Clinical Protocol

Urodynamic and clinical efficacy of Mirabegron among neurogenic bladder patients

Version Date
Sept 30, 2014

Table of Contents

Contact Information

Principle Investigator

Blayne Welk, MD FRCSC MSc
Assistant Professor, Division of Urology
Western University

Room B4-667
St Joseph's Health Care
268 Grosvenor Street London ON N6A 4V2
Phone: 519 646-6367
Fax: 519 646-6037
Blayne.welk@sjhc.london.on.ca

Participating Investigators

Dr Duane Hickling
Assistant Professor, Division of Urology
Ottawa University

The Ottawa Hospital Civic Campus
Department of Urology
1053 Carling Avenue
Ottawa ON K1Y 4E9
Phone: 613 761-4000
Fax: 613 761-4350
duanehickling@gmail.com

Dr Karen Ethans
Associate Professor, Department of Medicine
University of Manitoba

Room RR143A
Health Sciences Centre
800 Sherbrook St
Winnipeg, MB R3A 1M4
Phone: 204 787-5135
Fax: 204 787-1476
KEthans@exchange.hsc.mb.ca

Clinical Protocol Overview

The proposed study is a randomized, double blind placebo controlled multicenter study to determine the effectiveness of mirabegron in the treatment of neurogenic bladder dysfunction. Patients will be randomized into one of two trial arms: mirabegron 25mg for two weeks, with escalation to 50mg for the remaining 8 weeks, or matched placebo capsule for two weeks, with placebo escalation for the remaining 8 weeks. Each of these trial arms will be stratified based on whether the patient is already taking an anticholinergic medication or not. The study will treat a total of 144 patients (72 with placebo, 72 with mirabegron). The study hypothesis is that mirabegron will result in a statistically superior (increased) urodynamic bladder capacity.

The study duration is 12 weeks, with a 1-4 week run in period where no active or placebo treatment will be administered. The primary outcome measure will be based on an increase in urodynamic bladder capacity. Secondary outcome measures will be additional urodynamic parameters, urinary symptom scales, urinary quality of life indices, and voiding diary results.

Patients who are over 18 years of age with a diagnosis of multiple sclerosis or spinal cord injury will be eligible to participate. All eligible patients will have urodynamic studies performed within 4 weeks of trial enrollment, and at the end of study (week 9-10). Adverse events and study outcomes will be assessed at predefined study time points.

Background

A variety of neurologic diseases can lead to bladder dysfunction, however spinal cord injury (SCI) and multiple sclerosis (MS) are most often associated with significant bladder dysfunction and urinary morbidity (renal dysfunction, incontinence, and urinary tract infection)(1). In addition to conservative measures, first line therapy for many neurogenic bladder patients involves the use of anticholinergic medications. Anticholinergic medications have been primarily studied for the more common indication of overactive bladder(2). In small clinical trials and case series, these medications have demonstrated improvements in urgency incontinence, and urodynamic parameters (such as bladder capacity and detrusor pressure) among neurogenic bladder patients(3). However, anticholinergic medications have a number of undesirable side effects, including dry mouth and constipation. This has been shown to significantly limit medication compliance among both the general population(4), and neurogenic bladder patients(5). Despite treatment with anticholinergic medication, many patients still have bothersome urinary symptoms(3).

Mirabegron is a Beta-3 agonist, which is the first of a new class of overactive bladder medication. It was approved by Health Canada for the treatment of overactive bladder in 2012. Beta-3 receptors are primarily found in the bladder, and mediate bladder relaxation. Mirabegron has 33-100x selectivity for the Beta-3 receptor compared to Beta-1 or Beta-2(6). Clinical trials have shown it is efficacious for the treatment of overactive bladder symptoms in the general population with minimal side effects and an excellent safety profile(7,8). Common adverse events related to mirabegron appear to be limited to urinary tract infection, hypertension, headache and gastrointestinal upset, which all occur at rates similar to placebo(9). There is currently no evidence (or registered clinical trials) evaluating the use of mirabegron among neurogenic bladder patients, making this a novel and exciting area of study.

Objectives

Primary objective

Examine the change in urodynamic bladder capacity associated with mirabegron use among neurogenic bladder patients.

Urodynamics are a clinical study of bladder function. A small catheter is placed in the bladder and another in the rectum, and saline is infused into the bladder at a standard rate while a pressure transducer measures bladder pressure. Standard and accepted operating procedures for the performance of urodynamic testing have been established(10).

Urodynamic studies are an essential part of the urologic evaluation of patients with neurogenic disease due to the risk of urologic complications such as renal dysfunction and urinary incontinence related to impaired bladder compliance and high pressure neurogenic detrusor overactivity(11). It is a recommended test in the guidelines published by the American Urologic Association(12). It is standard practice to perform this study in order to assess baseline bladder function, and to assess treatment response.

Given the fact that many patients with neurogenic bladder dysfunction do not have normal perception of urinary function, an objective measure of bladder function is essential. Urodynamic bladder capacity is a good parameter to evaluate as the primary outcome for this study given the known effect of alternative medications on bladder capacity, and the desirable associated clinical benefit of increased bladder capacity (such as increased time between voids, reduced risk of renal damage, and reduced risk of urinary incontinence). Patients are often followed with further urodynamic studies to assess the effectiveness of interventions aimed at improving bladder function. Among neurogenic bladder patients, urodynamic parameters have good measurement characteristics(13).

Secondary objectives

Examine the clinical effectiveness of mirabegron for treating the symptoms of urinary frequency, urgency, and urge incontinence among neurogenic bladder patients.

The assessment of voiding function is complex, and individual measures may be inadequate. Multiple secondary outcomes are included to assess for a clinically meaningful level of improvement in bladder function.

