SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Diaphragm Pacing Stimulator

Device Trade Name: NeuRx DPS™, Diaphragm Pacing System

Applicant's Name and Address: Synapse Biomedical, Inc.
300 Artino Street
Oberlin, OH 44074

Humanitarian Device Exemption (HDE) Number: H100006

Humanitarian Use Device (HUD) Designation Number: 10-0242

Date of Humanitarian Use Device (HUD) Designation: September 17, 2010

Date(s) of Panel Recommendation: Not applicable

Date of Good Manufacturing Practice Inspection: November 27, 2007 and
April 23, 2008

Date of Notice of Approval to Applicant: September 28, 2011

II. INDICATIONS FOR USE

The NeuRx Diaphragm Pacing System (DPS)™ is a percutaneous, intramuscular, diaphragm motor point stimulating device intended for use in amyotrophic lateral sclerosis (ALS) patients with a stimulatable diaphragm (both right and left portions) as demonstrated by voluntary contraction or phrenic nerve conduction studies, and who are experiencing chronic hypoventilation (CH) , but not progressed to an FVC less than 45% predicted. For use only in patients 21 years of age or older. The right and left phrenic nerves are the conductive path from the spinal cord to the diaphragm. Both, right and left nerves, must be at least partially intact for the NeuRx DPS™ to work. Phrenic nerve function can be tested by neurophysiological testing, by visualizing diaphragm contraction with fluoroscopy (a full motion x-ray) or by other radiographic techniques (such as ultrasound). Chronic hypoventilation can be detected with standard tests. These tests include pulmonary function tests (sometimes referred to as PFT's) for measurement of forced vital capacity (FVC, a measure of maximum air movement) and maximum inspiratory pressure (MIP or PImax, a measure of the maximum strength of inspiration). Also, blood gases may be tested for carbon dioxide (PCO_2) levels and oxygen levels may be tested during sleep with oximetry (SaO_2). The levels, of any one of these measurements that identify chronic hypoventilation are:

- FVC less than 50% predicted
- MIP less than 60 cm H_2O
- PCO_2 greater than or equal to 45 mm Hg

- SaO_2 less than 88% for 5 consecutive minutes during sleep

III. CONTRAINDICATIONS

None known

IV. WARNINGS AND PRECAUTIONS

See labeling for warnings and precautions.

V. DEVICE DESCRIPTION

The NeuRx DPS™ is a percutaneous, intramuscular, diaphragm motor point stimulation system. It is implanted using standard laparoscopic surgical techniques in an outpatient procedure. The implanted intramuscular diaphragm electrodes are connected to a four channel external stimulator at a percutaneous exit site. The stimulator provides a capacitively coupled, charge balanced, biphasic stimulation to each electrode with a common indifferent electrode that is placed subcutaneously. The stimulator controls the charge delivered through clinician programmed parameters of pulse amplitude, pulse duration, pulse frequency, pulse ramp, inspiration time, and respiratory rate. The clinician uses a clinical station to characterize electrode response to stimulation and program the external stimulator with the patient specific parameters. The user connects the stimulator and turns it on for use; no other controls are available or necessary for operation.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The standard therapies for ALS patients are pharmacologic, nutrition and respiratory management followed by palliative care. Pharmacological interventions are predominately for management of symptoms with riluzole, having a modest survival benefit, targeting one of the hypothesized mechanisms of the disease. Non-invasive ventilation (NIV), and mechanical ventilation (MV) via a tracheostomy are the only approved treatments for respiratory symptoms.

Riluzole

The only approved drug to slow the progression of ALS is riluzole, which has been shown in trials, and is currently acknowledged, to have a modest survival benefit of approximately three months.[1, 2] The action of this drug is as a glutamate inhibitor, which is believed to be one of the mechanisms of cause of the disease.[3] It is also known that glutamate acts as an afferent signal transmitter for respiration.[4] Thus, while providing an overall benefit, riluzole may have some negative effects on the patient when respiratory dysfunction begins to occur.

Non-invasive ventilation

Non-invasive ventilation (NIV) is currently the first line treatment for patients experiencing symptoms of respiratory insufficiency. A number of recent publications[5-11] have

identified the probable benefit of NIV in advancing survival and improving quality of life in patients with ALS. Additionally, while NIV has become the standard of care for those patients with advanced respiratory insufficiency[5], it is also being considered as an appropriate treatment for earlier intervention[5, 12, 13]. NIV (also referred to as NPPV or NIPPV) commonly takes the form of bilevel or continuous positive airway pressure (BiPAP or CPAP) devices. These are applied with nasal, oronasal, full-face masks or mouth pieces. The choice of mask depends on patients' facial structure, ability to eliminate air leaks, cosmesis concerns, and claustrophobic tolerance.

The Practice Parameter of the American Academy of Neurology[14, 15] suggests that all patients with ALS and respiratory symptoms, or an FVC <50%, should be offered NIV. NIV has been shown to decrease dyspnea, and improve quality of life. Although it may delay the need for invasive mechanical ventilation, there is evidence to suggest that dependence on NIV may increase with use. [16] NIV is usually applied at night due to greater convenience and the high frequency of sleep-disordered breathing that it might ameliorate. Patients often add daytime hours as their disease progresses and many eventually use NIV for 24 hours per day. The fact that NIV does not require a surgical procedure helps with acceptance, although compliance is an issue. Some patients experience claustrophobia or find it difficult to tolerate the 8-15 cm H_2O force of air that is typically delivered with an inspiration. Historically, most patients in Europe and the US had not received non-invasive ventilation, with acceptance rates reported as low as 2% - 15% due to issues with implementation [7, 17]. A side effect may be diaphragm deconditioning

Mechanical ventilation.

At some point, ALS affects the respiratory muscles so severely that bulbar paresis is combined with severe expiratory and inspiratory muscle weakness. There is a significant risk of impending respiratory failure or death below 25 – 30% FVC[14] and invasive ventilation becomes the only option for survival[18]. Invasive ventilation or mechanical ventilation (MV) requires placement of a tracheostomy that is connected to a ventilator and can prolong life for up to 20 years.

VII. MARKETING HISTORY

The NeuRx DPS™, Diaphragm Pacing System, has been CE Marked (EC Certificate # 518356) since November 20, 2007, and actively marketed in Europe (EEA) since January 2008. The device was approved by FDA on June 17, 2008, under HDE H070003, for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but who lack control of their diaphragms. Synapse began actively marketing the device in the U.S. immediately following approval. The device was approved by TGA in Australia on January 20, 2009, and the first patients were treated there in late October 2009. The device has been used in other countries in compliance with provisional regulatory approvals in those countries. Full regulatory approval is being pursued in Canada, Israel, Jordan, Saudi Arabia, and Brazil. The NeuRx DPS™ has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. ADVERSE EFFECTS

Overview

Table 1 summarizes the adverse events reported for the 86 implanted patients who met the HUD Group definition and were not otherwise excluded (see section X. Clinical Investigations and Experience). In summary:

- There have been no reports of serious unanticipated adverse device effects in these studies.

