**Response to Diaphragmatic Pacing in Subjects with Pompe Disease**

**NCT02354651**

**Document Date: 12/05/2016**

# Protocol

## 1. Project Title

Response to Diaphragmatic Pacing in Subjects with Pompe Disease

## 2. Investigators:

Barbara Smith, PT, PhD

### Sub-Investigators:

Barry Byrne, MD, PhD
Manuela Corti, PT, PhD
Saleem Islam, MD
Terry Sexton, MSN, ARNP
Chasen Croft, MD
Brittany Knight, MSN, ARNP, CPNP-PC
Kara Godwin, MSN, ARNP, CPNP-PC

## 3. Abstract:

Diaphragm pacing is approved for replacing positive-pressure ventilators in neurodegenerative conditions including spinal cord injury and amyotrophic lateral sclerosis. Evidence shows that neurodegeneration plays a vital role to chronic ventilatory insufficiency in Pompe disease, which suggests that pacing may also benefit Pompe patients. This strategy has been shown to replace the role of mechanical ventilation during waking hours in patients with Pompe disease. The proposed study will evaluate the duration and pattern of spontaneous, versus paced ventilation in patients with Pompe disease and respiratory insufficiency. Medical records will be reviewed to document chemistry and hematology labs, chest x-ray, and review of symptoms for comorbidity. Functional outcomes include tolerance to breathing without positive pressure ventilators, and clinical and electrophysiological tests of respiratory muscle function.

## 4. Background:

The NeuRx DPS (Diaphragm Pacer) is a medical device approved for use in ventilator-dependent patients with spinal cord injury and patients with moderate ventilatory insufficiency due to amyotrophic lateral sclerosis. Pacing acts by bypassing the descending corticobulbar drive through the phrenic motor system to directly depolarize the diaphragm [1]. Diaphragm electrodes are implanted laparoscopically near the motor point of each hemi-diaphragm [2,3]. An external generator is connected to the externalized wire electrodes and emits an electrical impulse that directly stimulates the diaphragm muscle. In patients with phrenic neural insufficiency and yet residual contractility of the diaphragm, pacing can serve as an electrical ventilatory prosthesis, reducing or replacing positive pressure ventilation [4]. In occasional patients, spontaneous recovery of motor function has been reported after pacing, which has enabled removal of the pacing wires to restore fully independent breathing [5].
The preponderance of the preclinical and clinical evidence illustrates that respiratory insufficiency in Pompe disease is due to diminished phrenic motor function [6-9]. We evaluated an adult who

transferred to our center with Pompe disease and >four years of ventilator dependence. A multidisciplinary evaluation confirmed diaphragm paresis as the principal cause of his ventilatory insufficiency. In August 2011, a diaphragm pacing implantation was performed under guidelines of the FDA Humanitarian Device Exemption (HDE HO70003) for a Humanitarian Use Device (HUD 06-0165), following Institutional Review Board approval (UF-IRB-01# 399-2011). Five days after implantation of the device, progressive diaphragm conditioning was initiated. By post-operative day #65, the patient was pacing continuously, breathing without the ventilator for 12 hours per day, and was discharged home. We have since completed diaphragm pacing for infantile onset disease with similar functional results. In light of the early successes with diaphragm pacing, patient interest in the procedure has surged. However, the widespread use of this modality requires a further understanding of the magnitude of the clinical benefit as well as possible mechanisms behind the gains.

## 5. Specific Aims:

The global objective of this study is to determine the effect of diaphragm pacing on respiratory function in subjects with Pompe disease.

**Aim 1: to test the hypothesis that even a single bout of diaphragm pacing transiently augments diaphragm/phrenic activation and increases breathing capacity.**
The timing, flow, volume, and pressure generated during resting breathing, along with diaphragm EMG will be recorded throughout six months of diaphragm pacing and progressive diaphragm conditioning.

**Aim 2: to test the hypothesis that prolonged diaphragm pacing elicits prolonged rehabilitative effects on minute ventilation and ventilator weaning.**
Breath timing and volume in spontaneous breathing, breath strength, minute ventilation, ventilator weaning, diaphragm EMG, and sleep hypoventilation will be recorded throughout six months of diaphragm pacing and progressive diaphragm conditioning.