- Secondary urodynamic characteristics will be assessed (volume at first episode of detrusor overactivity, maximum detrusor pressure, volume at maximum detrusor pressure, bladder sensation, and bladder compliance).
- The 3 day voiding diary is a simple patient maintained record of fluid intake, voided volume and incontinence episodes. This measure has an acceptable reliability when used in clinical study(14). This will be used to assess number of episodes of urgency incontinence, urinary frequency, longest time between voids, functional capacity, and mean voided volume.
- Quantification of urinary incontinence will be assessed with pad weights(15). This will determine the amount of urinary incontinence that occurs over a 24hr period. The 24hr pad test is stable over time, and has good reliability(16).
- Patient reported outcome measures will be used to assess incontinence related quality of life, overall urinary quality of life, and specific urinary symptoms.

    - Quality of life will be measured with the Incontinence quality of life measure (I-QOL), and the SF-Qualiveen. The I-QOL is an incontinence specific quality of life tool that has been shown to be a valid, reliable and responsive measurement among patients with neurogenic bladder dysfunction(17). The SF-Qualiveen is a urinary specific quality of life measure developed and studied specifically for neurogenic bladder patients; validity, reliability and responsiveness have been established(18) (19,20).
    - The Neurogenic bladder symptom score (NBSS) is a symptom specific measure of urinary symptoms developed for patients with neurogenic bladder dysfunction with demonstrated validity and reliability (Reference in press, Journal of Urology).
- The patient perception of bladder condition is a commonly used measure in the assessment of oral medications for the treatment of overactive bladder symptoms(21).

- Examine the tolerability and adverse effects associated with mirabegron use among neurogenic bladder patients.

    - Adverse events related to mirabegron will be monitored. Patients will be actively monitored for hypertension, tachycardia, and urinary retention. Other adverse events will be monitored by passive reporting.

Specific Hypothesis

The primary hypothesis for effectiveness is that patients treated with mirabegron will have an increased urodynamic bladder capacity at 10 weeks compared to the placebo group. The null hypothesis is H0: $p_{mirabegron} - p_{placebo} \leq 0$. The alternative hypothesis is HA: $p_{mirabegron} - p_{placebo} > 0$.

Product Description

Mirabegron is a selective beta-3 agonist that is indicated for the treatment of overactive bladder, with symptoms of frequency, urgency and urgency incontinence. It is provided as a single extended release oral pill that may be taken with or without food. It has no significant affinity for other pharmacologic targets. Peak plasma concentrations occur at 3-5 hrs among health adults. Steady state concentrations occur within 7 days of once daily dosing. Mirabegron has been studied in over 10,000 human subjects, at doses from 25-200mg. The incidence of adverse events in the mirabegron 25-50mg dose groups is comparable to placebo groups. The most frequently reported adverse event was hypertension. Most of the events were mild or moderate in intensity.

Mirabegron is registered for the treatment of OAB in Canada. No actions have been required for safety reasons concerning withdrawal, rejection, suspension or failure to obtain a renewal of a marking authorization. There have been no restrictions on distribution, clinical study suspension, dosage modification, indications, or formulation changes.

Further product details are included in the product monograph (Appendix 5).

Study Justification

Patients with neurogenic bladder dysfunction consist primarily of patients with spinal cord injuries (SCI) or multiple sclerosis (MS)(1). These conditions lead to damage to the upper motor neurons, which can cause varying patterns of bladder dysfunction. Common symptoms among patients with MS include urgency, urgency incontinence, and increased urinary frequency, which is the result of neurogenic detrusor overactivity. Common symptoms among patients with SCI depend on the level of the injury and the method of bladder management. Most patients will have neurogenic detrusor overactivity, and often will have coexisting detrusor-sphincter dyssynergia. This leads to an inability to both store and void urine. Given the lack of urinary sensation, the primary symptom for these patients is often urinary incontinence. Patients may be started on intermittent catheterization to improve voiding.

For both MS and SCI patients, the symptoms of urinary incontinence or urgency/frequency are usually treated with anticholinergic medication. There are several medications available (such as oxybutynin and tolterodine). Health Canada approval of these medications is based on a labeled indication for the treatment of overactive bladder symptoms, however these medications have been studied in patients with neurogenic bladder dysfunction(3). These studies have demonstrated patient perceived improvement, increased bladder capacity, and lower maximum detrusor pressure, however they are also associated with a higher incidence of adverse events related to anticholinergic side effects.

Previous clinical experience with mirabegron has been in clinical trials for the treatment of overactive bladder (OAB) symptoms. Three large randomized trials have been completed(7,8,22). In these OAB studies, there was a trend towards better efficacy with the 50mg dose, and given the increased dose requirements for anticholinergic medications in the neurogenic bladder population(23), a dose titration to a maximal dose of 50mg was selected. Mirabegron has been evaluated in a Phase II RCT in combination with solifenacin (an anticholinergic medication) for OAB patients(24). The combination of mirabegron and solifenacin resulted in an improvement in voided volume and a reduction in voiding frequency, with adverse events in keeping with monotherapy. Synergy between anticholinergic medications and mirabegron has not been evaluated in the neurogenic bladder population.

Mirabegron is hypothesized to be effective in reducing the symptoms of neurogenic bladder dysfunction. In an animal model of SCI, mirabegron has a beneficial effect on urodynamic parameters without affecting voiding parameters(25). Mirabegron may have a beneficial safety and tolerability profile among patients with neurogenic bladder dysfunction. Evidence from patients with overactive bladder suggests adverse events with mirabegron are very similar to placebo(7,9).

