:
Astellas Scientific & Medical Affairs is now called Astellas Pharma Global Development, Inc., Medical Affairs, Americas.
2. Edited the definition for the exclusion criteria #1 of bladder outlet obstruction (BOO).
DESCRIPTION OF CHANGE:
Clarification for the exclusion criteria #1 of subjects with BOO was updated to be subjects who have ongoing symptoms of BOO or have a history of BOO, that is not well-controlled.
RATIONALE:
These statements were added to provide further clarification to the sites regarding exclusion of BOO.
3. Edited the exclusion criteria #4 for stress incontinence.
DESCRIPTION OF CHANGE:
Clarification for the exclusion criteria #4 of subjects with a history of stress incontinence may be included as long as they pass the cough provocation test.
RATIONALE:
This statement was added to provide further clarification to sites regarding exclusion of subjects with regards to stress incontinence.

4. Updated urinary tract infection (UTI), urine cultures and sensitivity (exclusion criteria #6).
DESCRIPTION OF CHANGE:
Clarification of the determination of UTI and when urine cultures and sensitivity would be conducted.
RATIONALE:
Additional urinalysis criteria were necessary to trigger appropriate urine culture and sensitivity procedures.
5. Updated the definition of creatinine clearance (exclusion criteria #14).
DESCRIPTION OF CHANGE:
Clarified renal impairment is defined as estimated creatinine clearance (determined by Estimated Glomerular Filtration Rate [eGFR] or Cockroft-Gault or MDRD formulae) less than 29 mL/min.
RATIONALE:
These statements were added to provide further clarification to the sites that a 24-hour urine was not required to measure creatinine clearance.
6. Edited QTcF to QTc (exclusion criteria #16).
DESCRIPTION OF CHANGE:
Removed the requirement to use QTcF to calculate QT prolongation (exclusion criteria #16).
RATIONALE:
Local ECG machines are used for the study and most sites were unable to provide the correction factor used on their machines. Some use Bazetts, not all sites will utilize the QTc corrected by the Fredericia method.
7. Removed exclusion criteria for completion of all 3-day micturition diaries.
DESCRIPTION OF CHANGE:
Exclusion criteria 3. Subject did not complete all 3 days of the 3-day micturition diary.
RATIONALE:
Subjects will be asked to complete 3-day micturition diaries, but the completion of all 3 days as an inclusion criterion will no longer be be required. This will be consistent with other previous Astellas mirabegron clinical trials.
8. Updated Identification of Investigational Product(s)
DESCRIPTION OF CHANGE:
Manufacturing of test and placebo by Astellas Pharma Technologies, Inc. and packaging of aluminum blisters have been removed.
RATIONALE:
The information provided in the protocol is not correct- it had been carried over from another protocol. Astellas Pharma Technologies, Inc. is not manufacturing the test or placebo drugs.

In addition, the study product is only being provided in bottles and not with aluminum blisters. There is no change to the IP supply, just correction of the wording.
9. Updated Study Drug Handling
DESCRIPTION OF CHANGE:
The addition that any study drug handling procedures is authorized by Astellas.
RATIONALE:
This was an omission in the original protocol and provides additional clarification of the study drug handling.
10. Updated Prohibited Medications
DESCRIPTION OF CHANGE:
Current or previous use of mirabegron at any time was added to Prohibited Medication Appendix 1, part A.
RATIONALE:
Mirabegron was previously listed in Appendix A but adding the statement provides further clarification to the sites that current or previous use of mirabegron at any time is prohibited.
11. Updated Section V. Table 1.
DESCRIPTION OF CHANGE:
• Edited Baseline Visit Windows (Days) • Edited Visit Windows (Days) footnote • Added footnote for urine cultures and sensitivity • Added footnote for ultrasound or bladder scan measurement • Updated footnote to include measure of urine volume voided and sleep interruption will be recorded in the 3-day micturition diary.
RATIONALE:
These edits, additions and updates provide further clarification of study procedures that are elsewhere described in the protocol for the sites to provide easier scheduling, proper subject care, and necessary data collection. There is no change to the originally planned data collection.
12. Included measure of urine volume voided to be collected with the electronic diary.
DESCRIPTION OF CHANGE:
Table 1 Schedule of Assessments was updated to provide more specific information the ePRO device will record that in oversight left out of the original table. The addition included measure of urine volume voided and sleep interruption.
RATIONALE:
Addition of measure of urine volume voided is required to obtain data for the following secondary endpoint: • Change from baseline to the end of treatment in mean volume voided per micturition.

