A Pilot Study of Mirabegron and Behavioral Modification including Pelvic Floor Exercise for Overactive Bladder in Parkinson Disease (MAESTRO)

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Phase	IV
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2. SYNOPSIS

STUDY DRUG:	Mirabegron 25-50 mg daily
STUDY TITLE:	A pilot study of Mirabegron and behavioral modification including pelvic floor exercise for overactive bladder in Parkinson Disease (PD)
STUDY OVERVIEW:	This study is a randomized 1:1 placebo-controlled 10-week study of mirabegron as add-on therapy to an educational intervention of behavioral modification including pelvic floor exercise (PFE) in a cohort of 40 PD subjects over the age of 30 with overactive bladder (OAB). Active drug will be mirabegron 25 mg daily with up-titration to 50 mg daily after 5 weeks. Subjects will be enrolled based on response to an overactive bladder questionnaire at baseline –visit 2. Voiding diaries (72-hr) will be utilized following the screening visit and phone visits 1 and 2. In the diaries, subjects will record the time of each micturition and/or urgency episode, urine volume with each void, any episode of incontinence, and the severity of urgency (according to the scale used in the Overactive Bladder Symptom Composite Score, OAB-SCS): 1 = no urgency (normal voiding); 2 = mild (could postpone voiding for as long as necessary without fear of incontinence); 3 = moderate (could postpone voiding for a short while without fear of leakage); 4= severe (could not postpone, had to rush to the toilet); 5= urgency incontinence (could not make it to the toilet without some leakage). Diaries will also record pelvic floor exercises. Primary outcome will be change in mean daily OAB-SCS (summation of all urgency scores recorded at all voids throughout the 72hr diary recording averaged over 3 days), visit 4 vs. baseline.
STUDY HYPOTHESIS:	Treatment with Mirabegron will improve urinary urgency control beyond that achieved with pelvic floor exercises alone.
STUDY SUBJECTS:	40 subjects with Parkinson disease and OAB complaints.
DESIGN:	Multiple-dose, randomized, placebo-controlled prospective, single-site, investigator-initiated trial.
DURATION OF STUDY:	10 weeks (active treatment)
TREATMENT REGIMEN:	Group A will receive Mirabegron 25mg daily; at visit 3, those who up-titrate will receive two 25mg tablets Group B will receive placebo; at visit 3, those who up-titrate will receive two placebo tablets Group A and B will receive the same baseline education in pelvic floor exercise based on viewing of an instructional PowerPoint presentation plus take-home printed material.

TREATMENT PERIOD:	Treatment Period: • Screening = Screening to baseline (1-2 weeks) • Active period = Baseline to final visit (10-12 weeks) Number of Visits: 4 (screening, randomization, visit 3 (titration) and visit 4 (final) Two phone visits. Phone visit 1 at 7-14 days post visit 1. Phone visit 2 at 70-74 days post visit 2
INCLUSION AND EXCLUSION CRITERIA:	Inclusion Criteria • Diagnosis of PD by UK brain bank criteria • Age ≥ 30 years old • No change in PD medications during the 4 weeks preceding screening, with no dose changes during the study, except that PRN (as needed) doses of carbidopa/levodopa will be allowed to address periodic worsening of parkinsonian symptoms. • Patient willing and able to complete micturition diary • Urinary urgency (≥ 8 entries of bladder urgency score ≥ 2) in 72hr voiding diary during screening period • Micturition frequency ≥ 8 / 24hr or incontinence ≥ 2 episodes in 72hr voiding diary during screening period • Use of other medication that could influence bladder function, other than those specifically prohibited (see below), will be permitted as long as the dose is stable for 4 weeks preceding screening, with no dose changes during the study. • Patient expects to have valid health insurance for the duration of the study period Exclusion Criteria • Women who are breast-feeding, pregnant or have potential to become pregnant during the course of the study (fertile and unwilling/unable to use effective contraceptive measures). • Cognitive deficits that in the opinion of the investigator would interfere with the subject's ability to give informed consent or perform study testing. • Screening blood pressure > 165 systolic or 100 diastolic • Heart rate > 100 • History of allergy to Mirabegron. • Screening post-void residual > 200ml • Evidence of urinary tract infection at screening • History of chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs • Intravesical botulinum toxin treatment within the previous six

	months of screening. • Presence of Interstim device • Use of indwelling catheter or self-catheterization • Concurrent use of thioridizine, flecainide, propafenone, or Digoxin • Concurrent use of warfarin (Coumadin) • Use of one of the anti-cholinergic bladder medications specified below within 14 days of the screening visit. Subjects who have used one of these medications in the past but discontinued it at least 14 days prior to the screening visit can be enrolled. • Screening estimated glomerular filtration rate (eGFR) < 60, AST or ALT > 2x upper limit of normal • Any other serious and/or unstable medical condition • Participation in other drug studies or use of other investigational drugs within 30 days prior to Screening Visit.
PROHIBITED MEDICATIONS:	Warfarin (Coumadin) Thioridizine Flecainide Propafenone Digoxin Intravesical botulinum toxin Anticholinergic bladder agents Darifenacin (Enablex) Fesoteridine (Toviaz) Flavoxate (Urispas) Oxybutynin (Ditropan, Ditropan XL, Oxtyrol, Uromax, Apo-Oxybutynin, Riva-Oxybutynin, Cystrin) Solifenacin (Vesicare) Tolterodine (Detrol, Detrol LA, Detrusitol, Unidet) Trospium (Sanctura, Sanctura XR)
LOCATION:	Booth Gardner Parkinson's Care Center EvergreenHealth Suite 300 12039 Northeast 128th Street Kirkland, Washington 98034, United States Ph: 425-899-3123 Fax: 425-899-3114
NO. OF SUBJECTS:	N= 40. This will include 20 subjects taking Mirabegron and 20 subjects taking placebo.