- There were no reports of any serious adverse effects related to the patients' use of the device following discharge.

- There were 3 reports of serious adverse effects related or possibly related to the surgical implantation procedure in 3 patients (3/86 or 3.5%):
  (1) capnothorax requiring intravenous catheter and an extended hospital stay;
  (2) capnothorax requiring intraoperative placement of an angiocathether; and
  (3) respiratory failure following complications from surgery.

  Additionally, in one enrolled subject (not implanted) there was a report of serious anesthesia reaction which led to cancellation of the implantation surgery. These serious adverse effects were previously identified as potential risks in the IDE and are typical of risks associated with other common laparoscopic or general surgical procedures.

- Overall, there have been 61 serious adverse events (other than death or tracheostomy with permanent mechanical ventilation) reported in the trial. Three of those events, as discussed above, were considered device or procedure related. In total there were 36 patients (42%) that experienced a serious adverse event during the study. The three serious events related to the device occurred in different patients (3.5%) and were all related to the surgical procedure. The cumulative hazard is provided in Figure 1A for all of the non-endpoint serious events and Figure 1B for the device related serious events. The line listing by patient and month is provided in Appendix B.

- During the standard 12-month protocol, 14 patients (16%) died and 5 patients (6%) underwent tracheostomy and initiated permanent mechanical ventilation. No patient died or had tracheostomy with permanent mechanical ventilation within the 30-day peri-implant period. After the standard 12-month protocol, 26 patients (30%) died and 8 patients (9%) underwent tracheostomy and initiated permanent mechanical ventilation. In all, 40 patients (47%) have reached the study endpoint of death and 13 patients (15%) have reached the endpoint of tracheostomy and permanent mechanical ventilation.

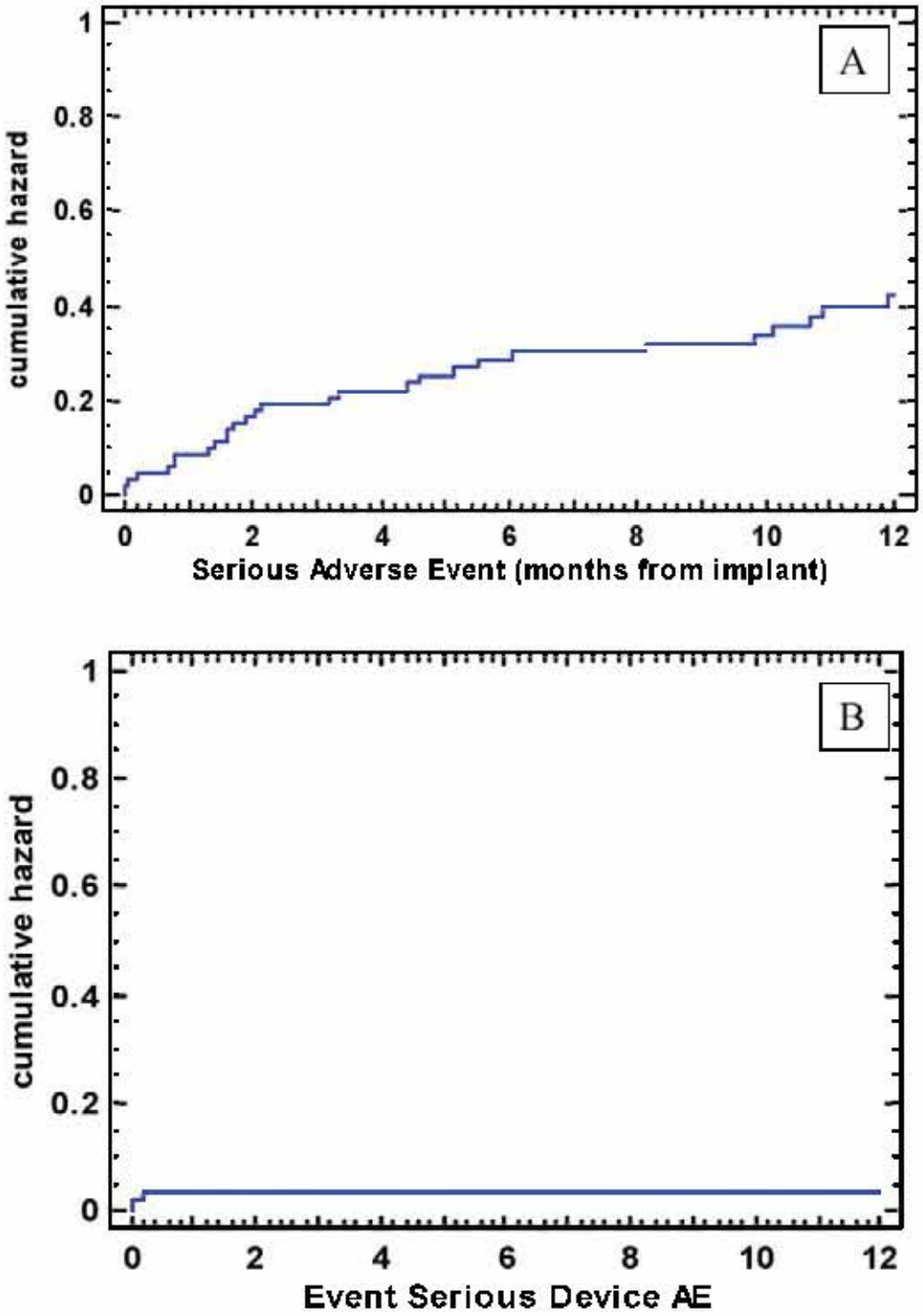

Figure 1: A) Hazard of All Serious Adverse Event (other than endpoint event); B) Device Related Serious Adverse Events

Capnothorax

The most commonly occurring surgical adverse event was air tracking into the pleural cavity caused by CO2 used to inflate the abdomen during surgery, e.g. a capnothorax. This event is related to the electrode implantation procedure. In the 86 HUD Group patients, capnothoraces were reported in 16 patients (19%). Two of these events were classified as serious (as discussed above). In one case, a pigtail intravenous catheter was placed intraoperatively to aspirate the air and the patient was admitted to the hospital for 3 days until the capnothorax resolved. In another case, the patient had a mild decrease in his oxygen saturation and mild eventration of the diaphragm suggestive of the capnothorax. An angiocatheter was placed into the intrapleural space, the CO2 was evacuated, the patient's oxygen saturation returned to 100%, and the diaphragm eventration was completely resolved.

