CLINICAL PROTOCOL

Title:

A clinical trial of mirabegron for overactive bladder symptoms in patients with Parkinson Disease and impaired cognition (MICT-PD)

Compound Name:	Mirabegron
ClinicalTrials.gov Number:	
Document Date:	June 29, 2016
Protocol Version:	1.0, Amendment 05
Phase:	4
Sponsor:	Struthers Parkinson's Center, HealthPartners Institute

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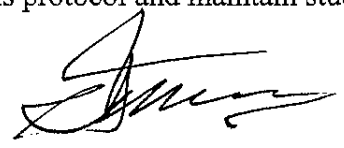
STATEMENT OF COMPLIANCE

This document is a protocol for a human research study. This study will be conducted according to US and International standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

All individuals responsible for the design and conduct of this study have completed Human Participants Protection Training and are qualified to be conducting this research prior to the enrollment of any participants.

As Principal Investigator, I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. Modifications to the study are acceptable only with an approved protocol amendment. I agree to obtain approval from the IRB and/or regulatory bodies of competent jurisdiction, for the protocol and informed consent before initiating the study, to obtain consent from participants prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse event and study reports as required by this protocol and maintain study documentation for the period of time required.



Sotirios A. Parashos, MD, PhD

6/29/2016

Date

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TERMS AND ABBREVIATIONS

Abbreviation	Definition
3-day VD	Voiding diary
AE	Adverse event
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory-II
BOO	Bladder outlet obstruction
CI	Impaired cognitive function
CL_{cr}	Creatinine clearance
CQ	Constipation questions
CRF	Case Report Forms
DBP	Diastolic blood pressure
DSMC	Data Safety and Monitoring Committee
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
eGFR	Glomerular filtration rate
HRQL	Health-Related Quality of Life
HVLT	Hopkins Verbal Learning Test
MoCA	Montreal Cognitive Assessment
NYHA	New York Heart Association
OAB	Overactive bladder
OABQ	Overactive Bladder Questionnaire
PD	Parkinson Disease
PFS	Parkinson Fatigue Scale
PI	Principal Investigator
PIMS	Parkinson's Impact Scale
PPBC	Patient Perception of Bladder Condition
PVR	Post-void residual
SBP	Systolic blood pressure
SF	Semantic Fluency
TMT A	Trail Making Test, part A

TMT B	Trail Making Test, part B
UPDRS I, II, III, IV	Unified Parkinson's Disease Rating Scale parts I, II, II, IV
UPDRS-6	UPDRS Question 6 regarding excessive salivation
VS	Vital signs
WOCP	Women of childbearing potential

STUDY SYNOPSIS

Name of Sponsor: Struthers Parkinson's Center, Park Nicollet Institute
Name of Investigational Product: Mirabegron (Myrbetriq®) in 25 mg extended release tablets; matching placebo tablets.
Study Title: A clinical trial of mirabegron for overactive bladder symptoms in patients with Parkinson Disease and impaired cognition (MICT-PD)
Study Center: Struthers Parkinson's Center, Park Nicollet Methodist Hospital, Park Nicollet Health Services, Golden Valley, MN USA
Study Duration: Approximately 16 months (from enrollment of first subject to last subject completion)
Phase of Development: 4
Indication: Overactive bladder (OAB) symptoms in patients with Parkinson Disease (PD) and impaired cognitive function (CI)
Rationale: There is a high prevalence of OAB symptoms among patients with Parkinson's disease and a lack of pharmacotherapies with an acceptable side effect profile. Specifically, available anticholinergic medications have a high risk of cognitive side-effects, which preclude their use in PD patients with CI. PD can also cause a number of non-motor symptoms that are likely to be adversely affected by the currently available anticholinergic agents. Mirabegron is the first pharmacologic treatment which may not exacerbate CI, constipation, orthostatic hypotension (OH), somnolence, and dry mouth in PD.
Objectives: **Primary Objective:** • To assess cognitive tolerability of mirabegron while treating OAB in PD patients with CI. **Secondary Objectives:** • To assess the efficacy of mirabegron for treating OAB symptoms in PD with CI. • To assess the effect of mirabegron on health related quality of life in PD patients with OAB symptoms and CI. • To assess the effect of mirabegron on excessive daytime sleepiness in PD patients with OAB symptoms and CI. **Exploratory analyses:**

- To assess the effects of mirabegron on orthostatic changes in blood pressure in PD patients with OAB symptoms and CI.
- To assess the effect of mirabegron on depressive and anxiety symptomatology, excessive salivation, and constipation in PD patients with OAB symptoms and CI.
- To assess effects of mirabegron on PD motor symptom severity in PD patients with OAB symptoms and CI.

Study Design:
This is a pilot study conducted in one study center. Study design will be a randomized, double-blind, placebo-control study. Subjects will receive a two-week, single-blind placebo run-in followed by 2 weeks of a 1:2 randomized double-blind phase (placebo:25 mg mirabegron), followed by 10 weeks dose escalation (placebo:50 mg mirabegron), followed by a two-week washout period.

Study Duration:
Maximum participation will be 20 weeks, consisting of 2-4 weeks screening period, 2 weeks of placebo run-in, 12 weeks of double-blind placebo-controlled treatment, and 2 weeks of safety follow up.

Study Population:
Adult ambulatory outpatients with PD, CI, and OAB symptoms.

Statistical Analysis:
Descriptive statistics will be performed. The primary group for analysis will consist of all subjects who received at least one dose during the double-blind placebo-controlled phase. Analyses will compare change from randomization (visit 3) to end of treatment (visit 7). Tests of equivalence will be performed on primary, secondary and exploratory outcomes, with significance level of $p<.05$.

Study Procedures:
Refer to the Study Schedule/Flowchart, below.

Number of Subjects: 30 (20 active treatment, 10 placebo group).

Eligibility criteria:

INCLUSION CRITERIA:

1. Aged 25-80 at screening. Subjects older than 80 will be allowed at the discretion of the PI.
2. Ambulatory (defined as able to ambulate at least 10 meters, with or without assistance).
3. Clinical Diagnosis of PD based on the United Kingdom Brain Bank diagnostic criteria for PD.
4. At baseline visit (Visit 2) patients must have:
    a. At least 8 micturitions per 24 hours and

b. At least 3 urgency episodes per 3-day diary.

5. A MoCA score between 19 and 28 (inclusive) at screening. For those on cognitive enhancers (donepezil, rivastigmine, memantine, galantamine) a MoCA score between 19 and 29 (inclusive) at screening.
6. Provide informed consent to participate in the study and understand that they may withdraw their consent at any time without prejudice to their future medical care.
7. Be cognitively capable, in the opinion of investigator, to understand and provide such informed consent.
8. Be cognitively capable to complete the required questionnaires and assessments, OR have a care partner who is willing and capable to assist them in the completion of these tasks.
9. Be on a stable regimen of antiparkinson's medications at least 30 days prior to screening, and be expected to remain on a stable dose for the duration of the study.
10. If taking cognitive enhancers (donepezil, rivastigmine, memantine, galantamine), must be on stable dose at least 30 days prior to screening, and be expected to remain on a stable dose for the duration of the study.

EXCLUSION CRITERIA:

1. Known or suspected alcohol or substance abuse in the preceding 12 months.
2. Women who are pregnant or breastfeeding.
3. Women of childbearing potential (WOCP) who are not using at least one method of contraception.
4. Patients with severe renal impairment ($CL_{cr} \leq 29$ mL/min, or eGFR ≤ 29 mL/min/1.73 m^2), or moderate or severe hepatic impairment (Child-Pugh classes B or C).
5. Patients with bladder outlet obstruction (BOO) that, in the opinion of the study urologist, would expose them to risk of urinary retention during treatment with mirabegron.
6. Patients treated with drugs that require dose adjustment when co-administered with CYP2D6 inhibitors.
7. Patients with supine systolic blood pressure (SBP) ≥ 180 mm Hg, or diastolic blood pressure (DBP) ≥ 110 mm Hg.
8. Clinically significant, uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure (NYHA Class 3 or 4), or history of myocardial infarction in the preceding 2 years.
9. History of cancer in the preceding 2 years other than successfully treated, non-metastatic, squamous cell or basal cell carcinoma, or cervical cancer in situ.
10. Any major urological procedure in the preceding 90 days.
11. Any major surgical procedure in the preceding 30 days.
12. Previously treated with mirabegron within 60 days prior to the baseline visit (Visit 2), or previously having failed treatment with mirabegron regardless of duration and timing of treatment.

13. Current or previous, within the 60 days preceding the baseline visit (Visit 2), treatment with antimuscarinic agents for OAB symptoms; and, willingness to not use antimuscarinic agents for the duration of the study.
14. Currently receiving any other investigational drug or having received an investigational drug within the 60 days preceding the baseline visit (Visit 2).
15. Any condition or laboratory test result, which, in the opinion of the Investigator or the Study Urologist, might result in an increased risk to the patient, or would affect their participation in the study.
16. Any patient who, in the opinion of the Investigator, is not a good candidate for the study or will not be able to follow study procedures.

Dosage and Administration:
During the 2-week run-in placebo period all subjects will receive placebo tablets matching the 25 mg mirabegron extended release tablets. During the first two weeks of the double-blind placebo-controlled phase, subjects will be randomized to either 25 mg extended release mirabegron or matching placebo (2:1 ratio). During the following 10 weeks of the double-blind placebo-controlled phase, subjects tolerating treatment without side-effects will be escalated to 50 mg mirabegron (two 25 mg mirabegron extended release tablets) or matching placebo (two placebo tablets); subjects experiencing side-effects that do not preclude continuation of the study will continue at the dosage level of one 25 mg extended release mirabegron tablet or matching placebo daily. Subjects who have escalated to 50 mg mirabegron or matching placebo and experience side-effects at that level, will be allowed one dose reduction to 25 mg mirabegron or matching placebo.
Depending on dose level, one or two tablets will be administered daily, with or without food, swallowed whole with water; chewing, crushing or dividing is not allowed.

Primary Endpoint:
Relative mean change to the MoCA score between randomization visit (Visit 3) and week 14 visit (Visit 7).

Table 1. Schedule of Activities:

VISIT/PROCEDURE:	Screening Visit	Baseline Visit	Randomization	Low dose phase	Dose escalation	High dose phase	End of TX / Early Term	Follow-up / Week 16
Visit number	1	2	3	4 phone	5	6	7	8
Visit time	week -4 to -6	week -2	day 0	day 7	day 14	day 42	day 84	day 98
Informed consent	X							
Inclusion/Exclusion criteria	X							
Past history/demographic	X							
Neurological and physical exam	X	X			X		X	X
Urologic exam	X *				X*			X*
Cystoscopy	X*							
Concomitant medication	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Study drug compliance			X	X	X	X	X	
UPDRS	X				X		X	X
Vital signs (includes weight, height and orthostatics)	X	X	X		X		X	X
ECG	X				X		X	
Pregnancy test (for WOCP)	X							X
Urinalysis	X*				X*		X	X*
Blood samples (safety)	X						X	
OABQ	X		X		X	X	X	
3-day VD training and concordance	X							
3-day VD assessment		X	X		X	X	X	
PVR	X*				X*			X*
PPBC		X	X		X	X	X	X
CQ			X				X	
UPDRS-6			X				X	
MoCA	X		X				X	
Map Search			X				X	
HVLT			X				X	
TMT A and B			X				X	
BAI			X				X	
BDI-II			X				X	
ESS			X				X	
PFS			X				X	
PIMS			X				X	
Drug dispense		X	X			X		

* Procedures performed during the urology visit

1.0 INTRODUCTION

1.1 Background

1.1.1 Parkinson Disease

Parkinson disease (PD) is a chronic, progressive degenerative disease of the nervous system. The disease affects approximately 7 out of every 1000 persons above the age of 40, 3 out of every 100 persons older than 80, and its incidence increases dramatically with age.[1,2] Apart from the well-known motor dysfunction, PD causes numerous non-motor symptoms at every stage of the disease.[3]

1.1.2 PD and urinary tract symptoms

Bladder dysfunction in the form of lower urinary tract symptoms has been reported in 38-71% of patients with PD[4] and even in the early and untreated stages.[5] Various types of lower urinary symptoms have been reported in PD patients, but storage related symptoms are the most common, relating to detrusor overactivity and uninhibited external sphincter relaxation, which are the main contributors to overactive bladder in PD. Such bladder dysfunction has a well-recognized negative impact on the quality of life of patients suffering from chronic neurologic diseases.[6] In more general terms, beyond bladder dysfunction, PD pathology affects the entire sympathetic chain, and particularly adrenergic neurons, resulting in a variety of dysautonomic symptoms.

1.1.3 PD and cognitive dysfunction

Another category of non-motor symptoms of PD is that of cognitive deficits, which can be mild, yet often obtrusive in early PD, even in the absence of dementia. Such deficits may include impaired attention, impaired recall but not recognition, executive dysfunction, and visuospatial impairment,[7] and may affect activities of daily living, employment status, and quality of life.[8] Dementia occurs in more advanced stages of PD, and its prevalence in PD is reported between 11% and 36%.[9] When compared to their age-peers, patients with PD have a five- to six-fold risk for dementia.[10] As the presence of dementia adversely affects the natural history and prognosis of PD,[11,12] preserving cognition is an important element in the clinical management of PD.

1.1.4 Current treatment of overactive bladder in PD

Current treatment of overactive bladder (OAB) in PD relies primarily on the use of anticholinergic agents, such as oxybutynin, tolterodine, solifenacin and darifenacin.[13] Unfortunately, no clinical trials assessing efficacy and tolerability of these agents in the

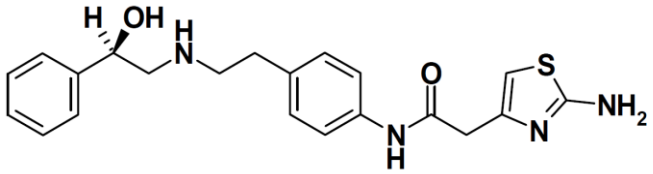
PD population have been conducted. None of these medications' list of adverse effects include the potential for cognitive dysfunction, yet this has been well demonstrated for the case of oxybutynin.[14] Tolterodine, solifenacin and darifenacin have virtually no information on their impact on patient populations vulnerable to cognitive adverse effects, so the current clinical practice is that they should be used "with caution".[15] The current clinical practice consensus is that such medications should be avoided in Parkinson patients with overactive bladder and cognitive dysfunction. Botulinum toxin injections have shown some effectiveness in this population, but this is an off-label use.[16]

1.1.5 Mirabegron

Mirabegron is a selective β_3 adrenoreceptor agonist approved in the USA for the treatment of overactive bladder symptoms under the brand name Myrbetriq®, produced by Astellas Pharma. A recent meta-analysis of the four phase III randomized clinical trials of mirabegron in the treatment of overactive bladder concluded that the compound is an effective and safe treatment for the treatment of overactive bladder symptoms, combining data from a total of 5,761 participants.[17]

1.1.6 Pharmacology (Myrbetriq Full Prescribing Information - Appendix I)

Mirabegron is a beta-3 adrenergic agonist. The chemical name is 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide with the empirical formula of C21H24N4O2S and molecular weight of 396.51. The structural formula of mirabegron is:



Mirabegron is a white powder. It is practically insoluble in water (0.082 mg/mL). It is soluble in methanol and dimethyl sulfoxide. Each Myrbetriq® extended release tablet for oral administration contains either 25 mg or 50 mg of mirabegron and the following inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide (25 mg tablet only).

1.2 Clinical experience with mirabegron: efficacy, safety, and tolerability

Mirabegron efficacy, safety and tolerability were evaluated in three 12-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trials. Long-

term safety and tolerability were further assessed in one 12-month, double-blind, randomized, active-control, parallel-group, multicenter clinical trial in patients with overactive bladder with symptoms of urinary incontinence and urinary frequency. Entry criteria for each of the four clinical trials required that patients had symptoms of overactive bladder ≥3 months, ≥8 micturitions per day, and ≥3 episodes of urgency with or without incontinence over a 3-day period.[18-21] (see Myrbetriq Full Prescribing Information, Appendix 1) It is estimated that over 10,500 subjects have received mirabegron in clinical trials over approximately 10 years, with over 5,500 patients with OAB symptoms having received the drug during Phase II and III clinical trials sponsored by Astellas.[22]

In Phase III clinical trials, mirabegron showed significant efficacy in treating the symptoms of OAB at daily doses of 25, 50, and 100 mg. Specifically, improvements were demonstrated in micturition frequency, urgency incontinence, and urgency. At daily doses of 50 and 100 mg of mirabegron, sustained improvements were attained as early as during week 4. Among responders, the magnitude of the therapeutic effect measured an at least 50% reduction in mean daily (24h) number of incontinence episodes, and in the proportion of patients with 8 daily (24h) micturitions or less. Of importance to the present discussion, patients aged 65 or older benefited from mirabegron 50 and 100 mg. Long-term clinical trials of up to 12 months demonstrated good long term safety and tolerability. The most common adverse events included hypertension, nasopharyngitis, and urinary tract infection. When looking specifically at anticholinergic side effects, the incidence of dry mouth was similar to placebo, and was between three and fivefold less than for tolterodine extended release 4 mg.