EFFICACY (Outcome measures):	Primary Outcome Measure Change in mean daily OAB-SCS, visit 4 vs. baseline. Secondary Outcome Measures based on voiding diary • Change in mean daily OAB-SCS, Visit 3 vs. baseline • Mean number of micturitions per 24 hours, Visit 3 and Visit 4 vs. baseline • Mean number of incontinence episodes per 24 hours, Visit 3 and Visit 4 vs. baseline • Mean volume voided per micturition, Visit 3 and Visit 4 vs. baseline Secondary Outcome Measures based on clinic visits • Overactive Bladder questionnaire symptom severity scale (OAB-q), Visit 3 and Visit 4 vs. baseline • Non-Motor Symptoms Scale (NMSS), which includes questions about cognition, psychosis, and constipation, in addition to urinary symptoms; Visit 3 and Visit 4 vs. baseline. • Patient Perception of Bladder Condition at Visit 3 and Visit 4 vs. baseline • Subject's Global Impression of Change at Visit 3 and Visit 4 vs. baseline
STATISTICAL METHODS:	Demographics and baseline disease characteristics, including age, gender, duration of disease, modified Hoehn and Yahr stage, MDS-UPDRS motor (part 3) subscore, PD medications including levodopa-equivalent daily dose (LEDD), and other medications for OAB will be compared between study groups. LEDD will be calculated according to standardized formulae (Tomlinson 2010). Analysis of primary and secondary outcome measures will include: • Summary statistics (n, mean, standard deviation, median, minimum and maximum) at baseline, visit 3 and visit 4 by treatment. • Summary of % change from baseline to visit 3 and 4. • Significance testing The primary time points for all comparative measures will be Baseline Visit (Visit 2), Titration Visit (Visit 3) and Final Visit (Visit 4). Outcome measures will be compared between groups using analysis of covariance (ANCOVA) or other method as deemed appropriate by the consulting statistician. Demonstration of superiority will depend on achieving statistical significance for the primary endpoint. Level of significance will be defined as $p = 0.05$. All statistical tests will be two-sided. Statistical

	assistance will be provided by a statistician consultant whose company is contracted with EvergreenHealth and whose services we have used on recent studies in PD. This is an exploratory study. Therefore, a small sample size is appropriate. Any treatment effect could be used to power a future larger study.
SAFETY:	Female subjects will undergo urine pregnancy testing if they are deemed to have any risk of being pregnant or becoming pregnant during the study. Baseline assessment of CBC, CMP, urinalysis, urine culture, and post-void residual will be conducted to address exclusion criteria. Adverse Event Monitoring: • This will be assessed at phone visits, visit 3 and 4 and continuously through phone contact and unscheduled visits as needed (see below) • Additionally, post-void residual will be assessed at screening, visit 3, and visit 4 to screen for urinary retention as an adverse event. Subjects will be monitored for adverse events throughout the trial. The occurrence of adverse events will be ascertained by observation, telephone monitoring if subjects call in, and by questioning by the investigator. Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy). Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Adverse events include adverse drug reactions, illness with onset during the study, exacerbations of pre-existing conditions or clinically significant changes in physical examination or significantly abnormal objective test findings. All adverse events will be recorded and graded as mild, moderate or severe by the principal investigator in accordance with general guidelines of clinical research. A serious adverse event is an undesirable sign, symptom or medical condition which: 1. is fatal or life-threatening, 2. requires or prolongs hospitalization, 3. results in persistent or significant disability/incapacity, 4. constitutes a congenital anomaly or a birth defect, 5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. If any serious adverse events occur, the treatment status of the subject(s) may be revealed, as clinically indicated. Subjects who discontinue medication use

	will be followed for adverse events until reaching the termination of adverse events. The frequency of adverse events (AE) will be under continuous scrutiny during the observation with comparison to AE rates that have been recorded in published PD drug trials.
SCHEDULE OF EVENTS:	Refer to the Schedule of Events for timing of procedures
STUDY TIMELINE:	Start-up 2 months, period of enrollment 24 months, data analysis and final report 3 months

3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BP	blood pressure
CBC	complete blood count
CMP	complete metabolic panel
eGFR	estimated glomerular filtration rate
FDA	United States Food & Drug Administration
GCP	good clinical practice
HEENT	head, eyes, ears, nose, & throat
hCG	human chorionic gonadotropin
HR	heart rate
HY	Hoehn & Yahr
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	institutional review board
LEDD	levodopa-equivalent daily dose
LUTS	lower urinary tract symptoms
MDS	Movement Disorder Society
MDS-UPDRS	MDS' Unified Parkinson Disease Rating Scale
NMSS	non-motor symptom assessment scale for PD
OAB	overactive bladder
OAB-q	OAB questionnaire symptom severity scale
OAB-SCS	OAB symptom composite score
PD	Parkinson disease
PFE	pelvic floor exercise
PPBC	patient perception of bladder condition
PVR	post-void residual
RR	respiratory rate

SAE	serious AE
SGI-C	subject's global impression of change
U/A	urinalysis
UK	United Kingdom