## 6. Research Plan:

**Subjects:**
The study group will consist of twelve male or female subjects 2-65 years of age with a diagnosis of Pompe disease as defined by mutational analysis, GAA enzyme activity assay in blood spot and/or fibroblast culture less than 40% of control values, as well as clinical symptoms. In addition, subjects will be eligible if they have met the clinical eligibility for NeuRx DPS implantation. All subjects will have a history of mechanical ventilation (MV) dependence, defined as a requirement of six or more hours invasive or non-invasive MV support daily for at least 21 days in duration [10]. Subjects currently on GAA replacement therapy will continue protein replacement during the study.

Subjects will be recruited either via self-referral to the research team (e.g. after discovering the study on ClinicalTials.gov), or referral from the surgeon who conducts the implantation surgery. The surgeon will provide subjects with the contact information of the study team, so that they may inquire to us about the study.

Exclusionary Criteria:
The subject must not:

- Be participating in another treatment study using a device for diaphragm pacing
- Be unable to complete pulmonary function testing
- Be pregnant, or become pregnant throughout participation in the study. If a subject may be pregnant, a pregnancy test will be performed, or results of a recent test will be used to confirm.

**Study design:**
Subjects with Pompe disease who are having NeuRx DPS implantation will be invited to participate in this study. This procedure is part of the subject's clinical care, and is not done for this or any other research project. Baseline data will be entered into the study record from clinical testing completed within 12 months of NeuRx DPS implant. After placement of DPS, study assessments will be completed at Days 3, 14, 90 and 180 per table of events on page 8.

**Testing:**
Pulmonary function testing equipment and test administration protocols will be standardized in accordance with ATS/ERS guidelines [12]. Pulmonary function testing will be conducted according to the schedule of assessments (page 8). During pulmonary function testing, baseline and exertional vital signs will be monitored (heart rate, respiratory rate, pulse oximetry). In addition, diaphragm EMG will be recorded, either with surface electrodes (global inspiratory muscle EMG) or by using an adaptor that enables direct EMG recording from the intramuscular pacing wires. These tests will be completed with support from any mechanical ventilation the subject may use. If the subject "sprints" routinely with reduced or no breathing support, we will also test breathing under these conditions. The following pulmonary function tests will be completed on all subjects:

*Forced expiratory tests:* Forced expiratory tests measure the maximal airflow and volume of gas that can be exhaled with the subject breathing or coughing forcefully. A nose clip, or cuffed tracheostomy with cuff inflated is used to prevent leakage. The subject deeply inhales and then exhales as forcefully and deeply as possible. Measurements will be obtained with the subject sitting upright and then repeated with the subject in the supine position, if tolerated. A minimum of three trials will be obtained in each position with <5% variability [13]. The highest value obtained in each position will be reported. Forced expiratory tests will be completed at Screening, Baseline, Day 14, Day 90, and Day 180.

*Maximal Inspiratory Pressure (MIP):* MIP will be measured with a manometer connected to the airway opening of the subject, which occludes the airway and prevents airflow. A nose clip will be used to prevent leakage and the subject is instructed to suck air from the tube with as much force as possible. Measurements will be obtained with the subject sitting upright. Transdiaphragmatic pressure (Pdi) may be calculated with esophageal and gastric manometry during MIP. The measurement will be taken three times and the best value will be reported. MIP will be completed at Screening, Baseline, Day 14, Day 90, and Day 180.

*Resting Breathing Pattern:* Resting ventilatory flow and timing will be recorded with a pneumotachograph and pressure transducer connected to the airway opening. If a patient

routinely uses MV throughout the day, the sensing equipment can be placed in series to the breathing tubes. Resting breathing will be recorded under the following conditions: (1) using the subject's routine daytime ventilatory support (ventilator, BiPAP, ETC); (2) using the subject's routine daytime ventilatory support plus the diaphragm pacer; (3) using no support or the lowest support needed to maintain baseline minute ventilation (if the subject uses reduced or no settings routinely); (4) using no support or the lowest support needed to maintain baseline minute ventilation plus the diaphragm pacer (if the subject uses reduced or no settings routinely). Subjects will rest for a minimum of 30 minutes between each condition, and tests may be scheduled over two consecutive days as needed. Resting Breathing Pattern will be completed at Screening, Baseline, Day 5, Day 14, Day 30, Day 90, and Day 180. During this testing, subjects will not be taken below their lowest tolerated ventilator settings.

