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

ClinicalTrials.gov Identifier: NCT02216214

Date of Statistical Analysis Plan: Sep 2017

Sponsor: Astellas Pharma Global Development, Inc.

Medical Affairs, Americas

1 Astellas Way

Northbrook, IL 60062

STATISTICAL ANALYSIS PLAN

Final dated June-2015

Update, Final Version 3.0, dated September 2017

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: 178-MA-1005
IND number: 69416

Astellas Scientific and Medical Affairs (ASMA)
1 Astellas Way
Northbrook, IL 60062

Table of Contents

I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviation	Description of abbreviations
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANCOVA	Analysis of Covariance
ASCM	Astellas Scientific Committee Meeting
ASMA	Astellas Scientific & Medical Affairs, Inc.
AST	Aspartate Aminotransferase (GOT)
ATC	Anatomical Therapeutic Chemical
AUST	Astellas U.S. Technologies, Inc.
BL	Baseline
BMI	Body Mass Index
Bpm	Beats per minute
CI	Confidence Intervals
CPMP	Committee for Proprietary Medicinal Products
CS	Classification Specifications
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoT	End of Treatment
ePRO	Electronic Patient Reported Outcomes
FAS-I	Full Analysis Set – Incontinence
HBPM	Home Based Blood Pressure Monitoring
HRQL	Health Related Quality of Life
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRT	Interactive Response Technology
Kg	Kilogram
LOCF	Last Observation Carried Forward
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MID	Minimally Important Difference
Min	Minutes
mL	Milliliter
MoCA	Montreal Cognitive Assessment
N/n	Number
OAB	Overactive Bladder
OAB-q	Overactive Bladder – questionnaire
OR	Odds Ratio
PBO	Placebo
PCS	Potential Clinically Significant

Abbreviation	Description of abbreviations
PD	Protocol Deviation
PK	Pharmacokinetics
PPBC	Patient Perception of Bladder Condition
PPIUS	Patient Perception of Intensity of Urgency Scale
PPS	Per Protocol Set
PT	Preferred Term
PVR	Post-Void Residual Volume
QoL	Quality of Life
RAS	Randomized Analysis Set
RR	Response Rate
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
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
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary
VES	Vulnerable Elders Survey

List of Key Terms

Terms	Definition of terms
Adverse Event	An adverse event is as any untoward medical occurrence in a subject administered a study drug and that does not necessarily have a causal relationship with this treatment.
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 Overactive Bladder (OAB) syndrome, urge syndrome or urgency-frequency syndrome.
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.
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.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to any of the following: study unblinding, database hard lock, interim analysis, or accumulation of substantial amount of data in an open-label study to ensure lack of bias. For operational efficiency an earlier time is usually targeted. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by [redacted] with accountability to the responsible biostatistician of Astellas Scientific & Medical Affairs, Inc. (ASMA). Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and Tables, Listings, and Graphs (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.

2 FLOW CHART AND VISIT SCHEDULE

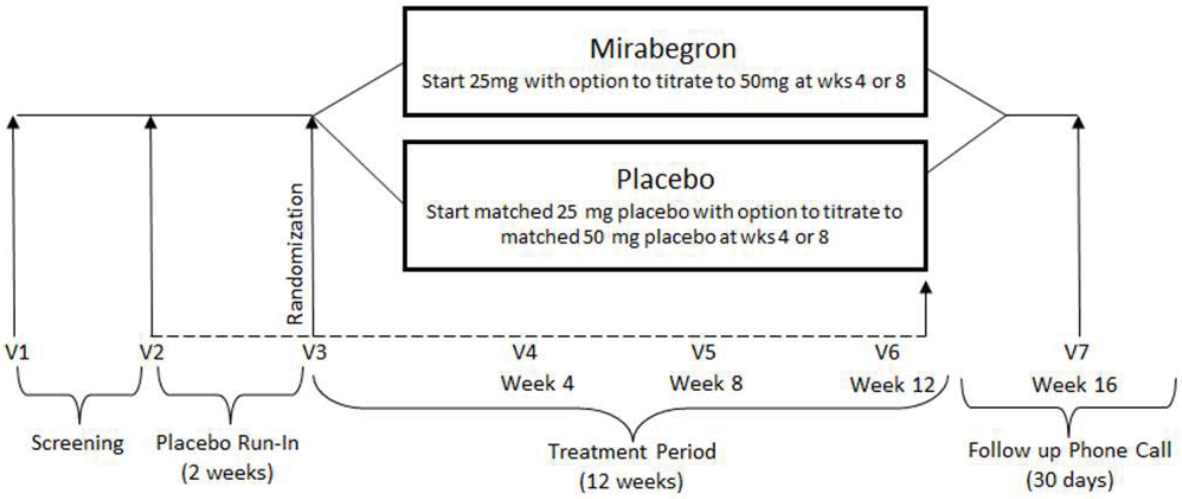


Table 1 Schedule of Assessments

	Screening	Placebo Run-In	Treatment Period				Follow-Up Call
Visit	1	2	3	4	5	6	7
Day	-28	-14	1	30	60	90	120
Week	-4	-2	0/BL	4	8	12/EoT	16
Visit Window (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 (includes pulse and blood pressure)	X	X	X	X	X	X	
Cough Provocation test (Females Only)	X						
Serum Chemistry, hematology, & urinalysis	X					X	
[redacted]	[redacted]						
12-Lead ECG	X	X	X	X	X	X	
Ultrasound or Bladder Scan (PVR)	X					X	

Table continues on next page							
	Screening	Placebo Run-In	Treatment Period				Follow-Up Call
Medication History and OAB Medication History	X		X				
Visit	1	2	3	4	5	6	7
Day	-28	-14	1	30	60	90	120
Week	-4	-2	0/BL	4	8	12/EoT	16
Visit Window (Days) [a]	+/- 10	+/- 3	+/- 3	+/- 7	+/- 7	+/- 7	+/- 3
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	X	
Drug Accountability			X	X	X	X	
Instruct Subject on 3-day Micturition Diary [f]	X	X	X	X	X	X	
Complete 3-day Micturition Diary including PPIUS [g]			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	

Table continues on next page

	Screening	Placebo Run-In	Treatment Period				Follow-Up Call
University of Alabama Birmingham Life Space Assessment (UAB-LSA)			X	X	X	X	
Barthel ADL Assessment			X			X	
Vulnerable Elders Survey 13 (VES-13)			X			X	
Review Subject Diary [i]			X	X	X	X	

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 the Screening visit (Visit 1), all subjects will be provided with an electronic patient reported outcomes (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 Screening (Visit 1) 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.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

3.1.1 Primary Objective

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

3.1.2 Secondary Objective

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

3.2 Study Design

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

After Screening, subjects will enter into a 2-week single-blind placebo run-in period prior to being randomized into the 12-week double-blind treatment period. Subjects will be asked to complete a 3-day training micturition diary during the placebo run-in period. Qualifying subjects will be randomized to 1 of 2 treatment groups (Mirabegron or PBO) for 12 weeks of treatment. Prior to Week 4, Week 8, and 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 and at Week 12/End of Treatment. Total study participation is approximately 20 weeks.

If the proportion of enrolled subjects ≥ 75 years of age is < 30%, measures may be taken to enhance enrollment of subjects ≥ 75 years of age.

3.3 Randomization

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). 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. After submitting certain information about the eligible subject, the randomized drug assignment will be provided by the IRT. Study drug assignment will remain blinded to all staff. Each study drug bottle will be preprinted with a Medication ID number that will be noted in the electronic case report form (eCRF). Once a subject number is assigned, if the corresponding subject does not receive study drug, the subject number will not be used again.

Subjects will be randomized to one of two treatment groups in a 1:1 ratio to either Mirabegron or 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.

4 SAMPLE SIZE

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 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 non-parametric 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 2 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 0.796 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.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

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

5.1 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 Quality of Life (QoL) instruments.

5.2 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 are defined in 5.2.1. Final judgments on exclusion of subjects from the PPS are to be made at the ASCM, held prior to unblinding.

The PPS will be a secondary analysis set for efficacy. Selected demographic and baseline characteristics may also be summarized for the PPS.

5.2.1 Reasons for Exclusion From PPS

The following criteria listed in Table 3 may lead to subject's exclusion from PPS.

Table 3. Criteria for Assessing Major Protocol Violations which could potentially Impact Efficacy Assessments

Number	MPV Criteria
Treatment Violations	
1	Double Blind treatment duration of less than 53 days
2	No measurement of the primary efficacy endpoint available at or after Visit 2
3	Treatment compliance of less than 70% between randomization and last visit
4	Administration of excluded concomitant treatment as described in the Study Protocol.
Inclusion Criteria Violations	

5	Subject did not experience at least one incontinence episode based on the 3-day micturition diary at baseline.
6	Subject did not experience at least 3 episodes of urgency (grade 3 or 4) based on the 3-day micturition diary at baseline.
7	Subject did not experience an average of greater than or equal to 8 micturitions/day based on the 3-day micturition diary at baseline.
Exclusion Criteria Violations	
8	Subject was non-compliant during 2-week placebo run-in period, defined as taking less than 80% or greater than 120% of study medication
9	Subject did not complete all 3 days of the baseline 3-day micturition diary
10	Unblinding of Study Drug
11	Error in Study Drug Administration
Other Exclusions from PPS	
12	Subject did not complete at least 2 days of the EOT 3-day micturition diary

5.3 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.

5.4 Randomized Analysis Set (RAS)

The Randomized Analysis Set (RAS) will consist of all randomized subjects. The RAS will be used to summarize disposition of subjects who were randomized to double-blind treatment.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy 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.

