Protocol Title: Pilot study of Mirabegron and behavioral modification including pelvic floor exercise for overactive bladder in multiple sclerosis (MIRROR)

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Protocol Summary

STUDY DRUG	Mirabegron 25-50mg daily
TITLE	Pilot study of mirabegron and behavioral modification including pelvic floor exercise for overactive bladder in multiple sclerosis (MIRROR)
STUDY OVERVIEW	A multi-center, randomized 1:1 placebo controlled 10-week study of mirabegron as add-on therapy to an educational intervention on behavioral modification including pelvic floor exercise (BM-PFE) to a cohort of 40 MS subjects with overactive bladder (OAB). Active drug will be mirabegron 25mg daily with optional up-titration to 50mg daily after approximately 5 weeks. Subjects will be randomized at the Baseline Visit based on recordings in a voiding diary kept for 72 continuous hours in the screening period. Voiding diaries of a 72 hour period each will be utilized during the screening period, between Phone Visit 1 and Titration and between Phone Visit 2 and Final Visit. In the diaries, subjects will record the time of each micturition and/or urgency episode, urine volume with each void (when available), any episode of incontinence, and the severity of urgency (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) Each voiding event is multiplied by the score for the event and then all events are summed to generate a total daily OAB-SCS cumulative score). Primary outcome will be average daily OAB-SCS total score, Final Visit vs. Baseline. This accounts for the frequency, urgency and incontinence components of OAB.
RATIONALE	This design will demonstrate the effects of behavioral modification, including pelvic floor exercise on OAB through the placebo arm of the study. Adding mirabegron may yield greater results than BM-PFE alone. The standard starting dose is 25mg daily. An optional up-titration to 50mg is included, since some patients may respond better to the higher dosage. This titration will occur at about 5 weeks to allow a balanced period of time for recording response to the two dosages.
STUDY HYPOTHESIS	Treatment with Mirabegron will improve urinary urgency control beyond that achieved with pelvic floor exercises alone.
STUDY SUBJECTS	40 subjects with multiple sclerosis and OAB complaints.
DESIGN	Multiple-dose, randomized, placebo-controlled prospective, single-site, investigator-initiated trial.
DURATION OF STUDY	Approximately 10 weeks (active treatment)

TREATMENT REGIMEN	Group A will receive Mirabegron 25mg daily Group B will receive placebo Group A and B will receive the same baseline education in pelvic floor exercise based on viewing of an instructional presentation plus take-home printed material.
TRIAL PERIODS	Screening Period • Screening to Baseline Treatment Period • Baseline to Final Visit (or Study Drug Discontinuation), includes Baseline, Phone Visit 1, Titration Visit, Phone Visit 2 and Final Visit
INCLUSION AND EXCLUSION CRITERIA	Inclusion Criteria • Confirmed diagnosis of MS (no sub-type restrictions) • Age ≥18 • No change in disease modifying therapy in 60 days. • Patient willing and able to complete micturition diary • Urinary urgency (8 or more entries of bladder urgency score ≥2) in 72hr voiding diary recorded during screening period • Micturition frequency ≥ 8 / day or incontinence ≥ 2 episodes in 72 hour voiding diary recorded during screening period • At least 36 hours of voiding activity recorded in 72 hour voiding diary during screening period • Non-antimuscarinic 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. • Discontinued use of antimuscarinics at least two weeks prior to screening • Able to give informed consent Exclusion Criteria • Females 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) • MS exacerbation within 30 days of screening • Cognitive deficits that would interfere with the subject's ability to give informed consent or perform study testing • Screening blood pressure > 165 systolic or 100 diastolic • History of allergy to Mirabegron • Screening post-void residual > 200ml • Evidence of urinary tract infection 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 • 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 (Mellaril® or Mellaril-S®, flecainide (Tambocor®), propafenone (Rythmol®) or digoxin (Lanoxin®) • Concurrent use of antimuscarinics: oxybutynin (Ditropan®, Ditropan XL ®), tolterodine (Detrol®, Detrol LA®), fesoterodine extended-release (Toviaz®), solifenacin (Vesicare®), trospium (Sanctura®, Sanctura XR®), darifenacin extended release (Enablex®) • Screening estimated glomerular filtration rate (eGFR) < 60, AST or ALT > 2x upper limit of normal • Any other serious and/or unstable medical condition
NO. OF SUBJECTS	N= 40. This will include 20 subjects taking mirabegron and 20 subjects taking placebo.
EFFICACY (Outcome measures)	Primary Outcome Measure: • Primary outcome will be Average daily OAB-SCS total score, Baseline vs. Final Visit Secondary Outcome Measures based on voiding diary, compared to Baseline: • Titration Visit: Average daily OAB-SCS total score • Titration and Final Visit: A) mean # of micturitions/day; B) Mean number of incontinence episodes/day; C) Mean volume voided/micturition Secondary Outcome Measures based on the following assessments at Titration Visit and Final Visit compared to Baseline: • Qualiveen Questionnaire • Subject Global Impression (single question) • PFE adherence question • Bladder Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0) Exploratory Outcome Measures based on the following assessments at Titration Visit and Final Visit compared to Baseline: • Bowel Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)
STATISTICAL METHODS	See Statistics section