The incidence of capnothoraces observed during implantation of the NeuRx DPS™, in ALS patients is lower than that for the 50 SCI patients described in the Summary of Safety and Probable Benefit (SSPB) for HDE H070003. The SCI patients had an incidence of capnothoraces of 21/50 (42%) and serious capnothoraces of 2/50 (4%), and were implanted an average of 5.6 years after their injury. This duration of disuse atrophy and subsequent thinning of the diaphragm possibly accounts for some of the difference between capnothoraces incidence in the SCI and the ALS studies. Nevertheless, the SCI HDE SSPB noted that the incidence was similar to that associated with other laparoscopic procedures.

While this complication is common, it is usually not clinically serious, and is acceptable within the context of the procedure and the patient population. This adverse event is specifically addressed in the firm's training program.

Respiratory Failure

One patient had respiratory failure following complications from surgery. The patient (#05-04) presented with abdominal pain and fever about one week post electrode implantation surgery. The patient was diagnosed with a large abdominal wall abscess in the rectus muscle consequent to the migration of a percutaneous endoscopic gastrostomy (PEG) tube outside of the stomach. The PEG was placed in the same surgery following electrode implantation. The abscess was drained in the operating room and stomach defect was subsequently closed and a feeding jejunostomy was then placed. The patient was placed on a mechanical ventilator and, after failing to wean, underwent tracheostomy. Attempts to use diaphragm pacing were made and five months later it appeared that the patient used diaphragm pacing partially during the day and mechanical ventilation at night. Due to lack of device use and follow-ups, this patient was not included in the efficacy analysis.

Reaction to Anesthesia

One patient had a serious reaction to anesthesia. After the induction of general anesthesia in the operating room, and before any incision was made, the patient had an episode of bradycardia and hypotension resulting in cancellation of the surgery. A subsequent stress echocardiogram performed on the patient showed no cardiac problems. A vasovagal event was suspected. Following this event, the patient was considered a high risk for general anesthesia and surgery and study participation was terminated.

Post-Operative Pain

One patient (who was not in the HUD Group) reported intermittent chest pain post-diaphragm pacing surgery. EKG indicated possible ischemic changes however cardiac catheterization was negative for coronary artery disease. The pain was determined to be secondary to the surgery and the patient was discharged to home on the second day post surgery.

Infection at Percutaneous Exit Site

Mild to moderate infection at the percutaneous exit site was reported in 8 patients (8/86 or 9.3%). Three patients had a recurrence of infection 1-3 months after the first report. All were described as mild except one which was described as moderate in severity. None were considered serious. Infections were primarily treated with antibiotics. One case resolved after the investigator externalized the wires at the epigastric port and another after the wires were re-routed. All other cases resolved with antibiotics. No cases required explant of the system.

Discomfort from Stimulation

There were no serious adverse events involving discomfort from stimulation and no reports of severe discomfort. Discomfort was reported in 22 patients (26%)—mild in 20 patients (23%) and moderate in 2 patients (2.3%). Resolution was achieved in most cases by adjusting stimulation parameters. In 2 patients (2.3%), discomfort was not resolved but both patients tolerated the discomfort and continued using DPS. In 2 patients (2.3%), discomfort was not resolved but both patients tolerated the discomfort and continued using DPS. As seen in Figure 2, the discomfort occurred primarily in the first months of use

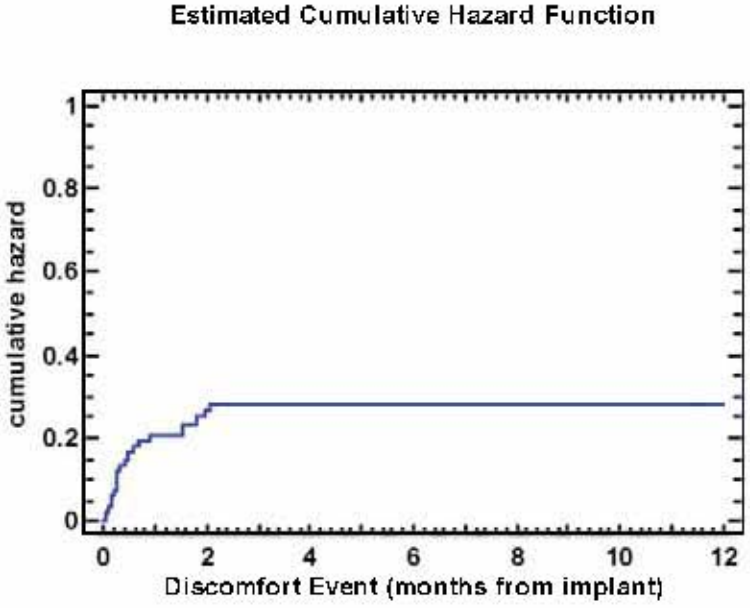

Figure 2: Stimulation discomfort

Discussion. In terms of discomfort from stimulation, diaphragm pacing was well tolerated, with the vast majority of discomfort described as mild and none described as severe. When it occurred, discomfort from stimulation tended to occur early on and was usually resolved promptly through stimulator reprogramming. This was anticipated in the protocol: "The programmed stimulus for the majority of patients implanted during this study has been far below the maximum output of the stimulator. As the patients remain sensory intact, the stimulus amplitude is reduced to provide a stimulus that can be comfortably tolerated during the conditioning sessions." The preponderance of early (peri-implant) versus late reports may reflect patients' initial discomfort until optimal stimulator settings were found or until some minimum level of conditioning was achieved.

Regarding the two patients whose discomfort was not resolved, we believe that the stimulation discomfort experienced by these patients may have been caused by unfused contractions of the diaphragm due to the stimulus settings. We have learned over the course of the clinical trial that these types of issues can potentially be resolved by adjusting the pulse amplitude and pulse frequency (rather than pulse amplitude and pulse width) to create a more fused or smooth contraction of the diaphragm. Unfortunately, the two participants experiencing unresolved discomfort have been unable, due to their disease progression, to return to the clinical site to attempt these settings adjustments. Nevertheless, both patients have tolerated the discomfort and have continued using DPS.