13. Added subjects to be contacted 3 days prior to visit in Patient Diary Instructions.
DESCRIPTION OF CHANGE:
Clarification was included in the Patient Diary description to include the subject is to be contacted 3 days prior to the scheduled Visit to remind the subject to complete the electronic diary, review completion instruction and review changes to concomitant medications and adverse events (if applicable).
RATIONALE:
The exact wording is extracted from the footnote of Table 1 Schedule of Assessments. There was an oversight to include it in Section 5.3.1 Patient Diary – Micturition and Incontinence.
14. Updated definition of an adverse event of hypertension.
DESCRIPTION OF CHANGE:
The definition that an adverse event of hypertension was updated to include that hypertension criteria needs to be met on 2 or more separate/consecutive visits.
RATIONALE:
This statement was added to provide further clarification and to the sites make it consistent throughout the protocol that the criteria of hypertension needed to be on consecutive visits and not any 2 visits throughout the course of the study.
15. Addition of INR in Table 3 Laboratory Assessment.
DESCRIPTION OF CHANGE:
Addition of INR in Table 3 Laboratory Assessment under Chemistry for Visit 1 and Visit 6.
RATIONALE:
Omission of INR in Table 3 was overlooked. INR is being analyzed and is specified in 12.2 Appendix 2: Liver Safety Monitoring and Assessment. It is already being collected and no increase in laboratory work is required.
16. Edited the positioning requirement for ECG measurement.
DESCRIPTION OF CHANGE:
Changed the positioning from sitting to either sitting or supine.
RATIONALE:
Subjects may not be able to be in the sitting position for an ECG due to anatomical or physical constraints. It is acceptable to have an ECG reading in either a sitting or supine position as long as the position is consistent throughout the study.

II. Amendment Summary of Changes:

Substantial Changes:

1. Addition of home based vital sign measurements.
III. List of Abbreviations and Key Terms, Page 11
ADDED:
HBPM Home based blood pressure monitoring **PR Pulse Rate**

1. Addition of home based vital sign measurements.
IV. Synopsis, Exclusion Criteria assessed after placebo run-in period at Visit 3 (Baseline), Page 18 *3.3 Exclusion Criteria, Exclusion Criteria assess after placebo run-in period at Visit 3 (Baseline), Page 38*
ADDED:
3. Subject has any systolic blood pressure measurement > 180 mmHg or diastolic blood pressure measurement > 110 in the 3-day diary or during the baseline visit.

1. Addition of home based vital sign measurements.
IV. Synopsis, Safety Variables, Page 20
ADDED:
• **Vital Signs: sitting systolic and diastolic blood pressure and pulse rate (home based measurements and office measurements**

1. Addition of home based vital sign measurements.
IV. Synopsis, Analysis on Secondary Endpoints, Page 24 *7.5.3 Vital Signs, Page 65*
ADDED:
• **Vital sign data will be analyzed separately based on the 3-day diary and the site assessment at each clinic visit. Change from baseline in vital sign variables will be analyzed using the same ANCOVA model as described for the analysis of change from baseline in mean number of micturitions per 24 hours. No p-values will be calculated.**

1. Addition of home based vital sign measurements.
V. Flow Chart and Schedule of Assessments – Table 1 Schedule of Assessments – Footnote, Page 26
WAS:

Visit
Day
Week
Visit Windows (Days) [a]

Informed Consent/HIPAA
Inclusion/Exclusion Criteria
Medical History and OAB History
Demographics
Enter 2-week Placebo Run-in [b]
Randomization [c]
Physical Exam (including height [d] and weight)
Vital Signs (includes pulse and blood pressure)
Cough Provocation test (Females only)
Serum chemistry, hematology & urinalysis
[redacted]
12-Lead ECG
Ultrasound or Bladder Scan (PVR)
Medication History and OAB Medication History
Clinical Assessment for Dose Increase
Concomitant Medications Assessment
Adverse Event Assessment
Dispense Study Drug
Drug Accountability
Instruct Subject on 3-day Micturition Diary [f]
Complete 3-day Micturition Diary including PPIUS [g]
OAB-q
Patient Perception of Bladder Condition Scores (PPBC)
TS-VAS
Montreal Cognitive Assessment Test (MoCA)
Univ Alabama Birmingham Life Space Assessment (UAB -LSA)

Table continues on next page

Barthel ADL Assessment
Vulnerable Elders Survey 13 (VES-13)
Review Subject Diary [i]

a. After Visit 2 (Placebo Run-In), visit windows/study days will be calculated based on the Visit 3 (Baseline) visit date.
b. Subjects must take at least 11 days, but no more than 17 days of placebo run-in medication.
c. Randomization is to occur after confirming all eligibility criteria and after performing all other visit procedures at Visit 3.
d. Height will only be assessed at the Screening Visit.
e. [redacted]
f. At Visit 2 (Placebo Run-In), all subjects will be provided with an ePRO device (electronic diary) that will be used to record the date and time of each of their micturitions, incontinence, and urgency episodes (micturition diary). Additionally, the diary will be used to record medication intake. Training on device use must be done at Visit 2 (Placebo Run-In) and as necessary throughout the study. Subjects will be instructed to begin completing the electronic micturition diary 3 days prior to each in-office study visit including Visits 3-6 (Treatment Period) and complete the diary for the full 3 days.
g. Subjects will complete the electronic micturition diary 3 days prior to the study visit and complete the diary for the full 3 days leading up to the visit.
h. During this activity, the subject will not come to the clinic for a visit. Site staff will contact the subject 3 days prior to the scheduled Visit to remind the subject they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable). The subject will need to complete the 3-day micturition electronic diary at

home the full 3 days leading up to Visits 3, 4, 5 & 6.