SAFETY	All subjects will undergo baseline blood testing, CBC and CMP. Subjects with screening estimated glomerular filtration rate (eGFR) < 60, or AST or ALT > 2x upper limit of normal will be excluded. At screening, subjects reporting dysuria, fever or abdominal pain will undergo urine analysis, culture and sensitivity at the discretion of the principal investigator. Subjects with blood pressure > 165 systolic or > 100 diastolic will be excluded at screening or will discontinue study drug if this occurs during treatment period. However, they may complete other elements of the study. Subjects with screening post-void residual > 200ml will be excluded. Symptoms of urinary retention will be monitored throughout the study and may lead to early discontinuation of study drug; however, such subjects may complete other elements of the study. 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. Female subjects will undergo urine pregnancy testing if they are deemed to have any risk of being pregnant or becoming pregnant during the study.
ESTIMATED BUDGET	A budget estimate will be provided separately
SCHEDULE OF EVENTS	Refer to the Schedule of Study Assessments, Appendix 2 for timing of procedures
STUDY TIMELINE	Start-up 2 months, period of enrollment 22 months, data analysis and final report 3 months

Appendices
Appendix 1: Subject Diary
Appendix 2: Schedule of Study Assessments
Appendix 3: Prohibited medications and medications that may not be initiated between screening and study completion, but may be continued with no dose changes during the study.

Objective
To assess the effect of pelvic floor exercise education with or without mirabegron (MBG) on overactive bladder symptoms in people with multiple sclerosis (MS) based on the OAB Symptom Composite Score.

Background
There are 400,000 Americans with MS and past and current surveys indicate that more than 80% report some bladder dysfunction, including 61% with urinary urgency.1,2,3 In MS, immune dysregulation and neurodegeneration in the central nervous system impairs normal micturition. Symptoms include frequency and/or urgency of urination, hesitancy in starting urination, nocturia and incontinence. Urological studies have shown the most common complaint is urinary urgency due to overactive bladder (OAB), with urinary retention less common. This is supported by urodynamic findings of detrusor hyperreflexia in 68% of a MS cohort.4,5 One study suggests that detrusor hyperreflexia is more severe when related to MS than when idiopathic.6 Urinary urgency and urge-incontinence symptoms have markedly negative impacts on physical functioning and mental-functioning health-related quality of life metrics in MS.7

Potential treatments for OAB include behavioral modification, pelvic floor rehabilitation, oral or intravesical anticholinergic medications, desmopressin, duloxetine, intravesical injection of botulinum toxins, medicinal cannabis, or placement of external or indwelling catheters.8,9,10,11,12,13,14,15 Mirabegron (MBG) is the first beta-3 adrenergic agonist drug indicated for OAB treatment with symptoms of urge urinary incontinence, urgency and urinary frequency (see prescribing information). This was based on studies conducted in general populations having OAB symptoms and not stress incontinence.16,17,18 MBG has not been studied in MS.

