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Subject Name:

Informed Consent Date:

Principal Investigators: Dr. Jill Wecht, EdD

VAMC: James J Peters

Protocol #: 1747301

Title of Study: Treatment of Orthostatic Hypotension in Individuals with Spinal Cord Injury (Study 1)

## INTRODUCTION

You are being asked to participate in a research study that is being performed at James J Peters VA Medical Center (JJPVAMC) and at the Kessler Foundation (KF). The JJPVAMC and KF are separate Institutions and independent of one another. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Please read the information below closely and discuss it with your family and friends if you wish. You can also ask one of the study staff members if there is anything that is not clear to you or if you would like more details. Please take your time to decide. If you do decide to take part in this study, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

### 1. Purpose of study and how long it will last:

The purpose of this study is to determine the dose of two different medications that is effective in increasing your blood pressure into a target range (111-139/70-85 mmHg). The two medications (midodrine and droxidopa) have been approved for experimental use in this study by the FDA. These medications will be given in three doses (midodrine: 5.0 mg, 10.0 mg, 15.0 mg and droxidopa: 400 mg, 500 mg, 600 mg) on successive study visits, depending on your blood pressure response. We will start you on the lowest dose and if your blood pressure stays below the target range, the dose will be increased on the next visit. Whether droxidopa or midodrine is administered first will be randomized, and you will not know which is being administered, but the investigator and study team will not be blinded. You are being asked to participate in the study because you have a spinal cord injury (SCI) and are between the age of 18 years and older. If you choose to participate in this study, you will be one of 50 participants with SCI screened for eligibility. If you are screened eligible you will be one of approximately 25 participants with SCI in this study. After the screening visit and if you qualify, your participation will last for no fewer than 2 visits and no more than 6 visits over the course of about six weeks. Each study visit will take about 3-4 hours each. A copy of this form will be given to you and a copy will be kept by the JJPVAMC research team. This study is sponsored and funded by the Craig H. Neilsen Foundation and is supported by the VA.

You will be eligible for the screening visit if you meet the following inclusion/exclusion criteria:

#### Inclusions:

- You are the age of 18 years and older
- You have a spinal cord injury at C1-T6
- You have a duration of injury more than 1 year

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- You are wheelchair dependent
- You have an American Spinal Injury Association (AIS) A, B, C
- You can provide written or verbal consent
- You are non-ventilator dependent

**Exclusions:** If any of the following statements apply to you, you need only tell the researcher that one or more of the statements pertain to you. To ensure your privacy and confidentiality, you need not reveal which of the statements apply to you. If you choose to tell the investigator which of the statements apply to you, the information will be kept strictly confidential. Please inform the researcher if any of the following statements apply to you.

- You are a current smoker
- You have a neurological condition other than SCI (Alzheimer's disease, dementia, stroke, multiple sclerosis, Parkinson's disease, etc.)
- You have history of cardiovascular disease (coronary heart and/or artery disease, hypertension, diabetes, unmanaged cardiac arrhythmias)
- You have a history of moderate or severe head trauma
- You have present or history of a psychological disorder
- You have a suspected or diagnosed malignancy
- You have a present or history of systemic, hepatic, or renal disease
- You have a recent history of substance abuse (within 6 months)
- You are currently ill or have an infection
- You are pregnant
- You have any allergies to study medications midodrine hydrochloride or droxidopa

## 2. Description of the Study Including Procedures to be Used:

If you consent to participate in this research study, you will visit the research center in Suite 7A-13 of the JJPVAMC main hospital building located in the Bronx, NY or you will visit the KF located in West Orange, NJ for a maximum of 7 visits. During the day of testing, you will report to the laboratory in the morning, after a normal breakfast and a good night sleep. For each visit you will be asked to empty your bladder upon arrival prior to testing, if needed. You will be asked to avoid caffeinated and alcoholic beverages and heavy exertion, smoking for 12 hours prior to arrival and you will refrain from taking sildenafil (Viagra), tadalafil (Cialis), or other similar medications, for 2-days prior to your study visit.