6.1.2 Secondary Efficacy Endpoints

Secondary endpoints are:

- Change from baseline (Week 0) to the end of treatment (Week 12) 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 Overactive Bladder-questionnaire (OAB-q).
- Change from baseline to the end of treatment in Patient Perception of Bladder Condition (PPBC).

6.1.3 Other Efficacy 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
- Barthel Index of Daily Living
- Vulnerable Elders Survey (VES-13)
- Patient Perception of Intensity of Urgency Scale (PPIUS)
- Subscale score from OAB-q scores
- Treatment Satisfaction – Visual Analog Scale (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
- Responder analysis defined by less than 8 micturitions per 24 hours post-baseline.
- Responder analysis defined as zero incontinence episodes at final visit
- Number of pads used

6.1.3.1 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 Screening (Visit 1) 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 Screening (Visit 1) 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).

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, 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.

Definitions of efficacy variables based on the 3-day micturition diary are presented in Table 4.

Table 4. Micturition Diary Definitions and Calculations

Measurement	Definition	Calculation
Micturition	Any voluntary micturition (excluding incontinence only episodes).	A micturition episode is counted as micturition regardless of whether volume voided was recorded or not. A micturition recorded before midnight of the first day or after midnight on the 3rd day of the 3-day micturition diary period will not be counted. A micturition will also be counted if the subject assessed an episode as both micturition and incontinence.
Valid Diary Day	A diary day in which at least one voluntary micturition	A diary day is considered valid if at least one

	episode occurs. A diary day with episodes of incontinence only is not considered a valid diary day.	micturition was recorded on this calendar day. Days of visits to the clinic (determined by the date of questionnaire completion) will not be counted as valid diary days.
Number of Valid Diary Days	Number of valid diary days per each 3-day micturition diary period.	Count of the valid diary days during the 3-day micturition diary period. Days of visits to the clinic will not be counted as valid diary days.
Valid Diary	A valid diary is a diary with at least 2 valid diary days within the analysis visit window. If more than 3 valid diary days are recorded then the last 3 days will be used in the calculations.	Not applicable.
Mean Number of Micturitions per 24 hours	Average number of times a subject urinates (excluding incontinence only episodes and excluding duplicate records [same time and episode characteristics]) per day during the 3-day micturition diary period.	Number of micturitions recorded on valid diary days during the 3-day micturition diary period divided by the number of valid diary days during the 3-day micturition diary period.
Urinary Incontinence Episode or Incontinence Episode	The complaint of any involuntary leakage of urine.	An incontinence episode is counted if it was recorded in the diary on a valid diary day. An incontinence will also be counted if the subject assessed an episode as both micturition and incontinence.
Number of Incontinence Episodes	Number of times a subject records an incontinence episode during the 3-day micturition diary period.	Total number of incontinence episodes recorded during the 3-day micturition diary period.
Mean Number of Incontinence Episodes per 24 hours	Average number of times a subject records an incontinence episode per day during the 3-day micturition diary period.	Number of incontinence episodes recorded on valid diary days during the 3-day micturition diary period divided by the number of

		valid diary days during the 3-day micturition diary period.
Mean Volume Voided per Micturition	Mean volume voided (mL) per micturition during 3 days of the 3-day micturition diary period.	Sum of each volume voided for each record with volume voided > 0 on valid diary days divided by the total number of records with a volume voided > 0 on valid diary days during 3 days with volume measurements in the 3-day micturition diary period.
Severity of Urinary Urgency (based on PPIUS)	Each micturition and/or incontinence episode is graded using the following 5 point scale based on PPIUS: 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 = Urgency incontinence, I leaked before arriving to the toilet.	Not applicable.
Urgency Urinary Incontinence Episode or Urgency Incontinence Episode	The involuntary leakage of urine accompanied by or immediately preceded by urgency.	One urgency incontinence episode is counted for each record of the diary in which the following occurs:

		incontinence episode is recorded AND severity of urinary urgency recorded is 3 or 4 NOTE: Only urgency incontinence episodes recorded on a valid diary day will be counted.
Number of Urgency Incontinence Episodes	Number of times a subject records an urgency incontinence episode during the 3-day micturition diary period.	Number of urgency incontinence episodes recorded on valid diary days of the 3-day micturition diary period.
Mean Number of Urgency Incontinence Episodes per 24 hours	Average number of times a subject records an urgency incontinence episode per day during the 3-day micturition diary period.	Number of urgency incontinence episodes recorded on valid diary days during the 3-day micturition diary period divided by the number of valid diary days during the 3-day micturition diary period.
Urgency Episodes (severity of 3 or 4)	The complaint of a sudden, compelling desire to pass urine, which is difficult to defer.	One urgency episode is counted for each record of the diary in which the following occurs: micturition or incontinence episode is recorded AND severity of urinary urgency recorded is 3 or 4 NOTE: Only urgency episodes recorded on a valid diary day will be counted. If an episode was recorded as both a micturition and an incontinence episode with a urinary urgency of 3 or 4, it will be counted as one urgency episode.

Mean Number of Urgency Episodes (severity of 3 or 4) per 24 hours	Average number of times a subject records an urgency episode (severity of 3 or 4) with or without incontinence per day during the 3-day micturition diary period.	Sum of each record with an urgency episode (severity of 3 or 4) recorded on a valid diary day divided by the number of valid diary days during the 3-day micturition diary period.
Nocturia	Waking at night one or more times to void (i.e. any voiding associated with sleep disturbance between the date/time the subject goes to bed with the intention to sleep until the date/time the subjects gets up in the morning with the intention to stay awake). A "night time" episode of incontinence only is not considered a nocturia episode.	A nocturia episode is counted for each micturition record which occurred between the date/time of going to bed with the intention to sleep (exclusive) and the date/time of getting up with the intention to stay awake (exclusive) on a valid diary day and which was accompanied by a sleep interruption. Nocturia will only be determined for subjects who are not night-shift workers.
Number of Nocturia Episodes	Number of nocturia episodes during the 3-day micturition diary period.	Sum of each nocturia episode recorded.
Mean number of nocturia episodes per 24 hours	Average number of times a subject records a nocturia episode per day during the 3-day micturition diary period.	Number of nocturia episodes recorded on valid diary days during the 3-day micturition diary period divided by the number of valid diary days during the 3-day micturition diary period.
Number of Pads Used	Number of times a subject records a new pad used during the 3-day micturition diary period.	Sum of each record with new pad checked. NOTE: Only records with new pad checked on a valid diary day will be counted.
Mean number of pads used per 24 hours	Average number of times a subject records a new pad used per day during the 3-day micturition diary period.	Number of new pads used during valid diary days during the 3-day micturition diary period divided by the number of valid diary days during the 3-day micturition diary period.

6.1.3.2 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 (See Appendix 2).

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

6.1.3.3 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 (See Appendix 3).

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

6.1.3.4 Patient Perception of Intensity of Urgency Scale

The 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.

The PPIUS micturition diary will be completed at Baseline (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5) and Week 12/EoT (Visit 6).

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

OAB has significant effects on health-related 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 OAB-q, the PPBC, TS-VAS, and UAB-LSA will be utilized.

6.1.3.5.1 Overactive Bladder-questionnaire

The OAB-q consists of a total of 33 questions, each with response options based on a 6-point Likert scale (1 through 6) and with a recall period of the past week. The items are grouped into Symptom Bother and each subscale of HRQL as described below.

Symptom Bother Answers on questions 1 through 8 will be summed which means the lowest and highest possible raw scores are 8 and 48, respectively, with a possible raw score range of 40. The following formula will be used to transform the Symptom Bother score which will range from 0 to 100 (=worst severity):

$$\text{Transformed Score} = \frac{(\text{Actual Raw Score} - \text{Lowest Possible Raw Score})}{\text{Possible Raw Score Range}} \times 100$$

A negative change from baseline to a scheduled visit in symptom bother score indicates an improvement.

For the HRQL subscales (coping, concern, sleep and social), raw scores will be calculated using the items described in the table below. The HRQL total score will be calculated by adding each individual HRQL subscale score together [Coyne et al, 2007], where a higher score indicates better HRQL.

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).

Calculation of HRQL Subscale Scores and HRQL Total Score Scale

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Coping	9+11+16+21+22+26+32+33	8, 48	40
Concern	12+13+14+19+23+25+29	7, 42	35
Sleep	10+15+17+24+30	5, 30	25
Social	18+20+27+28+31	5, 30	25
HRQL Total	Sum of HRQL subscales	25, 150	125

The raw scores will be transformed by the following formula with higher transformed scores indicating better quality of life [Coyne et al, 2007]:

$$\text{Transformed Score} = \frac{(\text{Highest Possible Score} - \text{Actual Raw Score})}{\text{Possible Raw Score Range}} \times 100$$

A positive change from baseline to a scheduled visit for a HRQL score indicates improvement.

For the symptom bother score and the subscale analysis, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing. If a subscale score for calculation of HRQL Total is missing, the HRQL Total score will not be calculated.

An example of the OAB questionnaire is given in Appendix 4.

6.1.3.5.2 Patient Perception of Bladder Condition

The 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 has the following response options, where a higher value equates a worse condition:

- 1 = My bladder condition does not cause me any problems at all
- 2 = My bladder condition causes me some very minor problems
- 3 = My bladder condition causes me some minor problems
- 4 = My bladder condition causes me (some) moderate problems
- 5 = My bladder condition causes me severe problems
- 6 = My bladder condition causes me many severe problems

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).

