

# BMJ Open Protocol for a phase II, open-label exploratory study investigating the efficacy of fesoterodine for treatment of adult patients with spinal cord injury suffering from neurogenic detrusor overactivity for amelioration of autonomic dysreflexia

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## ABSTRACT

**Introduction** Managing and preventing risk factors associated with cardiovascular and cerebrovascular impairment is well studied in able-bodied individuals. However, individuals with spinal cord injury (SCI) at or above the spinal segment T6 are prone to experience autonomic dysreflexia (AD) but also to suffer from neurogenic detrusor overactivity (NDO). Treatment of NDO would not only improve lower urinary tract function but could also reduce the severity and frequency of life-threatening episodes of AD. Fesoterodine, an antimuscarinic drug, has been successfully employed as a first-line treatment for detrusor overactivity in individuals without an underlying neurological disorder. Thus, our aim is to investigate the efficacy of fesoterodine to improve NDO and ameliorate AD in individuals with SCI.

**Methods and analysis** This phase II, open-label exploratory, non-blinded, non-randomised, single-centre study will investigate the efficacy of fesoterodine to improve NDO and ameliorate AD in individuals with chronic SCI at or above T6. During screening, we will interview potential candidates (with a previous history of NDO and AD) and assess their injury severity. At baseline, we will perform cardiovascular and cerebrovascular monitoring (blood pressure (BP), heart rate and cerebral blood flow velocity) during urodynamics (UDS) and 24-hour ambulatory BP monitoring (ABPM) during daily life to assess severity and frequency of AD episodes (ie, maximum increase in systolic BP). The primary outcome is a reduction of artificially induced (during UDS) and spontaneous (during daily life) episodes of AD as a display of treatment efficacy. To answer this, we will repeat UDS and 24-hour ABPM during the last cycle of the treatment phase (12 weeks overall, ie, three cycles of 4 weeks each). At the end of each treatment cycle, participants will be asked to answer standardised questionnaires (AD symptoms and quality of life) and present bladder and bowel diaries, which will provide additional subjective information.

## Strengths and limitations of this study

- This is the first study to evaluate the effect of fesoterodine on neurogenic detrusor overactivity (NDO), autonomic dysreflexia (AD), cerebral blood flow and cognitive function in individuals with spinal cord injury (SCI).
- This phase II, open-label exploratory, non-blinded, non-randomised, single-centre study will use a battery of urological, cardiovascular, cerebrovascular and quality-of-life assessments to investigate the relationship between urological, cardiovascular and cerebrovascular health in individuals with SCI.
- Pretreatment and on treatment comparison of assessments will provide evidence whether fesoterodine is a key element in reducing NDO and ameliorating detrimental cardiovascular responses associated with AD.
- Rigorous inclusion/exclusion criteria for participant enrolment.
- The study results will be limited by the participant's behavioural habits and lifestyle factors (which will not be controlled) such as water intake, alcohol and coffee consumption, exercise routine, work and availability of caregivers.

**Ethics and dissemination** The University of British Columbia Research Ethics Boards (H15-02364), Vancouver Coastal Health Research Institute (V15-02364) and Health Canada (205857) approved this study. The findings of the study will be published in peer-reviewed journals and presented at national and international scientific meetings. This protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials and CONSolidated Standards Of Reporting Trials statements.

**Trial registration number** NCT02676154; Pre-results.

## INTRODUCTION

Spinal cord injury (SCI) is one of the most debilitating chronic conditions, which immediately alters a person's life with a significant burden of disability.<sup>1,2</sup> Besides sensorimotor recovery, improvement of autonomic functions are among the primary priorities for individuals with SCI.<sup>3</sup>

Autonomic dysreflexia (AD), one devastating example of autonomic dysfunction following SCI, is defined according to the International Standards to document remaining Autonomic Function after SCI (ISAFSCI) as an increase in systolic blood pressure (SBP)  $\geq 20$  mmHg from baseline due to noxious or innocuous stimuli from below the level of injury.<sup>4,5</sup> This sudden increase in SBP, caused by an imbalanced sympathetic response, cannot be treated as essential hypertension. If AD is misdiagnosed or poorly managed, the consequences can be devastating,<sup>6</sup> that is, myocardial infarction,<sup>7</sup> stroke<sup>8</sup> and even death.<sup>9</sup>