### Visit 1: Screening:

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- Postural Change (Pos): While you are lying down, we will monitor your heart rate, breathing rate and blood pressure for 5 minutes, then we will move you to the seated position. You will be asked to remain very still and passive during this re-positioning from lying down to sitting up with your hips and knees at a 90 angle while your lower legs hang off the side of the table. Passive movement means that you should not use your muscles to move, even if you can. Your heart rate, breathing rate and blood pressure will be continuously recorded for 1 minute while you are laying down (0-60 seconds), during the repositioning, and for 4 minutes in the seated position. This test will take about 5 minutes.
- Heart rate & breathing rate: You understand that your heart rate and breathing rate will be continuously monitored at rest and during the Pos and you will be able to see changes in your heart and breathing rates during testing on a computer screen.
- Blood pressure: Your blood pressure will be measured on your right middle finger and right upper arm. You understand that measurement of your finger blood pressure will be continuous at rest and during the Pos and you will be able to see your blood pressure change during testing on a computer screen.
- ISAFSCI: we will monitor your heart rate and blood pressure for 10 minutes while you are lying down and for 10 minutes while you are seated. Your body temperature and the amount of air you are able to forcibly exhale will also be measured and recorded and we will ask you questions related to your ability to sweat, and to feel and control your bladder and bowel. In addition, you will be asked questions related to your ability to be sexually aroused, ejaculate (if applicable) and achieve an orgasm.
- ADFSCI Survey: You will be asked questions about your symptoms including dizziness, sweating, heart palpitations, anxiety, goosebumps, light headedness, blurred vision, nausea, weakness, confusion, fatigue, and passing out.

You will be eligible to participate in Study 1 if you meet the following criteria: your average supine SBP is  $\leq 90$  mmHg, your average seated BP meets the WHO definition of hypotension (i.e., SBP  $\leq 110$  mmHg for males or SBP  $\leq 100$  mmHg for females, DBP  $\leq 60$  mmHg), there is evidence of orthostatic hypotension (i.e., fall in BP  $\geq 20/10$  mmHg when you are moved from the supine to the seated position), you have a score or  $\geq 1$  on the cardiovascular section of the ISAFSCI or a score  $\geq 1$  on questions 16 and 22 of the ADSCI. This visit will take approximately 1-2 hours.

### Visit 2 - 7:

Upon arrival you will be transferred to a recumbent chair and will remain in the seated position while the research team applies instrumentation. Three sticky electrodes will be placed on your chest and

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abdomen area. A blood pressure cuff will be placed around your upper right arm and a small blood pressure cuff will be placed on your left middle or ring finger. Your blood pressure, respiration rate and heart rate will be recorded for 10-minutes while you rest quietly (baseline) before we administer the study medication. After baseline testing you will be asked to swallow a small pill with a glass of water. You will then be passively moved to the supine (laying down) position for 30-minutes, during which your blood pressure, respiration rate, heart rate and blood oxygen concentration will be recorded every minute. After the 30-minutes, you will be passively transitioned into the seated position for a 3-hour observation, during which time we will monitor your blood pressure, respiration rate, heart rate and blood oxygen concentration every 30 minutes. At each visit you will be randomized to receive either a midodrine (in a dose escalation manner) or droxidopa (in a dose escalation manner).

The table below displays the medication and dose escalation that will be administered on successive study visits, depending on your blood pressure response. Each of the medications has a short duration of action so any bad reaction should be observed during the 3-hour laboratory assessment. But if you feel unwell or if your heart rate, breathing rate, and blood pressure have not returned to baseline within the 3-hour study, we will ask that you remain in the laboratory, and we will continue to monitor you very closely until you recover.

Table 1: Medication Dose Schedule\*

| Drug      | Dose 1 | Dose 2 | Dose 3 |
|-----------|--------|--------|--------|
| Droxidopa | 400 mg | 500 mg | 600 mg |
| Drug      | Dose 1 | Dose 2 | Dose 3 |
| Midodrine | 5 mg   | 10 mg  | 15 mg  |

\*Once the target blood pressure is attained (i.e., 111-139/70-85 mmHg), you will not be administered a higher dose of that study medication.