5. INTRODUCTION (BACKGROUND AND RATIONALE)

5.1 OAB Symptoms in PD

Parkinson disease (PD) is the second most common neurodegenerative disease, behind only Alzheimer disease. Prevalence is estimated to be 0.3% of the general population and 1-2% of the population over the age of 60 (de Lau 2006, Kowal 2013). In 2005, 4 million people worldwide had PD, and that number is expected to more than double by 2030, to 8.7 million (Dorsey 2007). Estimates of prevalence in the United States vary from 340,000 (Dorsey 2007) to 630,000 (Kowal 2013). Prevalence in the US is expected to nearly double by 2030, with estimates ranging from 610,000 (Dorsey 2007) to 1.06 million (Kowal 2013) by 2030, and an estimate of 1.34 million by 2050 (Kowal 2013).

Urinary symptoms are common in PD. Prevalence estimates of lower urinary tract symptoms (LUTS) in PD range from 27% to 88% depending on severity threshold, screening tool, and sampling methods (Araki 2000b, Sammour 2009, Winge 2006, Winge 2012). LUTS include nocturia, urgency, frequency, and incontinence. LUTS increase morbidity (Balash 2005) and decrease quality of life (Araki 2000a, Sammour 2009) in PD.

Aside from the current study drug (Mirabegron), other FDA-approved oral medications for OAB have an anticholinergic mechanism of action. Patients with PD are especially sensitive to cognitive side effects of anticholinergic medications because they, by nature of their disease, have a significant cholinergic deficit. In addition, because of autonomic involvement in PD, these patients have a high rate of constipation, another symptom that may be significantly worsened by anticholinergic medications.

5.2 Pelvic Floor Exercises (PFE) in PD

There is limited research of PFE in PD. These are simple interventions that can be easily applied in a clinical setting (such as an educational video/handout). One uncontrolled pilot study in 20 patients with PD showed a significant improvement in episodes of urinary incontinence from baseline to follow-up after an 8-week, 5-visit course of PFE-based behavioral therapy (Vaughn 2011).

This design will demonstrate the effects of PFE on OAB in PD through the placebo arm of the study. Because PFE are possibly effective with virtually no risk, they are the preferred first-line intervention, but their efficacy has not been rigorously demonstrated. In addition,

including PFE in the protocol eliminates a possible confounder, as some, but likely not all, patients may have received training in PFE and be practicing them on their own.

5.3 Mirabegron for OAB

Adding mirabegron may yield greater results than PFE alone. Mirabegron is an FDA-approved treatment for OAB that has not been studied in Parkinson disease (PD). Importantly, mirabegron has a novel mechanism of action, activating Beta-3 adrenergic receptors in detrusor muscles (Chapple 2012). It is therefore expected to avoid anticholinergic side effects such as confusion, hallucinations, and constipation, to which PD patients are especially susceptible.

In phase 3 clinical trials, mirabegron demonstrated efficacy in treating OAB symptoms in a general adult population. In a sample of 1978 patients, mirabegron 50 mg daily and 100 mg daily produced statistically significant improvements over placebo in the number of incontinence episodes per 24 hours and number of micturitions per 24 hours (Khullar 2013). Incidence of adverse events (AEs) in the groups receiving mirabegron was not significantly different from AEs in a group receiving tolterodine ER 4 mg daily (Khullar 2013). This substantiated an earlier study (Chapple 2012) that found equivalent treatment effects and AE profile when comparing mirabegron 50 mg and 100 mg to tolterodine ER 4 mg in a sample of 2444 patients. This study was not placebo-controlled. Mirabegron efficacy was similarly demonstrated in a sample of 1329 patients (Nitti 2013), wherein mirabegron 50 mg and 100 mg showed statistically significant improvement over placebo in incontinence episodes and micturitions per 24 hours.

The standard starting dose of mirabegron is 25 mg daily (Prescribing Information, Astellas Pharma, Inc.). A higher dose of 50 mg daily is also approved for use, and titration to this dose will be allowed at the mid-point of the trial (after 5 weeks), as it is likely that some patients will respond better to the higher dosage.

6. STUDY OBJECTIVES

6.1 Primary Objective

- To compare the effects of mirabegron to the effects of placebo on the change from baseline to Visit 4 in mean daily OAB-SCS, the summation of all OAB-SCS urgency scores recorded at all voids throughout a 72-hour diary recording averaged over 3 days.

6.2 Secondary Objectives

Objectives based on micturition diary:

- To compare the effects of mirabegron to the effects of placebo on the change from baseline to Visit 3 in mean daily OAB-SCS

- To compare the effects of mirabegron to the effects of placebo on the change from baseline to visit 3 and to visit 4 in mean number of micturitions per 24 hours
- To compare the effects of mirabegron to the effects of placebo on the change from baseline to visit 3 and to visit 4 in mean number of incontinence episodes per 24 hours
- To compare the effects of mirabegron to the effects of placebo on the change from baseline to visit 3 and to visit 4 in mean volume voided per micturition.

Objectives based on clinic visits:

- To compare the effects of mirabegron to the effects of placebo on the change from baseline to visit 3 and to visit 4 in Overactive Bladder questionnaire symptom severity scale (OAB-q) score
- To compare the effects of mirabegron to the effects of placebo on the change from baseline to visit 3 and to visit 4 in Non-Motor Symptoms Scale (NMSS) score, which includes questions about cognition, psychosis, and constipation, in addition to urinary symptoms.
- To compare the effects of mirabegron to the effects of placebo on the change from baseline to visit 3 and to visit 4 in Patient Perception of Bladder Condition (PPBC).
- To compare the effects of mirabegron to the effects of placebo on the change from visit 3 and to visit 4 in Subject's Global Impression of Change (SGI-C).