*Respiratory Muscle Endurance Test:* This test will begin after subjects rest for a minimum of one hour. Subjects will be tested in the seated position while breathing through a mouthpiece with nose clip. When a steady state breathing pattern has been reached (noted by stable tidal volumes for at least 30 seconds), subjects will be instructed how to maintain the breathing rate and volume, with the use of visual feedback on a computer. A threshold inspiratory load equivalent to 35% of the maximal inspiratory pressure will be placed on the inspiratory port of the mouthpiece. Subjects will be instructed to maintain the established breathing pattern during loaded breathing. The test will end when the subject cannot open the threshold valve for 3 consecutive breaths, or when the subject can no longer subjectively tolerate the test and must remove the mouthpiece. Loaded breathing typically lasts between 2-10 minutes. Respiratory Muscle Endurance Testing will be completed at Screening, Baseline, Day 90, and Day 180.

*Magnetic stimulation:* Supramaximal, cervical magnetic stimulation of the phrenic nerves will be conducted with the subjects in upright with the head and trunk supported. Stimulations will be applied from end-expiratory lung volume. At least five stimulations will be delivered at the maximum stimulator output. The resulting twitch transdiaphragmatic pressure (Pdi) will be calculated from gastric and esophageal pressures obtained by catheter-mounted transducers, and compared to reference values [14]. Magnetic stimulation will be tested at screening.

*Sleep dysfunction:* Breathing during sleep will be assessed using the BioRadio, which has the ability to monitor oxygen saturation, electrocardiogram, and EMG while the subject is asleep. This will occur at Baseline and Day 90. Subjects will be given a monitor, sensors, and instructions for how to set up and record during one night's sleep, which will be returned at the end of their participation.

**Post-operative diaphragm conditioning:**
Typically diaphragm conditioning commences after a 5-day post-operative recovery period, when post-operative pain and inflammation have been controlled for >24 hours. Diaphragm conditioning will be progressed using an ordered protocol, which consists of gradual increases in:

(1) *The external stimulator settings.* The initial external stimulator settings will be set by the manufacturer's representative in the surgical suite, and any upper limits or restrictions in

parameters (e.g. threshold for PVC's) will be established. The stimulator settings will be increased as needed.

(2) *The duration of diaphragm stimulation.* Starting POD#5, the pacing system will be activated for one, or more30-minute trials, per day (maximum 5, 30 minute trials). The duration of diaphragm stimulation will be systematically increased as tolerated to accomplish three goals, including pain- and dyspnea-free pacing, overnight pacing, and continuous 24-hour pacing.

(3) *Off-ventilator spontaneous breathing (SB).* On POD#5, the patient will undergo an initial trial of unassisted breathing with the diaphragm pacer turned on. The duration of SB with pacing will be increased to tolerance, using a protocol. If the patient cannot complete at least 30-minute bouts of paced SB, then the focus of breathing trials will be reduced pressure support mechanical ventilation.

The subject will be instructed how to operate the pacemaker equipment and be provided with a diaphragm conditioning home exercise program. This is part of the patient's routine clinical care. Diaphragm conditioning will be completed five to seven days per week by the subject, based upon the subject's daily baseline level of fatigue.

**Diaphragm conditioning will routinely occur at home, yet an investigator will continue to monitor progress with the home program every 7 to 21 days by telephone. We will have experience in remote monitoring of RMST in ventilator-dependent children and adults, and remotely-supervised sessions enable investigators to monitor compliance, progress the diaphragm conditioning, and provide feedback.**

## SCHEDULE OF ASSESSMENTS

| | SCREENING | BASELINE | D5 | D14 | D30 | D90 | D180 | As Needed | Extension |
|---|---|---|---|---|---|---|---|---|---|
| Consent | X | | | | | | | | |
| Resting Breathing Pattern | X | X | X | X | X | X | X | X | X |
| Respiratory Muscle Endurance Test | X | X | | | | X | X | X | X |
| Phrenic Nerve-Magnetic Stimulation | | X | | | | | | X | |
| Maximal Inspiratory Pressure | X | X | | X | | X | X | X | X |
| Forced Expiratory Tests | X | X | | X | | X | X | X | X |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| EMG | | | X | X | X | X | X | X | X |
| Medical History/Record and Medications review, AE and Prescription Compliance assessment | ONGOING | | | | | | | | |
| Questionnaires | X | X | | | | X | X | X | |
| Physical exam | | | X | X | | X | X | X | X |
| Sleep dysfunction measure | | X | | | | X | | | |

Subjects will be asked to complete a daily pacemaker/ventilator diary documenting ventilator assistance use and pacemaker use. The Investigator or designee will contact the subject a minimum of two times per month to document adverse events, changes to medications, update the medical history, and assess compliance with diaphragm conditioning exercise prescription. This communication may be accomplished by email, telephone, or video conference calling.