Pelvic floor rehabilitation has a well-established role in the management of stress incontinence and idiopathic OAB.19 There is some evidence that pelvic floor exercise taught by physiotherapists over multiple sessions improves OAB in MS.20,21. However, access to pelvic floor physical therapy is limited by third-party payer coverage, availability of therapists with the necessary expertise and incurred expenses and time requirements for the patients. Behavioral modification, including pelvic floor exercise (BM-PFE) may be provided in a clinical setting using relevant educational materials. The BM-PFE component will offer an important educational benefit to all subjects interested in this study. Our center has a strong pelvic rehabilitation program with three therapists who are well-suited to produce the educational component of this study.

Adding MGB may yield greater results than BM-PFE alone. The standard starting dose is 25mg daily. An optional up-titration to 50mg is proposed, since some patients may respond better to the higher dosage, based on a Phase III trial including 25mg and 50mg daily treatment arms. This titration will occur at visit 3; 32-40 days post Baseline Visit, to allow a balanced period of time for recording response to the two dosages. Both dosages have been reported to be effective in treating OAB within 12 weeks.

This study explores the benefits of combining a brief BM-PFE educational program with a pharmacotherapy, MBG for OAB due to MS. Our objective is to determine the effect of BM-PFE with and without MBG in reducing the OAB Symptom Composite Score (OAB SCS). The OAB SCS is a validated measure that incorporates urinary frequency, urgency and incontinence episodes.22,23 The study design will also test differences in efficacy and tolerability between 25mg and 50mg doses of MBG.

Methodology

We propose a parallel-group, randomized, double-blind placebo-controlled trial of MBG as add-on therapy to an educational pelvic floor exercise (BM-PFE) intervention to a cohort of 40 MS subjects with overactive bladder (OAB).

Active drug will be MBG 25mg daily with optional up-titration to 50mg daily at Titration (visit 3). Subjects will be enrolled at Baseline (visit 2) based upon scores for urinary urgency and micturition frequency in subject diary recorded during screening period.

Voiding diaries of a 72 hour period each will be utilized during the screening period, between Phone Visit 1 and Titration and between Phone Visit 2 and Final Visit. 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 using the OAB-SCS. This score accounts for frequency and the urgency components of OAB, including incontinence episodes.

Number of centers & patients

Multicenter study with subject number = 40

Population

Inclusion criteria

- Confirmed diagnosis of MS (no sub-type restrictions)
- Age ≥18
- No change in disease modifying therapy in 60 days
- Patient willing and able to complete micturition diary
- Urinary urgency (8 or more entries of bladder urgency score ≥2) in 72hr voiding diary recorded during screening period
- Micturition frequency ≥ 8 / day or incontinence ≥ 2 episodes in 72hr voiding diary recorded during screening period
- At least 36 hours of voiding activity recorded in 72 hour voiding diary recorded during screening period
- Non-antimuscarinics 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.
- Discontinued use of antimuscarinics at least two weeks prior to screening
- Able to give informed consent

Exclusion criteria

- Females 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).
- MS exacerbation within 30 days of screening
- Cognitive deficits that would interfere with the subject's ability to give informed consent or perform study testing.
- Screening blood pressure > 165 systolic or 100 diastolic
- History of allergy to Mirabegron.
- Screening post-void residual > 200ml
- Evidence of urinary tract infection 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
- 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 antimuscarinics: oxybutynin (Ditropan®, Ditropan XL ®), tolterodine (Detrol®, Detrol LA®), fesoterodine extended-release (Toviaz®), solifenacin (Vesicare®), trospium (Sanctura®, Sanctura XR®), darifenacin extended release (Enablex®)
- Screening estimated glomerular filtration rate (eGFR) < 60, AST or ALT > 2x upper limit of normal
- Any other serious and/or unstable medical condition

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

We will utilize a 20 minute presentation, written by a physical therapist, utilizing a power point 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 power point presentation to take home for reference and to help them with a home bladder exercise regimen.
The following topics are part of this power point 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.

Investigational drug
The study medication and matching placebo will be provided by Astellas Pharma Inc. The active medication will be mirabegron (MBG) 25mg po daily from Baseline Visit to Titration Visit. At the Titration Visit subjects will be asked to choose to up-titrate to 50mg (or matching placebo) or to continue at 25mg dose (or matching placebo), while remaining blinded to treatment. 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.