6.1.3.5.3 Treatment Satisfaction – Visual Analog Scale

The 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 satisfied). 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).

6.1.3.5.4 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, where a higher score indicates greater mobility.

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).

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
- Adverse Events of Possible Hepatic Origin (See Appendix 1)
- Acute Urinary Retention
- Urinary Tract Infections
- Clinical laboratory variables (hematology, biochemistry including liver function tests, and urinalysis)
- Cardiovascular events, vital signs (systolic and diastolic blood pressure and pulse rate), MI, Stroke and serious arrhythmias.
- Montreal Cognitive Assessment (See Appendix 5)
- Physical Examination
- 12-lead electrocardiogram (ECG)
- Post-Void Residual Volume

TEAE is defined as an adverse event observed after starting administration of the test drug/comparative drug. If the adverse event occurs on Day 1 and the onset check box is marked “Onset after first dose of study drug” or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked “Onset before first dose of study drug”, then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as a TEAE only if it has worsened in severity (i.e. it is reported with a new start date). All adverse events collected that begin within 30 days after taking the last dose of study drug will also be counted as TEAEs.

A drug-related TEAE is defined as any TEAE with possible or probable relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

6.3 Other Variables

6.3.1 Duration of Exposure

For each subject the duration of exposure on double-blind treatment will be calculated in days using the following formula:

(Date of last dose of study drug – Date of first dose of study drug) + 1

where the dates of the first and last known double-blind treatment are recorded on the study drug dosing eCRF pages. If they are missing, then imputed dates as per Subsection 7.10.1.2 will be used. Any gaps in dosing will be included in the total number of days on double-blind treatment.

The duration of exposure during the placebo run-in will be calculated in a similar way based on the dates of first and last dose of the study drug administration.

6.3.2 Percent Overall Compliance

During the double-blind treatment period, subjects are supposed to take a 25mg tablet once daily, in the morning with the option to increase to 2 tablets (50mg) at 4 weeks and 8 weeks. Overall compliance to the dosing schedule will be examined for subjects in the safety population whose total tablet count and duration of exposure is known. The percent compliance is defined as the total number of tablets consumed divided by the total number of tablets that should have been taken times 100.

(Total number of tablets consumed) x 100% / [(Overall duration of exposure) + (Duration of exposure on 50mg)]

where total number of tablets consumed will be calculated as:

Total number of tablets dispensed – Total number of tablets returned

The quantity of study drug dispensed to and returned by the subject will be counted and recorded on the study drug dosing eCRF pages.

6.3.3 Previous, Prohibited, and Concomitant Medication

Previous Medication

Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug in the run-in period (i.e. first or last medication intake is prior to first placebo run-in dose date (exclusive)). All previous OAB medications, regardless of when they were taken, will be collected on the eCRF. Previous non-OAB medications will only be collected on the eCRF if taken within 30 days prior to screening.

Prohibited Medication

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).

Table 5. Part A –Prohibited Medications

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.

Concomitant Medication

Concomitant medication during the placebo run-in period is defined as medication with at least one dose taken between the date of first dose (inclusive) of run-in study medication and the date of first dose (not inclusive) of double-blind study drug

Concomitant medication during the double-blind treatment period is defined as medication with at least one dose taken between the date of first dose (inclusive) of double-blind study medication and the last dose of double-blind treatment (inclusive)

For above variables, imputation methods will be used in case of missing medication intake dates.

6.3.4 Demographics

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

6.3.5 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.

6.3.6 Diagnosis of the Target Disease and Duration of Disease

Diagnosis and duration of disease for each subject will be obtained at Screening (Visit 1).

7 STATISTICAL METHODOLOGY

7.1 General Considerations

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 diary measurements within a designated visit window will be used.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g. 10%, 25%, 75% and 90%) will be mentioned in the relevant section. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.

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.

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.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

For the definition of subgroups of interest please refer to section 7.8.

Unless specified otherwise, treatment groups will be displayed by placebo, Mirabegron 25 mg, and Mirabegron 50 mg. Mirabegron 25 mg will include the patients who has not titrated to 50 mg. Mirabegron 50 mg will include the patients who titrated to 50 mg at weeks 4 or 8. The group of Mirabegron 50 mg Titration at Week 4 and Mirabegron 50 mg Titration at Week 8 will also be displayed in the analysis of vital signs. Mirabegron 50 mg Titration at Week 4 will include the patients who titrated to 50 mg at weeks 4. Mirabegron 50 mg Titration at Week 8 will include the patients who titrated to 50 mg at weeks 8.

7.1.1 Last Observation Carried Forward (LOCF)

For the efficacy diary data the EoT value will be calculated as the average or the count of the valid diary measurements reported in the last 3 valid diary days of the analysis visit window prior to EoT. For subjects who withdraw before week 12, the last available post-baseline average of the diary data measurements will be carried forward as the EoT value (LOCF).

For the non-diary efficacy data and safety data, the EoT value will be the last measurement within the week 12 visit day windows. For subjects who withdraw before week 12 the last measurement within the analysis visit window of the last available post-baseline visit will be carried forward as the EoT value (LOCF).

7.1.2 Model Structure - Analysis of Covariance (ANCOVA)

Changes from baseline to a post-baseline visit for variables for which a normal distribution is assumed will be analyzed using the following ANCOVA model:

$$Ch_{ijks} = \beta_0 + \beta_1 Base_{ijks} + Trt_i + Gender_j + AgeGrp_k + \epsilon_{ijks}$$

Where Ch_{ijks} is the change from baseline for subject s from treatment group i, gender group j, and age group k. β_0 and β_1 are the intercept and the slope of Ch_{ijks} as a function of the baseline value and ϵ_{ijks} is the residual for each subject.

The ANCOVA model results will be presented with least squares (LS) means and two-sided 95% confidence intervals (CIs) for mean changes from baseline within each treatment group. Differences in LS means between Mirabegron versus placebo will be derived together with two-sided 95% CIs. T-statistics corresponding to the Type III sums of squares for the differences in the LS means will be used to obtain p-values for the comparisons. Distribution assumptions underlying the analysis will be assessed by residual plots.

The SAS code used to implement this test will be similar to that shown below:

```
PROC MIXED data=dataset COVTEST NOCLPRINT METHOD=ML;
CLASS Trt Gender AgeGrp;
MODEL Ch=Base Trt Gender AgeGrp / SOLUTION CLPARM;
LSMEANS Trt / CL OM AT MEANS;
ESTIMATE 'Mirabegron versus placebo Trt 1 -1 0 /est cl;
RUN;
```

SAS code used to implement the rank ANCOVA will be similar to that shown below:

```
PROC RANK data=dataset NPLUS1 TIES=MEAN OUT=RANK1;
VAR Base Ch ;
RANKS BASERANK CHRANK ;
BY AgeGrp ;
RUN ;

PROC MIXED data=RANK1 METHOD=ML /RESIDUAL OUTP=OUT
     (KEEP=AgeGrp Gender CHRANK BASERANK Trt Resid);
CLASS Gender ;
BY AgeGrp ;
MODEL CHRANK = BASERANK Gender ;
RUN ;

PROC FREQ data= out ;
TABLES AgeGrp*Trt*Resid /noprint CMH2 ;
ODS OUTPUT CMH = out2 ;
RUN ;
```

7.1.3 Logistic Regression

For the responder analyses, a logistic regression model for the response rate (*RR)* at a specified visit will be modeled with the logit link as follows:

$$logit(E(RR_{ijks})) = \beta_0 + \beta_1 Base_{ijks} + Trt_i + Gender_j + AgeGrp_k + \epsilon_{ijks}$$

where $(E(RR_{ijks}))$ is the probability that a subject *s* from treatment group *i*, gender group *j*, and age group *k* demonstrates a response.

The odds ratio (OR) as well as its two-sided 95% CIs and p-value for Mirabegron versus placebo use will be derived.

The SAS code used to implement this test will be similar to that shown below:

```
PROC GENMOD data=dataset order=data;
CLASS Trt Gender AgeGrp;
      MODEL Responder(event='1') =Base Trt Gender AgeGrp/ DIST=bin
      LINK=logit
      LRCI type3 wald;
      ESTIMATE 'Mirabegron versus placebo' Trt 1 -1 0 / EXP;
      LSMEANS Trt / DIFF CL CORR;
      RUN;
```

7.1.4 Mixed Effects Poisson (negative binomial) Regression Model

The analysis for count data ($Count_{ijks}$) at a specified visit e.g., the number of incontinence episodes prior to EoT will be performed using a Mixed Effects Poisson (Negative Binomial (NB)) regression model for a subject s from treatment group i, sex group j, age group k. The count data will be modeled with the log link function as follows:

$$log(E(Count_{ijks})) = log(Day_{ijks}) + \beta_0 + \beta_1 Base_{ijks} + Trt_i + Gender_j + AgeGrp_k + \epsilon_{ijks}$$

where the offset variable $log(Day_{ijks})$ is the log of the number of valid diary days of each subject with a slope=1.

The RR as well as its two-sided 95% CIs and p-value for each active treatment over placebo will be derived.