- Heart rate & breathing rate: You understand that your heart rate and breathing rate will be continuously monitored during each study visit. Heart and respiratory rate will be monitored and recorded for 10-minutes during the seated baseline period, every minute while you are laying down, and at 30-minute intervals in the seated position after administration of the study medication. You will be able to see changes in your heart rate and breathing rate during testing on a computer screen.
- Blood pressure: You understand that your blood pressure will be continuously monitored during each study visit on your right middle finger and right upper arm. Blood pressure will be monitored and recorded from your right upper arm for 10-minutes during the seated

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baseline period before taking the study medication, every minute while you are laying down, and at 30-minute intervals in the seated position after administration of the study medication. Finger blood pressure will be monitored continuously from your left middle or ring finger for 10-minutes during the seated baseline period, continuously while you are laying down, and at 30-minute intervals in the seated position after administration of the study medication. You will be able to see your blood pressure change during testing on a computer screen. Blood pressure will be taken by a trained research coordinator and will be reviewed by the study physicians Dr. Noam Harel and Dr. Marinella Galea, prior to increasing to the next dose level.

- Orthostatic Hypotension Likert Scale: Questions will be asked at 30-minute intervals in the seated position after administration of the study medication to report associated symptoms (dizziness, lightheadedness, blurry vision, nausea, feeling faint, weakness, trouble concentrating, head and neck discomfort).
- Autonomic Dysreflexia Likert Scale: Questions will be asked at 5-minutes in the supine position and at 30-minute intervals in the seated position after administration of the study medication to report associated symptoms (pounding in the head, goosebumps, sweating, ringing in the ears, vision problems, heart palpitations, nausea).

While you are a participant in this study, investigators may identify test results that they believe should be reviewed by your doctor. If that happens, they will call you within a week of the test to let you know. If you agree, the research team will send the test results to your doctor. You acknowledge that the researchers are not specifically looking for any medical problems, so it is unlikely that they will find any underlying issues. You understand that the tests for this study are not the same tests done as part of regular medical care.

### 3. Description of any Procedures that may Result in Discomfort or Inconvenience:

You have been told that the study described above may involve the following risks and/or discomforts:

Electrodes: The recording electrodes have adhesive backing. Therefore, skin irritation at the site of electrode application may occur. Areas with a lot of hair may be shaved prior to adhesive application.

Blood pressure: You may experience some discomfort when the blood pressure cuffs around your upper arm and finger are inflated.

Postural change (POS): You may feel uneasiness letting the staff passively reposition you from lying down to the seated position. Also, you may feel dizzy, lightheaded or nauseous while you are

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seated. A staff member will be supporting you during this 10-minute seated test, but if you feel very uncomfortable, we will stop the test.

Surveys: You could feel inconvenienced, frustrated, tired, or stressed when completing the study surveys

Autonomic Dysreflexia: There is a small chance that you could have an episode of autonomic dysreflexia while participating in this study. These episodes usually include headache, goose bumps, flushing (red face), and potentially dangerous increase in blood pressure. The investigators will be monitoring your blood pressure and other vital signs the entire time, and if there are significant symptoms or changes in your vital signs, they will halt the procedure immediately and provide appropriate medical care. The investigators are very experienced in treating episodes of autonomic dysreflexia.

#### Medications:

The medications (midodrine and droxidopa) may increase your blood pressure into a hypertensive range (i.e., systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 90$  mmHg), if this occurs, we will keep, or move you into the seated upright position and we will continue to monitor you until your blood pressure falls below hypertensive levels. If your blood pressure remains elevated, we will proceed through the AD algorithm to lower pressure, increase the orthostatic gradient and continue monitoring until your blood pressure returns to within 10/5 mmHg of your baseline blood pressure.

Common side-effects of midodrine include numbness and tingling, scalp itching, goosebumps, chills, rash, stomach pain, and urinary urgency.