Randomization
- Randomization will occur at the research pharmacy of EvergreenHealth (EH).
- Non-EH research sites will submit a randomization request to the EH Research Pharmacist.
- EH Research Pharmacist will assign randomization to placebo vs. active drug and record in randomization code book.
- EH Research Pharmacist will send the randomization assignment (placebo or active drug assignment) back to un-blinded staff at the enrolling site.
- Un-blinded staff at the enrolling site will dispense medication based on EH provided randomization assignment.
- The investigating physician, 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 have to be documented carefully.

Concomitant therapy
All concomitant therapy will be documented. Prohibited will be concurrent use of antimuscarinics listed in Appendix 3: oxybutynin (Ditropan®, Ditropan XL ®), tolterodine (Detrol®, Detrol LA®), fesoterodine extended-release (Toviaz®), solifenacin (Vesicare®), trospium (Sanctura®, Sanctura XR®), and darifenacin extended release (Enablex®) within the previous 2 weeks of screening. 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. This is listed as Appendix 3 and includes anticholinergic medications and drugs used in treatment of benign prostatic hypertrophy.

Interruption or discontinuation of treatment
Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study by the PI for any reason beneficial to his/her wellbeing or any other reason. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.

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.

Blinding
The subjects will receive identical appearing active or placebo study medication tablets, with identification known only to the research pharmacist.

Visit schedule and assessments
See schedule of assessments, Appendix 2

Enrollment
Subjects who may qualify for this study will be identified in the context of clinical care at the participating centers. Such eligible patients may receive a copy of the informed consent form at the time of their clinic visit. Recruitment may also occur through local promotional opportunities (doctor's programs, patient education programs). Patients may contact the participating centers without clinic visitation after reading a notice about the study on the centers' websites or other online postings, or after referral from an outside medical practitioner for study consideration. Such subjects 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.

Screening Visit
At this visit, subjects will be given ample time to read, review and ask questions about the study and the content of the informed consent form. After subjects have signed the informed consent form, they will undergo the following assessments:

- Review of Medical History
- Review of MS History
- Study Eligibility (Inclusion/Exclusion)
- Review of Concomitant Medications
- Physical Examination
- Vital Signs: Blood Pressure, Heart Rate and Temperature
- General and Neurological Evaluation
- Expanded Disability Status Scale (EDSS)
- Laboratory Testing: Complete Blood Count and Comprehensive Metabolic Panel
- Urine Pregnancy Testing for Female Subjects of Childbearing Potential

- Urine Analysis, including Culture and Sensitivity for Subjects Reporting Dysuria, Fever and/or Abdominal Pain (at the discretion of the principal investigator)
- Post-void Residual Urine Volume Using Ultrasound Scanner
- Subject Diary Training
- Void Volume Measurement Training

Subjects who meet all inclusion criteria will receive a diary with instructions to record information in their diaries for 72 continuous hours prior to Baseline Visit, during the screening period. Subjects will receive a urine receptacle ("hat" or hand-held urinal, patient preference) and will be trained on how to measure urine volume and record in diary whenever possible during the 72 hour diary period.

Baseline Visit
This visit will be scheduled 7 to 14 days post Screening Visit. The following assessments will be performed:

- Study Eligibility (Inclusion/Exclusion)
- Review of Concomitant Medications
- Adverse Event Assessment
- Vital Signs: Blood Pressure, Heart Rate and Temperature
- Physical Examination (if deemed necessary by investigator)
- Subject Diary Review

Subjects who meet all inclusion criteria will complete the following assessments:

- Qualiveen Questionnaire - pages #1-6 & #9-10 (pages #7-8 are N/A)
- Subject Global Impression
- Bladder Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)
- Bowel Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)
- Pelvic Floor Exercise Adherence Question
- Pelvic Floor Exercise Presentation
- Randomization to Group A or Group B
- Drug Dispensing and Training
- Subject Diary Training (if needed)
- Void Volume Measurement Training (if needed)

Phone Visit 1
Study staff will contact each subject 28-32 days post Randomization Visit. The following assessments will be performed:

- Adverse Event Assessment
- Prompting to Resume Subject Diary
- Subject Diary Training (if needed)
- Void Volume Measurement Training (if needed)

Subjects will be instructed to complete the 72 continuous hours of diary entries prior to the Titration Visit. Study staff will reconfirm scheduled dates for follow-up study visits.