Neurogenic lower urinary tract dysfunction (NLUTD), another example of autonomic dysfunction following SCI, often results in urgency and urinary incontinence, and thereby significantly reduces the quality of life (QoL) of affected individuals.<sup>10</sup> Urodynamic studies (UDS), considered as the gold standard to evaluate lower urinary tract function (in order to protect the upper urinary tract, ie, preserve renal function),<sup>11</sup> is a frequent trigger of artificially induced AD.<sup>12,13</sup> Given the fact that bladder filling occurs several times a day, individuals might experience multiple episodes of AD each day. Spontaneous uninhibited contractions of the detrusor, known as neurogenic detrusor overactivity (NDO), are a leading trigger of life-threatening episodes of AD (ie, affecting more than 80% of individuals with a supraspinal SCI).<sup>12</sup>

Considering the AD-related health risks,<sup>6</sup> this condition is potentially dangerous to individuals living with SCI suffering from NDO. In addition, inflammation of the urinary bladder, such as a urinary tract infection or irritation caused by bladder stones, can elicit episodes of AD.<sup>14,15</sup>

By treating NDO and therefore preventing peripheral afferent stimulation to the spinal cord, we could potentially decrease irritation of the spinal autonomic circuits that are responsible for triggering AD, ameliorate symptoms of this condition and consequently reduce chronic cardiovascular and cerebrovascular complications in this population. Reducing chronic cardiovascular and cerebrovascular complications of SCI would dramatically improve the health and well-being of individuals with SCI and positively affect healthcare costs.

In line with this, our research team conducted a pilot study where intradetrusor onabotulinumtoxinA injections, which is a standard second-line treatment option for NDO, reduced the frequency and severity of AD in patients with SCI at or above T6.<sup>16</sup>

Despite this evidence, there are no guidelines currently available that support the use of pharmacological treatment for the management of NLUTD with the purpose of ameliorating life-threatening episodes of AD. It is

unknown, whether antimuscarinic treatment for NDO, such as fesoterodine, affects the severity and frequency of AD. Potentially this treatment may therefore protect cerebrovascular health, maintain (or even improve) cognitive function and finally lower stroke risk after SCI. The study medication, fesoterodine, an antimuscarinic drug, is currently approved by Health Canada for the treatment of idiopathic overactive bladder (OAB) in individuals without an underlying neurological disorder. The choice of using fesoterodine is driven by its promising results in the management of NDO (in children only)<sup>16</sup> and idiopathic OAB (children and adults).<sup>17,18</sup> Its molecular structure results in a reduced capacity to cross the blood brain barrier, hence the potential to provide further benefit to individuals by lowering centrally mediated side effects compared with other antimuscarinic drugs, such as darifenacin, solifenacin, tolterodine and oxybutynin.<sup>19</sup> It is important to note that in head-to-head placebo-controlled trials, fesoterodine (8 mg) showed superior efficacy over tolterodine extended-release (4 mg) and placebo in reducing urgency and urinary incontinence episodes (primary endpoint).<sup>20,21</sup>

There is a paucity of data on the use of antimuscarinics in the SCI population (in contrast to the general population) and the total absence of evidence on the possible effects of fesoterodine on NDO and associated life-threatening episodes of AD. Thus, we propose an open-label exploratory study to gather preliminary information on the efficacy of fesoterodine treatment on NDO and AD in individuals with SCI. In this study, we are aiming to determine whether fesoterodine is effective in reducing the incidence and severity of AD episodes that are triggered by NDO in individuals with SCI.

This study will enable us to identify whether fesoterodine has a positive influence on short-term cardiovascular and cerebrovascular responses related to life-threatening episodes of AD. Furthermore, episodes of AD are considered as one of the major risk factors for cardiovascular morbidity and mortality in this population.<sup>22</sup> If successful, fesoterodine as a treatment of NDO-related AD could potentially ameliorate cardiovascular and cerebrovascular health in this population long-term. By reducing the incidence and severity of AD, fesoterodine could also potentially lower the frequency of hospitalisations related to AD. This may substantially reduce the costs of care associated with secondary consequences in this population.

## METHODS AND ANALYSIS

### Study design

This phase II, open-label exploratory, non-blinded, non-randomised, single-centre study will investigate the efficacy of fesoterodine (ie, flexible dose from 4 to 8 mg) to improve NDO and ameliorate AD in adults with SCI. This study will be conducted at the University of British Columbia, Vancouver, Canada.