Malfunction of Device Components

There were no serious adverse events involving malfunctioning device components. No patients had to return for surgical correction of malfunctioning electrodes. In the cases of the diaphragm electrodes, all malfunctions occurred external to the body at the connector holder. While this is a significant rate of occurrence, there was no cause for revision surgeries and most were repaired in an office visit. There were 18 reports of external anode breaks in 18 patients (21%) and 44 reports of external electrode breaks in 28 patients (33%).

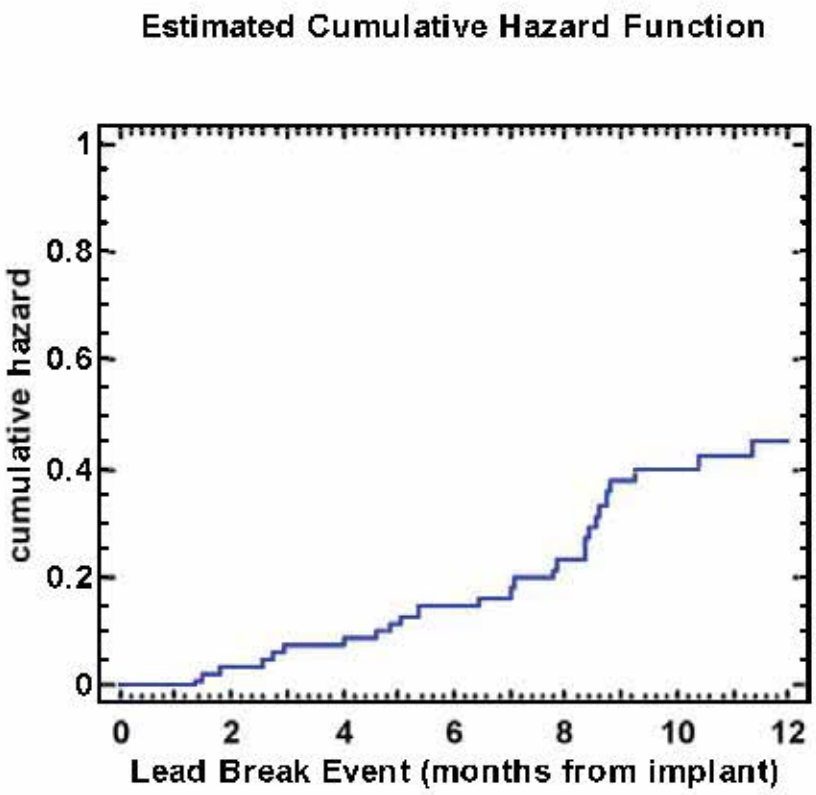

Figure 3: Lead (anode or electrode) break external to body

There were also eight anodes that came out of the body in six patients (7%). This required reinsertion in the subcutaneous tissue in a physician office under topical anesthetic or use of a surface anode until the subcutaneous one could be replaced.

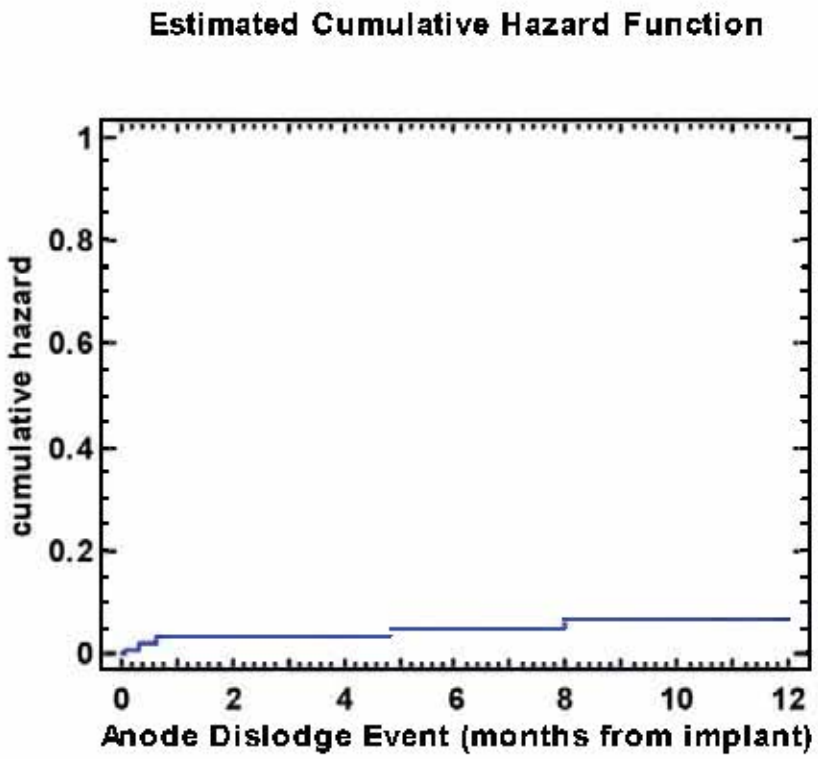

Figure 4: Anodes requiring replacement

There were only six broken stimulators (7% of patients) and four broken cables (5% of patients) reported. The cables are intended to be disposable and two are provided with each kit. The stimulators are easily replaced with a reprogrammed device that the investigator can deliver overnight to the patient.

Cumulative hazard graphs for lead (electrode or anode) breakage and anode dislodgement are shown in Figure 3 and Figure 4.

Discussion. There were no serious adverse events involving malfunctioning device components. Dislodgement of the electrode from the diaphragm was never reported in this study. All reports of device malfunction were able to be resolved and no surgical revision was ever required. Broken stimulators or patients cables were able to be replaced with spares. Malfunctioning electrodes were resolved through repair of the external connections. Malfunctioning anodes were resolved through replacement of the subcutaneous lead in an office visit or replacement with an external surface anode.

The proportion of ALS patients in the IUD Group who experienced lead breaks (35/86; 41%) exceeds the proportion of patients in the SCI study (HDE H070003) who experienced anode malfunction (3/50, 6%) and electrode malfunction (7/50, 14%). This is probably due to the relative mobility of the ALS patients.

In practical terms in the ALS, malfunctioning components resulted in a loss or diminution of conditioning therapy until the malfunction was able to be resolved. While the proportion of

patients experiencing anode or lead malfunction at some point in their DPS use is substantial, malfunction tends to occurs relatively late when it does occur and it can be resolved. Also, in contrast to SCI patients, the ALS patients are mainly using DPS for diaphragm conditioning, not for primary ventilatory assistance.

Based on the experience in this study, design improvements have been implemented in an effort to improve reliability or to simplify malfunction resolution. These changes focus on the cable to electrode interface. This includes making the cable more robust by improving the strain relief at the electrode connector end, creating a strain relief boot for the electrode lead wires as the exit the connector block, and providing a back-up surface anode in the patient kit. All of these changes do not modify the function of the device, but are rather intended to improve reliability as part of continuous improvement efforts in the design and development process.