A placebo controlled trial is the most methodologically sound trial design for this clinical study. Among all trials involving over active bladder symptoms, there is a significant placebo response (usually 20-30%)(26), which makes a noninferiority trial design impractical at this preliminary stage. In addition, there are no adequately powered and well conducted randomized clinical trials that have established the efficacy of anticholinergic medication among this population, and meta-analyses of the available data on anitcholinergics have confidence intervals with large bounds, indicating the imprecision of our current knowledge about their effect sizes(3). This also makes direct comparison to another medication in a clinical trial setting difficult. As this is the first study to investigate the efficacy of this medication in this population, it is important to establish basic efficacy before proceeding with further study. The placebo arm is limited to 10 weeks, which allows for a dose titration and an adequate medication trial of 6-8 weeks of the full dose mirabegron (in the OAB trials the maximum effect of this medication was seen after 4-6 weeks(22)), at which point if there is no response the trial is over, and different therapy can be pursued at the discretion of the treating physician. Although urinary

symptoms are often bothersome in this population, they are not dangerous, and current clinical practice would include a trial of anticholinergic medication in a similar manner.

Risk Assessment

All activities performed within the scope of this study will comply with recognized Good Clinical Practice guidelines and applicable regulatory requirements.

Potential specific risks

Potential risks related to the use of mirabegron include:

- Hypertension
- Increased heart rate
- Urinary retention
- Unknown effect on sperm, ovum, and pregnancy

Potential risks related to urodynamic studies include:

- Urinary tract infection
- Hematuria
- Mild pelvic discomfort
- Autonomic dysreflexia (among SCI patients only)

Methods to minimize risk

Potential risks related to the use of mirabegron will be minimized by exclusion criteria and active monitoring. Mirabegron has an acceptable safety profile based on previous animal and human studies(9).

Patients with uncontrolled hypertension (defined as screening visit BP >180mmHg systolic or >110mmHg diastolic) will be excluded at screening. BP will be monitored at the +2 week followup, and if a normotensive patient becomes hypertensive, or there is a significant increase in blood pressure after multiple readings, the medication will be discontinued and considered an expected adverse event (details in safety monitoring section). In clinical studies for OAB, a mean increase of 1mmHg was seen in systolic and diastolic BP; new onset hypertension was reversible upon discontinuation of the medication(9).

Patients will have their heart rate monitored at screening. Those with a resting heart rate >100bpm after repeat measurements will be excluded. Patients with a history of tachyarrhythmia's will be excluded. HR will be monitored at the 2 week followup, and if their resting HR is >100 bpm after multiple readings, the medication will be discontinued and considered an expected adverse event.

A clinical safety study in patients with bladder outlet obstruction did not demonstrate an increase in urinary retention(27), however it has been reported in postmarketing experience with mirabegron. Patients with a post void residual >250mL who are not already using intermittent catheters will be excluded from the study. All patients will be instructed on the signs and symptoms of urinary retention. Post void residual will be reassessed at the 2 week followup. Patients who develop urinary retention (defined as signs and symptoms of urinary retention with a post void residual >250mL, or an asymptomatic PVR >400mL) will discontinue medication and be considered as an expected adverse event.

Patients of child bearing potential will have a pregnancy test done on screening and monitored throughout the trial through health review at each visit. Male and female patients who are planning on

conceiving will be excluded from this study. Female patients must agree to use an effective form of contraceptive between the screening visit and continued throughout the study period and for 28 days after the final dose of study drug. Male subjects with a partner of childbearing potential must also use an effective form of contraceptive between the Screening visit and continued throughout the study period and for 28 days after the final dose of study drug. All male participants will be provided with Letters of Information to be given to all of their female sexual partner(s) who are of child bearing potential. Male subjects also must not donate sperm starting at screening and throughout the study period and for 28 days after the final study drug is taken.

All patients will be counseled about the risks related to urodynamic studies. Urodynamic studies are performed under the supervision of a urologist, and carried out by nurses trained in the urodynamic equipment. The risks are generally mild and infrequent(10,28). Patients will be assessed for symptomatic urinary tract infection prior to urodynamics, and if necessary, the urodynamic study will be delayed in order to initiate antibiotic treatment. After urodynamics, the urine will be assessed and if there is significant hematuria, this will be monitored and treated if necessary. Patients will be informed that there may be some mild pelvic discomfort associated with bladder filling that will be relieved at the end of the study. SCI patients with complete injuries above the level of T6 will be monitored for symptoms of autonomic dysreflexia related to bladder filling (headache, flushing, sweating, nausea). If these symptoms occur, the study will be terminated, and the bladder drained.

Patients will have baseline laboratory tests (creatinine, AST, ALT, GGT, total bilirubin), ECG, and urinalysis done prior to randomization, and at visit 3 (2 weeks after the initiation of the study medication).

Study Design

This clinical study will be a randomized, double blind placebo controlled multicenter study to determine the effectiveness of mirabegron for the symptoms of neurogenic bladder dysfunction among patients with SCI or MS. Patients will be randomized at study enrollment to either placebo or mirabegron treatment arms. The proposed study size is 144 patients, with an included 20% margin to account for those that may withdraw or be lost to followup. Randomization of SCI and MS patients will be stratified to ensure approximately equal distribution of these patient groups between trial arms, and approximately equal distribution of patients who are currently taking bladder specific anticholinergic medication versus those who are not taking anticholinergics. This study has been registered with clintrials.gov NCT02044510.