**Table 1** Inclusion and exclusion criteria for all participants

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>▶ Chronic SCI (at least 1 year post traumatic SCI).</li> <li>▶ Traumatic SCI at or above the T6 spinal segment.</li> <li>▶ Sex (female and male).</li> <li>▶ Age (18–60 years).</li> <li>▶ Documented presence of AD and NDO during UDS.</li> <li>▶ Hand function sufficient to perform CIC or a committed caregiver to provide CIC.</li> <li>▶ Documented 2 weeks of bladder and bowel history prior to baseline visit.</li> <li>▶ Willing and able to comply with all clinic visits and study-related procedures.</li> <li>▶ Able to understand and complete study-related questionnaires (must be able to understand and speak English or have access to an appropriate interpreter).</li> <li>▶ Women of childbearing potential must not be intending to become pregnant, currently pregnant or lactating.</li> <li>▶ Sexually active males with female partners of childbearing potential must agree to use effective contraception during the period of the trial and for at least 28 days after completion of treatment.</li> <li>▶ Must provide informed consent.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Pregnancy or breast feeding.</li> <li>▶ Any clinically significant: renal or hepatic disease; active acute urinary tract infections; pressure sores; active heterotopic ossification; newly changed or started antidepressant medications; or unstable diabetes.</li> <li>▶ Any severe acute medical issue that in the investigator's judgement would adversely affect the patient's participation in the study.</li> <li>▶ Moderate and severe forms of renal dysfunctions (GFR below 60 mL/min).</li> <li>▶ Clinically significant abnormal laboratory tests (ALT; alkaline phosphatase; bilirubin (total); GGT) as judged by the investigator.</li> <li>▶ A hypersensitivity to tolterodine (available as Detrol, Detrol LA), soya, peanuts or lactose.</li> <li>▶ Recent treatment with onabotulinumtoxinA (within 9 months of the baseline visit) into detrusor muscle.</li> <li>▶ Recent treatment with other anticholinergic medications (within 3 weeks of the baseline visit).</li> <li>▶ Use of any medication or treatment that in the opinion of the investigator indicates that it is not in the best interest of the patient to participate in this study, such as ketoconazole, itraconazole, miconazole and clarithromycin and rifampicin as indicated.<sup>36</sup></li> <li>▶ Patient is a member of the investigational team or his/her immediate family.</li> </ul>

AD, autonomic dysreflexia; ALT, alanine aminotransferase; CIC, clean intermittent catheterisation; GFR, glomerular filtration rate; GGT, gamma-glutamyltransferase; NDO, neurogenic detrusor overactivity; SCI, spinal cord injury; T, thoracic; UDS, urodynamic studies.

### Study population and recruitment

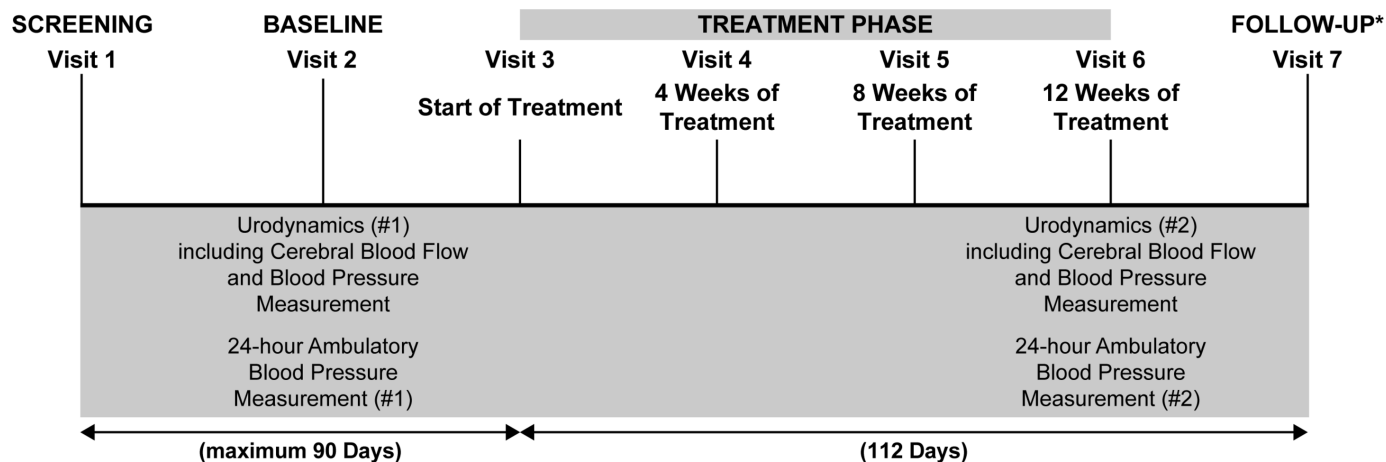
According to inclusion and exclusion criteria (table 1), individuals with chronic traumatic SCI, at or above the level of spinal segment T6, with documented AD triggered by NDO will be investigated. Eligible participants will act as their own controls and will undergo baseline evaluations that will be repeated after 12 weeks (–2 weeks) of treatment. Appropriate washout periods of medications and treatments for NDO will be undertaken if required, that is, 9 months for any type of botulinum toxin injected into the detrusor and 3 weeks for any antimuscarinic drug or any other drug, such as mirabegron. Individuals with SCI living in British Columbia will be recruited. Eligible individuals (with an established history of AD and NDO) will be invited to a first visit (screening) during which detailed information about the study, in particular the aims, methods, possible risks and side effects as well as alternative treatment options, will be provided. After obtaining written informed consent, individuals will be assigned a unique study number and the following data will be collected: a detailed medical history, a 14-day bladder and bowel diary, urine sample (urinalysis and pregnancy test), UDS, 24-hour ambulatory blood pressure monitoring (ABPM), as well as standardised questionnaires (assessing cognitive abilities, neurogenic bowel dysfunction (NBD), faecal and urinary incontinence and AD health-related QoL (AD HR-QoL)).