Common side-effects of droxidopa include feverish, muscle stiffness, confusion, sweating, rash, itching/swelling, and trouble breathing.

#### 4. Expected Risks of Study:

Autonomic Dysreflexia: There is a small chance that you could have an episode of autonomic dysreflexia while participating in this study. These episodes usually include headache, goose bumps, flushing (red face), and potentially dangerous increase in blood pressure. The investigators will be monitoring your blood pressure and other vital signs the entire time, and if there are

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significant symptoms or changes in your vital signs, they will halt the procedure immediately and provide appropriate medical care. The investigators are very experienced in treating episodes of autonomic dysreflexia.

#### Medications:

The medications (midodrine and droxidopa) may increase your blood pressure into a hypertensive range (i.e., systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 90$  mmHg), if this occurs, we will keep you in the upright position and monitor cardiovascular parameters until the blood pressure falls below hypertensive levels. If your blood pressure remains elevated, we will proceed through the AD algorithm to lower pressure, increase the orthostatic gradient and continue monitoring until within 10/5 mmHg of your baseline blood pressure.

Common side-effects of midodrine include numbness and tingling, scalp itching, goosebumps, chills, rash, stomach pain, and urinary urgency.

Common side-effects of droxidopa include feverish, muscle stiffness, confusion, sweating, rash, itching/swelling, and trouble breathing

As with any research, there may be unforeseen risks and discomforts. A medical doctor associated with the study will be available to treat any medical emergency that may develop.

#### 5. Expected Benefits of the Study

There may be no direct benefit to you from this study, but any information that the researchers get from this study may help others.

#### 6. Other Treatments Available:

Participation in the study is voluntary and the alternative to this study is to not participate and seek clinical advice from your doctor.

#### 7. Use of Research Results:

The researchers will let you and your physician know of any significant new findings made during this study which may affect your willingness to participate in this study. All research material generated from the study will remain in the possession of Dr. Jill Wecht and her study team at the JJP VAMC. Your medical records will be maintained according to this medical center's requirements and all electronic and hardcopy. All electronic and hardcopy Research Records will

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be retained according to National Archives and Records Administration, Records Schedule RCS-10-1.

Access to the research materials generated from the study will be restricted to Dr. Jill Wecht and her study team. If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. No information by which you can be identified will be released or published unless required by law. In order to comply with federal regulations, research records identifying you may be reviewed by the following:

☐ \_\_\_\_\_ By checking this box and initialing, you agree to be contacted by the Principal Investigator or her investigative team at a future date for additional studies being conducted in the Research Center.

Authorized representatives of the JJPVAMC (e.g., Institutional Review Board, Research Compliance Officer) and VA, including the Office of Research Oversight (ORO), Federal Agencies such as the Government Accounting Office (GAO), VA Office of Inspector General (OIG), and Office for Human Research Protections (OHRP) may have access to your research records. If this research involves articles regulated by the FDA, the FDA may choose to inspect and copy research records that identify individual research subjects.

### **Clinical Trials:**

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time using the NCT# (NCT05839652) to locate this study.

### **8. Special Circumstances:**

Your participation in this study will be included in the VHA health record. A copy of the signed informed consent form and signed HIPAA authorization for participation in the study will be in your health record. The study staff has no real or apparent conflicts of interest involving this study

### **9. Compensation and/or Treatment in the Event of Injury:**

The VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one

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or more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center.

### 10. Voluntary Participation:

You are not required to take part in this study; your participation is entirely voluntary. You can refuse to participate in this study or withdraw your participation in this study after you consent without penalty or loss of VA or other benefits to which you are entitled.

### 11. Termination of Participation:

You can refuse to participate now, or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment if you are a patient. The investigator also has the right to withdraw you from the study at any time for reasons including, but not limited to, medical concerns (your health and safety are in jeopardy with continued participation in the study), non-compliance (you miss several scheduled appointments without notification) and protocol deviations (exclusion/inclusion criteria change and you are no longer eligible to participate).