The SAS code used to implement this test will be similar to that shown below:

```
PROC GENMOD data=dataset order=data;
      CLASS Trt Sex AgeGrp;
      MODEL Count= Base Trt Sex AgeGrp/ type3 LINK=log DIST=negbin
      offset=lday;
      ESTIMATE 'Mirabegron versus placebo' Trt 1  -1 / EXP;
      ESTIMATE 'Mirabegron versus placebo' Trt 1  -1/ EXP;
      LSMEANS Trt / DIFF CL CORR;
      RUN;
```

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number of subjects with informed consent, discontinued before randomization, randomized (overall only);
- Number and percentage of subjects randomized in each analysis set, by treatment group and overall;
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation for randomized subjects, by treatment group;
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation for randomized subjects and by treatment group;
- Number and percentage of subjects excluded from PPS by reason for exclusion defined in section 5.2.1, by treatment group for FAS-I.

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all randomized subjects. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment group and total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. 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:

Protocol Deviation (PD)1 - Entered into the study even though they did not satisfy entry criteria,

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

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics.

Number and percentage of subjects randomized in each country and site will be presented by treatment group for the SAF.

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.

Descriptive statistics for age, weight, body mass index (BMI) and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (<75, >=75) and race will be presented. This will be done for the SAF, FAS-I and PPS by treatment group.

Demographic variables are based on the last available value prior to first dose of double-blind treatment.

BMI is calculated as BMI (kg/m^2) = weight (kg) / $height^2$ (m).

OAB related baseline characteristics summarized in Table 6 and recorded on the eCRF from the Screening Visit will be summarized for the FAS-I, and PPS, by treatment group.

Duration of the OAB symptoms in months is calculated as the number of months from onset date of OAB symptoms at diagnosis to the informed consent date at the screening.

(*Date of Informed Consent - onset date of OAB symptoms at diagnosis* + 1) / 30.44

Table 6 OAB Related Baseline Characteristics from eCRF

Characteristic	Summarized as	Categories
Duration of OAB symptoms (in months)	Continuous	N/A
OAB Symptoms	Categorical	• Urgency Incontinence Only • Mixed Stress/Urgency Incontinence With Urgency as a Predominant Factor • Frequency/Urgency Without Incontinence

Characteristic	Summarized as	Categories
Number of previous OAB medications (prior to screening) group	Categorical	• 0 • 1 • >=2
OAB Severity at Baseline Based on Number of Micturition per 24 hours	Categorical	• <8 • 8-<10 • >=10 - <=15 • >15
OAB Severity at Baseline Based on Number of Incontinence Episodes per 24 hours	Categorical	• >0 - <=2 • >2 - <4 • >=4
Type of OAB at Screening	Categorical	• Urgency Incontinence Only • Mixed Stress/Urgency Incontinence with Urgency as Predominant Factor
Previous OAB Medication	Categorical	• Yes • No
Effectiveness of Previous OAB Medication	Categorical	• At Least One Effective • None Effective
Discontinuation of Previous OAB Medication Due to Insufficient Effect	Categorical	• Yes • No
Discontinuation of Previous OAB Medication Due to Poor Tolerability	Categorical	• Yes • No
Previous Treatment with Solifenacin	Categorical	• Yes • No
Previous Treatment with Mirabegron	Categorical	• Yes • No
Previous non-drug treatment for OAB (prior to screening)	Free Text	• Yes →Biofeedback →Exercises →Electrical Stimulation →Behavioral →Pessaries →Implants →Surgery • No

OAB related baseline characteristics derived from the 3-day micturition diary prior to the Run-in Visit and the Randomization Visit will be summarized as continuous variables overall for the FAS-I, and PPS with following listed characteristics in Table 7. Only patients with a baseline value > 0 will be included in each individual summary.

Table 7 OAB Related Baseline Characteristics from 3-Day Micturition Diary

Characteristic	Summarized as	Categories
Number of incontinence episodes reported during the 3-day diary	Continuous	N/A
Mean number of incontinence episodes per 24 hours	Continuous	N/A
Number of urgency incontinence episodes reported during the 3-day diary	Continuous	N/A
Mean number of urgency incontinence episodes per 24 hours	Continuous	N/A
Mean number of micturitions per 24 hours	Continuous	N/A
Number of pads reported during the 3-day diary	Continuous	N/A
Mean number of pads per 24 hours	Continuous	N/A
Mean number of urgency episodes (grade 3 or 4) per 24 hours	Continuous	N/A
Number of nocturia episodes reported during the 3-day diary	Continuous	N/A
Mean number of nocturia episodes per 24 hours	Continuous	N/A

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by treatment group for the SAF.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with World Health Organization – Drug Dictionary (WHO-DD), and will be summarized by therapeutic subgroup (Anatomical Therapeutic Chemical (ATC) 2nd level) and chemical subgroup (ATC 4th level) and preferred World Health Organization (WHO) name by treatment group for the SAF.

As with previous medication, concomitant medication will be summarized for each treatment group by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication that can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

7.3 Study Drugs

7.3.1 Exposure

The following information on drug exposure will be presented for each treatment group for the SAF:

- Descriptive statistics for number of days treatment was received will be presented by treatment group
- Number and percent of subjects with dose increase from 25mg to 50mg by treatment group. Overall and split by those whose dose increased at 4 weeks versus 8 weeks.

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented by treatment group.
- Counts and percentages of exposure time will be categorized according to the following categories by treatment group:

- 1 to 6 days
- 7 to 13 days
- 14 to 27 days
- 28 to 55 days
- 56 to 83 days
- 84 days or more
- Unknown.

- Counts and percentages of cumulative exposure will be categorized according to the following categories by treatment group:
  - >=7 days
  - >=14 days
  - >=28 days
  - >=56 days
  - >=84 days

Counts and percentages of subjects in each of these categories will be summarized for each treatment group for the SAF.

7.3.2 Treatment Compliance

Overall compliance will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by treatment group.
- Percent compliance will be categorized according to the following categories by treatment group:
  - less than 50%
  - at least 50%, less than 70%
  - at least 70%, less than 90%
  - at least 90%, less than 110%
  - greater than 110%
  - Unknown.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoints

The primary analysis set for efficacy analyses will be the 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.

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.

If the two co-primary endpoints are statistically significant at the same alpha level ($\alpha = 0.05$), the secondary endpoint of mean volume voided per micturition will then be carried out.

Mean number of micturitions per 24 hours

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

> H0: Mean change from baseline in number of micturitions per 24 hours at end of treatment is the same for placebo and Mirabegron.
>
> H1: 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 an 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, gender, and age group (<75, >=75) as fixed factors and baseline mean number of micturitions episodes per 24 hours as the covariate in the model. 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;

> H0: Mean change from baseline in number of incontinence episodes per 24 hours at end of treatment is the same for placebo and Mirabegron.
>
> H1: 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 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.

7.4.2 Secondary Analysis of Primary Endpoints

Residual plots will be produced to check the assumptions of the underlying statistical models for mean number of micturitions and incontinence episodes 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. Outliers are defined and handled per section 7.10.2. If outliers are present, then additional sensitivity analyses will be performed with the outliers excluded to assess their impact on the results.

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.

All primary analyses will be repeated for the PPS which is considered secondary. These will be performed to assess the robustness of the primary analysis findings.

<u>Responder Analysis for Incontinence Episodes and Improvement in Patient Perception of Bladder Condition</u>

Two responder analyses based on incontinence episodes and two responder analyses based on PPBC will be performed at weeks 4, 8, 12, and EoT 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 and p-values.

The four 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.

<u>Responder Analysis for Less than 8 micturitions</u>

A responder analyses based on less than 8 micturitions will be performed at weeks 4, 8, 12, and EoT 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 and p-values.

Sub-group Analysis

Sub-group analysis of the co-primary endpoints will be conducted using ANCOVA models with an interaction term. The interaction terms will be the treatment arm and the subgroup. These subgroup analyses will only be performed for baseline to EoT. Please see Section 7.8 for the categories of the subgroups of interest.

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, two-sided 95% CIs, and p-values for mean changes from baseline within each subgroup will be provided.

7.4.3 Analysis of Secondary Endpoints

The secondary efficacy variables are:

- The change from baseline to week 4, 8, 12, and end of treatment in mean volume voided per micturition,
- 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 PPBC.

The analysis for secondary endpoints will be performed in FAS-I and PPS population.

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 an 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, gender, and age group (<75, >=75) as fixed factors and baseline mean volume voided as the covariate in the model. 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 mean voided volume. 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 an ANCOVA model. The response variable will be the change from baseline in symptom bother and total health related quality of life scores. Treatment group, gender, and age group (<75, >=75) will be fixed factors in the model and baseline score will be included as covariates. 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 PPBC

Differences in change from baseline of PPBC between Mirabegron and placebo will be analyzed using an ANCOVA model. The response variable will be the change from baseline in PPBC. Treatment group, gender and age group (<75, >=75) will be fixed factors in the model while the baseline scores will be included as covariates. 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 EoT using a logistic regression model. This will be based on the change in 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) of a 10-point improvement in OAB-q while a non-responder will be a subject with a MID of a less than 10-point improvement in OAB-q.

Two responder analyses will be performed for PPBC at Week 12 or EoT using a logistic regression. One analysis will look at symptom bother and another will look at HRQL total. The 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

The final responder analysis will examine the response outcome defined as zero incontinence episodes post baseline.

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

Poisson (Negative Binomial) Regression for Count Variables

Other secondary variables including the number of incontinence episodes, number of urgency incontinence episodes, number of nocturia episodes and number of pads used will be analyzed using the Mixed Effects Poisson (negative binomial) regression model.

7.4.4 Analysis of Exploratory Endpoints

[redacted]

7.4.5 Analysis of Other Variables

The analysis of change from baseline scores (to weeks 4, 8, 12, and EoT) for the following additional efficacy endpoints will be analyzed in the same way as described for the mean number of micturitions (ANCOVA), with the exception of urgency incontinence episodes which will be analyzed using a stratified rank ANCOVA.