### Determination of sample size

As this is a phase II, exploratory open-label study, we are not providing any sample size calculations. Previously published studies involving the use of antimuscarinics in SCI populations have also been relatively small. It has to be recognised that other neurological disorders, such as stroke, have a much greater prevalence compared with SCI. The most recently reported single-site clinical trials evaluating the effect of antimuscarinics on NDO in the SCI population typically did not include more than 24 participants (Ethans *et al* n=10<sup>23</sup>; and Kennelly *et al* n=24).<sup>24</sup> In a previous pilot study (n=17), our research team provided significant evidence on the treatment efficacy of onabotulinumtoxinA on AD and NDO.<sup>16</sup> Multicentre trials have been able to provide similar results, with a larger number of individuals (Stohrer *et al* n=131<sup>25</sup> and n=66),<sup>26</sup> but with undoubtedly considerably greater financial costs.

### Study location

- ▶ International Collaboration On Repair Discoveries, University of British Columbia (UBC), Vancouver, Canada.
- ▶ The Bladder Care Centre, UBC Hospital, UBC, Vancouver, Canada.
- ▶ Brenda & David McLean Integrated Spine Clinic, Blusson Spinal Cord Centre, Vancouver General Hospital, Vancouver Coastal Health (VCH), Vancouver, Canada.



**Figure 1** Study timeline. The study timeline is showing each study visit and the expected duration of study participation. \*The follow-up visit should be conducted via telephone 4 weeks following the end of treatment (ie, visit 6) or last scheduled visit in case of early termination of treatment.

### Partners

- ▶ Pfizer Canada, Kirkland, QC, Canada.
- ▶ Michael Smith Foundation for Health Research, Vancouver, BC, Canada.
- ▶ Rick Hansen Foundation, Vancouver, BC, Canada.
- ▶ VCH Research Institute, Vancouver, BC, Canada.

### Investigation

#### Study protocol

Following screening (visit 1) and baseline assessments (visits 1 and 2), prospective individuals meeting all inclusion and exclusion criteria will be enrolled into the study and be scheduled for upcoming visits. An outline of the study is illustrated in [figure 1](#) with study assessments and procedures presented by visit in [table 2](#). The study drug will be dispensed at visit 3 and the dose evaluated at visits 4 and 5, as illustrated in [figure 2](#).

#### Study assessments

- ▶ International Standards For Neurological Classification of Spinal Cord Injury<sup>27</sup>: neurological evaluations of patients with SCI will be performed using the American Spinal Injury Association Impairment Scale (AIS) unless available in the patients' chart at the discretion of the investigator. The level and severity of damage to motor and sensory pathways will be determined by a trained physician using the standard AIS examination.
- ▶ UDS ([figure 3](#))
  - All methods, definitions and units regarding UDS will be performed and recorded according to the standards recommended by the International Continence Society (ICS).<sup>28</sup> Urodynamics will be performed according to good urodynamic practices recommended by the ICS to detect/confirm NDO.<sup>29</sup>
  - Cardiovascular monitoring during UDS: brachial blood pressure (BP) will be measured episodically, that is, every minute, on the right brachial artery.<sup>16</sup> Furthermore, continuous 'beat-to-beat' recording

of SBP, diastolic BP and heart rate, synchronous to the ongoing UDS, will capture even short AD episodes.<sup>12 13</sup> Electrocardiography and blood velocity in the left middle and right posterior cerebral arteries will be acquired.<sup>30</sup>