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

IS AMENDED TO:

Visit
Day
Week
Visit Windows (Days) [a]
Informed Consent/HIPAA
Inclusion/Exclusion Criteria
Medical History and OAB History
Demographics
Enter 2-week Placebo Run-in [b]
Randomization [c]
Physical Exam (including height [d] and weight)
Vital Signs – **in office** (includes pulse and blood pressure)
Cough Provocation test (Females only)
Serum chemistry, hematology & urinalysis [e]
[redacted]
12-Lead ECG
Ultrasound or Bladder Scan (PVR)
Medication History and OAB Medication History
Clinical Assessment for Dose Increase
Concomitant Medications Assessment
Adverse Event Assessment
Dispense Study Drug
Drug Accountability
Instruct Subject on 3-day Micturition Diary [g]
Complete 3-day Micturition Diary including **Vital Sign measurements and** PPIUS [h,i]
OAB-q
Patient Perception of Bladder Condition Scores (PPBC)
TS-VAS
Montreal Cognitive Assessment Test (MoCA)
Univ Alabama Birmingham Life Space Assessment (UAB -LSA)

Table continues on next page

Barthel ADL Assessment
Vulnerable Elders Survey 13 (VES-13)
Review Subject Diary [j]

a. **Visits 1 and 2 are negatively scheduled from the Baseline (Visit 3) date. A subject has a combined timeframe of up to 38 days to complete both Visits 1 and 2; however, Baseline (Visit 3) must occur at least 18 days but no more than 38 days after Visit 1 (Screening) and at least 11 days but no more than 17 days after Visit 2 (Placebo Run-In).** After Visit 2 (Placebo Run-In), visit windows/study days will be calculated based on the Visit 3 (Baseline) visit date. **Study procedures (e.g. bladder scan) for a particular visit do not need to be completed on the visit date if this is not feasible for the subject, as long as, study procedures are performed per protocol within the applicable visit window. Any procedure not done or performed outside the applicable visit window will be noted as a protocol deviation.**

b. Subjects must take at least 11 days, but no more than 17 days of placebo run-in medication.

c. Randomization is to occur after confirming all eligibility criteria and after performing all other visit procedures at Visit 3.
d. Height will only be assessed at the Screening Visit.
e. Urine culture and sensitivity will be performed for positive leukocytes, or nitrites, or turbidity, or at the discretion of the PI. If a subject has a UTI, the subject can be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).
f. [redacted]
g. At Visit 2 (Placebo Run-In), all subjects will be provided with an ePRO device (electronic diary) that will be used to record the date and time of each of their micturitions, incontinence, urgency episodes, **measure of urine volume voided, and sleep interruption** (micturition diary). Additionally, the diary will be used to record medication intake **and home measurements of am and pm pulse rate and systolic and diastolic blood pressure**. Training on device use must be done at Visit 2 (Placebo Run-In) and as necessary throughout the study. Subjects will be instructed to begin completing the electronic micturition diary 3 days prior to each in-office study visit including Visits 3-6 (Treatment Period) and complete the diary for the full 3 days.
h. Subjects will complete the electronic ~~micturition~~ diary 3 days prior to the study visit and complete the diary for the full 3 days leading up to the visit.
i. During this activity, the subject will not come to the clinic for a visit. Site staff will contact the subject 3 days prior to the scheduled Visit to remind the subject they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable). The subject will need to complete the 3-day ~~micturition~~ electronic diary at home the full 3 days leading up to Visits 3, 4, 5 & 6.
j. Investigator, or designee, must review the subject's diary with the subject to ensure completion compliance and discuss data captured.

1. Addition of home based vital sign measurements.

5.4.1 Vital Signs, Page 47

ADDED:

5.4.2 Patient Diary – Subject Measurement Vital Signs

During Visit 2 (Placebo Run-In), the Investigator should instruct the subject onhow to perform and document in the electronic diary the self-measurement of BP and PR. The subject will have an opportunity to familiarize him/herself with the self-measurement of BP and PR and recording of the data.

Diaries for vital signs (measured at home) will be completed in both am and pm for 3 consecutive days prior to each visit: Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment (Visit 6).

Validated devices for measuring BP and PR will be provided to subjects along with detailed operating instructions. The Investigator should measure the circumference of the upper arm in order to give the subject the device with the correct cuff type (Adult: 25-35 cm; Adult Plus: 33-40 cm arm circumference).

At home, according to the "The ABCD's of Blood Pressure Measurement" [American Heart Association, April 2012], the subject should rest for at least 5 minutes before taking the measurements. The subject should be quiet and relaxed, sitting in a chair with feet on the floor, legs should not be crossed, and arms should be bare and supported at heart level. The cuff should be put on according to the instructions of the Investigator. The subject should not move and should remain silent during the reading as moving and talking can affect the reading.

The subject should measure his/her BP and PR in triplicate during the 3 consecutive days prior to the next visit, on the arm chosen from the Screening measurements.