Comment on PEG Placement at Time of DPS Implant

Early in the study, it was recognized that there was an overlap in the candidates for diaphragm pacing and those patients in need of, or at a stage when they should be considering use of, PEG feeding. Two primary issues were considered prior to placement of a PEG tube during the DPS implant procedure. First was the consideration of device contamination and potential for infection since PEG placement is a non-sterile procedure. Second, the mortality and morbidity of patients following PEG placement is substantial [19-22] with 30-day mortality rates as high as 25% and complications in up to 18% of patients.

Simultaneous PEG and DPS were performed in 24 HUD Group patients (28% of implanted patients). With the appropriate surgical handling of the laparoscopic port entries and PEG entry, the potential for infection is drastically reduced and there has been only one occurrence of a problem with the PEG placement at the same time as DPS (4.2%). In that case, the PEG was not inserted properly and caused leakage into the abdominal cavity and subsequent sepsis. The patient was unable to continue with the DPS follow-up and was thus excluded from efficacy evaluation.

Regarding mortality, there has been a remarkable 100% 30-day survival rate of patients with simultaneous PEG and DPS.

Comment on Extubation and Recovery

Early in the course of the studies, it was identified that the ALS patients were being extubated more easily than expected. The combination of the non-paralytic anesthetics and use of DPS to increase respiratory system compliance are suspected as the primary source. These operative techniques have been described in the literature.[23] There were no failures to extubate in any of the patients. In patients qualifying for the lead-in studies, there were no 30-day mortalities and no perioperative pneumonias. In the five compassionate use patients, there was one 30-day mortality from respiratory failure and one patient that entered hospice and withdrew support having been satisfied, with her family, that she had tried everything, short of tracheostomy, to prolong survival.

Comment on Respiratory System Compliance

At the end of each procedure, the DPS system is also used to increase the respiratory system compliance. By stimulating to create a negative pressure in conjunction with the positive pressure ventilation, posterior lobe atelectasis is decreased. Since ALS patients have little respiratory reserve, increasing respiratory compliance decreases their work of breathing. The respiratory system compliance was observed on the anesthesia ventilator prior to use of DPS. The DPS was then turned on synchronously with the delivery of ventilator gas and respiratory system compliance was again observed. The result of this finding, in a group of six spinal cord patients and four ALS patients, has been previously reported at the American Thoracic Society meeting. There was a 19% increase in respiratory compliance with DPS and is thus routinely used at the end of the procedure to help with extubation.

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Table 1: Adverse Event (AE) Frequency for Implanted HUD Group Subjects (N=86) – All AEs, Serious AEs, and Device/Procedure Related AEs

AE Frequency for Implanted HUD Group Subjects (N=86)	All AEs			Serious AEs			Device/Procedure Related AEs			Serious Device/Procedure Related AEs (Intersection)			
Adverse Event	**# AEs**	**# Pts.**	**Proportion. of Pts. w/AE (N= 86)**	**# AEs**	**# Pts.**	**Proportion. of Pts. w/AE (N= 86)**	**# AEs**	**# Pts.**	**Proportion. of Pts. w/AE (N= 86)**	**# AEs**	**# Pts.**	**Proportion. of Pts. w/AE (N= 86)**	**# Serious UADEs**
† other infections / conditions normally seen in ALS	74	36	41.9%	21	18	20.9%	1	1	1.2%	1	1	1.2%	--
† discomfort from stimulation	40	22	25.6%	--	--	--	40	22	25.6%	--	--	--	--
† broken percut lead - connect holder/ exit site	44	28	32.6%	--	--	--	44	28	32.6%	--	--	--	--
† death (endpoint)	40	40	46.5%	40	40	46.5%	--	--	--	--	--	--	--
† tracheostomy/mechanical ventilation (endpoint)	13	13	15.1%	13	13	15.1%	--	--	--	--	--	--	--
† death after (trach/mv endpoint)	3	3	3.5%	3	3	3.5%	--	--	--	--	--	--	--
† tracheostomy/mechanical ventilation (non-endpoint)	4	4	4.7%	6	4	4.7%	2	1	1.2%	2	1*	1.2%	--
† broken anode lead at connector holder or exit site	18	18	20.9%	--	--	--	18	18	20.9%	--	--	--	--
† dislodged anode lead	8	6	7.0%	--	--	--	8	6	7.0%	--	--	--	--
fall	17	8	9.3%	--	--	--	--	--	--	--	--	--	--
† surgical - capnothorax	15	15	17.4%	2	2	2.3%	15	15	17.4%	2	2	2.3%	--
† pneumonia / pneumonitis	11	8	9.3%	11	8	9.3%	--	--	--	--	--	--	--
† infection at percutaneous exit site	11	8	9.3%	--	--	--	11	8	9.3%	--	--	--	--
† respiratory infection (other than	11	10	11.6%	1	1	1.2%	--	--	--	--	--	--	--

AE Frequency for Implanted HUD Group Subjects (N=86)	All AEs		
Adverse Event	**# AEs**	**# Pts.**	**Propor-tion. of Pts. w/AE (N= 86)**
pneumonia)			
† surgical - pain	6	5	5.8%
urinary tract infection	6	5	5.8%
† broken external stimulator	7	6	7.0%
prolonged post-op. recovery - PEG placement	4	4	4.7%
† broken external cable / connector	4	4	4.7%
pain at percutaneous lead exit site	3	3	3.5%
general malaise	3	2	2.3%
stomach pain	3	1	1.2%
deep vein thrombosis	2	2	2.3%
skin irritation	5	5	5.8%
anxiety and/or depression	4	3	3.5%
drainage at gastrostomy site	2	2	2.3%
headache	2	2	2.3%
nausea	2	2	2.3%
temporomandibular joint syndrome	2	1	1.2%
constipation	3	2	2.3%