- Confirmation of AD during UDS: an attending physician will confirm episodes of AD, which is defined according to the ISAFSCI<sup>3</sup> as an increase in SBP  $\geq 20$  mmHg from baseline. AD will be resolved with the implementation of an AD management protocol (ie, identifying and resolving triggering stimuli or changes in body position).
- ▶ 24-hour ABPM<sup>31</sup>:
  - Automatic recordings will be taken every 15 min from 07:00 to 23:00 (daytime period), and every hour from 23:00 to 07:00 (nighttime period). Manual BP measurements will be documented in an activity log before and after each (self-) catheterisation and suspected AD episode. The number of bladder-related events will be documented, such as perception of a full bladder (if possible) and (self-) catheterisation. Participants will also note the time of waking and falling asleep.
- ▶ Laboratory tests:
  - Blood samples will be collected and standard haematology and biochemistry laboratory tests will be performed by a local laboratory to rule out any contraindication for receiving the study drug. Additionally, urinalysis and urine pregnancy tests (for women of childbearing potential) will be performed as indicated in the schedule of events ([table 2](#)).
- ▶ Participant diaries:
  - Medication: study drug compliance will be monitored using a diary, which identifies missed doses. Participants will be asked to indicate the days where a dose is missed. Non-adherence will be considered when an individual fails to intake fesoterodine consecutively (>5 days) or intermittent (>50%

**Table 2** Study event schedule

Study procedures	Screening		Baseline			Treatment phase			EOT	FUP*
	V1	V2	V3	V4	V5	V6	V7			
Day (D)	-90 to -1	-90 to -1	D1†	D28†	D56†	D84	D112			
Week (W)			W1†	W4†	W8†	W12	W16			
Visit window (D)				-7 to -2	-7 to -2	-14 to 0	-7 to +30			
Informed consent	X									
Inclusion/exclusion	X	X								
Medical history/demographics	X	X								
Laboratory blood tests (fasting)		X								
Urine dip stick		X								
Weight	X									
Height	X									
Treatment										
Study drug dispensing			X	X	X					
Study drug accountability				X	X	X				
Evaluate dose				X	X					
Diary of missed doses‡				X	X	X				
Assessments										
Urodynamics§		X					X			
24-hour ABPM		X¶					X			
24-hour BP diary		X					X			
ISNCSCI	X									
Autonomic dysreflexia HR-QoL; I-QoL		X					X			
Montreal cognitive assessment	X			X	X	X				
Bristol Stool Scale**	X		X	X	X					
Bladder and bowel diary**	X		X	X	X					
Neurogenic bowel dysfunction score		X		X	X	X				
Safety										
Pregnancy test (women of childbearing potential)	X		X	X	X	X††	X	X		
Adverse events	X	X	X	X	X	X	X	X		
Concomitant medication/procedures	X	X	X	X	X	X	X	X		
Honorarium paid out							X			

\*The follow-up visit should be conducted via telephone 4 weeks following the end of treatment (ie, visit 6) or last scheduled visit in case of early termination of treatment.

†Treatment start date=day 1, week 1 (cycle 1); visits 4, 5 and 6 will be scheduled based on treatment start date.

‡Diary of missed doses will be reviewed (ie, medication adherence) and a decision for future participation will be made.

§During urodynamics, we will perform electrocardiography, cerebral blood flow measurement and cardiovascular monitoring (blood pressure and heart rate).

¶Baseline 24-hour ABPM is only performed if autonomic dysreflexia is confirmed with the baseline urodynamics.