Inclusion criteria

- Diagnosis of traumatic or nontraumatic suprasacral SCI or multiple sclerosis (based on a neurologist assessment and/or the McDonald criteria)(29)
- Age >18 years
- Stable method of bladder management for >3months (either spontaneous or provoked voiding, or intermittent catheterization).
- Bothersome urinary symptoms (urinary frequency, urgency, or urgency incontinence based on standard ICS definitions(30)) and completed 3 day voiding diary demonstrating at least 1 episode of non-stress based urinary incontinence over the 72hr period (this may be urgency based incontinence or unaware incontinence).
- Patient is able to read and speak English

Exclusion criteria

Based on Screening visit history:

- Participation in another drug or device study in the 60 days prior to the screening visit.
- Previous urologic surgery: Transurethral prostatectomy, bladder augmentation, sphincterotomy, bladder neck sling, artificial urinary sphincter, catheterizable channel, implantable electrostimulator/neuromodulator
- Current use of suprapubic catheter/foley catheter
- Unstable cardiac disease (uncontrolled hypertension, myocardial infarction, unstable angina, severe congestive heart failure (NYHA 3 or 4), ventricular arrhythmia (such as torsades de pointes), or stroke within the last 6 months)
- Clinically significant abnormal ECG
- The investigator believes the patient has an increased risk of QT prolongation (based on review of the screening ECG and patients concurrent medications)
- History of significant renal dysfunction within 1 year, or serum creatinine >150umol/L at screening visit (visit 1).
- History of significant liver disease within 1 year, or serum AST/ALT >2 times upper limit of normal, GGT >3 times upper limit of normal, total bilirubin >2 times upper limit of normal at screening visit (visit 1).
- History of pelvic radiation
- History of bladder cancer
- History of a concurrent malignancy or cancer (except noninvasive skin cancer) within the last 5

years. Subjects with a history of cancer are considered eligible if the subject has undergone potentially curative therapy and the subject has been considered disease free for at least 5 years (with the exception of basal cell or squamous cell carcinoma of the skin).

- Patient has a history of interstitial cystitis/pelvic pain syndrome
- Patient has a history of acute or chronic urinary retention within the last 3 months, and is currently not using intermittent catheters
- Patient has a history of a tachyarrhythmia
- Patient has a history of glaucoma
- Patient has a medical condition that may cause noncompliance with the study protocol
- In the opinion of the Investigator the patient has a history of significant stress urinary incontinence
- Patient has signs and symptoms of an active urinary tract infection (symptoms of dysuria, foul smelling urine, cloudy urine, increased spasticity, increased autonomic dysreflexia, self reported fever, increased incontinence, back/suprapubic pain).
    - Patient will submit urine for culture and sensitivity, undergo treatment, and will be eligible for rescreening after treatment.
- Female patient who is pregnant or breastfeeding, or plans to become pregnant.
- Male patient who is planning on fathering a child during the study or for 28 days after the last dose of study drug, or who is planning to donate sperm
- Patient refuses to provide written consent
- Patient will be unable or unwilling to complete the questionnaires and study visits
- In the opinion of the study investigator, it is not in the patient's best interest to be enrolled in this study.

Based on medication and allergy review

- The new addition of an anticholinergic medication, or a change to anticholinergic dose, within the last 30 days, (bladder specific anticholinergics include oxybutynin, tolterodine, fesoterodine, solifenacin, darifenacin, trospium, hyoscine, oxybutynin gel or patch, atropine, benzatropine). If previously used and discontinued, these medications must have been stopped for >2 weeks
- Newly added bladder active medication (or dose change) within the last 2 months (Tamsulosin, Silodosin, Terazosin, Baclofen, Diazepam, amitriptyline, Finasteride, Dutasteride, DDAVP/desmopressin)
- Use of flecainide, propafenone, donepezil, thioridazine, tramadol, aripiprazole, desipramine, imipramine, venlafaxine or digoxin
- Intravesical onabotulinum toxin use within the last 1 year
- Intravesical oxybutynin within the last 3 months
- Patient has a previous history of treatment with mirabegron
- Patient has a known allergy to mirabegron or a previous adverse reaction to a beta 3 agonist.

Based on physical exam

- Patient has a postvoid residual > 250mL at study enrollment after repeated tested (1 attempt to re-void to ensure complete emptying of the bladder) and is not using intermittent catheters
- Patient has a resting BP >180 mmHg systolic and/or >110 mmHg diastolic after 2 minutes of sitting quietly
- Patient has a resting heart rate >100bpm after 2 minutes of sitting quietly
- In the opinion of the study investigator, it is not in the patient's best interest to be enrolled in this study based on a clinically significant abnormality on physical exam.

Point of enrollment

Patients who meet the inclusion/exclusion criteria are eligible for entry into the study. They will have the study protocol and potential risks and benefits explained to them. Patients who agree to participate will be given a letter of information, and required to sign an informed consent document. Official enrollment and randomization occurs at the initial urodynamic appointment, after completion of the urodynamics study. If a patient withdraws between screening and enrollment, that spot will reopen in order to achieve the total study sample size of 144 randomized patients.

Sample size

A two sample t-test was used to calculate sample size. Patients on anticholinergics versus those not on anticholinergics will be analyzed as separate populations. Based on previous clinical trials in SCI and MS patients(31,32), an estimated mean end of study bladder capacity of 250mL (placebo) versus 325mL (mirabegron), and a standard deviation of 100 was assumed; a two sided alpha of 0.05, and 80% power would require a total of 58 patients. Accounting for a dropout rate of 20%, and to equal stratification among SCI and MS patients, and anticholinergic users versus anticholinergic nonusers a total sample size of 144 patients is required (36/group: SCI on anticholinergics, MS on anticholinergics, SCI not on anticholinergics, MS not on anticholinergics).

Medication Preparation and Allocation

Medication preparation will be done by the clinical trial pharmacists at St Joseph's Health Care London. Commercially sourced mirabegron (myrbetriq) 25mg and matching inert placebo pill (both supplied by Astellas Inc) will be repackaged and dispensed in a blinded manner. Medication will be placed in identical containers, and labeled by study treatment assignment number (TAN). The clinical trial pharmacist at St Joseph's Health Care London, who will not be involved in any study data collection or interpretation, will maintain a master list of treatment allocations for emergency unblinding. This clinical pharmacist will provide medication kits for other participating centers and will be responsible for appropriate labeling of the medication containers. These medication kits will be shipped to participating centers using a commercial temperature sensitive shipping service.