Serious AEs			Device/Procedure Related AEs			Serious Device/Procedure Related AEs (Intersection)			
# AEs	# Pts.	Proportion. of Pts. w/AE (N= 86)	# AEs	# Pts.	Proportion. of Pts. w/AE (N= 86)	# AEs	# Pts.	Proportion. of Pts. w/AE (N= 86)	# Serious UADEs
--	--	--	6	5	5.8%	--	--	--	--
1	1	1.2%	--	--	--	--	--	--	--
--	--	--	7	6	7.0%	--	--	--	--
--	--	--	--	--	--	--	--	--	--
--	--	--	4	4	4.7%	--	--	--	--
--	--	--	3	3	3.5%	--	--	--	--
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--	--	--	--	--	--	--	--	--	--
1	1	1.2%	--	--	--	--	--	--	--
--	--	--	5	5	5.8%	--	--	--	--
1	1	1.2%	--	--	--	--	--	--	--
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--	--	--	2	1	1.2%	--	--	--	--
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AE Frequency for Implanted HUD Group Subjects (N=86)	**All AEs**		
Adverse Event	**# AEs**	**# Pts.**	**Propor-tion. of Pts. w/AE (N= 86)**
† embolism	2	2	2.3%
† systemic infection	1	1	1.2%
abdominal wall abscess	1	1	1.2%
cardiac arrest	1	1	1.2%
respiratory arrest	1	1	1.2%
colon cancer	1	1	1.2%
diabetic ketoacidosis	1	1	1.2%
infection, kidney	1	1	1.2%
myocardial infarction	1	1	1.2%
perforated diverticulum	1	1	1.2%
spasm	2	2	2.3%
ventricular tachycardia	1	1	1.2%
† surgical - infection	1	1	1.2%
blister under connecter patch	1	1	1.2%
difficulty speaking while stimulator on	1	1	1.2%
elevated temperature	1	1	1.2%
palpitations (no cardiac connotation)	1	1	1.2%
perioperative - lead wire drawn in subcutaneously at exit site	1	1	1.2%

Serious AEs			Device/Procedure Related AEs			Serious Device/Procedure Related AEs (Intersection)			
# AEs	# Pts.	Proportion. of Pts. w/AE (N= 86)	# AEs	# Pts.	Proportion. of Pts. w/AE (N= 86)	# AEs	# Pts.	Proportion. of Pts. w/AE (N= 86)	# Serious UADEs
1	1	1.2%	1	1	1.2%	--	--	--	--
1	1	1.2%	--	--	--	--	--	--	--
1	1	1.2%	--	--	--	--	--	--	--
1	1	1.2%	--	--	--	--	--	--	--
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--	--	--	1	1	1.2%	--	--	--	--
--	--	--	1	1	1.2%	--	--	--	--
--	--	--	1	1	1.2%	--	--	--	--

AE Frequency for Implanted HUD Group Subjects (N=86)	**All AEs**		
Adverse Event	**# AEs**	**# Pts.**	**Propor-tion. of Pts. w/AE (N= 86)**
pruritus	1	1	1.2%
shock while pacing while wet	1	1	1.2%
abdominal pain	2	2	2.3%
acid reflux	1	1	1.2%
baclofen pump malfunction	1	1	1.2%
benign fibrous nodule - diaphragm	1	1	1.2%
bleeding at tracheostomy site	1	1	1.2%
decubitus ulcer	1	1	1.2%
fever	1	1	1.2%
folliculitus	1	1	1.2%
hypertension	1	1	1.2%
infection, rectal	1	1	1.2%
insomnia	1	1	1.2%
abscessed tooth	1	1	1.2%
diarrhea	1	1	1.2%
gastroenteritis	1	1	1.2%
hemorrhoids	1	1	1.2%
kidney stone	1	1	1.2%
laceration, head	1	1	1.2%
lack of appetite	1	1	1.2%

Serious AEs			Device/Procedure Related AEs			Serious Device/Procedure Related AEs (Intersection)			
# AEs	# Pts.	Propor-tion. of Pts. w/AE (N= 86)	# AEs	# Pts.	Propor-tion. of Pts. w/AE (N= 86)	# AEs	# Pts.	Propor-tion. of Pts. w/AE (N= 86)	# Serious UADEs
--	--	--	1	1	1.2%	--	--	--	--
--	--	--	1	1	1.2%	--	--	--	--
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1	1	1.2%	--	--	--	--	--	--	--
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1	1	1.2%	--	--	--	--	--	--	--
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AE Frequency for Implanted HUD Group Subjects (N=86)	All AEs			Serious AEs			Device/Procedure Related AEs			Serious Device/Procedure Related AEs (Intersection)			
Adverse Event	**# AEs**	**# Pts.**	**Proportion. of Pts. w/AE (N= 86)**	**# AEs**	**# Pts.**	**Proportion. of Pts. w/AE (N= 86)**	**# AEs**	**# Pts.**	**Proportion. of Pts. w/AE (N= 86)**	**# AEs**	**# Pts.**	**Proportion. of Pts. w/AE (N= 86)**	**# Serious UADEs**
rash	1	1	1.2%	--	--	--	--	--	--	--	--	--	--
shingles	1	1	1.2%	--	--	--	--	--	--	--	--	--	--
stomach nodule	1	1	1.2%	--	--	--	--	--	--	--	--	--	--
† surgical - nausea	--	--	--	--	--	--	--	--	--	--	--	--	--

† = Adverse event code included in list of anticipated adverse events identified in the IDE

* = Adverse event code includes multiple entries for same patient split by tracheostomy and mechanical ventilation in detailed listing

IX. PRECLINICAL STUDIES

The following summary is identical to that found in the SSPB for HDE H070003 which covers the same device except that the indications relate to spinal cord injury (SCI).

Long-term Biocompatibility

Implanted components of the system were tested as long-term implant. ISO 10993 recommends cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, subacute toxicity, genotoxicity and implantation testing.

Test	Description	Results
Cytotoxicity	MEM Elution Test	Grading from 1-4 was used. The test sample article graded 0 while the positive controls graded 4.
Sensitization	Guinea Pig Maximization Test	The test criteria of grades 1 or better are presumed to be due to sensitization. The grading was 0 for all experimental articles and 1, 2 or 3 for the positive controls.
Intracutaneous Reactivity	ISO Method of Intracutaneous Reactivity Test	The average reaction was not appreciably greater than the reaction to the blank.
Systemic Injection Test	ISO Method of Systemic Injection Test	There was not a significant difference in biological reactivity between test groups and their corresponding negative controls.
Pyrogen Test	Material Mediated Rabbit Pyrogen Test	The individual temperature rise of each individual rabbit was below the test criteria of 0.5 degrees C. The test material was demonstrated to be non-pyrogenic.
Implantation Test	Thirty Day Muscle Implantation Test	The results indicate that the negative control and test article mean scores are in the same overall Toxicity rating (Not exceeding 1).
Implantation Test	Twenty-Six Week Muscle Implantation Test	The results indicated that the negative control and the test article mean scores were in the same overall toxicity rating.
Mutagenicity	Ames Assay Test	As none of the tester strains treated with the test article extract showed mean revertant frequencies greater than two fold when compared to the concurrent negative control, the test article was considered non-mutagenic.