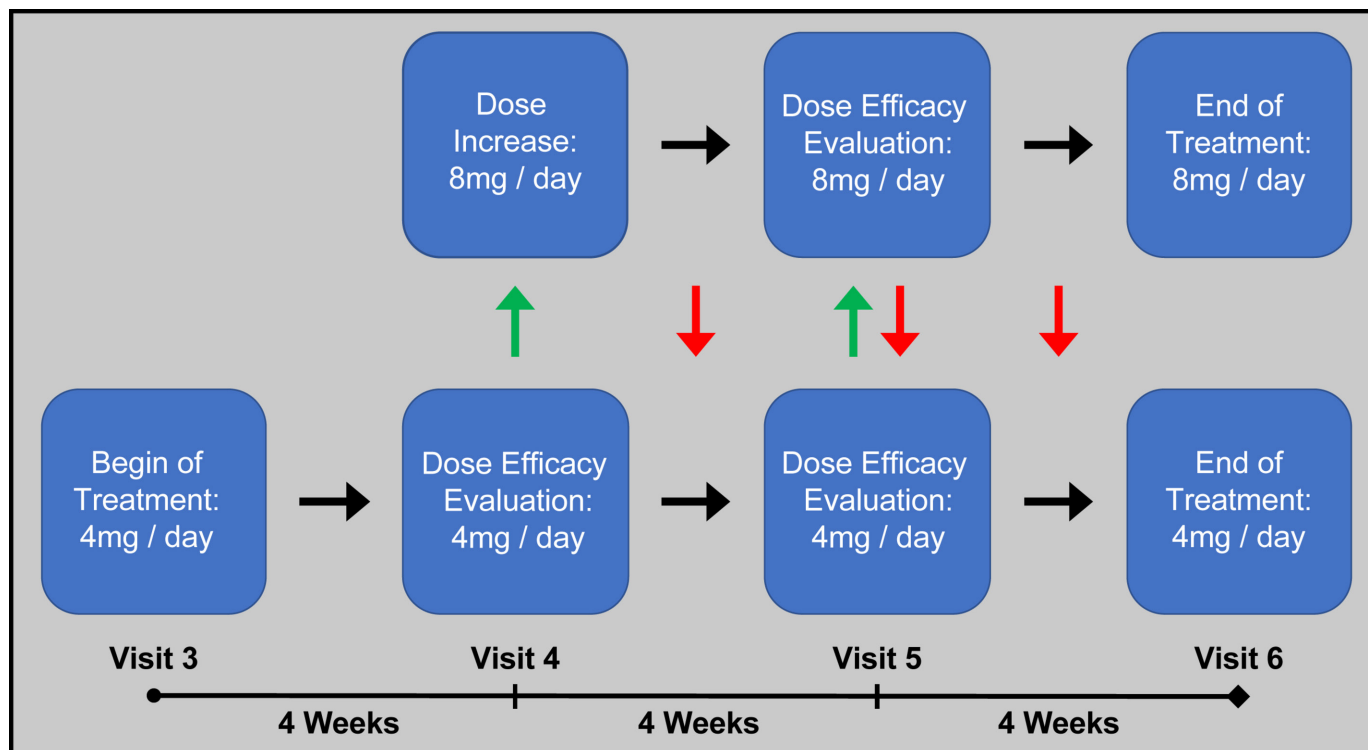
\*\*Bladder and bowel diary and the Bristol Stool Scale will be provided at screening and at visits 3, 4 and 5 for evaluation during screening and while on study medication (weeks 3, 4, 7, 8, 11 and 12).

††A home pregnancy test will be provided to women of childbearing potential at the EOT visit to be performed for the FUP telephone call.

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; EOT, end of treatment; FUP, follow-up; HR-QoL, health-related quality of life; I-QoL, Incontinence Quality of Life; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury.

of all days within one cycle). Participants will also be encouraged to note the start and stop date of any adverse events (AEs) and make comments regarding their observations.

– Bladder routines will be monitored for 14 days prior to taking the study drug, as well as for 14 days at the end of each 28-day cycle. Participants will be asked to provide information which is in accordance with



**Figure 2** Drug administration protocol. Beginning of treatment at visit 3. Eligible individuals will receive a 4-week supply of 4 mg daily doses of fesoterodine. They will also receive instructions for use of medication and reporting adverse events. During the treatment period, individuals will return to the clinic, at least 2 days before their supply runs out, for visits 4 and 5. During these visits, individuals will be assessed for dose efficacy. In consultation with the investigator, individuals will have a choice to either increase the dose of the study drug to 8 mg (green arrow) or stay at the same dose. Individuals who elect to increase their dose to 8 mg per day may return to 4 mg at any time (red arrow). However, individuals may only increase their dose once. Meaning that following a dose reduction, no increases in dose will be permitted. Up to 14 days before the end of treatment period (ie, visit 6), individuals will undergo treatment efficacy evaluations in comparison to baseline (ie, visit 2).

the ICS recommendations on bladder diaries.<sup>28</sup> In addition, we will ask whether the participants experienced any pain during catheterisation.

- Bowel routines will be monitored for 14 days prior to taking the drug, as well as for 14 days at the end of each 28-day cycle to capture constipation and faecal incontinence, the number of bowel movements experienced or performed and classification of stool using the Bristol Stool Scale.<sup>32</sup>
- ▶ Questionnaires:
  - Montreal Cognitive Assessment (MoCA)<sup>33</sup>: a validated assessment of eight domains of cognitive functioning, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation.
  - AD HR-QoL<sup>31</sup>: a self-administered, validated questionnaire that measures frequency and severity of AD on (1) a daily basis and (2) related to bladder function.
  - Incontinence QoL (I-QoL)<sup>34</sup>: a self-administered, validated and disease-specific questionnaire that measures incontinence-related QoL, including avoidance and limiting behaviours, the psychosocial impact and social embarrassment.