Measurement should be taken after waking up in the morning and again in the evening. The subject should ensure that the morning measurements of vital signs are taken before breakfast and before study medication intake. **Three readings should be taken at every occasion, each about 2 minutes apart.** **The subject should keep adequate records of the readings. Date, time, systolic and diastolic BP, and PR should be documented in the electronic diary. The subject should take care to have a 30 minute rest after exercise or smoking or intake of caffeine or alcohol, prior to taking a measurement.** **An AE of tachycardia should be reported if the mean am or pm PR in the resting state from subject reported measurements at home over the last 3 days is >100 bpm.**

1. Addition of home base vital sign measurements.
5.4.1 Vital Signs, Page 48
WAS:
An AE of hypertension will be recorded if one of the following criteria is met on >= 2 separate/consecutive visits: 1. If the average systolic blood pressure is > 140 mmHg AND/OR the average diastolic blood pressure is > 90 mmHg at two consecutive visits after Baseline (Visit 3) in subjects who were normotensive (average systolic blood pressure < 140 mmHg and average diastolic blood pressure < 90 mmHg [WHO-ISH, 2003]) at Baseline (Visit 3). 2. If the average systolic blood pressure is increased > 20 mmHg AND/OR the average diastolic blood pressure is increased > 10 mmHg at two consecutive visits as compared to Baseline (Visit 3) in subjects with hypertension at Baseline (Visit 3). 3. If treatment with antihypertensive drugs is initiated for treatment of hypertension or if the dose of prior antihypertensive drugs is increased due to an increase in blood pressure. An AE of tachycardia should be considered if resting heart frequency (pulse rate) is > 100 bpm.
IS AMENDED TO:
An AE of hypertension will be recorded if one of the following criteria is met on ~~>~~ 2 **or more** ~~separate/~~consecutive visits: 1. If the average systolic blood pressure is > 140 mmHg AND/OR the average diastolic blood pressure is > 90 mmHg at two consecutive visits after Baseline (Visit 3) in subjects who were normotensive (average systolic blood pressure < 140 mmHg and average diastolic blood pressure < 90 mmHg [WHO-ISH, 2003]) at Baseline (Visit 3). 2. If the average systolic blood pressure is increased > 20 mmHg AND/OR the average diastolic blood pressure is increased > 10 mmHg at two consecutive visits as compared to Baseline (Visit 3) in subjects with hypertension at Baseline (Visit 3). 3. If treatment with antihypertensive drugs is initiated for treatment of hypertension or if the dose of prior antihypertensive drugs is increased due to an increase in blood pressure.

An AE of "increased" Blood Pressure should be considered if the above conditions are not met, but a high blood pressure is recorded." An AE of tachycardia should be considered if resting heart frequency (pulse rate) is > 100 bpm.

1. Addition of home based vital sign measurements.
7.5 Analysis of Safety, Page 63
WAS:
Safety analysis will be performed for adverse events (AEs) and vital signs using the SAF. No inferential comparison between treatment groups will be performed for the safety analysis in this study with the exception of the change from baseline in Montreal Cognitive Assessment Test (MoCA).
IS AMENDED TO:
Safety analysis will be performed for adverse events (AEs) and vital signs using the SAF. No inferential comparison between treatment groups will be performed for the safety analysis in this study with the exception of the change from baseline in Montreal Cognitive Assessment Test (MoCA) **and for vital signs analysis**.

1. Addition of home based vital sign measurements.
7.5 Analysis of Safety, Page 63
WAS:
Vital signs will be summarized by treatment group using descriptive statistics for baseline value, specific post-baseline time point values (Week 4, Week 8, Week 12/EOT), and change from baseline to each specified post-baseline time points.
IS AMENDED TO:
Vital signs will be summarized by treatment group **and by Home Based Blood Pressure Monitoring (HBPM) versus office based** using descriptive statistics for baseline value, specific post-baseline time point values (Week 4, Week 8, Week 12/EOT), and change from baseline to each specified post-baseline time points. **Office based and morning and evening blood pressure will be reported separately. For HBPM the first reading from each time period will be discarded and the subsequent two readings for each time period will be averaged over the 3-day diary. HBPM and office based monitoring will be reported separately (See Appendix 4).**

1. Addition of home based vital sign measurements.
7.5.3 Vital Signs, Page 64
ADDED:
Details on the averaging of the multiple vital sign measurements are located in Appendix 4. Vital sign data will be analyzed separately based on the 3-day diary and the site assessment at each clinic visit. Change from baseline in vital sign variables will be analyzed using the same ANCOVA model as described for the analysis of

change from baseline in mean number of micturitions per 24 hours. No p-values will be calculated.

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

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

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

1. Addition of home based vital sign measurements.
11 REFERENCES, page 74
ADDED:
The ABCD's of Blood Pressure Measurement. American Heart Association, April 2012.