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design

This study is a randomized, double-blind, placebo-controlled 10-week study of mirabegron as add-on therapy to an educational intervention of behavioral modification including pelvic floor exercise (PFE) in a cohort of 40 PD subjects over the age of 30 with overactive bladder (OAB). Active drug will be mirabegron 25mg daily with optional up-titration to 50mg daily at visit 3. . Subjects will be enrolled based on response to an overactive bladder questionnaire at baseline –visit 2. Voiding diaries (72-hr) will be utilized following screening visit, Phone visit 1, and phone visit 2. In the diaries, subjects will record the time of each micturition and/or urgency episode, urine volume with each void, any episode of incontinence, and the severity of urgency as measured by the Overactive Bladder Symptom Composite Score (OAB-SCS): 1 = no urgency (normal voiding); 2 = mild (could postpone voiding for as long as necessary without fear of incontinence); 3 = moderate (could postpone voiding for a short while without fear of leakage); 4= severe (could not postpone, had to rush to the toilet); 5= urgency incontinence (could not make it to the toilet without some leakage).

Diaries will also record pelvic floor exercises. The primary outcome measure will be mean daily OAB-SCS (summation of all urgency scores recorded at all voids throughout the 72hr diary recording averaged over 3 days), visit 4 vs. visit 2-baseline. This measure accounts for both the frequency and the urgency components of OAB.

The study is composed of 4 clinic visits and 2 phone visits over the course of 11-12 weeks.

7.2 Enrollment

Subjects who may qualify for this study will be identified in the context of clinical care at the EvergreenHealth Neuroscience Institute. Such eligible patients may receive a copy of the informed consent form (ICF) at the time of their clinic visit. Recruitment may also occur through local promotional opportunities, referrals from other area neurologists, urologists, EvergreenHealth Pelvic Health Rehab, and the Washington State Parkinson Disease Registry. Patients may contact the EvergreenHealth Neuroscience Institute without clinic visitation after reading a notice about the study on the Institute's website or other online postings. Subjects who are not established patients at EvergreenHealth will be offered the chance to undergo a telephone screening using an institutional review board (IRB) approved telephone screening text. Subjects will be requested to send pertinent outside medical records for chart review by the principal investigator and be scheduled for a screening visit.

7.3 Screening (Visit 1)

Visit 1 is the screening visit. At this clinic visit, patients will provide written, informed consent and be assessed for eligibility (excluding those eligibility criteria requiring completion of the voiding diary). A history of the patient's PD symptoms and LUTS will be taken, and the patient's past medical history will be reviewed. Diagnosis of PD will be confirmed based on UK PD Society Brain Bank criteria (Hughes 1992). Current medication list will be reviewed, and a levodopa-equivalent daily dose will be calculated based on the patient's current PD medication list and on published conversion factors (Tomlinson 2010). Eligible subjects will have a stable PD medication regimen for 4 weeks prior to the screening visit and remain on a stable regimen for the duration of the study. Eligible patients will also not be concomitantly taking any of the prohibited medications, including none of the prohibited bladder medications for at least 14 days prior to the screening visit. The patient's history of medication allergies will be reviewed.

Physical examination will be performed, both a general medical examination including vital signs and a neurological examination. Neurological exam will include MDS-UPDRS part 3 evaluation and modified Hoehn and Yahr (HY) staging of PD (Goetz 2004). Post-void residual (PVR) will be assessed. Laboratory testing will include CBC, CMP, and urinalysis (U/A) by dipstick with reflex to urine culture if positive. Pre-menopausal women will have urine hCG measured.

The voiding diary will be dispensed to the patient and training will be provided on how to complete the diary, including instruction on how to measure void volume. The PowerPoint presentation of pelvic floor exercises will also be shown to the patient and each patient will be provided a copy to take home.

7.4 Baseline-(Visit 2) -Treatment Initiation

7.4.1 Confirmation of Eligibility

Patients who are deemed eligible in the screening visit will go home to complete a 72-hour voiding diary and return for Visit 2 within 7-14 days after Visit 1. At visit 2, final eligibility will be confirmed by a review of the voiding diary. Subjects eligible to continue will have urinary urgency as evidenced by at least 8 episodes of urgency scores of 2 or greater in 72 hours AND will have urinary frequency as evidenced by having EITHER 8 or more episodes of micturition per 24 hours averaged over 72 hours OR 2 or more episodes of urinary incontinence in 72 hours. In addition to confirming eligibility, the diary scoring will provide the baseline values of mean daily OAB-SCS, number of micturitions per 24 hours, number of incontinence episodes per 24 hours, and mean volume per micturition.

In addition to the diary review, medications will be reviewed again to ensure stability of the PD medication regimen and absence of any prohibited medications. Vital signs will again be measured. At any visit, if a patient is found to have systolic blood pressure over 165, diastolic blood pressure over 100 or heart rate over 100, he or she will be withdrawn from the study.

7.4.2 Baseline Assessments

Following confirmation of eligibility, an eligible patient will complete the baseline assessments of the OAB-q, NMSS, and PPBC during Visit 2.