**Extension phase:**
Subjects who complete this study will have the opportunity to continue in an optional extension phase, wherein they would be evaluated annually, or at the request of their physician. These evaluations can include a physical exam, EMG recording, and pulmonary function testing. This extension phase will last six years, and will allow evaluation of long-term changes in ventilator dependence.

**Data analysis:**
We will evaluate changes in average respiratory rate and volume, integrated EMG, and daily independent breathing time, between 0 and 6 months. Since this is an observational pilot study, data will be largely descriptive. However, the data are largely quantitative and continuous. Sample distributions and summary statistics will be calculated for each of these outcomes. Data transformations will be done if non-linear distributions exist, and repeated measures ANOVA (or non-parametric) will quantify recovery at 6 months.

## 7. Possible Discomforts and Risks:

**Pulmonary Function Testing**
Pulmonary function testing is used routinely in clinical medicine and has no inherent complications. Pulmonary function testing will be completed by the study team on Day 5, 14 and 180 after NeuRx DPS implantation. If possible, the study team will complete pulmonary function testing the day prior to NeuRx DPS implantation.

Although sustained (several minutes to several hours), intensive inspiratory loading can produce elevations in oxygen consumption, mean arterial pressure and diminish cardiac output, brief

periods of loading (<30 seconds) have not been shown to cause significant changes in cardiac parameters (Coast et al., 1988). Nevertheless, we have designed the protocol to include strict limits on baseline and exertional vital signs, in order to minimize the imposed cardiorespiratory work. Due to the brief duration of testing and training procedures, the incidence of blood gas dysfunction is extremely low. Nevertheless, end-tidal $CO_2$ and oxygen saturation will be monitored continually.

Respiratory testing may elicit transient fatigue or shortness of breath that resolves within several seconds of completion. Frequent rests are included to prevent or minimize these systems.

**Phrenic Nerve Function Evaluation with EMG**
Anterior magnetic stimulation of the phrenic nerves is a recommended technique for subjects, because it is painless and reproducible, yields supra-maximal stimulation, and does not require uncomfortable positioning [12]. Phrenic latency and compound muscle action potential (CMAP) will be determined individually for the right and left phrenic nerves [19]. The phrenic latency is the time between the stimulus and the responding diaphragm CMAP. A normal phrenic latency is between 6-8 msec in adults [20] and 4.8-8.63 msec in children [21]. The diaphragm CMAP will be recorded using surface or esophageal electrodes. Alternatively, the CMAP may be captured by recording from the implanted pacer wires. In addition to measuring CMAP, the transdiaphragmatic pressure (Pdi) may be calculated with esophageal and gastric manometry during bilateral, supra-maximal magnetic stimulation and compared to reference values obtained in healthy adults [14]. Phrenic stimulation testing will be conducted at baseline and at Day 180, unless clinical care dictates more frequent assessments are needed.

EMG recording will be completed with the implanted wires on Day 0, 5, 14, 180 and PRN.

**Questionnaires**
Subjects will be asked to complete the Severe Respiratory Insufficiency Questionnaire at Screening, baseline, day 90 and day 180. This questionnaire was developed for use in subjects with respiratory failure from various etiologies who utilize mechanical ventilation. It is a self-administered test that will require approximately 20 minutes to complete.

## 8. Possible Benefits:

There are some potential benefits to the individual subject expected in this clinical research study. The anticipated benefit to subjects and the Pompe community is to determine the mechanism of action for respiratory insufficiency and ultimately respiratory failure in Pompe disease. Subjects who participate in this clinical research study will have personalized respiratory muscle strengthening routine prescribed with regular contact with the study team.