Non-Substantial Changes:

1. Updated Sponsor Name
Header and Footer *Section 14, Attachment 2: Sponsor Signatures*
WAS:
Sponsor ASMA
IS AMENDED TO:
Sponsor **APGD, Medical Affairs, Americas** ~~ASMA~~

1. Updated II. Contact Details of Key Sponsor's Personnel	
Title Page, Page 1 *II. Contact Details of Key Sponsor's Personnel, Page 9*	
WAS:	
24h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	[redacted]

	[redacted]
Clinical Research Contacts:	[redacted]
Study Physician:	[redacted]
IS AMENDED TO:	
24h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	[redacted]

	[redacted]
Clinical Research Contacts:	[redacted]
Study Physician:	[redacted]

2. Edited the definition for the exclusion criteria #1 of bladder outlet obstruction (BOO).
IV. Synopsis – Selection Criteria – Exclusion: Exclusion Criteria assessed at Visit 1 (Screening) *Section 3.3 – Exclusion Criteria: Exclusion Criteria assessed at Visit 1 (Screening), Page 37*
WAS:
1. Subject has symptoms suggestive of bladder outlet obstruction (BOO) or history of BOO.
IS AMENDED TO:
3. Subject has **ongoing** symptoms suggestive of bladder outlet obstruction (BOO) or history of BOO **that is currently not well controlled.**

3. Edited the exclusion criteria #4 for stress incontinence.
IV. Synopsis – Selection Criteria – Exclusion: Exclusion Criteria assessed at Visit 1 (Screening) *Section 3.3 – Exclusion Criteria: Exclusion Criteria assessed at Visit 1 (Screening), Page 37*
ADDED:
3. Subjects has significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor as determined by the Investigator (for female subjects confirmed by a cough provocation test). **Subjects with a history of stress**

incontinence that is currently treated (e.g. remote history of surgery for stress incontinence may be included as long as they pass cough provocation test.

4. Updated urinary tract infection (UTI), urine cultures and sensitivity (exclusion criteria #6).
IV. Synopsis – Selection Criteria – Exclusion: Exclusion Criteria assessed at Visit 1 (Screening) *Section 3.3 – Exclusion Criteria: Exclusion Criteria assessed at Visit 1 (Screening), Page 37*
WAS:
6. Subject has evidence of Urinary Tract Infection (UTI) (positive leukocyte esterase will be confirmed with a urine culture greater than 100,000 cfu/mL) as assessed at Screening (Visit 1). The subject can be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).
IS AMENDED TO:
6. Subject has evidence of Urinary Tract Infection (UTI). ~~(positive leukocyte esterase will be confirmed with a urine culture greater than 100,000 cfu/mL) as assessed at Screening (Visit 1).~~**Urine culture and sensitivity will be performed for positive leukocytes, or nitrites, or turbidity, or at the investigator's discretion and will be confirmed with a culture greater than 100,000 cfu/mL.** If a subject has a UTI at Screening (Visit 1) the subject can be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).

4. Updated urinary tract infection (UTI), urine cultures and sensitivity (exclusion criteria #6).
V. Flow Chart and Schedule of Assessments – Table 1 Schedule of Assessments – footnote, Page 26
ADDED:
e. Urine cultures and sensitivity will be performed for positive leukocytes, or nitrites, or turbidity, or at the discretion of the PI. If a subject has a UTI, the subject can be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).

4. Updated urinary tract infection (UTI), urine cultures and sensitivity (exclusion criteria #6).
5.4.4 Laboratory Assessments – Table 3 Laboratory Assessments footnote, Page 49
WAS:
*Urine culture will be done only for subjects with positive leukocyte esterase.
IS AMENDED TO:
*Urine culture ~~will be done only for subjects with positive leukocyte esterase~~**and sensitivity** will be done ~~only for subjects~~ **performed for positive leukocytes, or nitrites, or turbidity, or at the discretion of the PI.**

5. Updated the definition of creatinine clearance (exclusion criter1a #14).
IV. Synopsis – Selection Criteria – Exclusion: Exclusion Criteria assessed at Visit 1 (Screening) *Section 3.3 – Exclusion Criteria: Exclusion Criteria assessed at Visit 1 (Screening), Page 38*
WAS:
14. Subject has severe renal impairment defined as creatinine clearance less than 29 mL/min. A subject with end stage renal disease or undergoing dialysis is also not a candidate for the study.
IS AMENDED TO:
14. Subject has severe renal impairment defined as **estimated** creatinine clearance less than 29 mL/min **determined by Estimated Glomerular Filtration Rate (eGFR, Cockroft-Gault, or MDRD formulae)**. A subject with end stage renal disease or undergoing dialysis is also not a candidate for the study.

6. Edited QTcF to QTc (exclusion criteria #16).
IV. Synopsis – Selection Criteria – Exclusion: Exclusion Criteria assessed at Visit 1 (Screening) *Section 3.3 – Exclusion Criteria: Exclusion Criteria assessed at Visit 1 (Screening), Page 38*
WAS:
16. Subject has evidence of QT prolongation on ECG defined at QTcF greater than 450 msec for males, QTcF greater than 470 msec for females or known history of QT prolongation.
IS AMENDED TO:
16. Subject has evidence of QT prolongation on ECG defined as QTc~~F~~ greater than 450 msec for males, QTc~~F~~ interval greater than 470 msec for females or a known history of QT prolongation.