7.4.3 Phone visit 1

Phone visit 1 will take place 28-32 days after Visit 2 and no less than 72 hours prior to Visit 3. Patients will be prompted to resume the voiding diary for 72 hours. Screening for AEs will also take place during this phone visit.

7.5 Treatment titration

7.5.1 Visit 3

Visit 3 will occur 32-40 days after Visit 2. This visit will include the same assessments as Visit 2, including review and entry of data in the voiding diary (mean daily OAB-SCS, number of micturitions per 24 hours, number of incontinence episodes per 24 hours, and mean volume per micturition). Visit 3 will also include review of current medication list, measurement of vital signs, PVR, OAB-q, NMSS, PPBC, and SGI-C. Screening for AEs will also take place during this visit. This will include assessment of symptoms of urinary tract infection and if, in the opinion of the study physician, urinalysis is indicated, dipstick will be performed with reflex to urine culture if positive. In pre-menopausal women, screening for pregnancy risk will be performed and if, in the opinion of the study physician, pregnancy testing is indicated, urine hCG will be measured.

In addition, at Visit 3, all patients who have tolerated mirabegron 25 mg daily or matching placebo (no adverse events on this dose) will be up-titrated to mirabegron 50 mg daily (for those in the active drug arm) or matching placebo (for those in the placebo arm). This will be dispensed as two 25-mg tablets or, for those in the placebo arm, two placebo tablets. Only

those without any AE on 25 mg daily or matching placebo will be eligible to increase the dose.

7.5.2 Phone Visit 2

Phone Visit 2 will occur 70-74 days after Visit 2 and no less than 72 hours prior to Visit 4. Patients will be prompted to resume the voiding diary for 72 hours. Screening for AEs will also take place during this phone visit.

7.6 Final Assessment (Visit 4)

Visit 4, the final visit will occur 74-82 days after Visit 2. Visit 4 will include review and entry of data in the voiding diary, review of current medication list, physical examination including measurement of vital signs, PVR, OAB-q, NMSS, PPBC, and SGI-C. Screening for AEs will also take place during this visit. This will include assessment of symptoms of urinary tract infection and if, in the opinion of the study physician, urinalysis is indicated, dipstick will be performed with reflex to urine culture if positive. In pre-menopausal women, screening for pregnancy risk will be performed and if, in the opinion of the study physician, pregnancy testing is indicated, urine hCG will be measured.

7.7 Unscheduled Visits

Subjects may return to the clinic for safety evaluation or to receive additional study medication as needed. Unscheduled visits will include a review of concomitant medications and any adverse effects, and, if needed in the estimation of the study physician, physical examination in whole or in part.

8. STUDY POPULATION

The population for this study is PD patients with symptoms of OAB who meet all of the following inclusion criteria and who do not meet any of the following exclusion criteria.

8.1 Inclusion Criteria

An eligible patient:

- Has signed and dated an IRB-approved informed consent form before any protocol-specific screening procedures are performed.
- Has a diagnosis of PD consistent with UK PD Society Brain Bank criteria
- Is aged 30 years or older
- Has had no change in PD medications during the 4 weeks preceding screening, with no dose changes during the study, except that PRN (as needed) doses of carbidopa/levodopa will be allowed to address periodic worsening of parkinsonian symptoms.

- Is willing and able to complete micturition diary
- Has urinary urgency as defined by having 8 or more entries of bladder urgency score ≥ 2 in a 72-hr voiding diary during screening period
- Has micturition frequency as defined by having 8 or more episodes of micturition per 24 hours, averaged over 72 hours; OR by having at least 2 episodes of incontinence in 72 hours as documented in the voiding diary during screening period
- May use other medications that could influence bladder function, other than those specifically prohibited, as long as the dose is stable for 4 weeks preceding screening, with no dose changes during the study.
- Has valid health insurance coverage at the time of study enrollment and expects this coverage to remain valid for the duration of the study period.

8.2 Exclusion Criteria

A patient will be excluded from the study if he or she meets any of the following:

- Is a woman who is breast-feeding, pregnant, or has the potential to become pregnant during the course of the study (fertile and unwilling/unable to use effective contraceptive measures).
- Has cognitive deficits that, in the opinion of the study physician, would interfere with the subject's ability to give informed consent or perform study testing.
- Has at screening a systolic blood pressure > 165 or a diastolic blood pressure > 100
- Has at screening a heart rate > 100
- Has a history of allergy to Mirabegron
- Has at screening a post-void residual > 200ml
- Has at screening evidence of a urinary tract infection
- Has at screening evidence of chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs
- Has received intravesical botulinum toxin treatment within six months prior to screening.
- Has the presence of an Interstim device
- Uses an indwelling catheter or self-catheterization
- Concurrent use of thioridizine, flecainide, propafenone, or Digoxin
- Concurrent use of warfarin (Coumadin)
- Use of one of the anti-cholinergic bladder medications specified below within 14 days of the screening visit. Subjects who have used one of these medications in the past but discontinued it at least 14 days prior to the screening visit will not be excluded.
- Has at screening an estimated glomerular filtration rate (eGFR) < 60, or AST or ALT > 2x upper limit of normal
- Has any other serious and/or unstable medical condition
- Has participated in other drug studies or has used other investigational drugs within 30 days prior to Screening Visit
- Prohibited anti-cholinergic bladder medications:

Darifenacin (Enablex)
Fesoteridine (Toviaz)
Flavoxate (Urispas)
Oxybutynin (Ditropan, Ditropan XL, Oxtyrol, Uromax, Apo-Oxybutynin, Riva-Oxybutynin, Cystrin)
Solifenacin (Vesicare)
Tolterodine (Detrol, Detrol LA, Detrusitol, Unidet)
Trospium (Sanctura, Sanctura XR)

8.3 Removal of Patients from Study

A patient will be considered to have completed the study when he or she has completed all study visits through the final visit. Every patient has the right to discontinue study participation at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. Criteria for early termination include, but are not limited to, < 36 hours of time covered in a bladder diary, poor adherence to study medication (less than 70% of study medication consumed), loss of health insurance coverage, and safety issues related to study-related or non-study related adverse events.