All subjects who sign a consent form will received a subject number (01, 02, 03…). Once they are randomized, they will receive a treatment assignment number (TANs) based on having a diagnosis of either MS or SCI. There will be two block randomization schedules, one for MS patients, and one for SCI patients. Subjects will be assigned the next sequential TAN in either the MS or SCI group (so that approximately 36 SCI and 36 MS patients who are not on anticholinergics are randomly assigned placebo or mirabegron, and 36 SCI and 36 MS patients who are on anticholinergics are randomly assigned placebo or mirabegron). The randomization schedules will be computer generated by the clinical trial pharmacist, and kept confidential from all study investigators and other blinded study staff. TANs will be assigned so that 8 approximately equal groups of patients are created: placebo MS not on anticholinergics, placebo SCI not on anticholinergics, mirabegron MS not on anticholinergics, mirabegron SCI not on anticholinergics, placebo MS on anticholinergics, placebo SCI on anticholinergics, mirabegron MS on anticholinergics, mirabegron SCI on anticholinergics. Each TAN will correspond to a vial containing a 3 week supply of assigned medication (either placebo or mirabegron 25mg), and then a separate vial containing the 8 weeks of dose escalated medication (either placebo or mirabegron 50mg, matching the assignment from the initial 3 week phase). An extra

7 day supply of medication will be included.

If it is medically necessary to unblind a patient in an emergency, the St Josephs Hospital Pharmacist will be contacted to unblind the patient. The reason for unblinding shall be recorded, and the study investigator informed as soon as possible. Pharmacy staff may unblind patients without prior permission of the study investigator.

Description of study timeline and patient visits

Visit 1: Screening

- Review of letter of information
- Signing informed consent form
- Medical history/Physical exam
- Point by point review of inclusion and exclusion criteria
- Assessment of BP (2min of sitting quietly, BP measured using standard office equipment consisting of a noninvasive, appropriately sized BP cuff in both arms. The arm with the highest diastolic will be used for the duration of the study. If the first reading is >140/>90mmHg, then a second reading will be obtained).
- Assessment of HR (2min of sitting quietly, HR measured using radial pulse for 30 sec)
- Assessment of PVR (not applicable for patients using intermittent catheterization.) Patient will be asked to void to completion, and 3 measurements obtained using calibrated, noninvasive bladder scanner are performed. If the average of these measurements is >250mL, then patient is asked to revoid and measurements are repeated.
- Assessment of pregnancy by urine dip stick
- Serum bloodwork drawn for creatinine, AST, ALT, GGT, total bilirubin
- Urinalysis
- ECG
- Symptomatic UTI screening (symptoms of dysuria, foul smelling urine, cloudy urine, increased spasticity, increased autonomic dysreflexia, self reported fever, increased incontinence, back/suprapubic pain). If based on the clinical judgment of the supervising physician, a symptomatic UTI is suspected, a urine dip and urine culture will be done as per standard clinical practice. If the supervising physician wishes, they may wait for culture results, or initiate treatment, and reschedule study visit.
- Patient will complete the following questionnaires: I-QOL, SF-Qualiveen, NBSS, and PPBC (Appendix 1).
- Patients will be instructed on how to carry out the 24hr urinary pad test, and will return with this for the next visit (Appendix 2).
- Patients will be instructed on how to complete the 3 day voiding diary, and will return with this for the next visit (Appendix 3).

Visit 2 (within 1-4 weeks of screening. Set as week 0)

- Review of 3 day voiding diary to ensure patient meets voiding diary eligibility criteria
- Collection of 24hr urinary pad test material
- Review of medication or health changes
- Symptomatic UTI screening (symptoms of dysuria, foul smelling urine, cloudy urine, increased spasticity, increased autonomic dysreflexia, self reported fever, increased incontinence, back/suprapubic pain). If based on the clinical judgment of the supervising physician, a symptomatic UTI is suspected, a urine dip and urine culture will be done as per standard clinical practice. If the supervising physician wishes, they may wait for culture results, or initiate treatment, and reschedule urodynamics.

- Randomization and 3 week medication supply (blinded placebo or mirabegron 25mg provided). Reminded to bring pill container to next visit.
- Urodynamic assessment (Appendix 4)

Visit 3 (2-3 weeks)

- Review of medication or health changes/Physical exam
- Pill count to assess medication compliance
- Passive reporting of adverse events
- Measurement of HR, BP, and PVR
- Serum bloodwork drawn for creatinine, AST, ALT, GGT, total bilirubin
- Urinalysis
- ECG
- Symptomatic UTI screening (symptoms of dysuria, foul smelling urine, cloudy urine, increased spasticity, increased autonomic dysreflexia, self reported fever, increased incontinence, back/suprapubic pain). If based on the clinical judgment of the supervising physician, a symptomatic UTI is suspected, a urine dip and urine culture will be done as per standard clinical practice. If the supervising physician wishes, they may wait for culture results, or initiate treatment.
- 8 week medication supply with a dose escalation (placebo capsule or 50mg mirabegron provided). Reminded to bring pill container to next visit.
- Reminded to provide a voiding diary and 24hr pad test for next visit

Visit 4 (9-10 weeks)

- Review of medication or health changes
- Pill count to assess medication compliance
- Passive reporting of adverse events
- Measurement of HR, BP, and PVR
- Symptomatic UTI screening (symptoms of dysuria, foul smelling urine, cloudy urine, increased spasticity, increased autonomic dysreflexia, self reported fever, increased incontinence, back/suprapubic pain). If based on the clinical judgment of the supervising physician, a symptomatic UTI is suspected, a urine dip and urine culture will be done. If the supervising physician wishes, they may wait for culture results, or initiate treatment, and reschedule urodynamics.
- Assessment of pregnancy by urine dip stick
- Urodynamic assessment (Appendix 4)