6. Edited QTcF to QTc (exclusion criteria #16).
7.5.5 Electrocardiograms (ECG), Page 64
WAS:
ECG variable (heart rate, PR interval, RR interval, QRS interval, QT interval and QTcF interval) will be summarized using frequency tables and percentages for each treatment group at Baseline, Week 4, Week 8, and Week 12/End of Treatment, including changes from baseline to end of treatment.
IS AMENDED TO:
ECG variable (heart rate, PR interval, RR interval, QRS interval, QT interval and QTc~~F~~ interval) will be summarized using frequency tables and percentages for each treatment group at Baseline, Week 4, Week 8, and Week 12/End of Treatment, including changes from baseline to end of treatment.

7. Removed exclusion criteria for completion of all 3-day micturition diaries.
IV. Synopsis – Selection Criteria – Exclusion: Exclusion Criteria assessed after placebo run-in period at Visit 3 (Baseline) *Section 3.3 – Exclusion Criteria: Exclusion Criteria assessed after placebo run-in period at Visit 3 (Baseline), Page 38*
DELETED:
~~3. Subject did not complete all 3 days of the 3-day micturition diary.~~

8. Updated Identification of Investigational Product(s)
4.1.1 Test Drug, Paragraph 4, Page 39
DELETED:
~~The clinical trial material of mirabegron OCAS tablets have been manufactured for Astellas by Astellas Pharma Technologies, Inc.~~

8. Updated Identification of Investigational Product(s)
4.1.2 Placebo, Paragraph 2, Page 39
DELETED:
~~The PTM mirabegron OCAS tablets have been manufactured for Astellas by Astellas Pharma Technologies, Inc.~~

8. Updated Identification of Investigational Products(s)
4.1.2 Placebo, Paragraph 3, Page 39
WAS:
The mirabegron PTM tablets are package in a 30 cc round wide mouth white HDPE bottles sealed with white child resistant polypropylene caps. Each bottle contains 30 tablets. Both the aluminum blisters and HDPE bottles must be stored at room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
IS AMENDED TO:
The mirabegron PTM tablets are package in a 30 cc round wide mouth white HDPE bottles sealed with white child resistant polypropylene caps. Each bottle contains 30 tablets. ~~Both the aluminum blisters and~~ **The** HDPE bottles must be stored at room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

9. Updated Study Drug Handling
4.3 Study Drug Handling, Paragraph 1, Bullet 4, Page 40
WAS:
• that any unused study drug is returned to the Sponsor or standard procedures for the alternative disposition of unused study drug are followed.
IS AMENDED TO:
• that any unused study drug is returned to the Sponsor or standard procedures for the alternative disposition of unused study drug are followed **and authorized by**

Astellas.

10. Updated Prohibited Medications

IV. Synopsis – Concomitant Medication – Prohibited Medications (Appendix 1, part A)
5.1.2.2 Concomitant Medications (Drugs and Therapies) – Prohibited Medications, Page 43
12.1 Appendix 1: List of Prohibited and Restricted Medications, Page 75

ADDED:

Current or previous use of mirabegron at any time is prohibited.

11. Updated Section V. Table 1.

V. Flow Chart and Schedule of Assessments – Table 1 Schedule of Assessments – Footnote, Page 26

WAS:

Visit
Day
Week
Visit Windows (Days) [a]
Informed Consent/HIPAA
Inclusion/Exclusion Criteria
Medical History and OAB History
Demographics
Enter 2-week Placebo Run-in [b]
Randomization [c]
Physical Exam (including height [d] and weight)
Vital Signs (includes pulse and blood pressure)
Cough Provocation test (Females only)
Serum chemistry, hematology & urinalysis
[redacted]
12-Lead ECG
Ultrasound or Bladder Scan (PVR)
Medication History and OAB Medication History
Clinical Assessment for Dose Increase
Concomitant Medications Assessment
Adverse Event Assessment
Dispense Study Drug
Drug Accountability
Instruct Subject on 3-day Micturition Diary [f]
Complete 3-day Micturition Diary including PPIUS [g]
OAB-q
Patient Perception of Bladder Condition Scores (PPBC)
TS-VAS
Montreal Cognitive Assessment Test (MoCA)
Univ Alabama Birmingham Life Space Assessment (UAB -LSA)
Table continues on next page
Barthel ADL Assessment