1.3 Study rationale

Clinical trials of mirabegron found no central nervous system-related adverse events, such as confusion and somnolence. Its pharmacology would suggest that it has no central nervous system action, and hence should be well tolerated in patient populations vulnerable to cognitive adverse effects. This is of special interest to the PD population, because confusion, hallucinations and somnolence are common side effects among PD patients treated with anticholinergic agents (current standard of practice) for overactive bladder symptoms, although unfortunately this statement cannot be supported by clinical trials which do not exist yet constitute the experience of most experts treating PD patients. Apart from the cognitive issues, sympathetic dysfunctions are very common non-motor manifestation of PD, one of the most disruptive being orthostatic hypotension. Mirabegron is a peripheral sympathomimetic agent, and it is reasonable to assume that the use of mirabegron in PD patients may result in improved sympathetic function, conceivably lessening the burden of these symptoms.

1.3.1 Dose and schedule of administration

Current prescribing recommendations for mirabegron include an initial dose of 25 mg daily for 8 weeks with subsequent escalation to 50 mg depending on efficacy and tolerability. Daily doses of 25, 50, and 100 mg have been proven both efficacious and safe. Due to the limited duration of the present protocol, dose escalation was contracted to 2 weeks, allowing for a one-time dose reduction after escalation if problems with tolerability arise. Because of the pilot character of this study, the allowed daily dose was limited to 25 and 50 mg. No dose adjustment is necessary for age. This was a consideration as it is expected that the majority of the enrolled subjects will fall within this age demographic, simply because of the age effect on prevalence of PD. Dose adjustments are recommended for severe renal and moderate hepatic impairments. Again, given the pilot character of the present protocol, subjects with these impairments are excluded from participation.

1.3.2 Selection of primary outcome

Although it may seem unusual for a clinical trial on OAB, a global cognitive measure was selected as the primary outcome measure, since the essence of this trial lies in demonstrating cognitive tolerability of this medication in PD patients with overactive bladder. The Montreal Cognitive Assessment[23] (see Appendix II) was chosen as a concise, comprehensive, and sensitive global measure of cognitive dysfunction, with proven accuracy in PD.[24] In this patient group, it has been demonstrated to be superior to the Minimental State Examination (MMSE) and equivalent to the more extensive and time consuming Scales for Outcomes in Parkinson disease-Cognition (SCOPA-COG)[25] in detecting mild cognitive impairment. The instrument takes approximately 10 minutes to administer, and contains tests of the cognitive domains of attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Three versions are available to improve test-retest reliability and reduce practice effects. It is scored 0-30, with higher scores reflecting better cognitive function. Normative data have been developed and cut-off scores are available.[26] A score of <26 is considered a cutoff for both mild cognitive impairment and dementia.

In this protocol we use the MoCA both as an outcome measure and as an inclusion and exclusion criterion. The purpose of this study is to examine the cognitive tolerability of mirabegron in PD patients with some impaired cognitive function (CI), yet not having cognitive dysfunction of an extent that would a) interfere with the subject's ability to participate in study procedures and provide informed consent or b) affect the subject's

ability to control bodily functions and thus interfere with measures of efficacy. Additionally there is a mounting evidence in the literature that the cut off of 26 may be too strict, with 66% of subjects in a recent population based study falling below this suggested cutoff.[27]

2. STUDY OBJECTIVES

Study objectives will focus on cognitive tolerability of mirabegron in PD patients with CI and OAB, while demonstrating efficacy in this population; exploratory analyses will look for potential positive or negative impact of the intervention on motor and non-motor aspects of PD.

2.1 Primary objective

The primary objective of this experimental protocol is to assess cognitive tolerability of mirabegron while treating OAB symptoms in patients with PD and CI.

2.2 Secondary objectives

Secondary objectives will assess efficacy of mirabegron in PD and the impact of mirabegron on other non-motor symptoms in PD:

- To assess the efficacy of mirabegron for treating OAB symptoms in PD with CI.
- To assess the effect of mirabegron on health related quality of life in PD patients with OAB symptoms and CI.
- To assess the effect of mirabegron on excessive daytime sleepiness in PD patients with OAB symptoms and CI.

2.3 Exploratory analyses

As discussed earlier, PD has a number of non-motor symptoms resulting from peripheral sympathetic dysfunction, which could conceivably respond favorably to mirabegron. It is also of interest to ensure that mirabegron does not worsen any of the motor and non-motor symptoms of PD. Although as per protocol any worsening of these symptoms will be logged as an adverse event (AE), more specific evaluations utilizing dedicated measures will also be obtained and analyzed. Therefore, additional exploratory analyses will be performed:

- To assess the effects of mirabegron on orthostatic changes in blood pressure in PD patients with OAB symptoms and CI.
- To assess the effects of mirabegron on depressive and anxiety symptomatology, excessive salivation, and constipation in PD patients with OAB symptoms and CI.

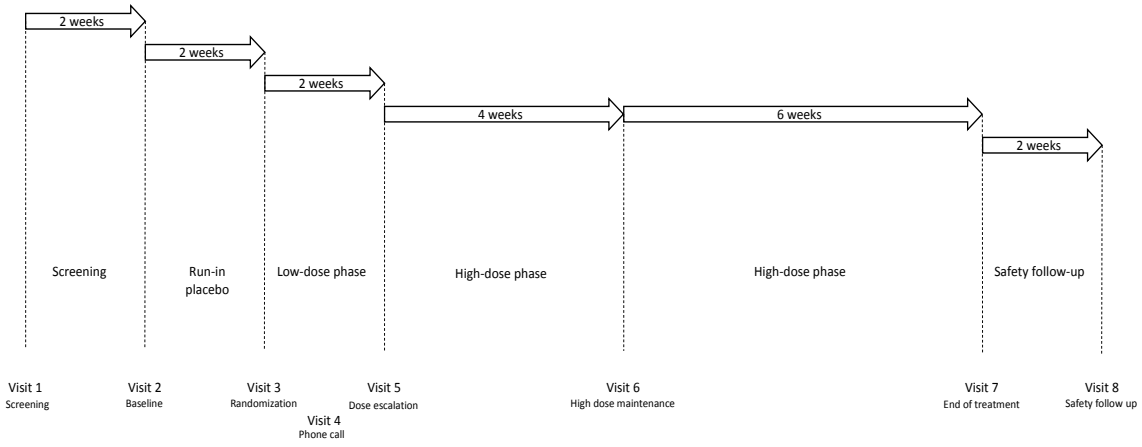
- To assess effects of mirabegron on PD motor symptom severity in PD patients with OAB symptoms and CI.

3.0 STUDY METHODOLOGY

3.1 Study design

This is a single-site, randomized, parallel-group, placebo-controlled, double-blind pilot study with a 12-week treatment period, consisting of an initial 2-week, single-blind placebo run-in, followed by 2-week randomization to low dose mirabegron (total daily dose of 25 mg) vs. placebo (2:1 active vs. placebo randomization), followed by 10-week, dose escalation randomization to high dose mirabegron (total daily dose of 50 mg) vs. placebo. Study design is outlined in figure 1.

Figure 1 Study design



3.2 Subject Selection

3.2.1 Number of subjects and assignment to treatment groups

A sufficient number of subjects will be screened and randomized until 30 subjects have received at least 1 dose of double-blind study medications (i.e. complete visit 3 and receive at least one dose of study drug after randomization). An effort will be made to assign equal proportions of men and women into the two treatment assignments. Randomization will be a 2:1 ratio between mirabegron and placebo.

3.2.2 Study site

The study will be conducted in a single study location: Struthers Parkinson's Center SPC), Park Nicollet Methodist Hospital, Park Nicollet Health Services, Golden Valley, Minnesota, United States of America. The center is nationally recognized for its team approach to PD management, and is a designated Center of Excellence of the National Parkinson Foundation. Staff includes 4 neurologists and 18 additional FTEs. The center is part of Park Nicollet Health Services, which recently merged with Health Partners. SPC research staff includes a Lead Physician for Clinical Research, a full-time Research Director, and two full-time RN/BSN-level Research Coordinators. SPC research staff have participated in numerous clinical trials of PD, Huntington disease and related disorders, continuously since 1998. The center currently provides medical and allied health services for approximately 1500 outpatients with PD. The immediate referral network includes 8 neurologists and numerous primary care providers of the Park Nicollet Health Services, and 34 neurologists of the Minneapolis Clinic of Neurology Ltd.

3.2.3 Study population

Adult ambulatory outpatients with PD and CI with OAB symptoms, who fulfill inclusion criteria. The degree of CI and OAB symptom severity necessary for participation are defined by the inclusion criteria. Subjects will be required to have been on a stable regimen of antiparkinsonian agents and/or cognitive enhancers for 30 days prior to screening, and be expected to remain so for the duration of the study.

3.3 Inclusion Criteria

1. Aged 25-80 at screening. Subjects older than 80 will be allowed at the discretion of the PI.
2. Ambulatory (defined as able to ambulate at least 10 meters, with or without assistance).
3. Clinical Diagnosis of PD based on the United Kingdom Brain Bank diagnostic criteria for PD.[28]
4. At baseline visit (Visit 2) patients must have:
    a. At least 8 micturitions per 24 hours and
    b. At least 3 urgency episodes per 3-day diary.
5. A MoCA score between 19 and 28 (inclusive) at screening. For those on cognitive enhancers (donepezil, rivastigmine, memantine, galantamine) a MoCA score between 19 and 29 (inclusive) at screening.
6. Provide informed consent to participate in the study and understand that they may withdraw their consent at any time without prejudice to their future medical care.

7. Be cognitively capable, in the opinion of investigator, to understand and provide such informed consent.
8. Be cognitively capable to complete the required questionnaires and assessments, OR have a care partner who is willing and capable to assist them in the completion of these tasks.
9. Be on a stable regimen of antiparkinson's medications at least 30 days prior to screening, and be expected to remain on a stable dose for the duration of the study.
10. If taking cognitive enhancers (donepezil, rivastigmine, memantine, galantamine), must be on stable dose at least 30 days prior to screening, and be expected to remain on a stable dose for the duration of the study.

3.4 Exclusion Criteria

1. Known or suspected alcohol or substance abuse in the preceding 12 months.
2. Women who are pregnant or breastfeeding.
3. Women of childbearing potential (WOCP) who are not using at least one method of contraception.
4. Patients with severe renal impairment ($CL_{cr} \leq 29$ mL/min, or eGFR ≤ 29 mL/min/1.73 m^2), or moderate or severe hepatic impairment (Child-Pugh classes B or C).
5. Patients with bladder outlet obstruction (BOO) that, in the opinion of the study urologist, would expose them to risk of urinary retention during treatment with mirabegron.
6. Patients treated with drugs that require dose adjustment when co-administered with CYP2D6 inhibitors.
7. Patients with supine systolic blood pressure (SBP) ≥ 180 mm Hg, or diastolic blood pressure (DBP) ≥ 110 mm Hg.
8. Clinically significant, uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure (NYHA Class 3 or 4), or history of myocardial infarction in the preceding 2 years.
9. History of cancer in the preceding 2 years other than successfully treated, non-metastatic, squamous cell or basal cell carcinoma, or cervical cancer in situ.
10. Any major urological procedure in the preceding 90 days.
11. Any major surgical procedure in the preceding 30 days.
12. Previously treated with mirabegron within 60 days prior to the baseline visit (Visit 2), or previously having failed treatment with mirabegron regardless of duration and timing of treatment.

13. Current or previous, within the 60 days preceding the baseline visit (Visit 2), treatment with antimuscarinic agents for OAB symptoms; and, willingness to not use antimuscarinic agents for the duration of the study.
14. Currently receiving any other investigational drug or having received an investigational drug within the 60 days preceding the baseline visit (Visit 2).
15. Any condition or laboratory test result, which, in the opinion of the Investigator or the Study Urologist, might result in an increased risk to the patient, or would affect their participation in the study.
16. Any patient who, in the opinion of the Investigator, is not a good candidate for the study or will not be able to follow study procedures.

3.5 Criteria for study discontinuation or early treatment termination

Study discontinuation may occur as a result of a decision from regulatory authorities, change of the opinion of the Park Nicollet Institutional Review Board (IRB), safety concerns raised by the Data and Safety Monitoring Committee (DSMC), or unavailability of the study drug.

The investigator retains the right to terminate the study at any time and for any reasons. Such study termination, however, will be subject to adequate consideration of the subjects' interests.

Individual subjects will be terminated from the study if they withdraw consent. In that instance, every effort will be made for the subject to attend an early termination visit and safety follow up.

Subjects may be withdrawn from the study at the discretion of the Investigator, for considerations relating to subject safety, or for non-adherence or loss of ability to comply with study requirements.

3.6 Registration

All materials and procedures will be approved by the Park Nicollet Institute Institutional Review Board (IRB) before recruitment begins. Over a 12 month period, all eligible patients will be screened by the research staff for enrollment. Informed consent will be signed prior to the performance of any study related procedures or assessments.

During screening, the investigator or designee is to assess the need and requirements for a caregiver during the course of the study, and to assure the commitment of the person(s) so designated.

Subjects will be considered enrolled into the study after they have signed the informed consent, have met all study mandated inclusion/exclusion criteria, and are enrolled at Visit 2 (Day 0, Baseline).

3.7 Randomization

After a 2-week run-in period in which all subjects take placebo in a single-blinded fashion, subjects will be randomized to a blinded dose of study drug at their randomization visit. This is a double-blind, pilot study. Neither the subject, treating physician, principal investigator, co-investigators, nor study coordinators will know to which group the subject has been randomized. The randomization scheme will be prepared by the study statistician. Study subjects will receive identical tablets in identical containers which will contain either 25 mg mirabegron extended release or placebo tablets, depending on which group they are randomized to. Study subjects will be instructed to take study drug in the morning with food and 8 ounces of water. A subject's dose assignment will be un-blinded if the Medical Monitor and PI determine it is medically necessary (for instance, allergic reaction).

3.8 Identification

At the time of study enrollment all subjects will be assigned a unique subject number. This identification number, in combination with the subject's initials, will be used as the identifier on all case report forms and study related documentation.

3.9 Visit and assessment schedule

3.9.1 Screening (Visit 1)

Written informed consent will be obtained before any study specific procedures are undertaken. Visit 1 has to be completed at least 2 weeks and no longer than 4 weeks prior to baseline visit, to allow sufficient time to review collected information and determine subject eligibility for participation. Urology screening procedures (urologic examination with cystoscopy, urinalysis and PVR) can be conducted anytime between Visit 1 and one week prior to baseline, including the same day as visit 1, but procedures for visit 1 have to precede urology visit.

Screening visit 1 will be conducted by the Investigator, or his designee, and will include:

- Review and signing of the written informed consent
- Assignment of patient identification number
- Review of inclusion and exclusion criteria

- Demographics
- Review of medical history
- Review of concomitant medications
- Vital signs, including weight, height, and orthostatics
- Physical examination
- Neurological Examination
- Unified Parkinson's Disease Rating Scale (UPDRS)
- 12-lead ECG recording
- Blood samples for chemistry and hematology (Na, K, Cl, HCO_3, blood glucose, BUN, creatinine, GFR, AST, ALT, total bilirubin, Alkaline phosphatase, GGT, CBC with differential and platelets)
- Montreal Cognitive Assessment (MoCA)
- Overactive Bladder Questionnaire (OABQ)
- 3-day VD training and concordance
- Serum pregnancy test (SPT) for WOCP
- Urologic examination with cystoscopy
- Urinalysis
- Post-void residual

All screening visit results must be reviewed by the Investigator or designee prior to Visit 2. In cases of screen failure resulting from treatable and reversible causes (e.g. urinary tract infection, other intercurrent illness during the screening period, etc.) or scheduling conflict, the screening period can be extended up to 56 days at the Investigator's discretion, provided subject still meets eligibility criteria. Screening assessments may need to be repeated at the Investigator's discretion.

3.9.2 Baseline (Visit 2; Day -14)

The baseline visit (Visit 2) will occur 14-28 days from Screening visit 1. Procedures will be conducted by the Investigator or designee:

- Concomitant medications
- Adverse events
- Vital signs, weight, height, and orthostatics
- Physical Examination
- Neurological Examination
- 3-day VD assessment
- Patient Perception of Bladder Condition (PPBC)
- Study drug dispense

At the end of the baseline visit, subjects will be dispensed study drug sufficient for the run-in period (to last until Visit 3). At this time, subjects will be dispensed placebo in a single-blinded fashion (subjects will be unaware that they are receiving placebo). Study drug will be in the form of mirabegron 25 mg extended release-matching placebo tablets, and will be given in a dose of 1 tablet daily. The intent of the single-blind, placebo phase is to minimize the impact of the placebo effect.

3.9.3 Randomization (Visit 3; Day 0)

Randomization visit procedures will aim at collecting data that will be utilized as baseline measures for the statistical analysis for primary and secondary outcomes, and exploratory analyses.