Study Timeline Summary

Event	**Visit 1** -1 to -4 wks *Screening*	**Visit 2** 0 wk *Randomization*	**Visit 3** +2-3 wks *Followup*	**Visit 4** +9-10 wks *End of Study visit*
Informed consent/LOI	X			
Medical History/Physical Exam	X		**X**	
Inclusion/Exclusion check	X			
Medication/Health review		X	X	X
BP/HR Measurement	X		X	X
PVR	X	X	X	X
Urine Pregnancy test	X			X
Bloodwork	X		X	
Urinalysis	X		X	
ECG	X		X	
Urine infection screen (Hx, Dip, C&S PRN)	X	X	X	X
IQOL	X			X
SF-Qualiveen	X			X
NBSS	X			X
PPBC	X			X
24hr urinary pad test	Provided & Return with visit 2	X	Provided & Return with visit 4	X
3 day voiding diary	Provided & Return with visit 2	X	Provided & Return with visit 4	X
Randomization		X		
Adverse event assessment			X	X
Medication compliance assessment			X	X
Initial study drug (3 week supply, placebo or mirabegron 25mg)		X		
Dose escalation (8 week supply placebo or mirabegron 50mg)			X	
Urodynamic study		X		X

Criteria and procedures for withdrawal

A patient may withdraw from the clinical trial at any time without prejudice or loss of care. The treating urologist may decide to withdraw a patient rom the clinical trial at any time based on their best medical judgment. Reasons for study exit will be obtained. If a patient is lost to followup or fails to appear for a scheduled post treatment assessment, every effort will be made to locate the patient before patient will be considered to have exited the trial.

Patient will stop participation in the clinical study, and the study medication will be discontinued if there is:

- An adverse event (an allergic reaction thought to be from the study medication, a significant increase in heart rate or blood pressure, an episode of acute urinary retention, a new asymptomatic PVR >400mL, a significant increase in serum liver function tests, (defined as an increase of serum AST/ALT >2 times upper limit of normal, GGT >3 times upper limit of normal, total bilirubin >2 times upper limit of normal), or a clinically significant abnormal ECG in the opinion of the investigator.
- A medical necessity to add an excluded medication before the termination of the study.
- A medical necessity to change the dose of an established anticholinergic medication used for bladder symptoms during the study.
- The patient voluntarily withdraws from the study. Patients who do not undergo randomization will be replaced.
- The subject is unable to mentally or physically tolerate the study medication or study procedures.
- Pregnancy during the study. The patient will be asked to immediately report this information to the study coordinator, and will be withdrawn from the study. The patient will be followed based on standard clinical practice.
- There is a new medical condition which in the judgment of the supervising urologist makes them ineligible for further participation.

Safety monitoring and reporting of adverse events

All adverse events (expected and unexpected) should be reported as soon as possible by trial personnel. Monitoring for adverse events will occur between randomization (visit 2) and the final study visit (visit 4). The appropriate adverse event record will be completed and submitted to the principle investigator (including information on the adverse event, onset date, duration, severity and course of action taken). The local investigator will be responsible for informing their local ethics committee, and the principle investigator will be responsible for informing his REB and Health Canada.

The following will be considered serious adverse events: any event that results in death or is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in significant disability/incapacity, or is an important medical event in the judgment of the treating physician.

Study specific expected adverse events that will be monitored include:

- Allergic reaction
- Tachycardia (>100bpm on the lowest of two measurements)
- Hypertension
    - Patient was previously normotensive (<140/<90 mmHg) and now has BP >140 mmHg systolic and/or >90mmHg diastolic with at least a 10mmHg increase in systolic and/or diastolic BP.

- BP has increased >20mmHg systolic or >10mmHg diastolic as compared to baseline.
- Elevated post void residual
  - >400mL without symptoms (pelvic pain, voiding small amounts, constant sense of bladder fullness, overflow incontinence)
- Urinary retention
  - >250mL with symptoms (pelvic pain, voiding small amounts, constant sense of bladder fullness, overflow incontinence)
- Liver function tests (an increase of serum AST/ALT >2 times upper limit of normal, GGT >3 times upper limit of normal, total bilirubin >2 times upper limit of normal) at visit 3.
- ECG (a clinically significant change in the opinion of the investigator).

Nonstudy specific expected adverse events that may occur include common medical complications associated with SCI and MS patients. These include development or worsening of pressure sores, spasticity, chronic pain, depression, renal stones, cardiac complications, pneumonia, autonomic dysreflexia, deep vein thrombosis, limb fractures, increased neurologic impairment, numbness, visual loss/double vision, impaired balance, and cognitive decline (33,34).

Specific expected minor adverse events that may occur include:
CNS: dizziness, headache
Cardiac: palpitations
ENT: nasopharyngitis, upper respiratory tract infection
Occular: dry eyes, blurred vision
GI: diarrhea, constipation, nausea, abdominal pain
GU: urinary tract infection
MSK: arthralgia, back pain
Other: fatigue
Urodynamic complications (urinary infection after urodynamics, gross hematuria, autonomic dysreflexia).

Estimated incidence of minor mirabegron related adverse events as listed below based on 1375 patients treated for overactive bladder symptoms(22).

	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.

Statistical considerations

The primary analysis set for efficacy will be the full analysis set (defined as all randomized subjects). Results will be stratified based on whether the patient is taking an existing anticholinergic medication or not, and these two groups will be analyzed as individual populations. The primary outcome will be maximum cystometric capacity, as determined by urodynamic studies. Cystometric capacity will be a continuous variable, measured to the nearest whole number. Analysis will be an intention to treat analysis; statistical analysis for the primary endpoint will be a linear regression model, with adjustment for any unbalanced covariates (such as baseline bladder capacity). The linear regression model will be the maximum cystometric capacity as predicted by placebo versus mirabegron randomization. The per protocol analysis (for efficacy) will consist of all patients who were compliant with mirabegron dosing (defined as 80-100% of medication compliance based on pill counts) compared to placebo. A planned subgroup analysis of the primary outcome among MS and SCI patients will also be performed. SAS 9.2 will be used for all statistical analysis.