Vulnerable Elders Survey 13 (VES-13)
Review Subject Diary [i]

a. After Visit 2 (Placebo Run-In), visit windows/study days will be calculated based on the Visit 3 (Baseline) visit date.
b. Subjects must take at least 11 days, but no more than 17 days of placebo run-in medication.
c. Randomization is to occur after confirming all eligibility criteria and after performing all other visit procedures at Visit 3.
d. Height will only be assessed at the Screening Visit.
e. [redacted]
f. At Visit 2 (Placebo Run-In), all subjects will be provided with an ePRO device (electronic diary) that will be used to record the date and time of each of their micturitions, incontinence, and urgency episodes (micturition diary). Additionally, the diary will be used to record medication intake. Training on device use must be done at Visit 2 (Placebo Run-In) and as necessary throughout the study. Subjects will be instructed to begin completing the electronic micturition diary 3 days prior to each in-office study visit including Visits 3-6 (Treatment Period) and complete the diary for the full 3 days.
g. Subjects will complete the electronic micturition diary 3 days prior to the study visit and complete the diary for the full 3 days leading up to the visit.
h. During this activity, the subject will not come to the clinic for a visit. Site staff will contact the subject 3 days prior to the scheduled Visit to remind the subject they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable). The subject will need to complete the 3-day micturition electronic diary at home the full 3 days leading up to Visits 3, 4, 5 & 6.
i. Investigator, or designee, must review the subject's diary with the subject to ensure completion compliance and discuss data captured.

IS AMENDED TO:

Visit
Day
Week
Visit Windows (Days) [a]
Informed Consent/HIPAA
Inclusion/Exclusion Criteria
Medical History and OAB History
Demographics
Enter 2-week Placebo Run-in [b]
Randomization [c]
Physical Exam (including height [d] and weight)
Vital Signs – **in office** (includes pulse and blood pressure)
Cough Provocation test (Females only)
Serum chemistry, hematology & urinalysis [e]
[redacted]
12-Lead ECG
Ultrasound or Bladder Scan (PVR)
Medication History and OAB Medication History
Clinical Assessment for Dose Increase
Concomitant Medications Assessment
Adverse Event Assessment
Dispense Study Drug
Drug Accountability
Instruct Subject on 3-day Micturition Diary [g]

Complete 3-day Micturition Diary including **Vital Sign measurements and** PPIUS [h,i]
OAB-q
Patient Perception of Bladder Condition Scores (PPBC)
TS-VAS
Montreal Cognitive Assessment Test (MoCA)
Univ Alabama Birmingham Life Space Assessment (UAB -LSA)
Table continues on next page
Barthel ADL Assessment
Vulnerable Elders Survey 13 (VES-13)
Review Subject Diary [j]

a. **Visits 1 and 2 are negatively scheduled from the Baseline (Visit 3) date. A subject has a combined timeframe of up to 38 days to complete both Visits 1 and 2; however, Baseline (Visit 3) must occur at least 18 days but no more than 38 days after Visit 1 (Screening) and at least 11 days but no more than 17 days after Visit 2 (Placebo Run-In).** After Visit 2 (Placebo Run-In), visit windows/study days will be calculated based on the Visit 3 (Baseline) visit date. **Study procedures (e.g. bladder scan) for a particular visit do not need to be completed on the visit date if this is not feasible for the subject, as long as, study procedures are performed per protocol within the applicable visit window. Any procedure not done or performed outside the applicable visit window will be noted as a protocol deviation.**
b. Subjects must take at least 11 days, but no more than 17 days of placebo run-in medication.
c. Randomization is to occur after confirming all eligibility criteria and after performing all other visit procedures at Visit 3.
d. Height will only be assessed at the Screening Visit.
e. **Urine culture and sensitivity will be performed for positive leukocytes, or nitrites, or turbidity, or at the discretion of the PI. If a subject has a UTI, the subject can be rescreened after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture).**
f. [redacted]
g. At Visit 2 (Placebo Run-In), all subjects will be provided with an ePRO device (electronic diary) that will be used to record the date and time of each of their micturitions, incontinence, urgency episodes, **measure of urine volume voided, and sleep interruption** (micturition diary). Additionally, the diary will be used to record medication intake **and home measurements of am and pm pulse rate and systolic and diastolic blood pressure**. Training on device use must be done at Visit 2 (Placebo Run-In) and as necessary throughout the study. Subjects will be instructed to begin completing the electronic micturition diary 3 days prior to each in-office study visit including Visits 3-6 (Treatment Period) and complete the diary for the full 3 days.
h. Subjects will complete the electronic ~~micturition~~ diary 3 days prior to the study visit and complete the diary for the full 3 days leading up to the visit.
i. During this activity, the subject will not come to the clinic for a visit. Site staff will contact the subject 3 days prior to the scheduled Visit to remind the subject they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable). The subject will need to complete the 3-day ~~micturition~~ electronic diary at home the full 3 days leading up to Visits 3, 4, 5 & 6.
j. Investigator, or designee, must review the subject's diary with the subject to ensure completion compliance and discuss data captured.