Titration Visit
This visit will be scheduled 35-40 days post Randomization Visit. The following assessments will be performed:

- Review of Concomitant Medications
- Adverse Event Assessment
- Vital Signs: Blood Pressure, Heart Rate and Temperature
- Physical Examination (if deemed necessary by investigator)
- Urine Pregnancy Testing for Female Subjects of Childbearing Potential (if deemed necessary by investigator)
- Subject Diary Review
- Qualiveen Questionnaire - pages #1-6 only
- Subject Global Impression
- Bladder Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)
- Bowel Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)
- Pelvic Floor Exercise Adherence Question
- Subject Diary Training (if needed)
- Void Volume Measurement Training (if needed)
- Drug Dispensing and Training
- Drug Return and Accountability
- Up-Titration Option Question

Subjects may receive increased dose of 50mg of MBG or matching placebo, or remain at 25mg of MBG or placebo, at their discretion and in consultation with the investigator.

Phone Visit 2

Study staff will contact each subject 70-74 days post Randomization Visit. The following assessments will be performed:

- Adverse Event Assessment
- Prompting to Resume Subject Diary
- Subject Diary Training (if needed)
- Void Volume Measurement Training (if needed)

Subjects will be instructed to complete the 72 continuous hours of diary entries prior to the Final Visit. Study staff will reconfirm scheduled dates for follow-up study visits.

Final Visit

This visit will be scheduled 74-82 days post Randomization Visit. The following assessments will be performed:

- Review of Concomitant Medications
- Adverse Event Assessment
- Vital Signs: Blood Pressure, Heart Rate and Temperature
- Physical Examination (if deemed necessary by investigator)
- Urine Pregnancy Testing for Female Subjects of Childbearing Potential (if deemed necessary by investigator)
- Subject Diary Review
- Qualiveen Questionnaire - pages #1-6 only
- Subject Global Impression
- Bladder Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)
- Bowel Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)
- Pelvic Floor Exercise Adherence Question
- Drug Return and Accountability

Unscheduled Visits
Subjects may return to the clinic for safety evaluation or to receive additional study medication as needed.

Laboratory tests
Screening blood testing will include complete blood count and comprehensive metabolic panel. At screening, subjects reporting dysuria, fever or abdominal pain will undergo urine analysis, culture and sensitivity at the discretion of the principal investigator. Urine pregnancy testing will be performed at Screening Visit and office visits thereafter, as indicated by female fertility status and as deemed necessary by investigator.

Screen failures / Rescreening
Subjects who screen fail due to not meeting inclusion criteria or due to certain exclusions, e.g. presence of urinary tract infection, may rescreen in 30 days at the discretion of the investigator.

Early Termination
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), safety issues related to study-related or non-study related adverse events, and at the request of the subject or at the discretion of the investigator.

Efficacy Assessment
Primary Outcome Measure
Average daily OAB-SCS total score based on OAB SCS at Final Visit vs. Baseline Visit. Every toilet void or incontinence episode will be recorded in a diary based on the OAB-SCS system: 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). Every incontinence episode is scored as 5. Each voiding event is multiplied by the score for the event and then all events are summed to generate a total daily OAB-SCS cumulative score. Each daily total score is averaged to generate the Average daily OAB-SCS total score. For incomplete days (e.g. went out for 6 hours and forgot to record voids) the sum score will be adjusted as follows: total score over 24 hours X 24 / actual # of hours included in documentation (see reference Zinner et al).

Secondary Outcome Measures based on diaries compared to Baseline Visit:
- Average daily OAB-SCS total score based on OAB SCS reviewed at Titration Visit
- Titration Visit and Final Visit mean number of micturition/day*
- Titration Visit and Final Visit mean number of incontinence episodes/day*
- Titration Visit and Final Visit mean volume voided/micturition*
  *missing blocks of time will not be included in the scoring

Secondary Outcome Measures based on Titration Visit and Final Visit compared to Baseline Visit:
- Qualiveen Questionnaire
  - The English version of the Qualiveen has been found to be a valid and responsive measure of bladder function in MS.24. Site will use pages

#1-6 & #9-10 at baseline and only pages #1-6 at other visits. Pages #7-8 will not be used as they are not applicable.