Study variables

Primary outcome

- Cystometric bladder capacity (continuous, mL). Measured as the infused volume + the diuresed volume, based on the amount of urine drained from the bladder at the end of the urodynamic study.

Secondary outcomes

- Urodynamic
    - Volume at first episode of detrusor overactivity (based on investigator interpretation of filling volume at which detrusor overactivity starts, continuous, mL)
    - Maximal detrusor pressure (based on investigator interpretation of change in Pdet from start of filling to end of filling once any detrusor overactivity has stopped, continuous, cmH2O)
    - Bladder sensation (based on patient reported first sensation, first desire to void, and strong desire to void; may only available for MS patients, continuous, mL)
    - Bladder compliance (based on investigator calculated change in volume / change in pressure, continuous, mL/cmH2O)
    - Bladder compliance (based on end fill pressure, cmH2O)

- Voiding diary
    - Number of episodes of urgency incontinence in 3 days (count)
    - Number of days without any urgency incontinence (count)
    - Average daily micturition frequency (count of number of voids from awakening in the morning to falling asleep at night averaged over 3 days), or Frequency of CIC (count, if applicable)
    - Average time between voids (each interval between daytime voids in minutes will be averaged over 3 days)
    - Maximal functional capacity (maximum voided volume over the 3 days, continuous, mL)
    - Median voided volume (median of all daytime voids over 3 days), or Median catheterized urine volumes (continuous, mL, if applicable)
    - Nocturia (number of voids/Catheters between falling asleep and awakening in the morning to start the day)

- 24hr pad weights (continuous measure of total weight of incontinence pads, sealed in plastic bags, minus the weight of each dry incontinence pad multiplied by the number of pads)

- PROM
    - IQOL total score
    - SF-Qualiveen total score
    - NBSS total score and domain scores (incontinence and storage & voiding domains)
    - PPBC score (continuous score, responder analysis with 2 point change (major change) being defined as response)

- Safety variables (frequency, severity, and causal likelihood of all adverse events)
    - Severity will be assessed based on the following scale:
        - Mild: no disruption of normal activities
        - Moderate: Effect on daily activities
        - Severe: inability to perform daily activities
    - Causal relationship
        - Not related: the adverse event's timing, nature, and patient's past history makes it unlikely that there is causal relationship to the study protocol/medication.
        - Possible: the adverse event's timing, nature, and patient's past history potentially represents a causal relationship to the study protocol/medication, but may also be explained by other illnesses or medications.
        - Probable: the adverse event's timing, nature, and patient's past history makes it likely that there is a causal relationship to the study protocol/medication.

Investigator Responsibilities

Each site investigator must ensure that the procedures outlined in this study protocol are adhered to. Study procedures are designed to ensure the investigator abides by GCP guidelines. Compliance with these regulations constitutes compliance with the ethical principles in the Declaration of Helsinki. All relevant Canadian legal and regulatory requirements will be met.

Each investigator must ensure that proper source documentation for all activities performed in relation to this study are properly maintained and stored in a secure location. The investigator will transfer relevant data from source documents to the case report forms. The following source documents must be kept for a minimum of 25 years after completion of the clinical trial:

- Signed consent forms
- Subject ID codes, screening log, and enrollment log
- REB communications
- Case report forms

The Investigator must ensure that institutional regulations and the Informed Consent Form clearly permit study-related monitoring and REB review by providing direct access to source data and documents.

Each site will need to obtain REB approval prior to initiating this study. The primary investigator will provide appropriate documentation and administrative assistance during the competition of the ethics form.

The principal investigator will be responsible for maintaining the clintrials.gov registration, and obtaining a Letter of No Objection from Health Canada. A copy of this letter will be provided to each site prior to start of the study.

Signature page

I have read this study protocol, I understand and agree to its content, and I will work according to this study protocol and according to the principles of good clinical practice.

Investigator

Name _____

Signature _____

Date _____

References

1. Stöhrer M, Blok B, CASTRO-DIAZ D, Chartier-Kastler E, Del Popolo G, KRAMER G, et al. EAU guidelines on neurogenic lower urinary tract dysfunction. European Urology. 2009 Jul;56(1):81–8.

2. Ouslander JG. Management of overactive bladder. N Engl J Med. 2004 Feb 19;350(8):786–99.

3. Madhuvrata P, Singh M, Hasafa Z, Abdel-Fattah M. Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis. European Urology. 2012 Nov;62(5):816–30.

4. Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. BJU Int. 2012 Dec;110(11):1767–74.

5. Manack A, Motsko SP, Haag-Molkenteller C, Dmochowski RR, Goehring EL, Nguyen-Khoa B-A, et al. Epidemiology and healthcare utilization of neurogenic bladder patients in a US claims database. Neurourol Urodyn. 2011 Mar;30(3):395–401.

6. Takasu T, Ukai M, Sato S, Matsui T, Nagase I, Maruyama T, et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]ethyl} acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. J Pharmacol Exp Ther. 2007 May;321(2):642–7.

7. Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a Randomized Phase III Trial of Mirabegron in Patients with Overactive Bladder. J Urol. 2012 Oct 16.

8. Khullar V, Amarenco G, Angulo JC, Cambronero J, Høye K, Milsom I, et al. Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. European Urology. 2013 Feb;63(2):283–95.

9. Tyagi P, Tyagi V, Chancellor M. Mirabegron: a safety review. Expert Opin Drug Saf. 2011 Mar;10(2):287–94.

10. Schafer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spångberg A, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn. 2002;21(3):261–74.