- 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 pads
- Change from baseline in mean number of nocturia episodes/24 hour
- Change from baseline in OAB-q subscale scores
- Change from baseline in TS-VAS
- Change from baseline in UAB-LSA
- Change from baseline in VES-13.

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 (MoCA).

7.5.1 Adverse Events

Summaries and listings of serious adverse events (SAEs) and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of 'Always Serious' terms if any upgrade was done.

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.

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with causally drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug, and
- Number of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment group. Summaries will be provided for:

- TEAEs
- Common TEAEs (>=2% in one group)
- drug related TEAEs,
- severe TEAEs
- serious TEAEs,
- drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of study drug,
- Non-serious TEAEs over 5% in any one treatment group

- TEAE by titration doses (prior to titration)
- TEAE by titration doses (post-titration)

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized for each treatment group and by the subgroups of interest found in Section 7.8.

The number of TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by severity. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity, then the subject will be counted only once with the worst severity, however, if any of the severity values are missing then the subject will be counted only once with missing severity. In the adverse event count, the adverse events will be presented in each category to which they were classified. Drug related severe TEAEs will be presented in a similar way.

Additional summaries will be provided for the following AEs of special interest:

- Cardiovascular events
- Vital signs (systolic and diastolic blood pressure and pulse rate)
- MI
- Stroke
- Serious Arrhythmias
- Urinary Tract Infection (UTI)
- Acute urinary retention
- Benign prostatic obstruction (BPO) requiring surgery

7.5.2 Clinical Laboratory Evaluation

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.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, and urinalysis will be summarized using mean, standard deviation, minimum, maximum, Q1, Q3, and median for each treatment group at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Laboratory results will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. Shift tables of reference range changes from Screening to Week 12/End of Treatment during the double-blind treatment period by treatment group will be summarized for all laboratory values.

Laboratory abnormalities will be evaluated based on the Potentially 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. The pre-defined criteria for PCS laboratory values are presented below.

Potentially Clinically Significant Laboratory Criteria			
Laboratory Parameter	**Unit**	**Low PCS Criterion**	**High PCS Criterion**
Hematology			
Hemoglobin	g/L	< 80	>180
Hematocrit	Fraction	< 0.25	> 0.55
Erythrocyte (Red Blood Cell Count)	$x10^{12}$/L	< 2.5	> 7.0
Platelet Count	$x10^{9}$ /L	< 120	> 500
Leukocyte (White Blood Cell Count)	$x10^{9}$ /L	< 2.5	> 18
Potassium	Meq/L	< 3.0	> 6.0

7.5.2.1 Liver function tests

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

Parameter	Criteria
ALT	> 3xUpper Llimit of Normal (ULN)
	> 5xULN
	> 10xULN
	> 20xULN
AST	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
ALT or AST	> 3xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver function tests during the investigational period will be presented by treatment group.

7.5.3 Vital Signs

The baseline visit is the last measurement taken prior to initial study drug administration.

Pulse rate, systolic blood pressure, and diastolic blood pressure will be summarized by treatment group, by Home Based Blood Pressure Monitoring (HBPM) and office based, and the subgroups of interest found in Section 7.8 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 point. Morning and evening blood pressure will be reported separately. The first reading of HBPM from each time period will be discarded and the subsequent two readings for each time period will be averaged over the 3-day diary. 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. Age group (<75, ≥75) will be included as the stratification factor. It should be noted that age group was omitted from the description of the analysis in the protocol. 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.

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 considred if resting heart frequency (pulse rate) is > 100 bpm.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest value obtained during treatment for each subject for each treatment group. 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.

The following Vital Sign data will be presented graphically by treatment group across visits:

- Change from baseline in vital sign results using mean (+/- 95% CI) plot
- Mean qualitative vital sign results using a bar chart
- Scatter plot of maximum vital sign results on treatment versus baseline value (separate plot for SBP, DBP, and pulse).

7.5.4 Montreal Cognitive Assessment Test (MoCA)

The observed values and change from baseline values for MoCA total points and its subscale items (Attention, Language, Naming Visuospatial/Executive, Abstraction Points, Delayed Recall Points, and Orientation Points) by treatment group will be presented in a by-patient listing and in a summary table.

Differences in change from baseline of MoCA scores between Mirabegron and placebo will be analyzed using a stratified rank 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.. A subset analysis by age group (<75, ≥75) will be included.. As part of the ANCOVA results, LS means, two-sided 95% CIs, and p-values for mean changes from baseline within each treatment group will be provided.

A simpler model will also be provided that includes only treatment, gender, and baseline MoCA values as covariates.

A shift table for MoCA total points by treatment group will be created by the following categories:

- >26: normal
- <=26: impaired
  - 18-26: mild cognitive impairment
  - 10-17: moderate cognitive impairment
  - <10: severe cognitive impairment.

The following MoCA data will be presented graphically by treatment group across visits:

- MoCA results using mean (+/- 95% CI) plot,
- Change from baseline in MoCA results using mean (+/- 95% CI) plot.

7.5.5 Electrocardiograms (ECGs)

ECG variables (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval) will be summarized using descriptive statistics 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.

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12 lead ECG will be tabulated by treatment group at each treatment visit and time point.

Shift tables that include number and percent of subjects will be presented for 12 lead ECG reading changes from normal at baseline to abnormal at week 4, 8, 12, and EoT by treatment group.

The QTc interval will be summarized by gender using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below. It will also be summarized by FDA Guidance categories.

	QTc Interval Criteria Value (msec)
Gender Splits	≤ 450 for males, ≤ 470 for females - Normal > 450 for males, >470 for females - Abnormal
FDA Categories	≤ 450 > 450 > 480 > 500

The QTc interval will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit and time point.

Variable	**Change from Baseline**
QTc Interval (msec)	<0 ≥ 0 >10 > 30 > 60

7.5.6 PVR Volume

PVR volume in mL and corresponding change from baseline values will be summarized by treatment group and visit (baseline and Week 12) for continuous values as well as using the following categories:

- >= 0 mL to < 150 mL
- >= 150 mL to < 300 mL

- >= 300 mL

A shift table for changes from baseline to each post-baseline visit for PVR volume based on the 3 categories above will be performed for each treatment group.

7.5.7 Weight, Height, and BMI

A descriptive summary for values of height (baseline only) weight in kg and BMI in kg/m^2 at each post-baseline visit and the changes from baseline will be provided at each visit. A listing will also be provided.

7.5.8 Pregnancies

A listing of pregnancy testing will be provided.

7.6 Analysis of Pharmacokinetics (PK)

Not applicable

7.7 Analysis of PD

Not applicable

7.8 Subgroups of Interest

Primary efficacy endpoints and selected safety variables (treatment emergent adverse events and vital signs) will be summarized by treatment group for the subgroups defined on the basis of the categorized variables listed below:

Grouping variable	Subgroups
Race	White
	Black or African American
	Asian
	American Indian/Alaskan Native
	Hawaiian or Other Pacific Islander
	Other
Age group	< 75 years
	>=75 years
Sex	Female
	Male

7.9 Other Analyses

Not applicable

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

7.10.1 Missing Data

Missing primary and secondary efficacy endpoints will be handled by LOCF for continuous variables, and non-responder imputation for binary variables.

For all OAB-q scales and subscales, if <50% of the items are missing, the scale/subscale should be retained with the mean scale score of the items present used to impute a score for the missing items. If >=50% of the items are missing, no scale/subscale score should be calculated, the scale/subscale score should be considered missing.

As a general principle, imputation of missing dates for variables will not be done. Exceptions are for start and stop dates of study drug intake, AEs and concomitant medications. The imputed dates will be used to determine whether the medication was taken prior to or during the double-blind treatment period. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

7.10.1.1 Imputation of Study Drug Start Dates and Study Drug End Dates

Imputation of Study Drug Start Dates

Run-In Period

For subjects who are not Screen Failures, the first dose date of placebo run-in will be imputed if both of the following criteria are met:

- There is a missing or partial date for the first dose of placebo run-in study drug AND
- The number of tablets dispensed at the Screening Visit does not equal the number of tablets returned (including missing values).

If both criteria are met, then the first dose date of placebo run-in study drug is defined as the first non-missing date in the following order:

- Dispense date at Screening Visit +1 day
- Date of the Screening Visit +1 day

Double-Blind Treatment Period

For subjects who are randomized to double-blind treatment, the first dose date of double-blind treatment study drug will be imputed if both of the following criteria are met:

- There is a missing or partial date for the first dose of double-blind treatment AND
- The number of tablets dispensed at the Randomization Visit does not equal the number of tablets returned (including missing values) AND
- Dispensed date is non-missing.

If all the above criteria are met, then the first dose date of double-blind treatment is defined as:

Dispense date at the Randomization Visit +1 day

Imputation of Study Drug End Dates

Run-In Period

For subjects who are not Screen Failures, the last dose date of placebo run-in will be imputed if both of the following criteria are met:

1. There is a missing or partial date for the last dose of placebo run-in study drug AND
2. The number of tablets dispensed at the Screening Visit does not equal the number of tablets returned (including missing values).

If both criteria are met, then the last dose date of placebo run-in study drug is defined as the first non-missing date in the following order:

- Date of the day before the first dose of double-blind treatment in the double-blind treatment period,
- Day of the dispense date at the randomization visit
- Day of the randomization visit (Visit 2)
- Date of the first dose of placebo run-in study drug + 1 day
- Dispensed date at the Screening Visit + 1 day
- Date of the Screening Visit + 1 day

Double-Blind Treatment Period

For subjects who are randomized to double-blind treatment, the last dose date of double-blind treatment study drug will be imputed if all the following criteria are met:

a. There is a missing or partial date for the last dose of double-blind treatment AND
b. The number of tablets dispensed at the Randomization Visit does not equal the number of tablets returned (including missing values).