- Concomitant medications
- Adverse events
- Study drug compliance
- Vital signs, weight, height, and orthostatics
- OABQ
- 3-day VD assessment
- PPBC
- CQ
- UPDRS-6
- MoCA
- Map Search
- Hopkins Verbal Learning Test (HVLT)
- Trail Making Test (TMT) parts A and B
- Beck Anxiety Inventory (BAI)
- Beck Depression Inventory version II (BDI-II)
- Epworth Sleepiness Scale (ESS)
- Parkinson Fatigue Scale (PFS)
- Parkinson's Impact Scale (PIMS)
- Study drug dispense

At the conclusion of the randomization visit, subjects will be randomized in a double-blind fashion in a ratio of 2:1 to mirabegron 25 mg daily vs. placebo. Study drug will be administered in the form of 1 mirabegron 25 mg extended release matching placebo tablet daily (placebo arm) or 1 mirabegron 25 mg extended release tablet daily (active treatment arm). Thus all subjects will continue to receive 1 tablet daily. Sufficient study drug will be dispensed to last until Visit 6.

3.9.4 Low-dose phase maintenance visit (Visit 4 - telephone call; Day 7)

The purpose of this telephone call is to assess adverse events and medication compliance. It can be conducted via telephone interview.

- Concomitant medications
- Adverse events
- Study drug compliance

3.9.5 Dose escalation visit (Visit 5; Day 14)

The purpose of this visit is to assess adverse events, medication compliance, and obtain interim measures for analyses.

- Concomitant medications
- Adverse events
- Study drug compliance
- Vital signs, weight, height, and orthostatics
- Physical Examination
- Neurological Examination
- ECG
- UPDRS
- Urologic examination
- PVR
- Urinalysis
- OABQ
- 3-day VD assessment
- PPBC
- Study drug dose escalation instructions

The urologic examination, PVR, and urinalysis may be obtained at a separate visit, within the 3 days preceding scheduled Visit 5. At the conclusion of Visit 5, subjects will be instructed to increase the dose to ge2 mirabegron 25 mg extended release - matching placebo tablets daily (placebo arm) or 2 mirabegron 25 mg extended release tablets daily (active treatment arm). Thus all subjects will begin receiving 2 identical looking tablets daily.

3.9.6 High-dose phase maintenance visit (Visit 6; Day 42)

The purpose of this visit is to establish interim overall tolerability of the medication, medication compliance, and obtain interim measures for analysis.

- Concomitant medications
- Adverse events
- Study drug compliance
- OABQ
- 3-day VD assessment
- PPBC
- Study drug dispense

At the conclusion of Visit 6, subjects will be dispensed mirabegron 25 mg tablets or matching placebo. Study drug will be administered in the form of 2 mirabegron 25 mg, matching placebo tablets daily (placebo arm) or 2 mirabegron 25 mg tablets daily (active treatment arm). Thus all subjects will continue to receive 2 identical looking tablets daily. Sufficient study drug will be dispensed to last until the end of treatment visit (Visit 7).

3.9.7 End of treatment / Early termination visit (Visit 7; Day 84)

During Visit 7, screening and baseline safety and tolerability as well as efficacy and outcome measures will be repeated.

- Concomitant medications
- Adverse events
- Study drug compliance
- Vital signs, weight, height, and orthostatics
- Physical Examination
- Neurological Examination
- ECG
- UPDRS
- Blood samples for chemistry and hematology (Na, K, Cl, HCO_3, blood glucose, BUN, creatinine, GFR, AST, ALT, total bilirubin, Alkaline phosphatase, GGT, CBC with differential and platelets)
- Urinalysis
- OABQ
- 3-day VD assessment
- PPBC
- CQ

- UPDRS-6
- MoCA
- Map Search
- Hopkins Verbal Learning Test (HVLT)
- Trail Making Test (TMT) parts A and B
- Beck Anxiety Inventory (BAI)
- Beck Depression Inventory version II (BDI-II)
- Epworth Sleepiness Scale (ESS)
- Parkinson Fatigue Scale (PFS)
- Parkinson's Impact Scale (PIMS)

If a subject at any point during the study requests to withdraw from treatment, they should return for an early termination visit. The procedures of visit 7 and visit 8 can be combined in a single visit for early termination subjects. It would be desirable that subjects continue to receive study drug until early termination procedures can be completed.

3.9.8 Safety follow up visit (Visit 8; Day 84+14)

The purpose of this visit will be to ensure lack of any delayed adverse events. These procedures can be combined with visit 7 for early termination subjects who request withdrawal from treatment.

- Concomitant medications
- Adverse events
- Vital signs, weight, height, and orthostatics
- Physical Examination
- Neurological Examination
- Urological Examination
- Urinalysis
- UPDRS
- PVR
- PPBC
- Serum pregnancy test (SPT) for WOCP

The urologic examination, PVR, and urinalysis may be obtained at a separate visit, within the 3 days preceding scheduled Visit 8.

3.9.9 Unscheduled visit

Unscheduled visits can be conducted at the Investigator's discretion. Procedures during these visits will be focused to the problem that precipitated the visit. If a subject develops intolerable side effects during the treatment period, but wishes to continue in the study, he/she may come in for an unscheduled visit. A dose reduction is permitted only once during treatment and only after the dose escalation to mirabegron daily dose of 50 mg vs. placebo. The dose can be decreased at that time to 25 mg of mirabegron vs. placebo. Subjects that require such dose reduction will be receiving one tablet daily. Further dose reductions will not be permitted, and, if deemed necessary, subjects will be brought in for early termination.

Changes in the antiparkinsonian agents or cognitive enhancers will only be permitted to a limited degree, and only if, in the opinion of the investigator, are not likely to alter the outcome measures of the study. Naturally, if these medication changes are triggered by worsening of the PD or cognitive symptoms, such worsening will have to be logged as an adverse event or serious adverse event as appropriate.

3.10 Efficacy Assessments

3.10.1 Procedures related to primary end point (cognitive tolerability)

3.10.1.1 Montreal Cognitive Assessment (Appendix II)

The Montreal Cognitive Assessment (MoCA)[23] is a brief cognitive battery, designed initially as a screening instrument for mild cognitive dysfunction. It has been standardized for use in Parkinson disease[24], and normative data have been developed with proposed cut-offs for both mild cognitive impairment and dementia.[26] It is generally sensitive to mild cognitive difficulties common in PD even in the absence of dementia. It assesses the following cognitive domains: attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Three versions are available to improve test-retest reliability and reduce practice effect. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. A one-point correction is added for education of less than 13 years.

3.10.1.2 Map Search

Map Search is a test of selective attention, developed as one of the components of Tests for Everyday Attention (TEA).[29] It is a 2-minute, timed task that involves searching a map for a target symbol among competing and irrelevant distracters. Subjects are

instructed to circle as many of the target symbols as possible. By the use of different colored pens the number of target symbols circled in 1 minute versus the total for 2 minutes can be counted. There are 80 of each type of symbol.

3.10.1.3 Hopkins Verbal Learning Test (HVLT)

The HVLT is a validated test of episodic verbal memory.[30] The revised HVLT-R will be utilized for this study.[31] It consists of a 12-item word list derived from three semantic categories, 4 words for each category. Categories are generally simple, straightforward and of common usage, e.g. 'precious stones', 'animals', etc. One of five available forms will be randomly administered to each subject as per the standard instructions. The list is read to the subject on three consecutive learning trials. After each trial, subjects are asked to recall the words. A delayed recall trial follows 20–25 minutes after the third learning trial. Finally, subjects are presented with a 24-word list composed from the 12 original words together with 12 novel, distractor words, and are asked to respond with 'yes' or 'no' to the question of which words were part of the original list. The following scores will be calculated: (a) sum of words correctly recalled on the three learning trials, (b) number of words recalled on the delayed recall trial, and (c) recognition discrimination index (true positive minus false positive responses).

3.10.1.4 Trail Making Test (parts A and B)

The Trail Making Test (TMT) is a measure of attention, speed and mental flexibility.[32] It requires the subject to connect, by making pencil lines, 25 encircled numbers randomly arranged on a page in proper order (Part A) and 25 encircled numbers and letters in alternating order (Part B). Subjects are presented with one example prior to the administration of each part. Mistakes are counted and the subject is told when they have made a mistake by the examiner, and are directed to correct the mistake. The time to complete each part in seconds is the main measure obtained from this test. No penalty is given for mistakes.

3.10.2 Procedures related to secondary end points

3.10.2.1 Overactive Bladder Questionnaire (OABQ – Appendix III)

Overactive bladder (OAB) is characterized by symptoms of urinary frequency and urgency, with and without incontinence. The Overactive Bladder Questionnaire[33] (OABQ) is a 33-item, self-administered instrument that contains a symptom bother scale (8 items to be administered during visits 1, 3, 5, 6, and 7) and a health-related quality of life scale (HRQL-to be administered during visits 3 and 7), pertaining to OAB symptoms

impact on HRQL. The OABQ was developed from an initial version of 62 items to its final form and has been shown to be a valid and reliable instrument in distinguishing normal from clinically diagnosed continent and incontinent patients. In addition to measuring the severity of symptom bother, the OABQ is also useful in quantifying the negative impact of both continent and incontinent symptoms on HRQL. This instrument has been used as an efficacy outcome in the pivotal randomized clinical trials of mirabegron, and the drug's efficacy was indeed accurately reflected in the instrument. The OABQ has also been studied and found useful in PD. [34]

3.10.2.2 3-Day Voiding Diary (Appendix IV)

A 3-day voiding diary will be implemented to collect additional efficacy measures of average daily incontinence episodes, micturition frequency, and volume voided per micturition. Subjects will be trained in the diary completion. A toilet hat will be supplied for volume measurement. Subjects are instructed to record the times of every voiding event during three consecutive days; amount voided with each event; instances of leaking including incontinence; whether there was associated urge to void with any voiding event; and, whether they had to get out of bed to void.

3.10.2.3 Patient Perception of Bladder Condition (PPBC – Appendix V)

The PPBC is a validated, patient-reported, single question measure of OAB severity.[35] This measure has demonstrated validity, but also good responsiveness to change. It consists of one single question with 6 possible answers, in which the subject is asked to indicate if his or her bladder dysfunction cause him or her no problems at all, or very minor, minor, moderate, severe, or very severe problems.

3.10.2.4 Parkinson's Impact Scale (PIMS – Appendix VI)

There are 10 areas (self, feelings, family, community, work, travel, leisure, safety, financial security and sexuality) in the validated, self-reported, Parkinson's Impact Scale (PIMS)[36], with four identified factors:

- psychological
- social
- physical
- financial

Subjects are asked to consider how much impact their Parkinson's symptoms have had on each area of the PIMS, scored from 0 to 4 points. There is a maximum possible score of 40, with higher scores indicating greater impact. This is one of six quality of life scales

recommended by the Movement Disorder Society for use in Parkinson's Disease. Administration time is approximately 5-10 minutes.

3.10.2.5 Epworth Sleepiness Scale (Appendix VII)

The Epworth Sleepiness Scale has been used repeatedly in PD and is one of the best available methods to measure excessive daytime sleepiness in these patients.[37,38] It is comprised of 8 everyday activities (such as 'Watching TV') and the respondent is to determine the chance of dozing or sleeping during the activity. There are four possible responses ranging from 0 to 3 points. The maximum possible score is 24, with higher scores indicating a greater chance of dozing or sleeping during activities. Self-reported administration times is approximately less than 5 minutes.

3.10.2.6 Parkinson's Fatigue Scale (Appendix VIII)

The Parkinson's Fatigue Scale[39] is a 16-item self-report instrument designed to measure the physical aspects of fatigue and its impact on the patient's daily function. Each item has four possible responses ranging from 1 to 5 points, with higher scores indicating greater fatigue. An average score of greater or equal to 2.95 optimally distinguished those who experienced fatigue from those who did not. Administration time is approximately 5-10 minutes.

3.10.3 Procedures related to exploratory analyses

3.10.3.1 Orthostatic Blood Pressure and Heart Rate measurements

Supine blood pressures (systolic and diastolic) will be obtained after 5 minutes of reclining, along with heart rate. Immediately following these measurements the subject will arise to full standing position, and systolic and diastolic blood pressures and heart rate will be obtained at 3 minutes after arising. Supine measurements will be obtained with the subject reclining with the head elevated at 30^{o} from the horizontal. If the investigator determines that the subject will be unable to stand for 3 minutes, then standing measurements will be obtained as close to the 3 minute time as possible. Blood pressure measurements will be obtained manually using a sphygmomanometer, always using the same side upper extremity for each subject (either left or right, but always the same side in the same subject).[40]

Heart rate will be manually counted for 30 seconds in the radial artery on the same side, and will be obtained after the blood pressure measurement. Presence of orthostatic hypotension will be documented for a drop in systolic blood pressure equal or greater

than 20 mm Hg, or in diastolic blood pressure equal or greater than 10 mm Hg. Symptomatic orthostatic hypotension will be documented if the subject also experiences presyncopal or syncopal symptoms.

3.10.3.2 Beck Depression Inventory version II (BDI-II – Appendix IX)

The Beck Depression Inventory[41] (BDI) has been used in a number of studies in Parkinson's disease and is an established screening tool that reliably discriminates depression from anxiety in various populations. It consists of 21 questions scored from 0-3 with higher scores indicating greater severity; a total score of all 21 questions provides an indicator of depressive symptomatology. Administration time is approximately 5-10 minutes. Interpretation guidelines for the BDI[41,42]:

0-9 Normal range
10-15 Minimal depressive symptomatology
16-19 Mild-moderate depressive symptomatology
20-29 Moderate-to-severe depressive symptomatology
30-63 Severe depressive symptomatology

Scores greater than 15 may indicate symptoms of depression which may impair cognitive abilities.

3.10.3.3 Beck Anxiety Inventory (BAI – Appendix X)

The Beck Anxiety Inventory[43] (BAI) was developed to address the need for an instrument that would reliably discriminate anxiety from depression while displaying convergent validity. The scale consists of 21 items, each describing a common symptom of anxiety. The respondent is asked to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 to 3. The items are summed to obtain a total score that can range from 0 to 63 (higher scores indicate greater anxiety). The scale has high internal consistency and item-total correlations ranging from .30 to .71 (median=.60). Administration time is approximately 5-10 minutes.

3.10.3.4 Constipation Questions (CQ – Appendix XI)

Subjects will be asked a series of 6 questions to establish if they meet the Rome II criteria for constipation.[44] The Rome II committee defined functional constipation as occurrence of 2 or more of the symptoms listed in Appendix XI for at least 12 weeks, which need not be consecutive, in the preceding 12 months and in the absence of structural and biochemical explanation. The criteria exclude subjects presenting with loose stool episodes and irritable bowel syndrome. For the purpose of this study, the reference period will be the preceding 2 weeks to conform with the timeline of the study. The questions will be administered by the investigator or designee.

3.10.3.5 Unified Parkinson's Disease Rating Scale (UPDRS) – Appendix XII

The UPDRS assesses motor and functional abilities of the subjects.[45] The total UPDRS will be completed (defined for this study as the sum of Parts I, II, III, and IV (I-Mentation, behavior, and mood section; II-Activities of Daily Living (ADL); III-motor section; and IV-complications section) will be completed by history and examination. The UPDRS parts III and IV evaluation will be conducted by a trained neurologist or other senior trained research staff with at least 10 years' experience in conducting the UPDRS. All attempts will be made to ensure that the same trained research staff member performs the UPDRS parts III and IV at all visits for each subject and at approximately the same time of the day and time following administration of medication. The UPDRS parts I and II may be completed by trained research staff as delegated by the PI.

3.10.3.6 Excessive Salivation Question (Unified Parkinson's Disease Rating Scale Question 6 - UPDRS-6) – Appendix XII

This is question 6 on the UPDRS[45] which refers specifically to excessive salivation. It is rated 0-4 and can be self-administered.

3.11 Safety assessments

3.11.1 Physical Examination and Neurological Examination

A complete physical exam (consisting of a review of all body systems) and neurological exam (including evaluation of mental status; motor function; balance and coordination; sensory function; reflexes and cranial nerves) at screening and end of treatment/early termination (visit 7) will be conducted by the study neurologist (primary investigator or sub-investigator). On other visits (baseline, dose escalation (visit 5), follow-up (visit 8) and unscheduled visit) a symptom-directed physical and neurological exam will be performed by the study neurologist.

3.11.2 12-Lead Electrocardiography

12-lead ECG's will be performed to evaluate the cardiovascular system. A standard 12-lead ECG will be performed at screening, dose escalation (visit 5) and end of treatment/early termination (visit 7). Additional ECGs will be performed if clinically indicated. ECGs will be conducted after approximately 5 minutes supine or recumbent rest using a standard ECG machine equipped with computer-based interval measurements.

The Investigator is responsible for evaluating the ECG. ECG findings will be assessed by the Investigator as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS), as appropriate. All abnormalities, whether assessed as clinically significant or not, will be recorded. The ECG tracing should be initialed and dated by the Investigator.