If a patient has a clinical necessity to alter their standard PD medications, the patient will be withdrawn from the trial so that changes may be made, except that occasional additional doses of carbidopa/levodopa will be allowed if needed to address periodic worsening of parkinsonian symptoms. Additional doses of carbidopa/levodopa taken during the 72-hour diary periods will be recorded in the diary. If a patient is withdrawn due to an adverse event, the event will be followed, when possible, until resolution. Patients who withdraw from the study may be replaced, but withdrawn patients will not be re-entered into the study.

All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.

8.4 Screen failures / Rescreening

Subjects who screen fail because they do not meet inclusion criteria or because of certain exclusions, e.g. presence of urinary tract infection, may rescreen after 30 days at the discretion of the investigator.

9. TREATMENTS

9.1 Behavioral Modification with Pelvic Floor Exercise (BM-PFE) Educational Material

We will produce a 15-20 minute presentation, written by a physical therapist, utilizing a PowerPoint presentation. Slides will include images such as pelvic floor anatomy as well as outlines of key points. Participants will be given a paper copy of the presentation to take

home for reference and to help them with a home bladder exercise regimen. The following topics are part of this presentation:

- Bladder health: What's normal?
- Bladder dietary irritants
- Bladder retraining and urge delay techniques
- Pelvic floor anatomy and function
- How to perform a "Kegel"
- "Kegel" home exercise program
- Pelvic floor exercises with functional activities
- Maintaining your home exercise program

Subjects will have the opportunity to ask the study physician follow-up questions as needed.

9.2 Investigational drug

The study medication and matching placebo will be provided by Astellas. The active medication will be mirabegron 25 mg po daily from Baseline Visit (Visit 2) to Titration Visit (Visit 3). At the Titration Visit, all patients who have tolerated mirabegron 25 mg daily (no adverse events on this dose) will be up-titrated to mirabegron 50 mg daily. This will be dispensed as two 25-mg tablets or, for those in the placebo arm, two placebo tablets. Only those without any AE on 25 mg daily or matching placebo will be eligible to increase the dose. The research pharmacist will dispense the active or placebo medication at randomization and again at the Titration Visit. An extra 5-day supply of medication will be provided for each study period to allow a window for scheduling of appointments.

9.3 Randomization and Blinding

Following confirmation of eligibility at Visit 2, an eligible patient will be randomized in a 1:1 randomization scheme to receive mirabegron 25 mg daily or placebo. Randomization will occur at the research pharmacy of EvergreenHealth using a computer-generated randomization list. The pharmacist will maintain a codebook indicating the treatment allocation of each subject. Study medication will be delivered by the research pharmacist to the research study staff from the research pharmacy (a separate locked room containing only research medications). The investigating physicians, nurse and research coordinator will be blinded as to treatment arm until the code is broken. The randomization code may be broken by the investigator only in a medical emergency. The reasons for this will be documented carefully. The subjects will receive identical appearing active or placebo study medication tablets, with identification known only to the research pharmacist.

9.4 Concomitant Therapy

All concomitant therapy will be documented. Prohibited will be concurrent (defined as "within 14 days of screening") use of antimuscarinics listed in Appendix 3: oxybutynin (Ditropan®, Ditropan XL ®, Oxytrol ®, Uromax ®, apo-oxybutynin, riva-oxybutynin,

Cystrin ®), tolterodine (Detrol®, Detrol LA®, Detrusitol ®, Unidet®), fesoterodine extended-release (Toviaz®), solifenacin (Vesicare®), trospium (Sanctura®, Sanctura XR®), flavoxate (Urispas®), and darifenacin extended release (Enablex®). Also prohibited will be concurrent use of thioridizine, flecainide, propafenone or Digoxin; and intravesical botulinum toxin treatment within the previous six months. Medications that are likely to influence bladder function may not be initiated between screening and study completion. They may be continued with no dose changes during the study.

9.5 Treatment Compliance

Patients will be asked to return all unused medication and all medication bottles, including empty bottles, at each visit and at the end of the study and the quantity of returned medication will be documented.

10. DESCRIPTION OF ASSESSMENTS

10.1 Safety Monitoring

Safety will be monitored by adverse event (AE) reporting, physical examination, vital signs, laboratory evaluation, and evaluation of post-void residual.

10.1.1 Physical Examination

A general physical examination will be performed at Visit 1 (Screening Visit) and Visit 4 (Final Visit). This exam will include, at minimum, HEENT, heart, lungs, abdomen, musculoskeletal, and neurologic systems. Subjects with a range of health conditions that may put the patient at risk for adverse outcomes will be excluded, as listed under Exclusion Criteria.

10.1.2 Vital Signs

Vital signs (blood pressure, heart rate, and respiratory rate) will be measured at each clinic visit. Subjects with BP > 165 systolic or > 100 diastolic or those with HR > 100 will be excluded at screening or discontinue study medication if this occurs while on study medication. However, they may complete other elements of the study.