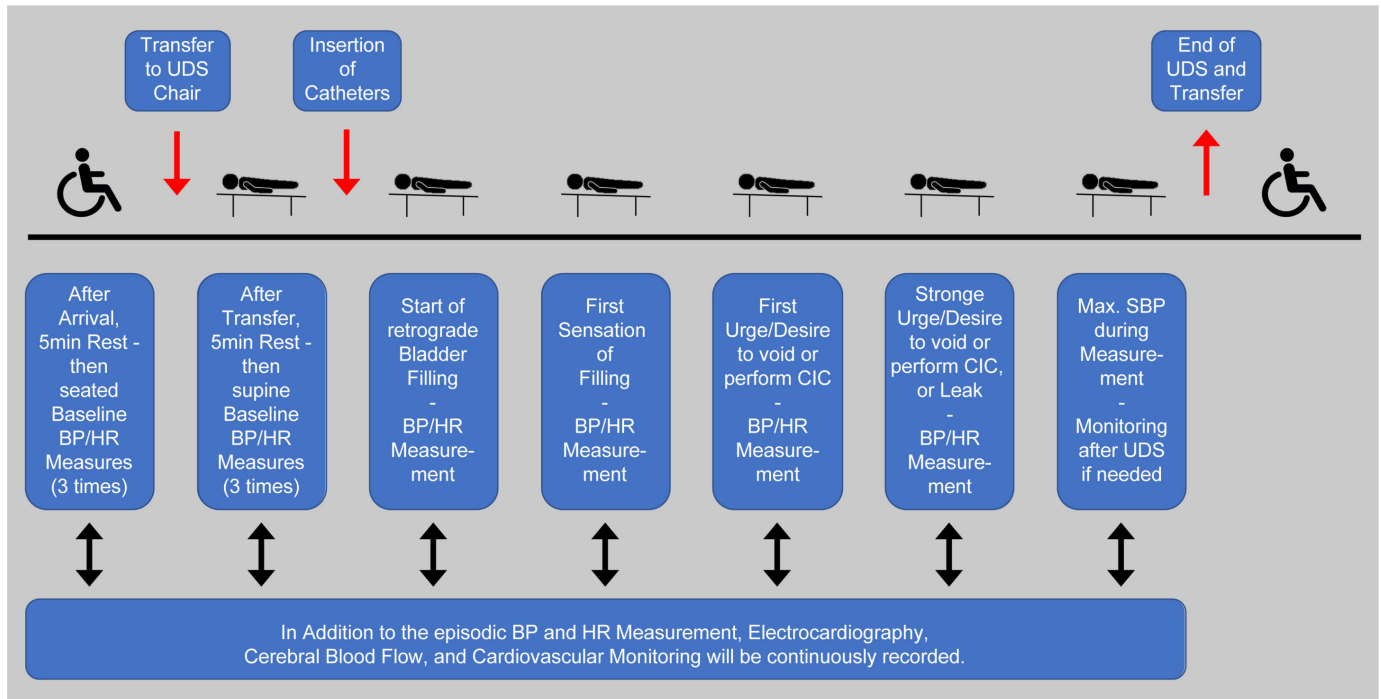
- NBD Score<sup>35</sup>: a self-administered, validated measure of both constipation and faecal incontinence for individuals with SCI.

#### Data handling

Following informed consent, participants will be assigned a unique study code and study initials that are not derived from, or related to, the information about the individual (ie, name). Deidentified data collected as part of the study will be entered into an electronic database. The latter is hosted at a high security data centre, located in Canada, and guaranteed to remain within Canada. Data encryption, two-factor authentication and role-based security will ensure the data are kept safe. Only authorised study personnel will have access to the electronic data. Once the study is completed and closed, all research-related study documents will be held on site for the Health Canada-mandated 25-year record retention period.

#### Safety

Fesoterodine is approved for sale in Canada for the symptomatic relief of OAB in patients with symptoms of urinary frequency, urgency or urge incontinence.<sup>36</sup> We will collect and report any AEs or severe AEs (SAEs). For safety variables, two observation periods are defined:



**Figure 3** Protocol for the evaluation of autonomic dysreflexia (AD) during urodynamic studies. After arrival and a 5 min rest, blood pressure (BP) and heart rate (HR) measurements will be recorded three times from the right brachial cuff. The individual will be placed in the urodynamic studies (UDS) chair in a supine position. After another 5 min rest, BP and HR measurements will be recorded again three times from the right brachial cuff. Thereafter, urethral and rectal measuring catheters will be inserted. Episodic BP/HR measurement and monitoring for symptoms of AD will be assessed at given time points (ie, start of bladder filling, first sensation, first urge/desire, strong urge/desire or leakage point). In addition, we will continuously record the following: cardiovascular changes ‘beat-to-beat’ of BP and HR from the left finger cuff, electrocardiography and cerebral blood flow. In case of prolonged AD after UDS, BP/HR measurements will be continued until SBP returns to a value below the individual’s threshold for AD. CIC, clean intermittent catheterisation.