3.11.3 Urologic examination

The urologist will exam the subject for organic causes of OAB and to determine if the subject has bladder outlet obstruction (BOO). The urologist will also perform cystoscopy during screening and obtain post-void residuals.

3.11.4 Post-void Residual (PVR)

The post-void residual (PVR) urine test measures the amount of urine left in the bladder after urination. The test is used to help evaluate incontinence in women and men, problems with urination, and benign prostatic hyperplasia. The amount of leftover (residual) urine will be measured using cystoscopy or ultrasound.

3.11.5 Vital signs and weight

Blood pressure and heart rate will be measured as described in section 3.10.3.1. Height will be performed at screening only and weight will be measured at all visits.

3.11.6 Clinical laboratory parameters

The safety laboratory tests (hematology, chemistry and urinalysis tests) will be performed as general measures of health. Methodist Hospital Laboratory services will be responsible for testing of all laboratory samples. Instructions will be included in the laboratory manual. Any clinically important abnormal laboratory values noted at the Screening visit will be recorded as medical history. In addition, in order for the Sponsor to collect additional information about clinically important laboratory abnormalities, at minimum, the following laboratory abnormalities should be captured at Unscheduled Visits or End of Treatment/Early Term on the non-serious or serious AE pages of the CRF as appropriate:

- Any laboratory test result that meets the criteria for an AE or SAE;
- Any laboratory abnormality that requires the subject to have study drug discontinued or interrupted;

- Any laboratory abnormality that requires the subject to receive specific corrective therapy.

All clinically important abnormal laboratory tests occurring during the study will be repeated in appropriate intervals until (1) the value returns to Baseline, (2) the value is judged to be clinically acceptable by the Investigator, (3) a diagnosis that explains the abnormal laboratory is made or (4) subject is lost to follow-up. When possible, the Investigator should report the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin.)

4.0 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

The two categories of adverse reactions that will be reported to the FDA for review on form 3500A are “serious and unexpected” and “unexpected fatal or life threatening”, which are assessed by the Principal Investigator as Possibly Related, Probably Related or Definitely Related to the study drug. Serious and unexpected events will be submitted to the FDA’s Center for Drug Evaluation and Research (CDER) for review within 15 days of learning of the event. Unexpected fatal or life threatening events will be submitted to the FDA’s Center for Drug Evaluation and Research (CDER) for review within 7 days of learning of the event.

Serious Adverse Event (SAE): An adverse event is considered serious if, in the view of the Medical Monitor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse event.
- Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life threatening" if, in the view of either the Principal Investigator or the Medical Monitor, its occurrence places the

subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

AE Identification: The NCI Common Terminology Criteria for Adverse Events (CTCAE) provides a descriptive terminology that is to be utilized for AE reporting. The grading (severity) scale which is provided for each AE term will be used to grade the severity of the event. For this study, CTCAE version 4 will be used.

Attribution: An assessment of the relationship between the AE and the study drug**.** After naming and grading the event, the Medical Monitor will assign an attribution to the AE. Attributions include:

- Unrelated
- Unlikely Related
- Possibly Related
- Probably Related
- Definitely Related

Expectedness: An adverse event or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current protocol. For this study, the risks listed in the Myrbetriq® package insert will be used to determine expectedness (Appendix I). The Principal Investigator will be contacted as soon as possible after an event is identified at 612-993-5495 during regular business hours or paged at 612-818-5336 after regular business hours. The Principal Investigator is responsible for AE identification, documentation, grading and assignment of attribution to the study drug or the study procedures. The completed FDA 3500A form will be submitted to the following address for review:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reports will contain patient initials, age, sex, and specific information regarding the event.

All adverse events will be recorded in a study specific Adverse Event (AE) log. Written reports to the DSMC and the PN IRB will be submitted according to the PN IRB

Unanticipated Problems Involving Risks to Participants or Others (UPIRTSO) policy and only those events that meet the criteria of a UPIRTSO will be promptly reported the IRB within 10 calendar days of learning of the event.

5.0 DATA AND SAFETY MONITORING PLAN

An external data safety and monitoring committee (DSMC) will monitor the safety of study participants. The PI will report all adverse events to the DSMC that include clinically significant changes in physical exams, abnormal laboratory values and post study adverse events. Subject hospitalizations and all adverse events reported to the PN IRB will be reviewed by the DSMC. Interim analysis will be available to the DSMC after 15 participants have complete data and then again at study completion. The study biostatistician for this study will prepare the data for review by the committee and attend the DSMC meetings.

The study will be monitored according to FDA/GCP guidelines. The PI will allocate adequate time for such monitoring activities. The PI will also ensure that the Park Nicollet Institute study monitors and other compliance or quality assurance reviewers are given access to all the above noted study-related documents and study related facilities and have adequate space to conduct the monitoring. Work standards to monitor study procedures and data collection will be in accordance with Park Nicollet Institute internal investigator-initiated study audit policy and procedures.

6.0 STUDY DRUG SUPPLY

Study drug will be provided to study subjects free of charge.

6.1 Mirabegron

Mirabegron extended-release tablets will be supplied as 25 mg oval, brown, film coated tablets. Matching placebo will also be supplied.

6.1.1 Drug Manufacturer

Astellas Pharma US, Inc.
1 Astellas Way
Northbrook, Illinois 60062-6111

6.1.1.1 Distribution and Shipment

Study drug (mirabegron and placebo) will be shipped to study site by Astellas Pharma US, Inc.

All study drugs and materials will be packed in appropriate storage boxes. If, upon arrival at the study site, the study drugs appear to be damaged, the sponsor will be contacted immediately.

Each shipment of study drugs for the study will contain a shipment form describing the content of shipment. This form will assist in maintaining current and accurate inventory records. When a shipment is received, the coordinator will acknowledge receipt of the study drugs by signing and dating the relevant shipping documents.

6.1.2 Known Potential Toxicities

The most frequent adverse events (0.2%) leading to discontinuation in 3 clinical trials for the 25 mg or 50 mg dose were nausea, headache, hypertension, diarrhea, constipation, dizziness and tachycardia.

Atrial fibrillation (0.2%) and prostate cancer (0.1%) were reported as serious adverse events by more than 1 patient and at a rate greater than placebo.

Table 2 lists adverse reactions, derived from all adverse events that were reported in 3 clinical trials at an incidence greater than placebo and in 1% or more of patients treated with mirabegron 25 mg or 50 mg once daily for up to 12 weeks. The most commonly reported adverse reactions (greater than 2% of Myrbetriq patients and greater than placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.

Table 2 Percentages of Patients with Adverse Reactions, Derived from All Adverse Events, Exceeding Placebo Rate and Reported by 1% or More Patients Treated With mirabegron 25 mg or 50 mg Once Daily in 3 Clinical Trials

	Placebo (%)	Mirabegron 25 mg (%)	Mirabegron 50 mg (%)
Number of patients	1380	432	1375
Hypertension*	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3

Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

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

Other adverse reactions reported by less than 1% of patients treated with mirabegron in clinical trials included:

- Cardiac disorders: palpitations, blood pressure increased
- Eye Disorders: glaucoma
- Gastrointestinal disorders: dyspepsia, gastritis, abdominal distension
- Infections and Infestations: sinusitis, rhinitis
- Investigations: GGT increased, AST increased, ALT increased, LDH increased
- Renal and urinary disorders: nephrolithiasis, bladder pain
- Reproductive system and breast disorders: vulvovaginal pruritis, vaginal infection
- Skin and subcutaneous tissue disorders: urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, lip edema

Table 3 lists the rates of the most commonly reported adverse reactions, derived from all adverse events in patients treated with mirabegron 50 mg for up to 52 weeks in a fourth clinical trial. The most commonly reported adverse reactions (>3% of Myrbetriq patients) were hypertension, urinary tract infection, headache, and nasopharyngitis.

Table 3 Percentages of Patients with Adverse Reactions, Derived from all Adverse Events, Reported by Greater Than 2% of Patients Treated With Myrbetriq 50 mg Once Daily in Study 4

	Mirabegron 50 mg (%)	Active Control (%)
Number of patients	812	812
Hypertension	9.2	9.6
Urinary Tract Infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back Pain	2.8	1.6
Constipation	2.8	2.7
Dry Mouth	2.8	8.6
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

In Study 4, in patients treated with Myrbetriq 50 mg once daily, adverse reactions leading to discontinuation reported by more than 2 patients and at a rate greater than active control included: constipation (0.9%), headache (0.6%), dizziness (0.5%), hypertension (0.5%), dry eyes (0.4%), nausea (0.4%), vision blurred (0.4%), and urinary tract infection (0.4%). Serious adverse events reported by at least 2 patients and exceeding active control included cerebrovascular accident (0.4%) and osteoarthritis (0.2%). Serum ALT/AST increased from baseline by greater than 10-fold in 2 patients (0.3%) taking Myrbetriq 50 mg, and these markers subsequently returned to baseline while both patients continued Myrbetriq.

In the fourth clinical trial, serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with mirabegron 50 mg, mirabegron 100 mg and active control once daily, respectively. Neoplasms reported by 2 patients treated with mirabegron 100 mg included breast cancer, lung neoplasm malignant and prostate cancer.

In a separate clinical study in Japan, a single case was reported as Stevens-Johnson syndrome with increased serum ALT, AST and bilirubin in a patient taking mirabegron 100 mg as well as an herbal medication (Kyufu Gold).

6.1.2.1 Postmarketing Experience

Because these spontaneously reported events are from the worldwide postmarketing experience, from a population of uncertain size, the frequency of events and the role of mirabegron in their causation cannot be reliably determined. Urinary retention has been reported in association with mirabegron use in worldwide postmarketing experience.

6.1.3 Known Key Drug Interactions

Drug interaction studies were conducted to investigate the effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs (e.g., ketoconazole, rifampin, solifenacin, tamsulosin, and oral contraceptives). No dose adjustment is recommended when these drugs are co-administered with mirabegron.

The following are drug interactions which are listed as prohibited medications:

6.1.3.1 Drugs Metabolized by CYP2D6

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when Myrbetriq is co-administered with these drugs, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone. Subjects on CYP2D6 inhibitors will not be allowed to participate in the study. Subjects receiving drugs which are partly metabolized via CYP2D6, but which do not require dose adjustment when co-administered with CYP2D6 inhibitors will be allowed in the study at the discretion of the PI.

6.1.3.2 Digoxin

When given in combination, mirabegron increased mean digoxin C_{max} from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng.h/mL (27%). Therefore, for patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be considered. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. Subjects on digoxin will be allowed in the study at the Principal Investigators discretion.

6.1.3.3 Warfarin

The mean C_{max} of S- and R-warfarin was increased by approximately 4% and AUC by approximately 9% when administered as a single dose of 25 mg after multiple doses of 100 mg mirabegron. Following a single dose administration of 25 mg warfarin, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated. Subjects on warfarin will be allowed in the study at the Principal Investigators discretion.

6.1.4 Storage

Study drug will be stored in a secure, locked storage cabinet at room temperature (15°C to 30°C (59-86°F)). The cabinet temperature is monitored daily.

Only authorized personnel will have access to the study drugs. Study site personnel will be responsible for correct storage and handling of the study drugs. The study drugs will be dispensed by the study coordinator, under the supervision of the PI.

6.1.5 Formulation of study drug

Each Myrbetriq extended release tablet for oral administration contains 25 mg of mirabegron as the active ingredient, and the following inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide (25 mg tablet only). Matching placebo will contain the same inactive ingredients and have the same appearance as the active study drug, but will not contain mirabegron.

6.1.6 Route and administration

Each subject will take one to two tablets of Myrbetriq or matching placebo as follows: All subjects will receive one tablet of placebo daily for the first two weeks following baseline visit (visit 2). After randomization (visit 3), participants randomized to placebo will continue to receive one tablet of placebo daily until dose escalation (visit 5). At the dose escalation visit (visit 5), subjects randomized to placebo will take two placebo tablets until the end of active treatment (visit 7). Participants randomized to study drug will receive one Myrbetriq 25 mg tablet daily for two weeks, until dose escalation (visit 5). At the dose escalation visit (visit 5), subjects randomized to active treatment will have their regimen changed to 2 Myrbetriq 25 mg tablets daily until end of the active treatment phase (visit 7). Thus, all subjects will be receiving one or two identical appearing tablets daily for the entire active treatment phase. Subjects will remain blinded to treatment (placebo vs. active) for all 14 weeks of treatment.

Subjects will be instructed to take the tablets together, at the same time every morning, in one single dose. The tablets can be taken one at a time, with water, and can be taken with food or on empty stomach. Tablets should be swallowed whole and should not be chewed, cut, or crushed. To avoid confusion, subjects will be explained that although the Myrbetriq package insert instructs patients to only take one tablet a day, in this study they will be asked to take one to two tablets a day.

6.1.7 Dose schedule

Table 4 describes the daily dose schedule during each portion of the active treatment phase, by treatment assignment.

Table 4. Daily dose schedule

Treatment Assignment	From visit 1 to visit 2	From visit 2 to visit 3	From visit 3 to visit 5	From visit 5 to visit 7	From visit 7 to visit 8
Active Drug Group	none	1 placebo	1 Myrbetriq	2 Myrbetriq	none

Placebo Group	none	1 placebo	1 placebo	2 placebo	none

6.1.8 Dose increase / Dose reduction

One scheduled dose increase will occur for the active treatment group subjects as described above at visit 5. Dose de-escalations will not be allowed prior to dose escalation (visit 5). If the subject is not tolerating study drug prior to dose escalation then the Principal Investigator will consider their withdrawal from the study. One dose de-escalation will be allowed after the dose escalation has taken place (visit 5). Thus, subjects in both treatment groups will be allowed to reduce their daily dose to 1 tablet daily, at the discretion of the Investigator. No re-escalations will be allowed due to the short duration of the study. If subjects cannot tolerate 1 tablet a day, then the Principal Investigator will consider withdrawal of the subject from the study.

6.1.9 Drug accountability

The investigator is responsible for the control of study drugs under investigation. Adequate records of the receipt and disposition of the study drug must be maintained.

Study drug accountability records should contain the following information:

- Shipment number, kit numbers, batch number, number of kits and date received for all shipments of study drug received by the site.
- Subject number, medication kit number, the date, batch number, and quantity of study drug dispensed to AND returned by the subject (when applicable).
- Kits numbers, batch number, number of kits (undispensed study drug) or number of tablets (returned study drug) for all study drug returned to the Sponsor.

6.1.10 Subject compliance

Subjects will be instructed to bring their medication kit, including used and unused bottles, with them every post baseline visit during the treatment phase for compliance and accountability checks. During each study visit (visits 3-7), the investigator and/or site coordinator will assess the subject's compliance with the prescribed regimen for the study medication. This will include checks of protocol compliance and use of study drug in order to assess the reliability of subject-generated data. Subjects who fail to comply with the study requirements may be withdrawn from the study.

Compliance with the dosing regimen will be determined by performing study drug accountability of returned study drugs used and unused. The number of used, unused and

lost tablets will be recorded in the study drug accountability records and the CRF by site personnel at every visit during the treatment phase.

A subject will be considered non-compliant if he/she misses more than 4 doses of study medication within a 28 day period (less than 85% compliance) but not on the last week prior to a visit – unacceptable noncompliance will be reported to the Medical Monitor. Examples of acceptable reasons for missing a dose are 1) if a subject develops an adverse event that the Investigator believes requires the subject's dose to be held, or 2) if a subject loses their kit of study medication and a replacement kit is requested.

6.1.11 Prior and concomitant medications

All concomitant medication that the subject is taking from the screening visit should be recorded on the concomitant medications log. In addition, any changes in concomitant medication or new medications added, including as a result of an inter-current illness must be recorded in the case report forms at each visit.

6.1.12 Prohibited medications

The following medications will not be allowed during study participation. If treatment with one of these agents is clinically necessary, then subjects will have to be withdrawn from the study:

- CYP2D6 substrates that are significantly metabolized by CYP2D6 (Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine). Medications metabolized by CYP2D6 in small proportion, such that no dosage adjustment is necessary when co-administered with CYP2D6 inhibitors will be allowed at PIs discretion.
- Antidopaminergic agents (e.g. all neuroleptics, metoclopramide).
- Anticholinergic antiparkinsonian agents (e.g. trihexyphenidyl, benztropine, orphenadrine): such agents will be allowed if a subject has been on a stable dose for 30 days prior to screening; however, such medications will not be allowed to be initiated during the study. Dose adjustment or discontinuation will be at the discretion of the Principal Investigator.
- All other antiparkinsonian agents will be allowed, if, in the opinion of the Principal Investigator they will not affect the outcome measures.
- Antimuscarinic agents used to treat overactive bladder.
- Cognitive enhancers (donepezil, rivastigmine, galantamine and memantine) will be allowed, only if the subject has been on these medications and on stable dose for 30 days prior to screening. Dose adjustment or discontinuation will be at the discretion of the Principal Investigator.

- Any other medications that, in the opinion of the Principal Investigator, may alter the outcome measures may be prohibited from the study.