12. Included measure of urine volume voided to be collected with electronic diary.
V. Flow Chart and Schedule of Assessments – Table 1 Schedule of Assessments – Footnote, Page 26
WAS:
f. At Visit 2 (Placebo Run-In), all subjects will be provided with an ePRO device

(electronic diary) that will be used to record the date and time of each of their micturitions, incontinence, and urgency episodes (micturition diary). Additionally, the diary will be used to record medication intake. Training on device use must be done at Visit 2 (Placebo Run-In) and as necessary throughout the study. Subjects will be instructed to begin completing the electronic micturition diary 3 days prior to each in-office study visit including Visits 3-6 (Treatment Period) and complete the diary for the full 3 days.
IS AMENDED TO:
g. At Visit 2 (Placebo Run-In), all subjects will be provided with an ePRO device (electronic diary) that will be used to record the date and time of each of their micturitions, incontinence, urgency episodes, **measure of urine volume voided, and sleep interruption** (micturition diary). Additionally, the diary will be used to record medication intake. Training on device use must be done at Visit 2 (Placebo Run-In) and as necessary throughout the study. Subjects will be instructed to begin completing the electronic micturition diary 3 days prior to each in-office study visit including Visits 3-6 (Treatment Period) and complete the diary for the full 3 days.

12. Included measure of urine volume voided to be collected with electronic diary.
5.3.1 Patient Diary – Micturition and Incontinence, Paragraph 3, Page 44
WAS:
A diary day starts at midnight and ends at midnight the following day. Time to bed with intention to sleep, time to awake with intention of staying awake, type of episode (urinary/incontinence), time of episode, urgency severity (see Section 5.3.4) and sleep interruption will be recorded by the subject in the micturition diary.
IS AMENDED TO:
A diary day starts at midnight and ends at midnight the following day. Time to bed with intention to sleep, time to awake with intention of staying awake, type of episode (urinary/incontinence), time of episode, urgency severity (see Section 5.3.4), **measure of urine volume voided** and sleep interruption will be recorded by the subject in the micturition diary.

13. Added subjects to be contacted 3 days prior to visit in Patient Diary Instructions.
5.3.1 Patient Diary – Micturition and Incontinence, Paragraph 2, Page 44
ADDED:
During this activity, the subject will not come to the clinic for a visit. Site staff will contact the subject 3 days prior to the scheduled Visit to remind the subject they need to complete the electronic diary, review completion instructions and review changes to concomitant medications and adverse events (if applicable).

14. Updated definition of an adverse event of hypertension.
5.4.1 Vital Signs – Paragraph 3, Page 47
WAS:

An AE of hypertension will be recorded if one of the following criteria is met on >2 separate visits:
IS AMENDED TO:
An AE of hypertension will be recorded if one of the following criteria is met on 2 separate**, consecutive** visits:

15. Addition of INR in Table 3 Laboratory Assessment.

5.4.4 Laboratory Assessments – Table 3 Laboratory Assessments, Page 49

WAS:

Table 5 Laboratory Assessments

Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Hematology	CBC Hemoglobin Hematocrit
Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Chemistry	Sodium Potassium Calcium Chloride Glucose Creatinine Alkaline phosphatase AST ALT GGT Total bilirubin Total protein Albumin
Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Urinalysis	Protein Glucose pH Blood Urine Culture *
[redacted]	[redacted]	[redacted]

* Urine culture will be done only for subjects with positive leukocyte esterase.

IS AMENDED TO:

Table 6 Laboratory Assessments

Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Hematology	CBC Hemoglobin Hematocrit
Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Chemistry	Sodium Potassium Calcium Chloride Glucose Creatinine Alkaline phosphatase AST

		ALT GGT Total bilirubin Total protein Albumin **INR**
Screening (Visit 1) Week 12/End of Treatment (Visit 6)	Urinalysis	Protein Glucose pH Blood Urine Culture *
[redacted]	[redacted]	[redacted]

*Urine culture ~~will be done only for subjects with positive leukocyte esterase~~**.and sensitivity** will be done ~~only for subjects~~ **performed for positive leukocytes, or nitrites, or turbidity, or at the discretion of the PI.**

16. Edited the positioning requirement for ECG measurement.
5.4.6 Electrocardiogram (ECG), Paragraph 1, Page 49
WAS:
A 12-lead ECG will be recorded at Screening (Visit 1), the placebo run-in (Visit 2), Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12/End of Treatment 9Visit 6). ECGs will be taken with the subject in the sitting position.
IS AMENDED TO:
A 12-lead ECG will be recorded at Screening (Visit 1), the **P**lacebo **R**un-**I**n (Visit 2), Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), Week 12/End of Treatment (Visit 6). ~~ECGs will be taken with the subject in the sitting position.~~ **ECGs will be taken with the subject in the sitting or supine position. The patient's sitting or supine position for the ECG should be consistent throughout the course of the study.**

14 ATTACHMENT 2: SPONSOR'S SIGNATURES

14 ATTACHMENT 2: SPONSOR'S SIGNATURES

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Older Adult Subjects with Overactive Bladder (OAB)

ISN/Protocol 178-MA-1005 / Version 3.0 dated

Incorporating Substantial Amendment 2 / September 10, 2015

Signature: [redacted]

[redacted]
[redacted] APGD, Medical Affairs, Americas

[redacted]
Date

Signature: [redacted]

[redacted] MD
[redacted] APGD, Medical Affairs, Americas

[redacted]
Date

Signature: [redacted]

[redacted]
[redacted] APGD, Medical Affairs, Americas

[redacted]
Date