10.1.3 Laboratory Evaluations

All subjects will undergo baseline testing with CBC, CMP, and urinalysis by dipstick with reflex to urine culture if positive. Subjects with screening estimated glomerular filtration rate (eGFR) < 60, or AST or ALT > 2x upper limit of normal will be excluded.

10.1.4 Pregnancy Status

All pre-menopausal women will have pregnancy screening with urine hCG at baseline (Visit 1). At Visits 3 and 4, pre-menopausal women will have screening for pregnancy risk and if, in the opinion of the study physician, pregnancy testing is indicated, urine hCG will be measured. A positive urine hCG will result in discontinuation of the study drug and withdrawal of the subject from the study.

10.1.5 Post-void Residual

PVR will be measured by a bladder scan after urination at Visits 1, 3, and 4. Subjects with PVR > 200 mL will be excluded at screening or will discontinue study medication if this occurs while on study medication. Symptoms of urinary retention will be monitored throughout the study and may lead to early discontinuation of study medication; however, such subjects may complete other elements of the study.

10.1.6 Adverse Events

Subjects will be monitored for adverse events throughout the trial. The occurrence of adverse events will be ascertained by observation, telephone monitoring and questioning by the investigator. Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events.

An adverse event (AE) is any symptom, physical sign, or medical condition that emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause. Adverse events include adverse drug reactions, illness with onset during the study, exacerbations of pre-existing conditions or clinically significant changes in physical examination or significantly abnormal objective test findings. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. All adverse events will be recorded and graded as mild, moderate or severe by the principal investigator in accordance with general guidelines of clinical research, outlined here:

- **MILD**: An event that causes transient or minimal symptoms and that does not interfere with daily activities.
- **MODERATE**: An event that causes symptoms sufficient to interfere with but not prevent daily activities.
- **SEVERE**: An event that prevents normal, everyday activities.

Adverse events will also be classified by their relationship to the study medication by the principal investigator in accordance with general guidelines of clinical research, outlined here:

- **Definitely Unrelated**: The AE is definitely not related to the drug. This designation is reserved for those events that do not follow a reasonable temporal sequence following drug administration (e.g. occur prior to study treatment) or for those events that cannot be even remotely related to study participation.

- **Unlikely related**: There is no reasonable association between the study treatment and the suspected event and the event could have been produced by the patient's clinical state or other therapy administered to the patient.
- **Possibly related**: The suspected AE may or may not follow a reasonable temporal sequence from study treatment administration but seems to be the type of reaction that cannot be dismissed as unlikely. The event could have been produced or mimicked by the patient's clinical state or other therapy administered to the patient.
- **Probably related**: The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the patient's clinical state or other treatments.
- **Definitely related**: The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and, if appropriate, resumes upon re-introduction of the treatment. Additionally, the suspected AE cannot be reasonably explained by the known characteristics of the patient's clinical state or other treatments.

The principal investigator and all other research staff except the research pharmacist will be blinded towards randomization of active drug versus placebo until after completion of study.

10.1.7 Serious Adverse Events

A serious adverse event (SAE) is any AE that meets one of more of the following criteria:

- Is fatal or life-threatening
- Requires hospitalization or prolongs a current hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
- Requires medical or surgical intervention to prevent one of the above outcomes

If any SAE occurs, the treatment status of the subject(s) may be revealed, as clinically indicated. If a patient discontinues medication use due to an AE, the event will be followed, when possible, until resolution. No interim analysis of safety data is planned because the entire study will be conducted over 2 months. However, the frequency of AEs will be under continuous scrutiny during the trial with comparison to AE rates that have been recorded in published PD drug trials.

10.1.7.1 Serious Adverse Events Reporting

The FDA will be informed of SAEs as soon as possible or within 15 calendar days. In addition, the Investigator will notify the FDA of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible, or within 7 calendar days, by telephone or facsimile. When the principal investigator has determined that an SAE requires reporting to the FDA (unexpected and possibly related to study drug), the following actions will be taken:

- Telephone the FDA immediately (day of awareness) in the case of reportable death or life-threatening events.
- Complete FDA Form 3500.
- Send the completed Form 3500 to the FDA (preferably by fax at 1-800-FDA-0178) within the timelines mentioned above.
- Attach the photocopy of all examinations, medical notes and records related to the SAE and document the dates these were made. For laboratory results, include the laboratory normal ranges. For hospitalizations, Admission H&P, Discharge Summary, Consultative reports, etc. could be very helpful. In the case of a fatal event, provide an autopsy report, when it becomes available.

10.2 Efficacy Assessments

10.2.1 OAB-SCS

The primary outcome measure will be the change in the mean daily Overactive Bladder-Symptom Composite Score (OAB-SCS) from baseline to visit 4. . One of the secondary outcome measures will be the change in the mean daily OAB-SCS from baseline to visit 3. The OAB-SCS requires subjects to record the severity of urgency of each micturition over a 72-hour period as follows: 1 = no urgency (normal voiding); 2 = mild (could postpone voiding for as long as necessary without fear of incontinence); 3 = moderate (could postpone voiding for a short while without fear of leakage); 4= severe (could not postpone, had to rush to the toilet); 5= urgency incontinence (could not make it to the toilet without some leakage). The total score is derived by adding the urgency rating of each micturition over a 72-hour period as recorded in a voiding diary. In this way, the OAB-SCS accounts for both frequency and urgency in OAB, and is therefore a more accurate assessment of OAB than measurements of urgency alone (Starkman 2008). Mean daily OAB-SCS is total 72-hour score divided by 3. For incomplete days, the daily score will be adjusted to equal [(total score for the incomplete day / actual number of hours recorded) x 24 hours] (Zinner 2005).