If treatment with one of the prohibited medications is medically necessary during the study, then, in consideration of subject's interests, subject may be withdrawn from the study.

6.1.13 Blinding and Unblinding

Blinding will be maintained during the entire study. The investigators, study coordinators, monitors, analysis and data management will all be blinded to the subject assignment. The blind will be held by the statistician and the PI has the authority to unblind a subject.

7.0 DATA ANALYSIS AND STATISTICAL METHODS

7.1 Sample size

As this is a pilot study, no formal sample size calculation was performed. For feasibility reasons, a total of 30 participants will be enrolled with 10 in the placebo group and 20 in the active treatment group.

7.2 Randomization

The randomization scheme will be prepared by the study statistician per standard statistical procedures. Randomization will be a 2:1 ratio between mirabegron and placebo, and aim at equivalent sex distribution in the active treatment and placebo groups.

7.3 Analysis population

The analysis population is based on intent-to-treat and will consist of all participants who received at least one dose during the double-blind placebo-controlled phase. Participants who withdraw from the study or are withdrawn by the study PI will be described by screening/baseline characteristics, but excluded from analyses.

7.4 Data summary

Data will be collected on case report forms for each participant at each visit and double-entered into a secure study database. A quality check of data will occur after the first five

records and prior to analysis, looking for out-of-range values and inconsistent data. The study statistician will conduct additional quality checks prior to data analyses including consistency between rounds of data entry, checking for duplicate entries, truncation of data, out-of-range values, inconsistent data and amount of missing data. Data discrepancies will be resolved and documented prior to data analysis. Missing data will not be imputed. After quality checks have been completed, a final database will be created with proper formatting and any appropriate mathematical algorithms applied including change from randomization visit (Visit 3).

Descriptive summaries will be generated for all demographic and clinical variables by study visit and treatment group including number, mean, median, standard deviation, minimum and maximum for continuous variables and number and percent for categorical variables. Summaries for change from randomization visit will also be generated. The number and screening/baseline characteristics of withdrawn participants will be recorded.

Subgroups for analyses may include treatment group, time point/study visit, age group and sex. A significance level of 0.05 will be used throughout with no adjustment for multiplicity. Normality will be tested throughout using the Shapiro-Wilk test. All analyses will be conducted on the final dataset in SAS version 9.3 or higher.

7.4.1 Summary of primary outcome data

The primary objective of this experimental protocol is to assess cognitive tolerability of mirabegron while treating OAB symptoms in patients with PD and CI. The hypothesis is that mirabegron will not impact cognitive impairment. The goal is to demonstrate equivalent cognitive impairment prior to and following treatment with mirabegron as well as change compared to the placebo group. To assess this primary objective, a test of equivalence will be performed using the two one-sided tests approach on change from visit 3 to visit 7 in MoCA total score within groups as well as between the two groups. Normality will be assessed by the Shapiro-Wilk test and the appropriate t-test or non-parametric alternative will be used. The equivalence range will be set at (-2, 2).

Other measures of cognitive impairment will follow similar analyses, but will not be considered the primary endpoint. Equivalence ranges will be determined for each measure based on available literature prior to data analysis.

7.4.2 Summary of efficacy data

The first secondary objective of this project is to assess the efficacy of mirabegron for treating OAB symptoms in PD with CI. The hypothesis is that participants in the

treatment group will experience improved OAB symptoms compared to placebo group. As this is a superiority objective, a 2-sample t-test or the Mann-Whitney-Wilcoxon test will be used as appropriate to determine significant differences between treatment groups on change in OABQ subscale scores from visit 3 to visit 7. Other measures of OAB symptoms (including PPBC and the average daily values from the diary) will follow similar analyses.

The rest of the secondary objectives are to assess efficacy of mirabegron in PD and the impact of mirabegron on other non-motor symptoms in PD including health related quality of life and excessive daytime sleepiness in PD patients with OAB symptoms and CI. The related hypotheses are that mirabegron will not impact these non-motor symptoms. The goal is to demonstrate equivalent non-motor symptoms prior to and following treatment with mirabegron as well as change compared to the placebo group. Tests of equivalence will be performed using the two one-sided tests approach on change from visit 3 to visit 7 in related variables within groups as well as between the two groups. Equivalence ranges will be determined for each measure based on available literature prior to data analysis.

7.4.3 Summary of exploratory data

The exploratory objectives are to assess effects of mirabegron on orthostatic changes in blood pressure, depressive and anxiety symptomatology, excessive salivation, constipation and PD motor symptom severity in PD patients with OAB symptoms and CI. The related hypotheses are that mirabegron will not impact these symptoms. The goal is to demonstrate equivalent symptoms prior to and following treatment with mirabegron as well as change compared to the placebo group. Tests of equivalence will be performed using the two one-sided tests approach on change from visit 3 to visit 7 in related variables within groups as well as between the two groups. Equivalence ranges will be determined for each measure based on available literature prior to data analysis.

7.4.4 Summary of safety data

Safety data and adverse events will be summarized, overall and by group, prior to each DSMB meeting and reported in the final study report.

7.4.5 Interim analysis

Interim analyses will not be conducted.

7.4.6 Subject replacement policy

Subjects who withdraw consent or are withdrawn from the study prior to randomization (complete visit 3) will be replaced. After randomization (visit 3), subjects will not be replaced.

8.0 STUDY DOCUMENTATION, CRF, AND RECORD KEEPING

8.1 Case report forms

Data will be collected on case report forms (CRFs). All the information collected during the study will identify subjects by unique subject identification number and subject initials.

8.2 Management of data

All the information collected during the study will be recorded on CRFs identified by subject initials and subject ID number, for each subject enrolled. It is the responsibility of the Investigators to ensure that the CRFs are properly and completely filled in.

The following regulations will be followed:

- FDA 21CRF part 11 rule
- ICH, Good Clinical Practice, Consolidated guideline

8.3 Monitoring

Study monitoring will be conducted according to a monitoring plan.

9.0 ADMINISTRATIVE PROCEDURES

9.1 Compliance with Good Clinical Practice, and ethical considerations

All aspects of the study will be carefully monitored with respect to Good Clinical Practices (GCP) and SOPs for compliance with applicable government regulations. Study monitoring will be conducted according to a monitoring plan. This study will be registered with ClinicalTrials.gov.

9.2 Confidentiality of subject information

All subject data will be identified only by a unique subject identification number and subject initials. However, all laboratory testing will be conducted at Park Nicollet Health

Services, Methodist Hospital Laboratory. Patient identifiers, including name, medical record number, and birth date, will be included on all lab samples sent to the Laboratory.

The subject's personal data (e.g. name and address) will be blinded in all data analyses.

9.3 Protocol amendments

Changes to the protocol will be approved by the IRB prior to implementation of the revisions.

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APPENDIX I: Myrbetriq® Full Prescribing Information (Prescribing information from astellas.com)

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Myrbetriq® is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose of Myrbetriq is 25 mg once daily with or without food. Myrbetriq 25 mg is effective within 8 weeks. Based on individual patient efficacy and tolerability the dose may be increased to 50 mg once daily *[see Clinical Studies (14)]*.

Myrbetriq should be taken with water, swallowed whole and should not be chewed, divided, or crushed.

2.2 Dose Adjustments in Specific Populations

The daily dose of Myrbetriq should not exceed 25 mg once daily in the following populations:

- Patients with severe renal impairment (CL_{cr} 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m^2) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.
- Patients with moderate hepatic impairment (Child-Pugh Class B) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

Myrbetriq is not recommended for use in patients with end stage renal disease (ESRD), or in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Myrbetriq extended-release tablets are supplied in two different strengths as described below:

- 25 mg oval, brown, film coated tablet, debossed with the (Astellas logo) and “325”
- 50 mg oval, yellow, film coated tablet, debossed with the (Astellas logo) and “355”

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increases in Blood Pressure

Myrbetriq can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Myrbetriq is not recommended for use in patients with severe uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mm Hg) *[see Clinical Pharmacology (12.2)]*.

In two, randomized, placebo-controlled, healthy volunteer studies, Myrbetriq was associated with dose-related increases in supine blood pressure. In these studies, at the maximum recommended dose of 50 mg, the mean maximum increase in systolic/diastolic blood pressure was approximately 3.5/1.5 mmHg greater than placebo.

In contrast, in OAB patients in clinical trials, the mean increase in systolic and diastolic blood pressure at the maximum recommended dose of 50 mg was approximately 0.5 - 1 mmHg greater than placebo. Worsening of preexisting hypertension was reported infrequently in Myrbetriq patients.

5.2 Urinary Retention in Patients with Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Medications for OAB

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in Myrbetriq patients; however, Myrbetriq should be administered with caution to patients with clinically significant BOO. Myrbetriq should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB *[see Clinical Pharmacology (12.2)]*.

5.3 Patients Taking Drugs Metabolized by CYP2D6

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In three, 12 week, double-blind, placebo-controlled, safety and efficacy studies in patients with overactive bladder (Studies 1, 2, and 3), Myrbetriq was evaluated for safety in 2736 patients [*see Clinical Studies (14)*]. Study 1 also included an active control. For the combined Studies 1, 2, and 3, 432 patients received Myrbetriq 25 mg, 1375 received Myrbetriq 50 mg, and 929 received Myrbetriq 100 mg once daily. In these studies, the majority of the patients were Caucasian (94%), and female (72%) with a mean age of 59 years (range 18 to 95 years).

Myrbetriq was also evaluated for safety in 1632 patients who received Myrbetriq 50 mg once daily (n=812 patients) or Myrbetriq 100 mg (n=820 patients) in a 1 year, randomized, fixed dose, double-blind, active controlled, safety study in patients with overactive bladder (Study 4). Of these patients, 731 received Myrbetriq in a previous 12 week study. In Study 4, 1385 patients received Myrbetriq continuously for at least 6 months, 1311 patients received Myrbetriq for at least 9 months, and 564 patients received Myrbetriq for at least 1 year.

The most frequent adverse events (0.2%) leading to discontinuation in Studies 1, 2 and 3 for the 25 mg or 50 mg dose were nausea, headache, hypertension, diarrhea, constipation, dizziness and tachycardia.

Atrial fibrillation (0.2%) and prostate cancer (0.1%) were reported as serious adverse events by more than 1 patient and at a rate greater than placebo.

Table 1 lists adverse reactions, derived from all adverse events that were reported in Studies 1, 2 and 3 at an incidence greater than placebo and in 1% or more of patients treated with Myrbetriq 25 mg or 50 mg once daily for up to 12 weeks. The most commonly reported adverse reactions (greater than 2% of Myrbetriq patients and greater than placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.

Table 1: Percentages of Patients with Adverse Reactions, Derived from All Adverse Events, Exceeding Placebo Rate and Reported by 1% or More Patients Treated With Myrbetriq 25 mg or 50 mg Once Daily in Studies 1, 2, and 3

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

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

Other adverse reactions reported by less than 1% of patients treated with Myrbetriq in Studies 1, 2, or 3 included:

Cardiac disorders: palpitations, blood pressure increased *[see Clinical Pharmacology (12.2)]*
Eye Disorders: glaucoma *[see Clinical Pharmacology (12.2)]*
Gastrointestinal disorders: dyspepsia, gastritis, abdominal distension
Infections and Infestations: sinusitis, rhinitis
Investigations: GGT increased, AST increased, ALT increased, LDH increased
Renal and urinary disorders: nephrolithiasis, bladder pain
Reproductive system and breast disorders: vulvovaginal pruritis, vaginal infection
Skin and subcutaneous tissue disorders: urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, lip edema

Table 2 lists the rates of the most commonly reported adverse reactions, derived from all adverse events in patients treated with Myrbetriq 50 mg for up to 52 weeks in Study 4. The most commonly reported adverse reactions (>3% of Myrbetriq patients) were hypertension, urinary tract infection, headache, and nasopharyngitis.

Table 2: Percentages of Patients with Adverse Reactions, Derived from all Adverse Events, Reported by Greater Than 2% of Patients Treated With Myrbetriq 50 mg Once Daily in Study 4

	Myrbetriq 50 mg (%)	Active Control (%)
Number of Patients	**812**	**812**
Hypertension	9.2	9.6
Urinary Tract Infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back Pain	2.8	1.6
Constipation	2.8	2.7
Dry Mouth	2.8	8.6
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

In Study 4, in patients treated with Myrbetriq 50 mg once daily, adverse reactions leading to discontinuation reported by more than 2 patients and at a rate greater than active control included: constipation (0.9%), headache (0.6%), dizziness (0.5%), hypertension (0.5%), dry eyes (0.4%), nausea (0.4%), vision blurred (0.4%), and urinary tract infection (0.4%). Serious adverse events reported by at

least 2 patients and exceeding active control included cerebrovascular accident (0.4%) and osteoarthritis (0.2%). Serum ALT/AST increased from baseline by greater than 10-fold in 2 patients (0.3%) taking Myrbetriq 50 mg, and these markers subsequently returned to baseline while both patients continued Myrbetriq.

In Study 4, serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with Myrbetriq 50 mg, Myrbetriq 100 mg and active control once daily, respectively. Neoplasms reported by 2 patients treated with Myrbetriq 100 mg included breast cancer, lung neoplasm malignant and prostate cancer.

In a separate clinical study in Japan, a single case was reported as Stevens-Johnson syndrome with increased serum ALT, AST and bilirubin in a patient taking Myrbetriq 100 mg as well as an herbal medication (Kyufu Gold).

6.2 Postmarketing Experience
Because these spontaneously reported events are from the worldwide postmarketing experience, from a population of uncertain size, the frequency of events and the role of mirabegron in their causation cannot be reliably determined. The following events have been reported in association with mirabegron use in worldwide postmarketing experience:

Urologic: urinary retention *[see Warnings and Precautions (5.2)]*

7 DRUG INTERACTIONS
Drug interaction studies were conducted to investigate the effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs (e.g., ketoconazole, rifampin, solifenacin, tamsulosin, and oral contraceptives) *[see Clinical Pharmacology (12.3)]*. No dose adjustment is recommended when these drugs are co-administered with mirabegron.

The following are drug interactions for which monitoring is recommended:

7.1 Drugs Metabolized by CYP2D6
Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when Myrbetriq is co-administered with these drugs, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

7.2 Digoxin
When given in combination, mirabegron increased mean digoxin C_{max} from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng.h/mL (27%). Therefore, for patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be considered. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect *[see Clinical Pharmacology (12.3)]*.

7.3 Warfarin
The mean C_{max} of S- and R-warfarin was increased by approximately 4% and AUC by approximately 9% when administered as a single dose of 25 mg after multiple doses of 100 mg mirabegron. Following a

single dose administration of 25 mg warfarin, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies using Myrbetriq in pregnant women. Myrbetriq should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during Myrbetriq treatment are encouraged to contact their physician.

Risk Summary

Based on animal data, mirabegron is predicted to have a low probability of increasing the risk of adverse developmental outcomes above background risk. Reversible adverse developmental findings consisting of delayed ossification and wavy ribs in rats and decreased fetal body weights in rabbits occurred at exposures greater than or equal to 22 and 14 times, respectively, the maximal recommended human dose (MRHD). At maternally toxic exposures decreased fetal weights were observed in rats and rabbits, and fetal death, dilated aorta, and cardiomegaly were reported in rabbits.

Animal Data

In the rat embryo/fetal developmental toxicity study, pregnant rats received daily oral doses of mirabegron at 0, 10, 30, 100, or 300 mg/kg from implantation to closure of the fetal hard palate (7^{th} to 17^{th} day of gestation). Maternal systemic exposures were approximately 0, 1, 6, 22, or 96 times greater than exposures in women treated at the MRHD of 50 mg based on AUC. No embryo/fetal toxicities were observed in rats exposed up to 6 times the human systemic exposure at the MRHD of 50 mg. At systemic exposures equal to or greater than 22 times the human systemic exposure at the MRHD, delayed ossification and wavy ribs were observed in fetuses at an increased incidence. These findings were reversible.

In the rabbit embryo/fetal developmental toxicity study, pregnant rabbits received daily oral doses of mirabegron at 0, 3, 10, or 30 mg/kg from implantation to closure of the fetal hard palate (6^{th} to 20^{th} day of gestation). Maternal systemic exposures were 0, 1, 14, or 36 times that in women treated at the MRHD of 50 mg based on AUC. The embryo/fetal No Adverse Effect Level (NOAEL) was similar to the exposure in women at the MRHD and was established in this species based on reduced fetal body weight observed at systemic exposures that were 14-fold higher than the human systemic exposure at MRHD. At higher doses, where systemic exposures were 36-fold higher than the human exposure at MRHD, maternal body weight gain and food consumption were reduced, one of 17 pregnant rabbits died, the incidence of fetal death increased, and fetal findings of dilated aorta and cardiomegaly were reported.