Limited-Duration Contact Biocompatibility

System components used during surgery were tested as limited-duration contact devices. ISO 10993 recommends cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity and pyrogenicity testing.

Test	Description	Results
Cytotoxicity	MEM Elution Test	Grading from 1-4 was used. The test sample article graded 0 while the positive controls graded 4.
Sensitization	Guinea Pig Maximization Test	The test criteria of grades 1 or better are presumed to be due to sensitization. The grading was 0 for all experimental articles and 1, 2 or 3 for the positive controls.
Intracutaneous Reactivity	ISO Method of Intracutaneous Reactivity Test	The average reaction was not appreciably greater than the reaction to the blank.
Systemic Injection Test	ISO Method of Systemic Injection Test	There was not a significant difference in biological reactivity between test groups and their corresponding negative controls.
Pyrogen Test	Material Mediated Rabbit Pyrogen Test	The individual temperature rise of each individual rabbit was below the test criteria of 0.5 degrees C. The test material was demonstrated to be non-pyrogenic.

Patient Cable Biocompatibility

The Patient Cable (PN 22-0011) was tested as a surface device with potential for permanent-duration skin contact. ISO 10993 recommends cytotoxicity, sensitization and irritation testing.

Test	Description	Results
Cytotoxicity	MEM Elution Test	Grading from 1-4 was used. The test sample article graded 0 while the positive controls graded 4.
Sensitization	Guinea Pig Maximization Test	The test criteria of grades 1 or better are presumed to be due to sensitization. The grading was 0 for all experimental articles and 1, 2 or 3 for the positive controls.
Irritation	Primary Skin Irritation Test	The average reaction was not appreciably greater than the reaction to the blank.

Sterilization

The implantable portions of the device are sterilized by ethylene oxide (EO). The Sterility Assurance Level is 10^{-6}, The validation was performed in conformity with recommendations contained in ANSI/AAMI/ISO 11135:1994.

Ethylene Oxide and Ethylene Chlorohydrin residual testing was conducted, in accordance with ANSI/AAMIIISO 10993, Part 7. The residuals are within the recommended limits for implanted devices.

Shelf Life

An accelerated aging study was completed to establish a 2-year Shelf Life.

General Safety

General Safety testing was performed on the External Pulse Generator and the Clinical Station to ISO60601-1 and UL60601-1.

Electromagnetic Compatibility

Electromagnetic Compatibility testing was performed on the External Pulse Generator and the Clinical Station.

Testing of the NeuRx DPS™ was completed according to:

- EN60601-1-2 36.201.1/EN 55011 Radiated Emissions,
- EN60601-1-2, 36.202.2/EN 61000-4-2 Electrostatic discharge immunity,
- EN60601-1-2, 36.202,3/EN 61000-4-3 Radiated Electromagnetic Field Immunity,
- EN 60601-1-2, 36.202.6/EN 61000-4-6 Conducted RF immunity for I/O,
- EN 60601-1-2, 36.202.8/EN 61000-4-8. Magnetic Field Immunity

In each case, the device passed the standardized test.

As the NeuRx DPS™ is intended for out of the hospital transport, testing for the higher electric field immunity level of 20 V/m was performed on the External Pulse Generator. This testing was done in a shielded room with the frequency broadcast from 26MHz to 1 GHz, with both horizontal and vertical antenna polarization. No deviation to the selected operation modes was observed during this testing.

Programmable Electrical Medical System

Programmable Electrical Medical Systems testing was performed on the External Pulse Generator and the Clinical Station according to EN60601-1-4.

The software for each component runs independently and was validated with a predefined software validation procedure.

The software for the External Pulse Generator operates continuously under software control. The software processes the parameter data and generates the required timing in real-time.

The software for the Clinical Station has several functions. It provides for multi-mode functionality of the device. The three operating modes are described below: stimulator, programmer and surgical mapping modes.

STIMULATOR MODE
The Stimulator operating mode emulates the functionality of the NeuRx DPS™ External Pulse Generator. When the Clinical station is in this mode, it has the abilities of the stimulator.

PROGRAMMER MODE
The Programmer operating mode automatically uploads the current parameter values from a connected stimulator. It also automatically downloads display parameters to the connected stimulator, as they are modified.

SURGICAL MAPPING MODE
The Surgical mapping operating mode provides intra-operative stimulation and sensing of stimulated response. This mode provides twitch or burst stimulation and displays an indication of relative abdominal pressure response.

Environmental and Mechanical Testing of Pulse Generator

Temperature and Humidity Cycle Testing was performed on the External Pulse Generator and the Clinical Station to IEC 60068-2-1, IEC 60068-2-2, IEC 60068-2-27, IEC 60068-2-6, IEC 60068-2-34 and IEC 60068-2-78.

Mechanical Strength Testing of Electrode

Testing demonstrates the barb assembly of the electrode has the mechanical strength to remain intact during explantation of the electrode. Data submitted previously indicate the electrode Teflon insulation and Prolene (polypropylene suture) core retain their strength during simulated long-term exposure studies. Samples at simulated six month, 1, 2, 3, 4, 5, and 10 year exposures in phosphate buffered saline maintained strength characteristics not significantly different from un-aged (time 0) samples.

Animal Testing

Thirty-two electrodes have been implanted in the diaphragms of seven dogs. Five dogs were stimulated from 8-24 hours per day for 2-6 months. Two dogs were maintained as controls and did not receive stimulation. Graded inspiratory contractions of the diaphragm were achieved by applying bursts of stimulus pulses that were ramped in intensity from threshold to complete muscle recruitment. Diaphragm fatigue was prevented by using the minimum stimulus pulse rate and shortest burst needed to evoke the required tidal volume. Measurements of the airflows and pressures evoked by intramuscular diaphragm stimulation were made at regular intervals. The tidal volumes and trans-diaphragmatic pressures produced were repeatable in all animals throughout the study period. The induced tidal volume was sufficient to provide 167 percent (s.d. 48) of the ventilation required for basal metabolic needs without fatiguing the diaphragm. Airway resistance, lung compliance, and functional residual capacity were measured. No

significant changes were observed, indicating that pulmonary function was not adversely affected by the stimulation.

Stimulus parameters, transdiaphragmatic pressure and tidal volumes are shown for animals stimulated full time and part time. The tidal volume has been normalized to critical tidal volume. Critical tidal volume is the tidal volume required for full time basal ventilation without diaphragm fatigue.