10.2.2 Voiding Diary

In addition to the OAB-SCS, the voiding diary will be used to record number of micturition episodes per 24h, number of incontinence episodes per 24h, and volume per micturition. The change in these variables from baseline to visit 3 and from baseline to visit 4 will be secondary outcome measures. (The voiding diary will also record frequency of Kegel exercises and PRN doses of carbidopa/levodopa, but these will be controls, not outcome measures.)

10.2.3 OAB-q

The Overactive Bladder questionnaire symptom severity scale (OAB-q) measures the impact of bladder symptoms by asking patients to rate the severity of eight OAB symptoms on a 6-

point scale. The questionnaire has been validated for use in the general population (Coyne 2002) and in patients with Parkinson disease (Iacovelli 2010).

10.2.4 NMSS

The NMSS is a validated rating scale of non-motor symptoms in Parkinson disease (Chaudhuri 2007). It rates the severity and frequency of 30 symptoms in 9 domains, including 3 symptoms of overactive bladder. The other domains it evaluates are cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, sexual function, and miscellaneous (pain, sense of smell, change in weight, and excessive sweating). Severity is rated from 0 (none) to 3 (major source of distress) and frequency is rated from 1 (rarely, <1/week) to 4 (very frequent, at least daily). The score on each item is the product of the severity and frequency ratings. The total score for the NMSS is the sum of all item scores.

10.2.5 PPBC

The PPBC asks patients to rate the severity of their bladder symptoms on a 6-point scale, from "My bladder condition does not cause me any problems at all" to "My bladder condition causes me many severe problems." This single-item, global measure has been validated for use in a general population with OAB (Coyne 2006).

10.2.6 SGI-C

The Subject's Global Impression of Change will be assessed by asking a single question at visit 3 and visit 4.: "Since starting the study drug, how have your bladder symptoms changed?" Answers will be on a 7-point scale: 1 = much improved; 2 = somewhat improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = somewhat worse; and 7 = much worse.

11. DATA MANAGEMENT AND STATISTICAL ANALYSIS

Statistical analysis will be performed by a consulting statistician contracted with EvergreenHealth.

11.1 Sample Size Considerations

This is a prospective, double-blinded, randomized controlled pilot study. The purpose is to test a hypothesis in a preliminary fashion and to assess for safety in this population with a specific neurological disease. As such, a power calculation may be irrelevant. However, a small number of subjects (e.g. less than 10) may cause significant sampling error to miss a treatment effect or common safety issue. Some entities that establish criteria for level of evidence consider a sample size of 20 subjects in each arm to be a minimum representative population to be considered for Class III or better classification of Level of Evidence. Therefore, a sample size of 40 subjects is a reasonable number for a pilot study of this nature.

11.2 Study Population

The study population will include all patients who pass screening and undergo randomization. Data will be analyzed in an intent-to-treat fashion.

11.3 Baseline and Demographic Characteristics

The following characteristics will be summarized descriptively for placebo and drug groups:

- Demographics (age, gender, race)
- Parkinson disease characteristics at baseline (disease duration, date of onset, initial symptom, PD type [tremor-dominant or akinetic-rigid], modified Hoehn and Yahr stage in the ON state, and MDS-UPDRS part 3 score in the ON state)
- Levodopa-equivalent daily dose (LEDD)
- Other medications used for OAB

11.4 Safety Analysis

AEs will be summarized by treatment group (study drug or placebo) and by dose. Changes in vital signs (BP, HR, RR) and changes in post-void residual will be analyzed to detect differences between active drug and placebo.

11.5 Efficacy Analysis

Outcome measures are described in section 10.2. Analysis of primary and secondary outcome measures will include:

- Summary statistics (n, mean, standard deviation, median, minimum and maximum) at baseline, visit 3 and visit 4 by treatment.
- Summary of % change from baseline to visit 3 and 4.
- Significance testing

The primary time points for all comparative measures will be Baseline Visit (Visit 2), Titration Visit (Visit 3) and Final Visit (Visit 4). Outcome measures will be compared between groups using analysis of covariance (ANCOVA) or other method as deemed appropriate by the consulting statistician. Demonstration of superiority will depend on achieving statistical significance for the primary endpoint. Level of significance will be defined as $p = 0.05$. All statistical tests will be two-sided.

12. STUDY MANAGEMENT

12.1 Ethics and Good Clinical Practice

This study will be performed according to the principles of Good Clinical Practice [Chapter 2 of the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP)], the

declaration of Helsinki, and national laws and regulations about clinical studies. The study may not start without written approval from the appropriate Institutional Review Board or Independent Ethics Committee.

12.2 Informed Consent

For each trial patient, written informed consent will be obtained before any study-related activity is commenced. Both the informed consent form (ICF) and an oral explanation that occurs as part of the informed consent process will include information about the study objective, the nature and duration of the study, the action of the study drug, potential risks, inconveniences, adverse effects, and alternatives. The patient will be informed that he or she is free to withdraw from the study at any time without consequence.

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14. APPENDICES

14.1 Schedule of assessments
14.2 Voiding Diary

14.3 Prohibited meds