The effects of mirabegron on prenatal and postnatal development was assessed in pregnant rats dosed at 0, 10, 30, or 100 mg/kg/day from the seventh day of gestation until 20 days after birth. Maternal systemic exposures were 0, 1, 6, and 22 times the exposure in women at the MRHD based on AUC. Rat pups exposed to mirabegron in utero and through 21 days of lactation had no discernable adverse effects at maternal systemic exposures 6 times the MRHD. A slight but statistically significant decrease in the survival of pups was observed 4 days after birth at exposures 22 times the MRHD (92.7% survival) compared to the control group (98.8%), however, there was no effect on survival of pups 21 days after birth. Absolute body weight of pups was not affected on the day of birth. However, at the 30 mg/kg dose (22-fold higher systemic exposure than humans at MHRD) body weight gain of pups was reduced 5% to

13% from postnatal day 4 to 7 but not throughout the remainder of the lactation period. In utero and lactational exposure did not affect behavior or fertility of offspring at exposures up to 22 times the MRHD.

8.3 Nursing Mothers
It is not known whether Myrbetriq is excreted in human milk. Mirabegron was found in the milk of rats at concentrations twice the maternal plasma level. Mirabegron was found in the lungs, liver, and kidneys of nursing pups. No studies have been conducted to assess the impact of Myrbetriq on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. Because Myrbetriq is predicted to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of Myrbetriq in pediatric patients have not been established.

8.5 Geriatric Use
No dose adjustment is necessary for the elderly. The pharmacokinetics of Myrbetriq is not significantly influenced by age *[see Clinical Pharmacology (12.3)]*. Of 5648 patients who received Myrbetriq in the phase 2 and 3 studies, 2029 (35.9%) were 65 years of age or older, and 557 (9.9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies.

8.6 Renal Impairment
Myrbetriq has not been studied in patients with end stage renal disease (CL_{cr} <15 mL/min or eGFR <15 mL/min/1.73 m^2 or patients requiring hemodialysis), and, therefore is not recommended for use in these patient populations. In patients with severe renal impairment (CL_{cr} 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m^2), the daily dose of Myrbetriq should not exceed 25 mg. No dose adjustment is necessary in patients with mild or moderate renal impairment (CL_{cr} 30 to 89 mL/min or eGFR 30 to 89 mL/min/1.73 m^2) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
Myrbetriq has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), and therefore is not recommended for use in this patient population.

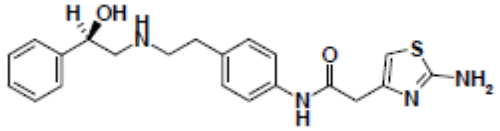
In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose of Myrbetriq should not exceed 25 mg. No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3)]*.

8.8 Gender
No dose adjustment is necessary based on gender. When corrected for differences in body weight, the Myrbetriq systemic exposure is 20% to 30% higher in females compared to males.

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

11 DESCRIPTION

Mirabegron is a beta-3 adrenergic agonist. The chemical name is 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide having an empirical formula of $C_{21}H_{24}N_4O_2S$ and a molecular weight of 396.51. The structural formula of mirabegron is:



Mirabegron is a white powder. It is practically insoluble in water (0.082 mg/mL). It is soluble in methanol and dimethyl sulfoxide.

Each Myrbetriq extended release tablet, for oral administration contains either 25 mg or 50 mg of mirabegron and the following inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide (25 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mirabegron is an agonist of the human beta-3 adrenergic receptor (AR) as demonstrated by in vitro laboratory experiments using the cloned human beta-3 AR. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity. Although mirabegron showed very low intrinsic activity for cloned human beta-1 AR and beta-2 AR, results in humans indicate that beta-1 AR stimulation occurred at a mirabegron dose of 200 mg.

12.2 Pharmacodynamics

Urodynamics

The effects of Myrbetriq on maximum urinary flow rate and detrusor pressure at maximum flow rate were assessed in a urodynamic study consisting of 200 male patients with lower urinary tract symptoms (LUTS) and BOO. Administration of Myrbetriq once daily for 12 weeks did not adversely affect the mean maximum flow rate or mean detrusor pressure at maximum flow rate in this study. Nonetheless, Myrbetriq should be administered with caution to patients with clinically significant BOO *[see Warnings and Precautions (5.2)]*.

Cardiac Electrophysiology

The effect of multiple doses of Myrbetriq 50 mg, 100 mg and 200 mg once daily on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-treatment-arm parallel crossover study in 352 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 msec. For the 50 mg Myrbetriq dose group (the maximum approved dosage), the mean difference from placebo on QTcI interval at 4-5 hours post-dose was 3.7 msec (upper bound of the 95% CI 5.1 msec).

For the Myrbetriq 100 mg and 200 mg doses groups (dosages greater than the maximum approved dose and resulting in substantial multiples of the anticipated maximum blood levels at 50 mg), the mean differences from placebo in QTcI interval at 4-5 hours post-dose were 6.1 msec (upper bound of the 95% CI 7.6 msec)

and 8.1 msec (upper bound of the 95% CI 9.8 msec), respectively. At the Myrbetriq 200 mg dose, in females, the mean effect was 10.4 msec (upper bound of the 95% CI 13.4 msec).

In this thorough QT study, Myrbetriq increased heart rate on ECG in a dose dependent manner. Maximum mean increases from baseline in heart rate for the 50 mg, 100 mg, and 200 mg dose groups compared to placebo were 6.7 beats per minutes (bpm), 11 bpm, and 17 bpm, respectively. In the clinical efficacy and safety studies, the change from baseline in mean pulse rate for Myrbetriq 50 mg was approximately 1 bpm. In this thorough QT study, Myrbetriq also increased blood pressure in a dose dependent manner (see *Effects on Blood Pressure*)**.**

Effects on Blood Pressure
In a study of 352 healthy subjects assessing the effect of multiple daily doses of 50 mg, 100 mg, and 200 mg of Myrbetriq for 10 days on the QTc interval, the maximum mean increase in supine SBP/DBP at the maximum recommended dose of 50 mg was approximately 4.0/1.6 mmHg greater than placebo. The 24-hour average increases in SBP compared to placebo were 3.0, 5.5, and 9.7 mmHg at Myrbetriq doses of 50 mg, 100 mg and 200 mg, respectively. Increases in DBP were also dose-dependent, but were smaller than SBP.

In another study in 96 healthy subjects to assess the impact of age on pharmacokinetics of multiple daily doses of 50 mg, 100 mg, 200 mg, and 300 mg of Myrbetriq for 10 days, SBP also increased in a dose-dependent manner. The mean maximum increases in SBP were approximately 2.5, 4.5, 5.5 and 6.5 mmHg for Myrbetriq exposures associated with doses of 50 mg, 100 mg, 200 mg and 300 mg, respectively.

In three, 12-week, double-blind, placebo-controlled, safety and efficacy studies (Studies 1, 2 and 3) in OAB patients receiving Myrbetriq 25 mg, 50 mg, or 100 mg once daily, mean increases in SBP/DBP compared to placebo of approximately 0.5 - 1 mmHg were observed. Morning SBP increased by at least 15 mmHg from baseline in 5.3%, 5.1%, and 6.7% of placebo, Myrbetriq 25 mg and Myrbetriq 50 mg patients, respectively. Morning DBP increased by at least 10 mmHg in 4.6%, 4.1% and 6.6% of placebo, Myrbetriq 25 mg, and Myrbetriq 50 mg patients, respectively. Both SBP and DBP increases were reversible upon discontinuation of treatment.

Effect on Intraocular Pressure (IOP)
Myrbetriq 100 mg once daily did not increase IOP in healthy subjects after 56 days of treatment. In a phase 1 study assessing the effect of Myrbetriq on IOP using Goldmann applanation tonometry in 310 healthy subjects, a dose of Myrbetriq 100 mg was non-inferior to placebo for the primary endpoint of the treatment difference in mean change from baseline to day 56 in subject-average IOP; upper bound of the two-sided 95% CI of the treatment difference between Myrbetriq 100 mg and placebo was 0.3 mm Hg.

12.3 Pharmacokinetics
Absorption
After oral administration of mirabegron in healthy volunteers, mirabegron is absorbed to reach maximum plasma concentrations (C_{max}) at approximately 3.5 hours. The absolute bioavailability increases from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean C_{max} and AUC increase more than dose proportionally. This relationship is more apparent at doses above 50 mg. In the overall population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 to 200 mg mirabegron increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold. Steady state concentrations are achieved within 7 days of once daily dosing with mirabegron. After once daily administration, plasma exposure of mirabegron at steady state is approximately double that seen after a single dose.

Effect of Food
Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron C_{max} and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC by 75% and 51%, respectively. In the phase 3 studies, mirabegron was administered irrespective of food contents and intake (i.e., with or without food) and demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose [*see Dosage and Administration (2.1)]*.

Distribution
Mirabegron is extensively distributed in the body. The volume of distribution at steady state (V_{ss}) is approximately 1670 L following intravenous administration. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. Based on *In vitro* study erythrocyte concentrations of ^{14}C-mirabegron were about 2-fold higher than in plasma.

Metabolism
Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of 14C-mirabegron. Two major metabolites were observed in human plasma and are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptor. Although *in vitro* studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, *in vivo* results indicate that these isozymes play a limited role in the overall elimination. In healthy subjects who are genotypically poor metabolizers of CYP2D6, mean C_{max} and AUC_{tau} were approximately 16% and 17% higher than in extensive metabolizers of CYP2D6, respectively. *In vitro* and *ex vivo* studies have shown the involvement of butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

Excretion
Total body clearance (CL_{tot}) from plasma is approximately 57 L/h following intravenous administration. The terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. Renal clearance (CL_R) is approximately 13 L/h, which corresponds to nearly 25% of CL_{tot}. Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary elimination of unchanged mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg. Following the administration of 160 mg ^{14}C-mirabegron solution to healthy volunteers, approximately 55% of the radioactivity dose was recovered in the urine and 34% in the feces. Approximately 25% of unchanged mirabegron was recovered in urine and 0% in feces.

Specific Populations
Geriatric Patients
The C_{max} and AUC of mirabegron following multiple oral doses in elderly volunteers (≥ 65 years) were similar to those in younger volunteers (18 to 45 years).

Pediatric Patients
The pharmacokinetics of mirabegron in pediatric patients have not been evaluated *[see Use in Specific Populations (8.4)*].

Gender

The C_{max} and AUC of mirabegron were approximately 40% to 50% higher in females than in males. When corrected for differences in body weight, the mirabegron systemic exposure is 20% - 30% higher in females compared to males.

Race
The pharmacokinetics of mirabegron were comparable between Caucasians and African American Blacks. Cross studies comparison shows that the exposure in Japanese subjects is higher than that in North American subjects. However, when the C_{max} and AUC were normalized for dose and body weight, the difference is smaller.

Renal Impairment
Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2 as estimated by MDRD), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m2), C_{max} and AUC were increased by 23% and 66%, respectively. In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2), mean C_{max} and AUC values were 92% and 118% higher compared to healthy subjects with normal renal function. Mirabegron has not been studied in patients with End Stage Renal Disease-ESRD (CL_{cr} less than 15 mL/min or eGFR less than 15 mL/min/1.73 m^2 or patients requiring hemodialysis).

Hepatic Impairment
Following single dose administration of 100 mg mirabegron in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC values were 175% and 65% higher. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Drug Interaction Studies
In Vitro Studies
Effect of Other Drugs on Mirabegron
Mirabegron is transported and metabolized through multiple pathways. Mirabegron is a substrate for CYP3A4, CYP2D6, butyrylcholinesterase, UGT, the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Sulfonylurea hypoglycemic agents glibenclamide (a CYP3A4 substrate), gliclazide (a CYP2C9 and CYP3A4 substrate) and tolbutamide (a CYP2C9 substrate) did not affect the *in vitro* metabolism of mirabegron.

Effect of Mirabegron on Other Drugs
Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron is unlikely to inhibit the metabolism of co-administered drugs metabolized by the following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 because mirabegron did not inhibit the activity of these enzymes at clinically relevant concentrations. Mirabegron did not induce CYP1A2 or CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations. Mirabegron is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport. Mirabegron did not affect the metabolism of glibenclamide or tolbutamide.

In Vivo *Studies*
The effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs was studied after single and multiple doses of mirabegron.

Most drug-drug interactions (DDI) were studied using mirabegron 100 mg extended-release tablets. However, interaction studies of mirabegron with metoprolol and with metformin were studied using mirabegron 160 mg immediate release (IR) tablets.

The effect of ketoconazole, rifampicin, solifenacin, tamsulosin, and metformin on systemic mirabegron exposure is shown in Figure 1.

The effect of mirabegron on metoprolol, desipramine, combined oral contraceptive-COC (ethinyl estradiol-EE, levonorgestrel-LNG), solifenacin, digoxin, warfarin, tamsulosin, and metformin is shown in Figure 2. In these studies, the largest increase in mirabegron systemic exposure was seen in the ketoconazole DDI study. As a potent CYP3A4 inhibitor, ketoconazole increased mirabegron C_{max} by 45% and mirabegron AUC by 80% after multiple dose administration of 400 mg of ketoconazole for 9 days prior to the administration of a single dose of 100 mg mirabegron in 23 male and females healthy subjects.

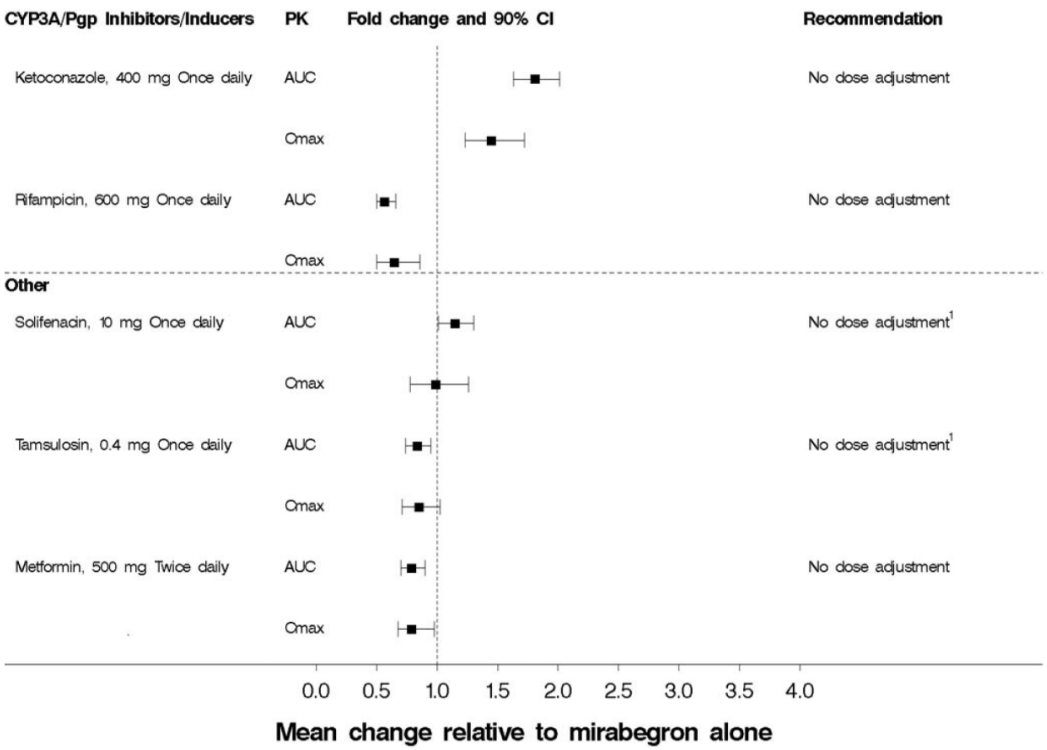
As a moderate CYP2D6 inhibitor, mirabegron increased the systemic exposure to metoprolol and desipramine:

- Mirabegron increased the C_{max} of metoprolol by 90% and metoprolol AUC by 229% after multiple doses of 160 mg mirabegron IR tablets once daily for 5 days and a single dose of 100 mg metoprolol tablet in 12 healthy male subjects administered before and concomitantly with mirabegron.
- Mirabegron increased the C_{max} of desipramine by 79% and desipramine AUC by 241% after multiple dose administration of 100 mg mirabegron once daily for 18 days and a single dose of 50 mg desipramine before and concomitantly with mirabegron in 28 male and female healthy subjects.

Caution is advised if Myrbetriq is co-administered with CYP2D6 substrates such as metoprolol and desipramine, and especially narrow therapeutic index drugs, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.3) and Drug Interactions (7.1)]*.