If only the day is missing for the last dose date of double-blind treatment, the last day of the month under consideration will be used.

If the month and/or year are missing for the last dose date of double-blind treatment, then the last dose date of double blind treatment is defined as the first non-missing date in the following order:

- Last dispense date of the double-blind period + 1 day

- Date of the first dose of double-blind treatment in the double-blind treatment period + 1 day
- Date of the randomization visit + 1 day.

For imputing the last dose date of placebo run-in study drug and double-blind treatment study drug, an imputed first dose date should not be used but the next imputation rule should be used instead.

7.10.1.2 Imputation of Adverse Event Onset Date

For AEs, a missing or incomplete onset date will be imputed according to the following conventions:

If an onset date is missing or only the year is known, the imputed onset date will be the **latest** of the following non-missing dates:

1. Date of first dose of double-blind treatment
2. Date of randomization visit + 1 day
3. Date of last dose of single-blind run-in study drug + 1 day

If only the month and year is known for onset date, set the surrogate onset date to the first day of that month and then apply the following rules:

- If the month and year of the onset date is prior to the month and year of the first dose of double-blind treatment, then the surrogate onset date will be the imputed onset date.
- If the month and year of the onset date is on or after the month and year of the first dose of double-blind treatment or if the first dose of double-blind treatment is missing, then the imputed onset date will be the **latest** of the following non-missing dates:

4. Date of first dose of double-blind treatment
5. Date of randomization visit + 1 day
6. Date of last dose of single-blind run-in study drug + 1 day
7. Surrogate onset date

If the imputed onset date is after a complete adverse event end date, the imputed onset date will be the same as the complete adverse event end date.

7.10.1.3 Imputation of Concomitant Medication and Non-Drug Treatment Start and End Date

Start and stop dates for all concomitant medications and non-drug treatment are collected on the eCRF. However, in case of missing or partial information in these dates, the following rules will be used:

If start date is missing or partial:

8. if month is missing, use January
9. if day is missing, use the first day of the month under consideration
10. if year is missing, use year of the informed consent date
11. if entire date is missing, use informed consent date

If stop date is missing or partial and the medication is not ongoing:

12. if month is missing, use December
13. if day is missing, use the last day of the month under consideration
14. if year or the entire date is missing, set to December 31st, 2099

If the imputed start date is after the stop date, then the imputed start date will be one day prior to the stop date.

If the medication or non-drug treatment is ongoing, the stop date will remain missing.

7.10.1.4 Imputation of OAB Symptoms Onset Date

If the onset date of OAB symptoms is partially missing, the following rules will take effect:

15. Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
16. Missing day and month, but year is present: the day and month will be imputed as 30 June of the year.
17. Missing year, but day and month are present: No imputations will occur, and the subject will be excluded from all summaries related to duration of OAB symptoms.
18. Missing day, month and year: No imputations will occur, and the subject will be excluded from all summaries related to duration of OAB symptoms.
19. If any such imputed date falls after the informed consent date, then the onset date will be taken as equal to the informed consent date.

7.10.2 Outliers

An outlier is defined as an observation for which the residual is more than three interquartile ranges above the 75th percentile or below the 25th percentile. Outliers will be identified based on diagnostics performed for the co-primary and secondary efficacy variables by using standardized residuals from ANCOVA model (Section 7.4.2). If outliers are present, then additional sensitivity analyses will be performed with the outliers excluded to assess their impact on the results.

7.10.3 Visit Windows

Subjects do not always adhere strictly to the visit timing in the protocol. Therefore, the designation of visits during the double-blind treatment period will be based on the day of

evaluation relative to the start of the double-blind treatment period (day of first dose of double-blind treatment in double-blind treatment period = Day 1 of double-blind treatment period) rather than the nominal visit recorded in the CRF.

To assign a measurement to a study visit during the double-blind treatment period, the first step consists of selecting all measurements falling within the double-blind treatment period as defined above. To further determine the study visit measurement, mutually exclusive relative day windows are used.

If a subject has more than one visit with a measurement included within a window, the assessment closest to the scheduled day will be used. In case of ties between observations located on different sides of the scheduled day, the later assessment will be used. In case of ties located on the same side of the scheduled day (i.e., more than one value for the same day), the mean of the values will be used for continuous variables and the worst value for categorical variables.

It should be noted that if more than one measurement for a parameter is recorded within the same visit window, the above conventions may not lead to the most conservative approach for the by-visit summaries of categorical or numerical variables. The worst individual categorical or numerical value within a visit window may not be identified as the value representative for the analysis visit due to the rules above. However, the worst individual categorical or numerical value will be accounted for in tables summarizing the worst individual categorical or numerical value reported during the double-blind treatment period. All individual values will be provided in a listing.

7.10.3.1 Analysis Visit Windows for Efficacy and Safety Variables

All the efficacy and safety assessments for a treatment period will be allocated based on the tables below.

Efficacy:

Analysis visit	Target day	Actual assessment day
Screening	Day -28	-38 to -18
Placebo Run-In	Day -14	-17 to 0
Baseline	Day 1	Day 1[a]
Week 4	Day 30	15-42
Week 8	Day 60	43-70
Week 12/End of Treatment	Day 90	71-98
Follow Up Phone Call	Day 120	EOT+14

[a] After Placebo Run-In, visit windows/study days will be calculated based on the Baseline (Visit 3) date.

Safety:

Analysis visit	Target day	Actual assessment day
Screening	Day -28	-38 to -18
Placebo Run-In	Day -14	-17 to 0
Baseline	Day 1	Day 1[a]
Week 4	Day 30	2-45
Week 8	Day 60	46-75
Week 12/End of Treatment	Day 90	76-97
Follow Up Phone Call	Day 120	EOT+14

1. After Placebo Run-In, visit windows/study days will be calculated based on the Baseline (Visit 3) date.

For efficacy variables recorded in the 3-day micturition diary, the following rules will apply:

1. As micturition diary data are to be recorded from midnight 3 days prior to a visit to midnight 1 day prior to a visit, micturition diary records which have the same date as a visit date should be excluded from the analysis. Non-micturition questionnaire assessment dates will be compared to the eDiary dates and used to flag which diary records should be excluded.
2. Any diary days which are > 7 days after the last dose of double-blind treatment will not be included in the analysis.
3. Average values or number of episodes for count data will only be calculated if at least 2 valid diary days are available within the specified window. In the case that only 1 valid diary day is available, then no value will be calculated.
4. If there are more than 3 valid diary days available for a visit, the average will be based on the last 3 days prior to the scheduled visit.
5. Duplicate records (same time and episode characteristics) per day during the 3-day micturition diary period will be excluded.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	03-SEP-2014	NA	Document Initialized
2.00	12-FEB-2016	YES	Changes in Protocol Amendment 2
3.00	08-SEP-2017	YES	Changes per sponsor's comments

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

10 APPENDICES

10.1 Appendix 1: Adverse Events of Possible Hepatic Origin

MedDRA Hepatic Disorders SMQ

- Congenital, familial, neonatal and genetic disorders of the liver (SMQ)
  - Accessory liver lobe
  - Alagille syndrome
  - Cerebrohepatorenal syndrome
  - Congenital absence of bile ducts
  - Congenital cystic disease of liver
  - Congenital hepatic fibrosis
  - Congenital hepatobiliary anomaly
  - Congenital hepatomegaly
  - Cystic fibrosis hepatic disease
  - Dilatation intrahepatic duct congenital
  - Glycogen storage disease type I
  - Glycogen storage disease type III
  - Glycogen storage disease type IV
  - Glycogen storage disease type VI
  - Hepatitis neonatal
  - Hepatocellular damage neonatal
  - Hepato-lenticular degeneration
  - Hepatosplenomegaly neonatal
  - Hereditary haemochromatosis
  - Neonatal cholestasis
  - Neonatal hepatomegaly
  - Polycystic liver disease
  - Porphyria acute
  - Hyperbilirubinaemia neonatal
  - Jaundice neonatal
  - Kernicterus
  - Porphyria non-acute
- Drug related hepatic disorders - comprehensive search (SMQ)
  - Cholestasis and jaundice of hepatic origin (SMQ)
    - Bilirubin excretion disorder
    - Cholaemia
    - Cholestasis
    - Cholestatic liver injury
    - Cholestatic pruritus
    - Drug-induced liver injury
    - Hepatitis cholestatic
    - Hyperbilirubinaemia
    - Icterus index increased
    - Jaundice

Jaundice cholestatic
Jaundice hepatocellular
Mixed liver injury
Ocular icterus
Deficiency of bile secretion
Yellow skin

Drug related hepatic disorders - severe events only (SMQ)

Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)

Acute hepatic failure
Acute yellow liver atrophy
Ascites
Asterixis
Bacterascites
Biliary cirrhosis
Biliary cirrhosis primary
Biliary fibrosis
Cholestatic liver injury
Chronic hepatic failure
Coma hepatic
Cryptogenic cirrhosis
Diabetic hepatopathy
Drug-induced liver injury
Duodenal varices
Gallbladder varices
Gastric varices
Gastric varices haemorrhage
Hepatectomy
Hepatic atrophy
Hepatic calcification
Hepatic cirrhosis
Hepatic encephalopathy
Hepatic encephalopathy prophylaxis
Hepatic failure
Hepatic fibrosis
Hepatic hydrothorax
Hepatic infiltration eosinophilic
Hepatic lesion
Hepatic necrosis
Hepatic steatosis
Hepatitis fulminant
Hepatobiliary disease
Hepatocellular foamy cell syndrome