1. The pretreatment period is defined as the time from signing the informed consent form to before the first dose of the study.
2. The treatment period is defined as day 1 of study treatment through to the end of the study.

In the situation of an AE or SAE, which are defined by the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (E6)<sup>37</sup> and International Organization for Standardization (14155),<sup>38</sup> appropriate actions will be executed and the appropriate party (principal investigator, ethics committee, Pfizer) will be informed. All AEs and SAEs will be followed as long as medically indicated.

### Study outcome measures

#### Primary

To assess the effect of fesoterodine in reducing AD (maximum increase in SBP) when induced artificially during UDS, as well as when occurring spontaneously in daily living as detected during the 24-hour ABPM. The primary endpoint will be the decrease in severity of AD (ie, maximum increase in SBP), which is artificially induced during UDS, by 50% from baseline in at least 50% of participants.

#### Secondary

- ▶ Number of participants that experience a decrease in the frequency and severity of AD from baseline (evaluated during the 24-hour ABPM)
- ▶ Number of participants that experience an improvement from baseline in self-reported AD severity and frequency as reported with the AD HR-QoL questionnaire and reflected by a decrease in score
- ▶ An improvement from baseline of self-reported bladder incontinence, as reported with the I-QoL questionnaire and reflected with an increase in score
- ▶ A change from baseline in cognitive function will be evaluated with the MoCA (a total score equal to or greater than 26 will be considered as unimpaired cognitive function)
- ▶ An improvement from baseline in bowel function/stool outcomes as reported with the Bristol Stool Scale and NBD Score
- ▶ An improvement from baseline in the following UDS parameters: for example, cystometric capacity and detrusor pressure
- ▶ An improvement from baseline in cerebral blood flow changes during UDS, that is, a reduction of BP allowing the maintenance of cerebral blood flow autoregulation

## Data analysis

Clinical data will be statistically analysed and compared (ie, pre/post treatment). Results will be presented with means and SD, 95% CI or medians and IQRs as appropriate (for non-parametric data).

Differences in continuous variables for primary outcome measures (AD severity during UDS and 24-hour ABPM) will be compared using repeated measures (pre/post treatment) analysis of variance. Differences in secondary outcome measures (AD frequency during 24-hour ABPM; bladder function parameters including: volume (mL) at first uninhibited detrusor contraction, compliance (mL/cmH<sub>2</sub>O), maximum detrusor pressure (cmH<sub>2</sub>O), the number of contractions before urinary leakage and volume at urinary leakage or maximum volume achieved (mL), will be assessed using the same method as for the primary outcome measure. The questionnaire data for the Bristol Stool Scale, MoCA, AD HR-QoL, I-QoL and NBD Score will be assessed using Wilcoxon signed-rank tests. For this feasibility study, we plan to present a treatment exposure analysis (ie, looking at the effectiveness of those who successfully completed the treatment phase). Alongside this, we will investigate whether there are any pertinent participant characteristics, that is, concurrent medication use, demographics and injury variables, which differ between participants that will complete the trial or not. A p value less than 0.05 will be considered as significant. Furthermore, we are aiming to calculate effect sizes (ES). Considering the limitation of not having a control group (ie, single-group pre-post ES), the following equation will be used:  $ES = (\text{Mean}_{\text{post}} - \text{Mean}_{\text{pre}}) / \text{SD}$ .<sup>39</sup>

## ETHICS AND DISSEMINATION

The sponsor investigator recognises that it is his responsibility to ensure that this clinical study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki,<sup>29</sup> and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements. Furthermore, handling of all personal data will strictly comply with the federal and provincial laws of data protection in Canada. This study has been registered at clinicaltrials.gov (NCT02676154). This protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials and CONSolidated Standards Of Reporting Trials statements.

## DISCUSSION

This study will assess the efficacy of flexible doses (4 to 8mg) of fesoterodine in reducing the severity of AD episodes, triggered by NDO in adults with SCI. Treatment of NDO will reduce, at best prevent, peripheral afferent stimulation to the spinal cord (resulting from bladder contractions) and therefore decrease potential irritation of the spinal autonomic circuits that are responsible for triggering AD. If successful in the short-term, fesoterodine could be a potential treatment option

to consequently reduce chronic cardiovascular and cerebrovascular complications in this population in the long-term. It is expected that this study will provide new insights on how and to what extent individuals with SCI can gain secondary benefits from NDO treatment.

Knowledge translation will include conference presentation and peer-reviewed publications. To extend the dissemination of study outcomes, we will get in direct contact with the SCI community, that is, patients, their families and caregivers through participation at public meetings.

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