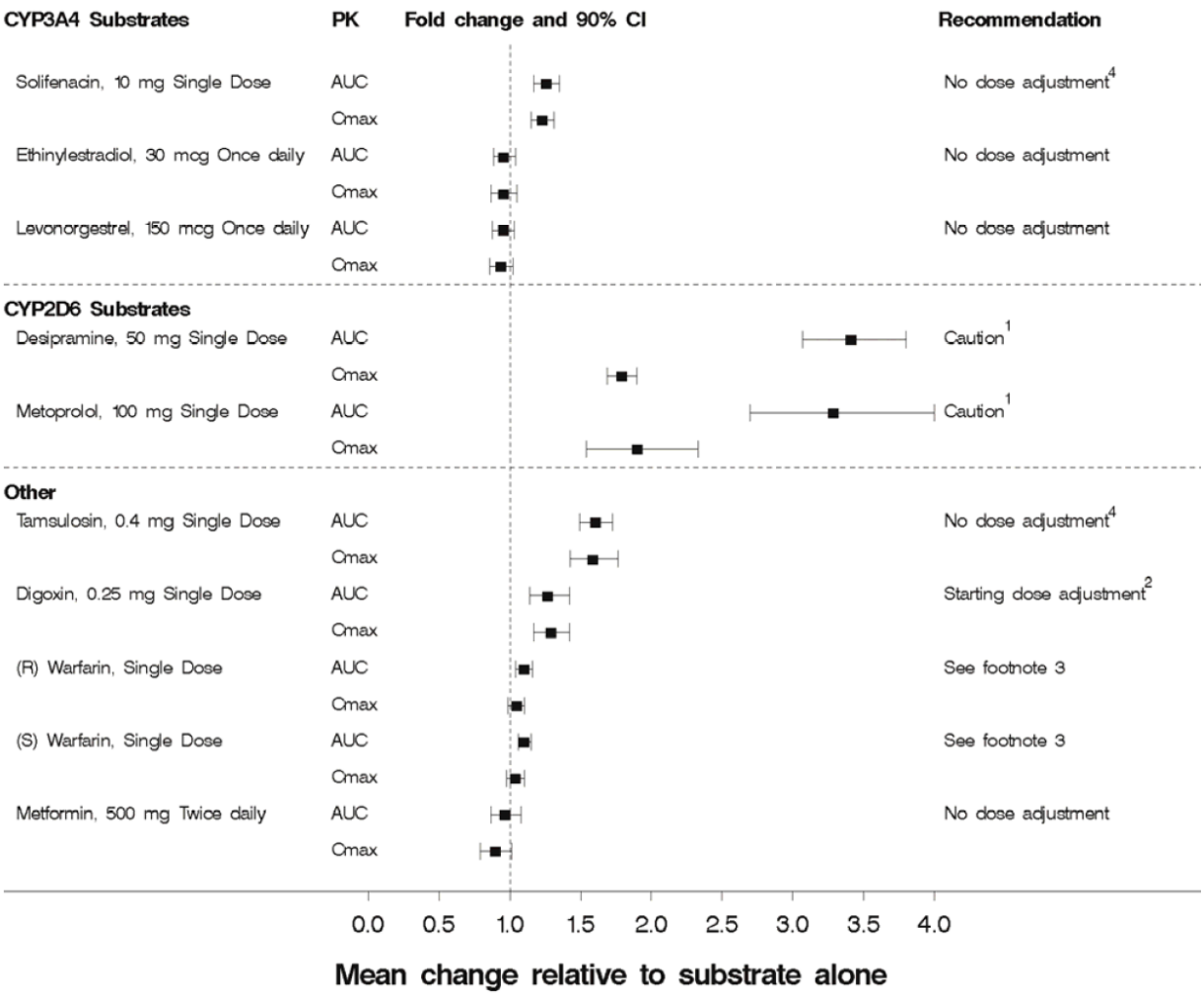
Figures 1 and 2 show the magnitude of these interactions on the pharmacokinetic parameters and the recommendations for dose adjustment, if any:

Figure 1: The Effect of Co-administered Drugs on Exposure of Myrbetriq and Dose Recommendation



(1) Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, Myrbetriq should be administered with caution to patients taking antimuscarinic medications for the treatment of OAB and in patients with clinically significant BOO because of the risk of urinary retention *[see Warnings and Precautions (5.2)]*.

Figure 2: The Effect of Myrbetriq on Exposure of Co-administered Medication



(1) Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.3) and Drug Interactions (7.1)]*.

(2) For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be prescribed. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect *[see Drug Interaction (7.2)]*.

(3) Warfarin was administered as a single 25 mg dose of the racemate (a mixture of R-warfarin and S-warfarin). Based on this single dose study, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as INR and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated *[see Drug Interactions (7.3)]*.

(4) Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, Myrbetriq should be administered with caution to patients taking antimuscarinic medications for the treatment of OAB and in BOO because of the risk of urinary retention *[see Warnings and Precautions (5.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity

Long-term carcinogenicity studies were conducted in rats and mice dosed orally with mirabegron for two years. Male rats were dosed at 0, 12.5, 25, or 50 mg/kg/day and female rats and both sexes of mice were dosed at 0, 25, 50, or 100 mg/kg/day. Mirabegron showed no carcinogenic potential at systemic exposures (AUC) 38 to 45-fold higher in rats and 21 to 38-fold higher in mice than the human systemic exposure at the 50 mg dose.

Mutagenesis

Mirabegron was not mutagenic in the Ames bacterial reverse mutation assay, did not induce chromosomal aberrations in human peripheral blood lymphocytes at concentrations that were not cytotoxic, and was not clastogenic in the rat micronucleus assay.

Impairment of Fertility

Fertility studies in rats showed that mirabegron had no effect on either male or female fertility at non-lethal doses up to 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg in female rats was estimated to be 22 times the MRHD in women and 93 times the MRHD in men.

14 CLINICAL STUDIES

Myrbetriq was evaluated in three, 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical trials in patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency (Studies 1, 2, and 3). Entry criteria required that patients had symptoms of overactive bladder for at least 3 months duration, at least 8 micturitions per day, and at least 3 episodes of urgency with or without incontinence over a 3 day period. The majority of patients were Caucasian (94%) and female (72%) with a mean age of 59 years (range 18 – 95 years). The population included both naïve patients who had not received prior antimuscarinic pharmacotherapy for overactive bladder (48%) and those who had received prior antimuscarinic pharmacotherapy for OAB (52%).

In Study 1, patients were randomized to placebo, Myrbetriq 50 mg, Myrbetriq 100 mg, or an active control once daily. In Study 2, patients were randomized to placebo, Myrbetriq 50 mg or Myrbetriq 100 mg once daily. In Study 3, patients were randomized to placebo, Myrbetriq 25 mg or Myrbetriq 50 mg once daily.

The co-primary efficacy endpoints in all 3 trials were (1) change from baseline to end of treatment (Week 12) in mean number of incontinence episodes per 24 hours and (2) change from baseline to end of treatment (Week 12) in mean number of micturitions per 24 hours, based on a 3-day micturition diary. An important secondary endpoint was the change from baseline to end of treatment (Week 12) in mean volume voided per micturition.

Results for the co-primary endpoints and mean volume voided per micturition from Studies 1, 2, and 3 are shown in Table 3.

Table 3: Mean Baseline and Change from Baseline at Week 12‡ for Incontinence Episodes, Micturition Frequency, and Volume Voided per Micturition in Patients with Overactive Bladder in Studies 1, 2, and 3

Parameter	Study 1		Study 2		Study 3		
	Placebo	Myrbetriq 50 mg	Placebo	Myrbetriq 50 mg	Placebo	Myrbetriq 25 mg	Myrbetriq 50 mg
Number of Incontinence Episodes per 24 Hours^							
n	291	293	325	312	262	254	257
Baseline (mean)	2.67	2.83	3.03	2.77	2.43	2.65	2.51
Change from baseline (adjusted mean†)	-1.17	-1.57	-1.13	-1.47	-0.96	-1.36	-1.38
Difference from placebo (adjusted mean†)	--	-0.41	--	-0.34	--	-0.40	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	--	(-0.66, -0.03)	--	(-0.74, -0.06)	(-0.76, -0.08)
p-value		0.003#		0.026#		0.005#	0.001#
Number of Micturitions per 24 Hours							
n	480	473	433	425	415	410	426
Baseline (mean)	11.71	11.65	11.51	11.80	11.48	11.68	11.66
Change from baseline (adjusted mean†)	-1.34	-1.93	-1.05	-1.66	-1.18	-1.65	-1.60
Difference from placebo (adjusted mean†)	--	-0.60	--	-0.61	--	-0.47	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	--	(-0.98, -0.24)	--	(-0.82, -0.13)	(-0.76, -0.08)
p-value		<0.001#		0.001#		0.007#	0.015#
Volume Voided (mL) per Micturition							
n	480	472	433	424	415	410	426
Baseline (mean)	156.7	161.1	157.5	156.3	164.0	165.2	159.3
Change from baseline (adjusted mean†)	12.3	24.2	7.0	18.2	8.3	12.8	20.7
Difference from placebo (adjusted mean†)	--	11.9	--	11.1	--	4.6	12.4
95% Confidence Interval	--	(6.3, 17.4)	--	(4.4, 17.9)	--	(-1.6, 10.8)	(6.3, 18.6)
p-value		< 0.001#		0.001#		0.15	<0.001#

‡ Week 12 is last observation on treatment
† Least squares mean adjusted for baseline, gender, and geographical region
^For incontinence episodes per 24 hours, the analysis population is restricted to patients with at least 1 episode of incontinence at baseline.
#Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment

Myrbetriq 25 mg was effective in treating the symptoms of OAB within 8 weeks, and Myrbetriq 50 mg was effective in treating the symptoms of OAB within 4 weeks. Efficacy of both 25 mg and 50 mg doses of Myrbetriq was maintained through the 12-week treatment period.

Figures 3 through 8 show the co-primary endpoints, mean change from baseline (BL) over time in number of incontinence episodes per 24 hours and mean change from baseline over time in number of micturitions per 24 hours, in Studies 1, 2 and 3.

Figure 3. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours –Study 1

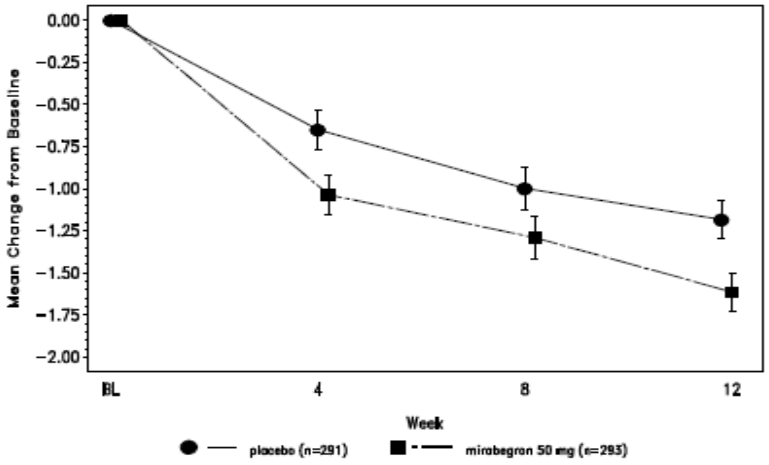


Figure 4. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 1

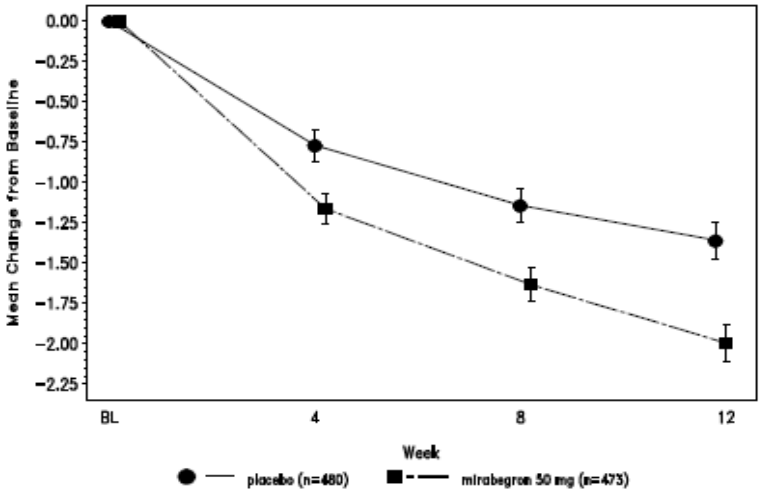


Figure 5. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 2

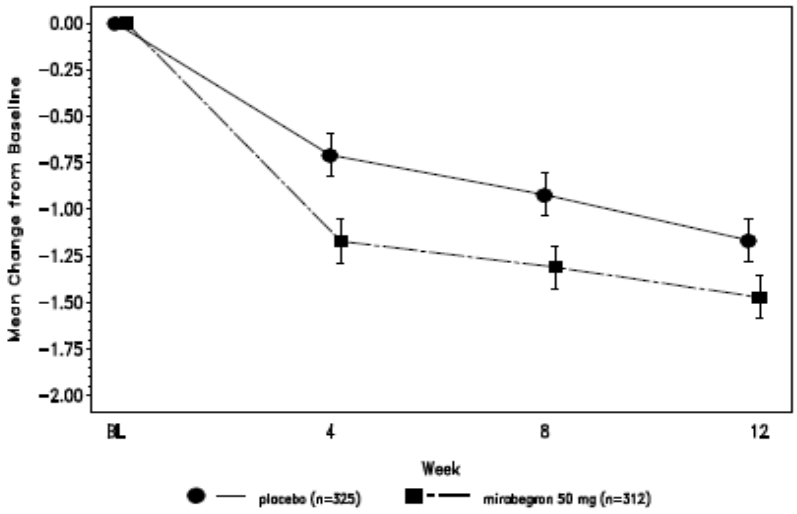


Figure 6. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 2

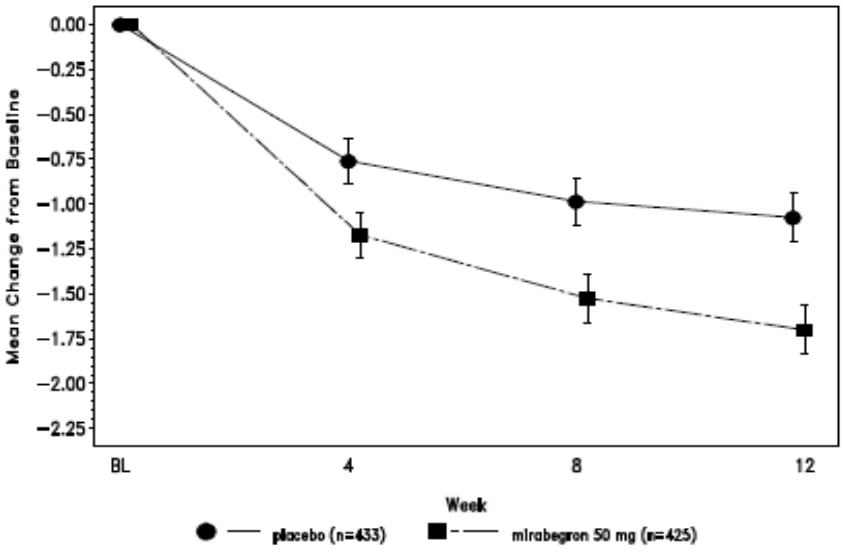


Figure 7. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 3

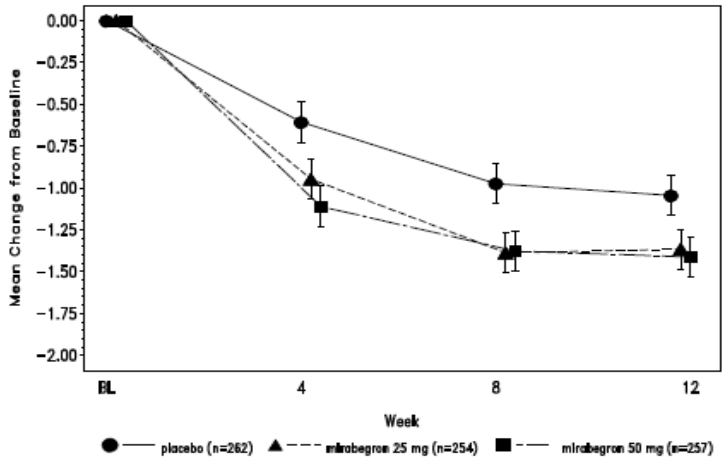
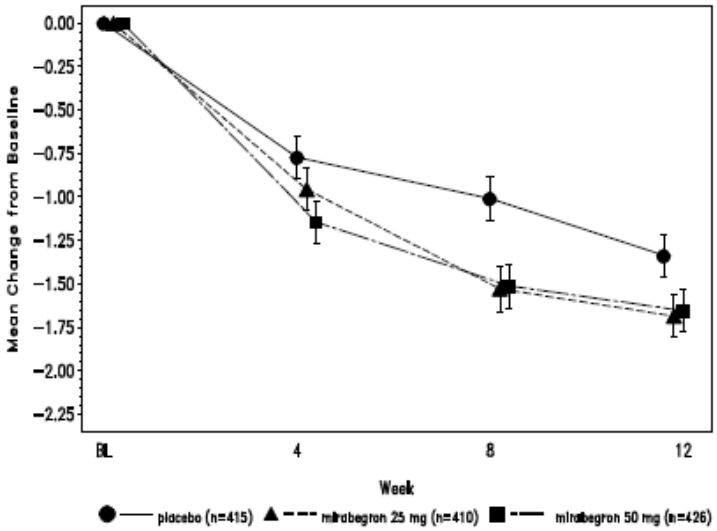


Figure 8. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 3



16 HOW SUPPLIED/STORAGE AND HANDLING

Myrbetriq is supplied as oval, film coated extended-release tablets, available in bottles and blister units as follows:

Strength	25 mg	50 mg
Color	brown	yellow
Debossed	logo, 325	logo, 355
Bottle of 30	NDC 0469-2601-30	NDC 0469-2602-30
Bottle of 90	NDC 0469-2601-90	NDC 0469-2602-90
Unit dose pack of 100	NDC 0469-2601-71	NDC 0469-2602-71

Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F). {see USP controlled Room Temperature}

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Inform patients that Myrbetriq may increase blood pressure. Periodic blood pressure determinations are recommended, especially in patients with hypertension. Myrbetriq has also been associated with infrequent urinary tract infections, rapid heart beat, rash, and pruritis. Inform patients that urinary retention has been reported when taking mirabegron in combination with antimuscarinic drugs used in the treatment of overactive bladder. Instruct patients to contact their physician if they experience these effects while taking Myrbetriq.