11. Rosier PFWM, Szabó L, Capewell A, GaJewski JB, Sand PK, Hosker GL, et al. Executive summary: The International Consultation on Incontinence 2008--Committee on: "Dynamic Testing;" for urinary or fecal incontinence. Part 2: Urodynamic testing in male patients with symptoms of urinary incontinence, in patients with relevant neurological abnormalities, and in children and in frail elderly with symptoms of urinary incontinence. Neurourol Urodyn. 2010;29(1):146–52.

12. Winters JC, Dmochowski RR, Goldman HB, Herndon CDA, Kobashi KC, Kraus SR, et al. Urodynamic Studies in Adults: AUA/SUFU Guideline. J Urol. 2012 Oct 19.

13. Ho CH, Linsenmeyer TA, Millis SR. The reproducibility of urodynamic studies of neurogenic bladders in spinal cord injury. J Spinal Cord Med. 2000;23(4):276–83.

14. Groutz A, Blaivas JG, Chaikin DC, Resnick NM, Engleman K, Anzalone D, et al. Noninvasive outcome measures of urinary incontinence and lower urinary tract symptoms: a multicenter study of micturition diary and pad tests. J Urol. 2000 Sep;164(3 Pt 1):698–701.

15. Ryhammer AM, Djurhuus JC, Laurberg S. Pad testing in incontinent women: a review. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(2):111–5.

16. FLISSER AJ, Figueroa J, Bleustein CB, Panagopoulos G, BLAIVAS JG. Pad test by mail for home evaluation of urinary incontinence. Neurourol Urodyn. 2004;23(2):127–9.

17. Schurch B, Denys P, Kozma CM, Reese PR, Slaton T, Barron R. Reliability and validity of the Incontinence Quality of Life questionnaire in patients with neurogenic urinary incontinence. Archives of Physical Medicine and Rehabilitation. 2007 May;88(5):646–52.

18. Bonniaud V, Bryant D, Parratte B, Guyatt G. Development and Validation of the Short Form of a Urinary Quality of Life Questionnaire: SF-Qualiveen. J Urol. American Urological Association; 2008 Dec 1;180(6):2592–8.

19. Costa P, Perrouin-Verbe B, Colvez A, Didier J, Marquis P, Marrel A, et al. Quality of life in spinal cord injury patients with urinary difficulties. Development and validation of qualiveen. European Urology. 2001 Jan;39(1):107–13.

20. Bonniaud V, Bryant D, Parratte B, Gallien P, Guyatt G. Qualiveen: a urinary disorder-specific instrument for use in clinical trials in multiple sclerosis. Archives of Physical Medicine and Rehabilitation. 2006 Dec;87(12):1661–3.

21. Coyne KS, Matza LS, Kopp Z, Abrams P. The validation of the patient perception of bladder condition (PPBC): a single-item global measure for patients with overactive bladder. European Urology. 2006 Jun;49(6):1079–86.

22. Chapple CR, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. European Urology. 2013 Feb;63(2):296–305.

23. Horstmann M, Schaefer T, Aguilar Y, Stenzl A, Sievert KD. Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. Neurourol Urodyn. 2006;25(5):441–5.

24. Abrams P, Kelleher C, Staskin D, Rechberger T, Kay R, Martina R, et al. Combination

Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-blind, Dose-ranging, Phase 2 Study (Symphony). European Urology. 2014 Feb 19.

25. Stackhouse D, Dolber P, PETERSON A, Fraser M. DRAMATIC EFFECTS OF A SELECTIVE BETA3-ADRENERGIC AGONIST ON NEUROGENIC DETRUSOR OVERACTIVITY IN SPINAL CORD INJURED RATS. J Urol. 4 ed. 2013;189:e703.

26. Zinner NR, Ammann LP, Haas GP, Janning SW, He W, Bukofzer S. Finding unrecognized information in overactive bladder clinical trial data: a new approach to understanding placebo and treatment effects. Neurourol Urodyn. 2013 Apr;32(4):308–13.

27. Nitti VW, Rosenberg S, Mitcheson DH, He W, Fakhoury A, Martin NE. Urodynamics and Safety of the β3-Adrenoceptor Agonist Mirabegron in Males with Lower Urinary Tract Symptoms and Bladder Outlet Obstruction. J Urol. 2013 Oct;190(4):1320–7.

28. Almallah YZY, Rennie CDC, Stone JJ, Lancashire MJM. Urinary tract infection and patient satisfaction after flexible cystoscopy and urodynamic evaluation. Urology. 2000 Jul 1;56(1):37–9.

29. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011 Feb;69(2):292–302.

30. Abrams P, Artibani W, Cardozo L, Dmochowski R, van Kerrebroeck P, Sand P, et al. Reviewing the ICS 2002 terminology report: the ongoing debate. Neurourol Urodyn. 2009;28(4):287.

31. Stohrer M, Madersbacher H, Richter R, Wehnert J, Dreikorn K. Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia--a double-blind, placebo-controlled clinical trial. Spinal Cord. 1999;37(3):196.

32. Deffontaines-Rufin S, Weil M, Verollet D, Peyrat L, Amarenco G. Botulinum toxin A for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients. Int braz j urol. SciELO Brasil; 2011;37(5):642–8.

33. Miller DH, Weinshenker BG, Filippi M, Banwell BL, Cohen JA, Freedman MS, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. 2008. pp. 1157–74.

34. Hitzig SL, Tonack M, Campbell KA, McGillivray CF, Boschen KA, Richards K, et al. Secondary health complications in an aging Canadian spinal cord injury sample. Am J Phys Med Rehabil. 2008 Jul;87(7):545–55.

35. Staskin D, Kelleher C, Avery K, Bosch R, Cotterill N, Coyne K, et al. Initial assessment of urinary and faecal incontinence in adult male and female patients. Incontinence 4th ed Plymouth, UK: Health Publications. 2009;:3311–412.