### 12. Costs and Reimbursements:

As a veteran or non-veteran, you will not be charged for any treatments or procedures that are part of this study. For veterans who are required to pay co-payments for medical care and services provided by VA, these co-payments will continue to apply for medical care and services provided by VA that are not part of this study.

You will receive up to \$650 compensation for participation in this research study according to the following schedule:

|                           |                |                |
|---------------------------|----------------|----------------|
| Visit 1 (screening): \$50 | Visit 4: \$100 | Visit 7: \$100 |
| Visit 2: \$100            | Visit 5: \$100 |                |
| Visit 3: \$100            | Visit 6: \$100 |                |

You will also receive up to \$100/per visit compensation for travel to cover mileage and tolls if you drive to the laboratory in your own vehicle. We will also cover the expense of ambulette service if needed.

As a participant in the study, you may receive payments for your participation to help support your participation in the clinical trial.

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Greenphire is a company working on behalf of The Bronx Veterans Medical Research Foundation (BVMRF) to support this reimbursement process. In order for you to get paid, Greenphire will need to process certain personal information about you. This information will be collected from you by the study staff study and given to Greenphire.

Greenphire will collect and use your information for the following purpose(s): ClinCard. You may be issued a Greenphire ClinCard, which is a debit card that your funds are loaded onto. When a study visit is completed, funds will be approved and loaded onto your ClinCard. The funds will be available within 1 business day and can be used to pay for anything you need. In order to assign a ClinCard to you and load funds onto the ClinCard, Greenphire will need your Name, Address, and Date of Birth.

Taxation: Payment received as compensation for participation in research is considered taxable income. If payment exceeds \$600 in any one calendar year, Greenphire will file a 1099 (Miscellaneous Income) form on behalf of BVMRF. Greenphire will need your Name, Address, and Social Security Number.

Greenphire has administrative, physical, and technical safeguards that reasonably and appropriately protect the confidentiality, integrity, and availability of your personal information. Your personal information will be used and disclosed only to support the described research activities, including to service providers who assist us in managing, administering, or delivering the Services. Your personal information will not be shared by Greenphire or sold, used, or distributed for any other purpose. Your information will be kept for as long as necessary to provide the described activities and for compliance with applicable laws. You can exercise your rights to access, correct, modify, or delete your information at any time by contacting the staff from this study. If you exercise your rights or take away your consent, the study staff will not further transfer your personal information to Greenphire; however, this may not affect processing that occurred before you took away consent.

#### Contact Person(s):

To obtain answers to questions about the research, report or seek treatment for a research -related injury, or to voice concerns or complaints about the research contact the following:

- During the Day: Jill Wecht, EdD (718) 584-9000 x.3122
- After Hours: Matthew Maher, MS (201)-566-0291

I understand that should I wish to discuss my participation in this study with any other doctor or layperson, I can contact Mary Sano, Ph.D., Associate Chief of Staff (ACOS) R&D Program at the JJP

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VAMC by requesting an appointment at (718)741-4228 hospital extension 4228, first floor in the research building, Room 1F-01 If I have questions, concerns, and/or complaints or to offer input.

**RESEARCH SUBJECTS' RIGHTS:** I have read or have had read to me all of the above. Dr. Jill Wecht or her delegate has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

**I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.**

The results of this study may be published, but my records will not be revealed unless required by law. This study has been explained to me. I have had a chance to ask questions. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

Subject Signature

Date

Time

Person Obtaining Informed Consent  
(Print Name)  
(Investigator or Delegate as  
indicated on Assurance Page)

Signature of Person  
Obtaining Informed  
Consent

Date

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### **VERBAL CONSENT IF THE PARTICIPANT LACKS UPPER LIMB FUNCTIONS TO COMFORTABLY WRITE**

\_\_\_\_\_ is unable to sign the consent form due to impaired arm function. I certify that I have carefully explained the purpose and nature of this research to him/her in appropriate language and he/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she has consented to participate in this research. I, therefore, am signing the consent form to document that he/she has given his/her consent to participate in this research study.

#### **Person Obtaining Consent:**

Name: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Witness Name: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_