Hepatocellular injury
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatotoxicity
Intestinal varices
Liver and small intestine transplant
Liver disorder
Liver injury
Liver operation
Liver transplant
Lupoid hepatic cirrhosis
Mixed liver injury
Nodular regenerative hyperplasia
Non-alcoholic steatohepatitis
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Peripancreatic varices
Portal hypertension
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal triaditis
Portal vein dilatation
Portopulmonary hypertension
Renal and liver transplant
Retrograde portal vein flow
Reye's syndrome
Reynold's syndrome
Splenic varices
Splenic varices haemorrhage
Subacute hepatic failure
Varices oesophageal
Varicose veins of abdominal wall
Anorectal varices
Anorectal varices haemorrhage
Intrahepatic portal hepatic venous fistula
Peritoneovenous shunt
Portal shunt
Small-for-size liver syndrome
Spider naevus

Hepatitis, non-infectious (SMQ)
Acute graft versus host disease in liver
Allergic hepatitis

- Autoimmune hepatitis
- Chronic graft versus host disease in liver
- Chronic hepatitis
- Graft versus host disease in liver
- Hepatitis
- Hepatitis acute
- Hepatitis cholestatic
- Hepatitis chronic active
- Hepatitis chronic persistent
- Hepatitis fulminant
- Hepatitis toxic
- Ischaemic hepatitis
- Lupus hepatitis
- Non-alcoholic steatohepatitis
- Radiation hepatitis
- Granulomatous liver disease
- Liver sarcoidosis

Liver neoplasms, benign (incl cysts and polyps) (SMQ)

- Benign hepatic neoplasm
- Focal nodular hyperplasia
- Haemangioma of liver
- Haemorrhagic hepatic cyst
- Hepatic adenoma
- Hepatic cyst
- Hepatic cyst ruptured
- Hepatic haemangioma rupture

Liver neoplasms, malignant and unspecified (SMQ)

- Liver malignant tumours (SMQ)
  - Hepatic angiosarcoma
  - Hepatic cancer metastatic
  - Hepatic cancer stage I
  - Hepatic cancer stage II
  - Hepatic cancer stage III
  - Hepatic cancer stage IV
  - Hepatoblastoma
  - Hepatoblastoma recurrent
  - Hepatocellular carcinoma
  - Mixed hepatocellular cholangiocarcinoma
- Liver tumours of unspecified malignancy (SMQ)
  - Hepatic neoplasm
  - Hepatobiliary neoplasm

Liver related investigations, signs and symptoms (SMQ)

- Alanine aminotransferase abnormal

Alanine aminotransferase increased
Ammonia abnormal
Ammonia increased
Ascites
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
Bacterascites
Bile output abnormal
Bile output decreased
Bilirubin conjugated abnormal
Bilirubin conjugated increased
Biopsy liver abnormal
Blood bilirubin abnormal
Blood bilirubin increased
Blood bilirubin unconjugated increased
Bromosulphthalein test abnormal
Child-Pugh-Turcotte score increased
Foetor hepaticus
Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gamma-glutamyltransferase abnormal
Gamma-glutamyltransferase increased
Guanase increased
Hepaplastin abnormal
Hepaplastin decreased
Hepatic artery flow decreased
Hepatic congestion
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic function abnormal
Hepatic hydrothorax
Hepatic mass
Hepatic pain
Hepatic sequestration
Hepatic vascular resistance increased
Hepatobiliary scan abnormal
Hepatomegaly
Hepatosplenomegaly
Hyperammonaemia
Hyperbilirubinaemia
Hypercholia
Hypertransaminasaemia

Kayser-Fleischer ring
Liver function test abnormal
Liver induration
Liver palpable subcostal
Liver scan abnormal
Liver tenderness
Mitochondrial aspartate aminotransferase increased
Molar ratio of total branched-chain amino acid to tyrosine
Oedema due to hepatic disease
Perihepatic discomfort
Retrograde portal vein flow
Total bile acids increased
Transaminases abnormal
Transaminases increased
Ultrasound liver abnormal
Urine bilirubin increased
X-ray hepatobiliary abnormal
5'nucleotidase increased
Blood alkaline phosphatase abnormal
Blood alkaline phosphatase increased
Blood cholinesterase abnormal
Blood cholinesterase decreased
Deficiency of bile secretion
Glutamate dehydrogenase increased
Haemorrhagic ascites
Hypoalbuminaemia
Leucine aminopeptidase increased
Periportal oedema
Peritoneal fluid protein abnormal
Peritoneal fluid protein decreased
Peritoneal fluid protein increased
Pneumobilia
Portal vein flow decreased
Portal vein pressure increased
Retinol binding protein decreased
Urobilinogen urine decreased
Urobilinogen urine increased

Liver-related coagulation and bleeding disturbances (SMQ)

Antithrombin III decreased
Blood fibrinogen abnormal
Blood fibrinogen decreased
Blood thrombin abnormal
Blood thrombin decreased

Blood thromboplastin abnormal
Blood thromboplastin decreased
Coagulation factor decreased
Coagulation factor IX level abnormal
Coagulation factor IX level decreased
Coagulation factor V level abnormal
Coagulation factor V level decreased
Coagulation factor VII level abnormal
Coagulation factor VII level decreased
Coagulation factor X level abnormal
Coagulation factor X level decreased
Hypocoagulable state
Hypofibrinogenaemia
Hypoprothrombinaemia
Hypothrombinaemia
Hypothromboplastinaemia
International normalised ratio abnormal
International normalised ratio increased
Protein C decreased
Protein S abnormal
Protein S decreased
Prothrombin level abnormal
Prothrombin level decreased
Prothrombin time abnormal
Prothrombin time prolonged
Prothrombin time ratio abnormal
Prothrombin time ratio increased
Thrombin time abnormal
Thrombin time prolonged

Hepatic disorders specifically reported as alcohol-related (SMQ)
Alcoholic liver disease
Cirrhosis alcoholic
Fatty liver alcoholic
Hepatitis alcoholic
Zieve syndrome

Liver infections (SMQ)
Acute hepatitis B
Acute hepatitis C
Adenoviral hepatitis
Asymptomatic viral hepatitis
Chronic hepatitis B
Chronic hepatitis C
Congenital hepatitis B infection

Cytomegalovirus hepatitis
HBV-DNA polymerase increased
Hepatic amoebiasis
Hepatic candidiasis
Hepatic cyst infection
Hepatic echinococciasis
Hepatic infection
Hepatic infection bacterial
Hepatic infection fungal
Hepatic infection helminthic
Hepatitis A
Hepatitis A antibody abnormal
Hepatitis A antibody positive
Hepatitis A antigen positive
Hepatitis A virus test positive
Hepatitis B
Hepatitis B antibody abnormal
Hepatitis B antibody positive
Hepatitis B core antibody positive
Hepatitis B core antigen positive
Hepatitis B DNA assay positive
Hepatitis B DNA increased
Hepatitis B e antibody positive
Hepatitis B e antigen positive
Hepatitis B surface antibody positive
Hepatitis B surface antigen positive
Hepatitis B virus test positive
Hepatitis C
Hepatitis C antibody positive
Hepatitis C RNA increased
Hepatitis C RNA positive
Hepatitis C virus test positive
Hepatitis D
Hepatitis D antibody positive
Hepatitis D antigen positive
Hepatitis D RNA positive
Hepatitis D virus test positive
Hepatitis E
Hepatitis E antibody abnormal
Hepatitis E antibody positive
Hepatitis E antigen positive
Hepatitis E virus test positive
Hepatitis F

Hepatitis G
Hepatitis H
Hepatitis infectious
Hepatitis infectious mononucleosis
Hepatitis mumps
Hepatitis non-A non-B
Hepatitis non-A non-B non-C
Hepatitis post transfusion
Hepatitis syphilitic
Hepatitis toxoplasmal
Hepatitis viral
Hepatitis viral test positive
Hepatobiliary infection
Hepatosplenic candidiasis
Herpes simplex hepatitis
Liver abscess
Schistosomiasis liver
Viral hepatitis carrier
Withdrawal hepatitis
Gianotti-Crosti syndrome
Portal pyaemia
Weil's disease
Pregnancy-related hepatic disorders (SMQ)
Acute fatty liver of pregnancy
Cholestasis of pregnancy

10.2 Appendix 2: Barthel Index of Activities of Daily Living

Barthel Index of Activities of Daily Living

Instructions: Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation. Refer to the Guidelines section on the following page for detailed information on scoring and interpretation.