- Subject Global Impression
  - This is a single question: "How would you rate your level of bladder control during the past week?" Please circle your choice:
    - Extremely good, Quite good, Better than average, Average, Below Average, Quite bad, Extremely bad"

- Pelvic Floor Exercise Adherence Question
  - This is a single question: "How many days did you perform pelvic floor exercises during the past two weeks? Please circle your choice:
    - Never, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, more than once a day"

- Bladder Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)
  - 8 multiple choice questions

Exploratory Outcome Measures based on Titration Visit and Final Visit compared to Baseline Visit:

- Bowel Management Difficulties Questionnaire – Short Form (SCI-QOL v1.0)25
  - 9 multiple choice questions

Questionnaires will be administered by the research coordinator or study nurse. See Schedule of Assessments above for timing of testing.

Safety Measures

All subjects will undergo baseline blood testing, CBC and CMP. Subjects with screening estimated glomerular filtration rate (eGFR) < 60, or AST or ALT > 2x upper limit of normal will be excluded. At screening, subjects reporting dysuria, fever or abdominal pain will undergo urine analysis, culture and sensitivity at the discretion of the principal investigator. Subjects with blood pressure > 165 systolic or 100 diastolic 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. Subjects with screening post-void residual > 200ml will be excluded. 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. 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. Female subjects will undergo urine pregnancy testing if they are deemed to have any risk of being pregnant or becoming pregnant during the study.

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.

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

Adverse events that arise between the Baseline Visit and Final Visit will be classified as acute therapy phase adverse events.

A serious adverse event is an undesirable sign, symptom or medical condition which: 1. is fatal or life-threatening, 2. required or prolonged 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. No interim analysis of safety data is planned because the entire study will be conducted over 2 months. However, 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 MS fatigue drug trials.

Serious Adverse Events Reporting
The FDA will be informed of serious unexpected adverse reactions (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 a Serious Adverse Event requires reporting to the FDA (unexpected and possibly related to study drug), the following actions will be taken:

1. Telephone the FDA immediately (day of awareness), in the case of reportable death or life threatening events.
2. Complete FDA Form 3500.
3. Send the completed Form 3500 to the FDA (preferably by fax at 1-800-FDA-0178) within the timelines mentioned above.
4. Attach the photocopy of all examinations, medical notes and records related to the Serious Adverse Event 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.

Any symptoms or signs that could be due to an MS exacerbation will prompt an unscheduled visit with the investigating physician to confirm or refute an MS exacerbation. Any confirmed exacerbations will be noted in the results, but will not lead to removal from the study unless it is deemed by the subject or the investigating physician to be in the subjects' best interest to do so. Treatment of exacerbation with IV methylprednisolone 1gm daily for three days with oral steroid taper may be provided at the investigator's discretion.

Sample Size Considerations

This is a prospective double-blinded, 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.

Statistical Analysis

Demographics and baseline disease characteristics, including age, gender, MS type and duration of disease, level of disability (EDSS), and disease modifying therapy status will be compared between study groups.

Summary and analysis of primary and secondary outcome measures will include

1. Summary statistics (n, mean, standard deviation, median, minimum and maximum) at baseline and week 5 and week 10 by treatment
2. Summary of % change from baseline to week 5 and 10.
3. Significance testing

For the primary outcome measure, Average daily OAB-SCS, each voiding event is multiplied by the score for the event and then all events are summed to generate a total daily OAB-SCS cumulative score. Each daily total score is averaged to generate the Average daily OAB-SCS total score. For incomplete days (e.g. went out for 6 hours and forgot to record voids) the sum score will be adjusted as follows: total score over 24 hours X 24 / actual # of hours included in documentation (see reference Zinner et al).

Mean OAB-SCS score at Baseline Visit will be included in the model as an independent variable. The primary time points for all comparative measures will be Baseline Visit, Titration Visit and Final Visit. Outcome measures will be compared between groups using analysis of covariance (ANCOVA) or other method. 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 two recent MS studies.

Aggregate, de-identified data from the Bladder and Bowel Management Difficulties Short Form Questionnaires (SCI-QOL v1.0) will be shared with the University of Washington in Seattle, WA. This will be done as a courtesy for giving the investigator permission to use these questionnaires in this protocol.

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 Institutional Review Board/Independent Ethics Committee/Research Ethics Board approval and the written informed consent of the patient.

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