Another potential benefit to participants is decreased ventilator dependence. Other respiratory muscle exercises have shown to be effective in adults with ventilator dependence and/or neuromuscular disease, as well as in children without neuromuscular diseases. The primary interest is whether and for how long strength and functional breathing patterns can improve for subjects after pacer conditioning. The training regimen may provide an alternative adjuvant treatment for subjects with Pompe disease who require assisted ventilation.

## 9. Conflict of Interest:

There are no declared conflicts of interest for the investigators.

## References:


1. DiMarco AF (2005) Restoration of respiratory muscle function following spinal cord injury. Review of electrical and magnetic stimulation techniques. Respir Physiol Neurobiol 147: 273-287.

2. Onders RP, Aiyar H, Mortimer JT (2004) Characterization of the human diaphragm muscle with respect to the phrenic nerve motor points for diaphragmatic pacing. Am Surg 70: 241-247; discussion 247.

3. Onders RP, Dimarco AF, Ignagni AR, Aiyar H, Mortimer JT (2004) Mapping the phrenic nerve motor point: the key to a successful laparoscopic diaphragm pacing system in the first human series. Surgery 136: 819-826.

4. Onders RP, Elmo M, Khansarinia S, Bowman B, Yee J, et al. (2009) Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients. Surg Endosc 23: 1433-1440.

5. Onders RP, Ponsky TA, Elmo M, Lidsky K, Barksdale E (2011) First reported experience with intramuscular diaphragm pacing in replacing positive pressure mechanical ventilators in children. J Pediatr Surg 46: 72-76.

6. DeRuisseau LR, Fuller DD, Qiu K, DeRuisseau KC, Donnelly WH, Jr., et al. (2009) Neural deficits contribute to respiratory insufficiency in Pompe disease. Proc Natl Acad Sci U S A 106: 9419-9424.

7. Lee KZ, Qiu K, Sandhu MS, Elmallah MK, Falk DJ, et al. (2011) Hypoglossal neuropathology and respiratory activity in pompe mice. Front Physiol 2: 31.

8. Burrow TA, Bailey LA, Kinnett DG, Hopkin RJ (2010) Acute progression of neuromuscular findings in infantile Pompe disease. Pediatr Neurol 42: 455-458.

9. Mah CS, Falk DJ, Germain SA, Kelley JS, Lewis MA, et al. (2010) Gel-mediated delivery of AAV1 vectors corrects ventilatory function in Pompe mice with established disease. Mol Ther 18: 502-510.

10. MacIntyre NR, Epstein SK, Carson S, Scheinhorn D, Christopher K, et al. (2005) Management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. Chest 128: 3937-3954.

11. Ireland D, Jennings R (2009) NC DMA: Durable Medical Equipment, Clinical Coverage Policy 5A. Durable Medical Equipment

12. ATS/ERS (2002) ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 166: 518-624.

13. Society AT (1995) Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 152: 1107-1136.

14. Mier A, Brophy C, Moxham J, Green M (1989) Twitch pressures in the assessment of diaphragm weakness. Thorax 44: 990-996.

15. Martin AD, Smith BK, Davenport P, Harman E, Gonzalez-Rothi RJ, et al. (2011) Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. Crit Care 15: R84.

16. Onders RP, Elmo MJ, Ignagni AR (2007) Diaphragm pacing stimulation system for tetraplegia in individuals injured during childhood or adolescence. J Spinal Cord Med 30 Suppl 1: S25-29.

17. Hulzebos EH, Helders PJ, Favie NJ, De Bie RA, Brutel de la Riviere A, et al. (2006) Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. Jama 296: 1851-1857.

18. Dronkers J, Veldman A, Hoberg E, van der Waal C, van Meeteren N (2008) Prevention of pulmonary complications after upper abdominal surgery by preoperative intensive inspiratory muscle training: a randomized controlled pilot study. Clin Rehabil 22: 134-142.

19. Luo YM, Moxham J, Polkey MI (2008) Diaphragm electromyography using an oesophageal catheter: current concepts. Clin Sci (Lond) 115: 233-244.

20. Chen R, Collins S, Remtulla H, Parkes A, Bolton CF (1995) Phrenic nerve conduction study in normal subjects. Muscle Nerve 18: 330-335.

21. Russell RI, Helps BA, Helms PJ (2001) Normal values for phrenic nerve latency in children. Muscle Nerve 24: 1548-1550.