The Barthel Index

Bowels
0 = incontinent (or needs to be given enemata)
1 = occasional accident (once/week)
2 = continent
Patient's Score: _____

Bladder
0 = incontinent, or catheterized and unable to manage
1 = occasional accident (max. once per 24 hours)
2 = continent (for over 7 days)
Patient's Score: _____

Grooming
0 = needs help with personal care
1 = independent face/hair/teeth/shaving (implements provided)
Patient's Score: _____

Toilet use
0 = dependent
1 = needs some help, but can do something alone
2 = independent (on and off, dressing, wiping)
Patient's Score: _____

Feeding
0 = unable
1 = needs help cutting, spreading butter, etc.
2 = independent (food provided within reach)
Patient's Score: _____

Transfer
0 = unable – no sitting balance
1 = major help (one or two people, physical), can sit
2 = minor help (verbal or physical)
3 = independent
Patient's Score: _____

Mobility
0 = immobile
1 = wheelchair independent, including corners, etc.
2 = walks with help of one person (verbal or physical)
3 = independent (but may use any aid, e.g., stick)
Patient's Score: _____

Dressing
0 = dependent
1 = needs help, but can do about half unaided
2 = independent (including buttons, zips, laces, etc.)
Patient's Score: _____

Stairs
0 = unable
1 = needs help (verbal, physical, carrying aid)
2 = independent up and down
Patient's Score: _____

Bathing
0 = dependent
1 = independent (or in shower)
Patient's Score: _____

Total Score: _____

(Collin et al., 1988)

Scoring:

Sum the patient's scores for each item. Total possible scores range from 0 – 20, with lower scores indicating increased disability. If used to measure improvement after rehabilitation, changes of more than two points in the total score reflect a probable genuine change, and change on one item from fully dependent to independent is also likely to be reliable.

Sources:

- Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud*. 1988;10(2):61-63.
- Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:61-65.
- Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *Int Disabil Stud*. 1988;10(2):64-67.

1

Guidelines for the Barthel Index of Activities of Daily Living

General

- The Index should be used as a record of what a patient ***does***, NOT as a record of what a patient ***could do***.
- The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
- The need for supervision renders the patient not independent.
- A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives, and nurses will be the usual source, but direct observation and common sense are also important. However, direct testing is not needed.
- Usually the performance over the preceding 24 – 48 hours is important, but occasionally longer periods will be relevant.
- Unconscious patients should score '0' throughout, even if not yet incontinent.
- Middle categories imply that the patient supplies over 50% of the effort.
- Use of aids to be independent is allowed.

Bowels (preceding week)

- If needs enema from nurse, then 'incontinent.'
- 'Occasional' = once a week.

Bladder (preceding week)

- 'Occasional' = less than once a day.
- A catheterized patient who can completely manage the catheter alone is registered as 'continent.'

Grooming (preceding 24 – 48 hours)

- Refers to personal hygiene: doing teeth, fitting false teeth, doing hair, shaving, washing face. Implements can be provided by helper.

Toilet use

- Should be able to reach toilet/commode, undress sufficiently, clean self, dress, and leave.
- 'With help' = can wipe self and do some other of above.

Feeding

- Able to eat any normal food (not only soft food). Food cooked and served by others, but not cut up.
- 'Help' = food cut up, patient feeds self.

Transfer

- From bed to chair and back.
- 'Dependent' = NO sitting balance (unable to sit); two people to lift.
- 'Major help' = one strong/skilled, or two normal people. Can sit up.
- 'Minor help' = one person easily, OR needs any supervision for safety.

Mobility

- Refers to mobility about house or ward, indoors. May use aid. If in wheelchair, must negotiate corners/doors unaided.
- 'Help' = by one untrained person, including supervision/moral support.

Dressing

- Should be able to select and put on all clothes, which may be adapted.
- 'Half' = help with buttons, zips, etc. (*check!*), but can put on some garments alone.

Stairs

- Must carry any walking aid used to be independent.

Bathing

- Usually the most difficult activity.
- Must get in and out unsupervised, and wash self.
- Independent in shower = 'independent' if unsupervised/unaided.

(Collin et al., 1988)

2

10.3 Appendix 3: Vulnerable Elder Survey

VES-13

1. Age _____

SCORE: *1 POINT FOR AGE 75-84*
3 POINTS FOR AGE ≥ 85

2. In general, compared to other people your age, would you say that your health is:

- ☐ Poor,* *(1 POINT)*
- ☐ Fair,* *(1 POINT)*
- ☐ Good,
- ☐ Very good, or
- ☐ Excellent

SCORE: *1 POINT FOR FAIR or POOR*

3. How much difficulty, on average, do you have with the following physical activities:

	No Difficulty	A little Difficulty	Some Difficulty	A Lot of Difficulty	Unable to do
a. stooping, crouching or kneeling?	☐	☐	☐	☐ *	☐ *
b. lifting, or carrying objects as heavy as 10 pounds?	☐	☐	☐	☐ *	☐ *
c. reaching or extending arms above shoulder level?	☐	☐	☐	☐ *	☐ *
d. writing, or handling and grasping small objects?	☐	☐	☐	☐ *	☐ *
e. walking a quarter of a mile?	☐	☐	☐	☐ *	☐ *
f. heavy housework such as scrubbing floors or washing windows?	☐	☐	☐	☐ *	☐ *

SCORE: *1 POINT FOR EACH * RESPONSE IN Q3a THROUGH f . MAXIMUM OF 2 POINTS.*

4. Because of your health or a physical condition, do you have any difficulty:

a. shopping for personal items (like toilet items or medicines)?

- ☐ YES → Do you get help with shopping? ☐ YES * ☐ NO
- ☐ NO
- ☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

b. managing money (like keeping track of expenses or paying bills)?

- ☐ YES → Do you get help with managing money? ☐ YES * ☐ NO
- ☐ NO
- ☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

Continued

c. walking across the room? USE OF CANE OR WALKER IS OK.

☐ YES → Do you get help with walking? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

d. doing light housework (like washing dishes, straightening up, or light cleaning)?

☐ YES → Do you get help with light housework? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

e. bathing or showering?

☐ YES → Do you get help with bathing or showering? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

SCORE: *4 POINTS FOR ONE OR MORE * RESPONSES IN Q4a THROUGH Q4e*

10.4 Appendix 4: Overactive Bladder Questionnaire

Participant Initials: _____ Participant ID #_____

OAB-q

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please place a ✓ or × in the box that best describes the extent to which you were bothered by each symptom during the past 4 weeks. There are no right or wrong answers. Please be sure to answer every question.

During the past 4 weeks, how bothered were you by. . .	Not at all	A little bit	Some-what	Quite a bit	A great deal	A very great deal
1. Frequent urination during the daytime hours?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. An uncomfortable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. A sudden urge to urinate with little or no warning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Accidental loss of small amounts of urine?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Nighttime urination?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Waking up at night because you had to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
7. An uncontrollable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
8. Urine loss associated with a strong desire to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

The above questions asked about your feelings about individual bladder symptoms. For the following questions, please think about your overall bladder symptoms in the past 4 weeks and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a ✓ or × in the box that best answers each question.

US English OAB-q, ver 1.0, 2004 1

Participant Initials: _____ Participant ID #_____

During the past 4 weeks, how often have your bladder symptoms . . .	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
9. Made you carefully plan your commute?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Caused you to plan "escape routes" to restrooms in public places?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
12. Caused you distress?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
13. Frustrated you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
14. Made you feel like there is something wrong with you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
15. Interfered with your ability to get a good night's rest?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
16. Caused you to decrease your physical activities (exercising, sports, etc.)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
17. Prevented you from feeling rested upon waking in the morning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
18. Frustrated your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
19. Caused you anxiety or worry?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
20. Caused you to stay home more often than you would prefer?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
21. Caused you to adjust your travel plans so that you are always near a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
22. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
23. Made you frustrated or annoyed about the amount of time you spend in the restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
24. Awakened you during sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

US English OAB-q, ver 1.0, 2004 2

Participant Initials: _____ Participant ID #_____

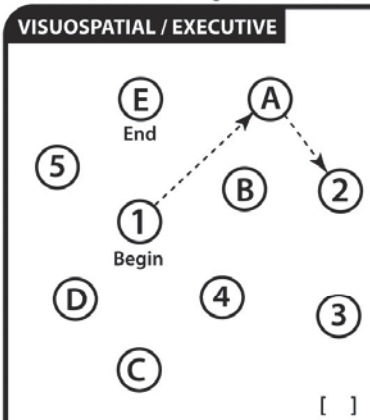
During the past 4 weeks, how often have your bladder symptoms . . .	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
25. Made you worry about odor or hygiene?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
26. Made you uncomfortable while traveling with others because of needing to stop for a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
27. Affected your relationships with family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
28. Caused you to decrease participating in social gatherings, such as parties or visits with family or friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
30. Interfered with getting the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
31. Caused you to have problems with your partner or spouse?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
32. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
33. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

10.5 Appendix 5: Montreal Cognitive Assessment

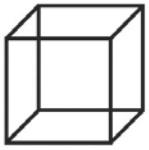
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



[ ] [ ]

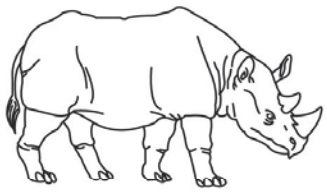
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

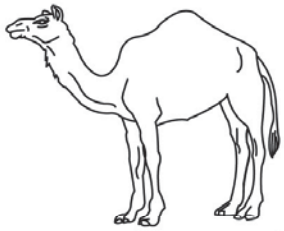
__/5

NAMING

[ ]



[ ]



[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2
__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**
__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]
__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)
__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler
__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
__/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

10.6 Appendix 6: Signatures

Prepared by: [redacted] Date: [redacted]

REASON: I approve this document

[redacted]

[redacted] Date (DD Mmm YYYY)

Reviewed by: [redacted]

REASON: approve this document

[redacted]

[redacted] Date (DD Mmm YYYY)

Approved by: [redacted]

REASON: I approve this document

[redacted]

[redacted] Date (DD Mmm YYYY)

Reviewed by: [redacted]

REASON: I approve this document

[redacted]

[redacted] Date (DD Mmm YYYY)