Patients should read the patient leaflet entitled “Patient Information” before starting therapy with Myrbetriq.

Patient Information
Myrbetriq (meer-BEH-trick)
(mirabegron)
extended-release tablets

Read the Patient Information that comes with Myrbetriq before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is Myrbetriq?
Myrbetriq is a prescription medicine for adults used to treat the following symptoms due to a condition called overactive bladder:

- Urge urinary incontinence: a strong need to urinate with leaking or wetting accidents
- Urgency: a strong need to urinate right away
- Frequency: urinating often

It is not known if Myrbetriq is safe and effective in children.

What should I tell my doctor before taking Myrbetriq?
Before you take Myrbetriq, tell your doctor if you:

- have liver problems
- have kidney problems
- have very high uncontrolled blood pressure
- have trouble emptying your bladder or you have a weak urine stream
- are pregnant or plan to become pregnant. It is not known if Myrbetriq will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Myrbetriq passes into your breast milk. You and your doctor should decide if you will take Myrbetriq or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Myrbetriq may affect the way other medicines work, and other medicines may affect how Myrbetriq works.

Tell your doctor if you take:

- thioridazine (Mellaril® or Mellaril-S®)
- flecainide (Tambocor™)
- propafenone (Rythmol®)
- digoxin (Lanoxin®)

How should I take Myrbetriq?

- Take Myrbetriq exactly as your doctor tells you to take it.
- You should take 1 Myrbetriq tablet 1 time a day.
- You should take Myrbetriq with water and swallow the tablet whole.
- Do not crush or chew the tablet.

- You can take Myrbetriq with or without food.
- If you miss a dose of Myrbetriq, begin taking Myrbetriq again the next day. Do not take 2 doses of Myrbetriq the same day.
- If you take too much Myrbetriq, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of Myrbetriq?
Myrbetriq may cause serious side effects including:

- **increased blood pressure.** Myrbetriq may cause your blood pressure to increase or make your blood pressure worse if you have a history of high blood pressure. It is recommended that your doctor check your blood pressure while you are taking Myrbetriq.

- **inability to empty your bladder (urinary retention).** Myrbetriq may increase your chances of not being able to empty your bladder if you have bladder outlet obstruction or if you are taking other medicines to treat overactive bladder. Tell your doctor right away if you are unable to empty your bladder.

The most common side effects of Myrbetriq include:

- increased blood pressure
- common cold symptoms (nasopharyngitis)
- urinary tract infection
- headache

Tell your doctor if you have any side effect that bothers you or that does not go away or if you have hives, skin rash or itching while taking Myrbetriq.

These are not all the possible side effects of Myrbetriq. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Myrbetriq?
• Store Myrbetriq between 59°F to 86°F (15°C to 30°C). Keep the bottle closed.
• Safely throw away medicine that is out of date or no longer needed.

Keep Myrbetriq and all medicines out of the reach of children.

General information about the safe and effective use of Myrbetriq.
Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflet. Do not use Myrbetriq for a condition for which it was not prescribed. Do not give Myrbetriq to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Myrbetriq. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Myrbetriq that is written for health professionals.

For more information, go to www.Myrbetriq.com website or call 1-800- 727-7003.

What are the ingredients in Myrbetriq?

Active ingredient: mirabegron

Inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide and red ferric oxide (25 mg Myrbetriq tablet only).

What is overactive bladder?
Overactive bladder occurs when you cannot control your bladder contractions. When these muscle contractions happen too often or cannot be controlled, you can get symptoms of overactive bladder, which are urinary frequency, urinary urgency, and urinary incontinence (leakage).

Rx Only

PRODUCT OF JAPAN

Manufactured by:
Astellas Pharma Technologies, Inc.
Norman, Oklahoma 73072

Marketed and Distributed by:
Astellas Pharma US, Inc.
Northbrook, Illinois 60062

*Myrbetriq® is a registered trademark of Astellas Pharma Inc. All other trademarks or registered trademarks are the property of their respective owners.

Revised: February 2014
13C011-MIR-WPI

APPENDIX II: The Montreal Cognitive Assessment (MoCA). REDACTED – can be accessed at www.mocatest.org

APPENDIX III: Overactive Bladder Questionnaire (OABQ)

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please circle the number 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 circle the number that best answers each question.

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 walking 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
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

APPENDIX IV: 3-day voiding diary

VOIDING DIARY/UROLOGY

This chart is a record of your voiding (urinating) and leakage (incontinence) of urine. Please complete this according to the following instructions prior to your visit to our office. Choose a 3 day period (if possible) to keep this record when you can conveniently measure your voids. If you are unable to keep the diary for a 24 hour period, try to keep it for as many hours as possible, say from early evening when you get home from work until you get up the next morning. Include all voids, even if they occur in the middle of the night.

EXAMPLE **VOIDING DIARY**

TIME	AMOUNT VOIDED	ACTIVITY	LEAK VOLUME	URGE PRESENT	AMOUNT/TYPE OF INTAKE
6:45 AM	10oz	Awakening			
7:00AM		Turned on H2O	2	Yes	2 cups coffee 6 oz orange juice

Record the time of all voiding (you can use a kitchen measuring cup- 4 cup capacity), leakage, and intake of liquids. Measure all intake and output in ounces or mL (30mL – 1oz). Describe activity you were performing at the time of leakage. If you were not actively doing anything, record whether you were sitting, standing, or lying down. Estimate the amount of leakage according to the following:

0 = no leakage
1 = damp, few drops only
2 = wet underwear or pad
3 = soaked or emptied bladder

If the urge to urinate accompanied (or preceded) the urine leakage, write Yes. If you felt no urge when the leakage occurred, write No. Record the amount and type of all liquid intake using ounces or mL (30mL = 1oz) (1 cup = 8oz = 240mL).

DO NOT FILL OUT: RESEARCH PERSONNEL USE ONLY
Bladder diary

Participant Identifier

Page 1 of 7

Data entry initials Data entry date

DAY #1: BLADDER DIARY **date __/__/____ (mm/dd/yyyy)**

- Please fill out for all urination episodes beginning with when you wake up, up until the next day when you wake up. **Use the back if necessary**
- Please also circle time when you went to bed, and when you woke up, for each day (for 3 days).
- Follow the example as a guide

TIME	AMOUNT VOIDED	ACTIVITY	LEAK VOLUME (circle)	URGE PRESENT (circle)	AMOUNT/TYPE OF INTAKE
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	

DAY #1: BLADDER DIARY cont.

TIME	AMOUNT VOIDED	ACTIVITY	LEAK VOLUME (circle)	URGE PRESENT (circle)	AMOUNT/TYPE OF INTAKE
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
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			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	

DAY #2: BLADDER DIARY **date __/__/____ (mm/dd/yyyy)**

- Please fill out for all urination episodes beginning with when you wake up, up until the next day when you wake up. **Use the back if necessary**
- Please also circle time when you went to bed, and when you woke up, for each day (for 3 days).
- Follow the example as a guide

TIME	AMOUNT VOIDED	ACTIVITY	LEAK VOLUME (circle)	URGE PRESENT (circle)	AMOUNT/TYPE OF INTAKE
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	

DAY #2: BLADDER DIARY cont.

TIME	AMOUNT VOIDED	ACTIVITY	LEAK VOLUME (circle)	URGE PRESENT (circle)	AMOUNT/TYPE OF INTAKE
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	

DAY # 3: BLADDER DIARY **date __/__/____ (mm/dd/yyyy)**

- Please fill out for all urination episodes beginning with when you wake up, up until the next day when you wake up. **Use the back if necessary**
- Please also circle time when you went to bed, and when you woke up, for each day (for 3 days).
- Follow the example as a guide

TIME	AMOUNT VOIDED	ACTIVITY	LEAK VOLUME (circle)	URGE PRESENT (circle)	AMOUNT/TYPE OF INTAKE
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
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			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
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			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	

DAY #3: BLADDER DIARY cont.

TIME	AMOUNT VOIDED	ACTIVITY	LEAK VOLUME (circle)	URGE PRESENT (circle)	AMOUNT/TYPE OF INTAKE
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
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			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
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			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	
			0 1 2 3	Yes / No	

APPENDIX V: Patient Perception of Bladder Condition (PPBC)

Which of the following statements describes your bladder condition best at the moment? Please mark "X" in one box only.

◯ My bladder condition does not cause me any problems at all.
◯ My bladder condition causes me some very minor problems.
◯ My bladder condition causes me some minor problems.
◯ My bladder condition causes me (some) moderate problems.
◯ My bladder condition causes me severe problems.
◯ My bladder condition causes me many severe problems.

APPENDIX VI: Parkinson's Impact Scale (PIMS) – **REDACTED – permission required**

APPENDIX VII: Epworth Sleepiness Scale (ESS) REDACTED License required http://epworthsleepinessscale.com/

APPENDIX VIII: Parkinson's Fatigue Scale (PFS)

REDACTED – can be accessed at www.parkinsons.org.uk/professionals/resources/parkinsons-disease-fatigue-scale

APPENDIX IX: Beck Depression Inventory-II (BDI-II)

REDACTED – Permission required. www.pearsonclinical.co.uk

APPENDIX X: Beck Anxiety Inventory (BAI)

REDACTED – Permission required. www.pearsonclinical.co.uk

APPENDIX XI: Constipation Questions

The following questions will be asked to establish the number of Rome II criteria each subject meets:

Over the last 2 weeks,

1. Did you have to strain at least 1 out of 4 times when having a bowel movement?
2. Did you have lumpy or hard stools at least 1 out of 4 times when having a bowel movement?
3. Did you have a sense of incomplete evacuation at least 1 out of 4 times when having a bowel movement?
4. Did you have a sensation of obstruction or blockage in your anal area at least 1 out of 4 time when having a bowel movement?
5. Did you have to use manual maneuvers to facilitate bowel movements at least 1 out of 4 times when having a bowel movement?
6. Did you have less than 3 bowel movements per week?

APPENDIX XII: Unified Parkinson's Disease Rating Scale (UPDRS)

Unified Parkinson's Disease Rating Scale

I. Mentation, Behavior and Mood

1. **Intellectual Impairment**
   - 0 = None.
   - 1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
   - 2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
   - 3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
   - 4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.
2. **Thought Disorder** *[Due to dementia or drug intoxication.]*
   - 0 = None.
   - 1 = Vivid dreaming.
   - 2 = "Benign" hallucinations with insight retained.
   - 3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
   - 4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.
3. **Depression**
   - 0 = Not present.
   - 1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
   - 2 = Sustained depression (1 week or more).
   - 3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
   - 4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.
4. **Motivation/Initiative**
   - 0 = Normal.
   - 1 = Less assertive than usual; more passive.
   - 2 = Loss of initiative or disinterest in elective (non-routine) activities.
   - 3 = Loss of initiative or disinterest in day to day (routine) activities.
   - 4 = Withdrawn, complete loss of motivation.

II. Activities of Daily Living *[For both "on" and "off."]*

5. **Speech**
   - 0 = Normal.
   - 1 = Mildly affected. No difficulty being understood.
   - 2 = Moderately affected. Sometimes asked to repeat statements.
   - 3 = Severely affected. Frequently asked to repeat statements.
   - 4 = Unintelligible most of the time.
6. **Salivation**
   - 0 = Normal.
   - 1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
   - 2 = Moderately excessive saliva; may have minimal drooling.
   - 3 = Marked excess of saliva with some drooling.
   - 4 = Marked drooling, requires constant tissue or handkerchief.
7. **Swallowing**
   - 0 = Normal.
   - 1 = Rare choking.
   - 2 = Occasional choking.
   - 3 = Requires soft food.
   - 4 = Requires NG tube or gastrostomy feeding.
8. **Handwriting**
   - 0 = Normal.
   - 1 = Slightly slow or small.
   - 2 = Moderately slow or small; all words are legible.
   - 3 = Severely affected; not all words are legible.
   - 4 = The majority of words are not legible.
9. **Cutting food and handling utensils**
   - 0 = Normal.
   - 1 = Somewhat slow and clumsy, but no help needed.
   - 2 = Can cut most foods, although clumsy and slow; some help needed.
   - 3 = Food must be cut by someone, but can still feed slowly.
   - 4 = Needs to be fed.
10. **Dressing**
    - 0 = Normal.
    - 1 = Somewhat slow, but no help needed.
    - 2 = Occasional assistance with buttoning, getting arms in sleeves.
    - 3 = Considerable help required, but can do some things alone.
    - 4 = Helpless.
11. **Hygiene**
    - 0 = Normal.
    - 1 = Somewhat slow, but no help needed.
    - 2 = Needs help to shower or bathe; or very slow in hygienic care.
    - 3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
    - 4 = Foley catheter or other mechanical aids.
12. **Turning in bed and adjusting bed clothes**
    - 0 = Normal.
    - 1 = Somewhat slow and clumsy, but no help needed.
    - 2 = Can turn alone or adjust sheets, but with great difficulty.
    - 3 = Can initiate, but not turn or adjust sheets alone.
    - 4 = Helpless.
13. **Falling** *[Unrelated to freezing.]*
    - 0 = None.
    - 1 = Rare falling.
    - 2 = Occasionally falls, less than once per day.
    - 3 = Falls an average of once daily.
    - 4 = Falls more than once daily.
14. **Freezing when walking**
    - 0 = None.
    - 1 = Rare freezing when walking; may have start-hesitation.
    - 2 = Occasional freezing when walking.
    - 3 = Frequent freezing. Occasionally falls from freezing.
    - 4 = Frequent falls from freezing.
15. **Walking**
    - 0 = Normal.
    - 1 = Mild difficulty. May not swing arms or may tend to drag leg.
    - 2 = Moderate difficulty, but requires little or no assistance.
    - 3 = Severe disturbance of walking, requiring assistance.
    - 4 = Cannot walk at all, even with assistance.

16. Tremor *[Symptomatic complaint of tremor in any part of body.]*
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. Motor Examination

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity *[Judged on passive movement of major joints with patient relaxed in sitting position; ignore cogwheeling.]*
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps *[Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.]*
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements *[Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.]*
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands *[Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, each hand separately.]*
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility *[Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.]*
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests inongoing movement.
4 = Can barely perform the task.

27 Arising from chair *[Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.]*
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability *[Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared, and can have had some practice runs.]*
0 = Normal.
1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia *[Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.]*
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. Complications of Therapy *[In the past week.]*

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? *[Historical information.]*
0 = None
1 = 1–25% of day.
2 = 26–50% of day.
3 = 51–75% of day.
4 = 76–100% of day.

33. Disability: How disabling are the dyskinesias? *[Historical information; may be modified by office examination.]*
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia *[Historical information.]*
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are any "off" periods predictable as to timing after a dose of medication?
0 = No
1 = Yes

37. Are any "off" periods unpredictable as to timing after a dose of medication?
0 = No
1 = Yes

38. Do any of the "off" periods come on suddenly, e.g., over a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1–25% of day.
2 = 26–50% of day.
3 = 51–75% of day.
4 = 76–100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Does the patient have any sleep disturbances, e.g., insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis? *[Record the patient's blood pressure, height and weight on the scoring form.]*
0 = No
1 = Yes

V. Modified Hoehn and Yahr Staging

Stage 0	No signs of disease.
Stage 1	Unilateral disease.
Stage 1.5	Unilateral plus axial involvement.
Stage 2	Bilateral disease, without impairment of balance.
Stage 2.5	Mild bilateral disease, with recovery on pull test.
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent.
Stage 4	Severe disability; still able to walk or stand unassisted.
Stage 5	Wheelchair bound or bedridden unless aided.

VI. Schwab and England Activities of Daily Living Scale

[It is O.K. to select a number in between the definitions.]

100%	Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90%	Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80%	Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70%	Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60%	Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50%	More dependent. Help with half of chores, slower, etc. Difficulty with everything.
40%	Very dependent. Can assist with all chores, but few alone.
30%	With effort, now and then does a few chores alone or begins alone. Much help needed.
20%	Nothing alone. Can be a slight help with some chores. Severe invalid.
10%	Totally dependent, helpless. Complete invalid.
0%	Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bed-ridden.