Histological studies have shown that the tissue reaction to the new electrode is well within acceptable limits. Morphological and histological studies performed on the diaphragm and surrounding tissue at the termination of each study indicated tissue ingrowth into the electrodes and fibrous encapsulation consistent with a mild foreign body response extending less than 100 microns beyond the implant. Cellular reaction in the area of stimulating tips showed no signs of tissue damage. There was no evidence of infection along the electrode tract. As expected, histochemical muscle fiber typing showed an almost complete conversion to type I fatigue-resistant fibers in chronically stimulated diaphragms.

GLP Statement

All of the non-clinical studies discussed above, with the exception of the animal studies were conducted in accordance with GLP. The animal studies followed standard university research laboratory protocols, and did not comply in every respect with the good laboratory practice regulations as described in 21 CFR 58. Each study was, however, carefully monitored and reviewed. All studies involving the use of animals were accepted by a peer review panel of the Case Western Reserve University School of Medicine.

X. CLINICAL INVESTIGATIONS AND EXPERIENCE

Study

The prospective study of the NeuRx Diaphragm Pacing Stimulation (DPS™) System of Motor-Point Stimulation for Conditioning the Diaphragm of Patients with Amyotrophic Lateral Sclerosis (ALS) has been approved at nine clinical centers in the U.S. and France with 144 patients enrolled and 106 patients implanted with the DPS therapy between 2005 and 2009. The primary inclusion criteria were demonstration of bilateral phrenic nerve function and forced vital capacity (FVC) below 85% at enrollment and above 45% at the time of DPS implantation. Otherwise the patients had to be suitable surgical candidates and not have co-morbidities that would affect their involvement. The study was initiated in two phases, initially as a pilot phase at University Hospitals of Cleveland then expansion to a multi-center pivotal phase at additional sites. Seven additional U.S. sites were approved for enrollment (IDE G040142) and one site in France enrolled under the protocol.

Data analysis

Analyses were performed to evaluate whether the NeuRx DPS device meets the criteria for Humanitarian Device Exemption in ALS, i.e., that the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Analyses were performed on subgroup (HUD Group) which meets the Humanitarian Use Designation (HUD #10-0242) population criteria, i.e., *ALS patients with a stimulatable diaphragm by voluntary contraction or phrenic nerve conduction studies, and who are experiencing chronic hypoventilation (CH).* Generally, study patients were included in the HDE analyses if their pre-implant FVC, PCO_2 and maximal inspiratory pressure (MIP) values met the criteria for chronic hypoventilation (CH) specified in the published guidelines [14, 24] Safety analyses involved 86 patients. Efficacy analyses involved 84 patients (excluding, from the safety analysis population, two patients lost to follow-up).

Safety

Generally DPS implantation surgery was uncomplicated and DPS therapy was well tolerated. There were no reports of serious unanticipated adverse device effects and no reports of any serious adverse effects related to the patients' use of the device following discharge. There were 3 reports of serious adverse effects related or possibly related to the surgical implantation procedure in 3 patients (3/86 or 3.5%): (1) capnothorax requiring intravenous catheter and an extended hospital stay; (2) capnothorax requiring intraoperative placement of an angiocathether; and (3) respiratory failure following complications from surgery. Additionally, in one enrolled subject (not implanted) there was a report of serious anesthesia reaction which led to cancellation of the implantation surgery. These serious adverse effects were previously identified as potential risks in the IDE and are typical of risks associated with other common laparoscopic or general surgical procedures.

Survival

Overall (N=84) the median survival (freedom from death or permanent tracheostomy ventilation—PTV) from onset is 56 months (4.7 years) using Kaplan-Meier survival analysis with 53 (63%) of the patients having reached an endpoint thus far. Surviving patients (N=31) were at a median of 62 months post onset of symptoms (interquartile range 49 – 84), at last contact. Overall (N=84), survival from diagnosis is a median of 39 months (3.3 years) and from DPS implant is median of 19 months (1.6 years) with Kaplan-Meier analysis. Surviving patients (N=31) were at a median of 23.9 months post implant (interquartile range 16.4 – 29.2), at last contact.

Survival versus NIV alone

The survival of patients treated with NeuRx DPS™ and NIV compares favorably to the survival of ALS patients treated with standard-of-care NIV alone in Lechtzin's study[5] ("Lechtzin Group"). DPS HUD Group patients having $45\% \leq FVC < 65\%$ were selected

(N=43) for comparison to the Lechtzin Group (N=43). The HUD Group patients showed a significant improvement in survival from diagnosis (by 16 months) and from the start of NIV (by 9 months). Survival from diagnosis was 21.4 months for the Lechtzin Group (consistent with the published result) and was 37.5 months for the HUD Group ($p<0.001$ by Log Rank and Wilcoxon tests). From NIV initiation the survival was 11.9 months for the Lechtzin Group and was 20.9 months for the HUD Group ($p<0.001$ by Log Rank and Wilcoxon tests). The 43 HUD Group patients in this sub-comparison had a survival of 19.7 months from implant, consistent with the survival of the overall 82 HUD Group patients.

For the overall DPS/Lechtzin set comparison of 86 patients (43 DPS & NIV + 43 NIV only), Cox proportional hazard estimates were identified for (a) survival from diagnosis and (b) survival from first respiratory intervention. Based on the model of survival from diagnosis (a), it is expected that DPS and riluzole have the greatest effect on the patients in the dataset. Based on the model of survival from first respiratory intervention (b), it is expected that DPS has the greatest effect on the patients in the dataset.

The results of these comparisons to Lechtzin's data suggest that NeuRx DPS™ benefits ALS patients over and above the benefit they may receive from NIV alone.

Survival after PEG

Simultaneous endoscopic gastrostomy (PEG) and DPS were performed in 24 HUD Group patients (28% of implanted patients in lead-in study). There has been a remarkable 100% 30-day survival rate of patients with simultaneous PEG and DPS and 79% of the patients were still surviving at six months. There is a 54% survival at 12 months of patients receiving a PEG at the same time as DPS and the eight patients still alive at the time of last contact were at a median of 29 months post implant (interquartile range 24.4 – 33.2). In contrast, Forbes's report on a study of 142 patients that had PEG insertion involved a review of several prior studies which showed a 30 day mortality, following PEG, ranging from 2% - 25%[19]. Median survival from PEG ranged from 4 months to 13 months in the studies reviewed by Forbes.

Sleep

The importance to sleep of losing diaphragm function has been well documented both in general[25, 26] and in ALS[27, 28]. In ALS, diaphragm dysfunction is associated with REM sleep related episodes of hypoventilation and deteriorated sleep architecture and efficiency[27, 28]. An ancillary study to our IDE study was undertaken by the investigators at Pitié Salpêtrière in Paris, France, to assess the impact of diaphragm conditioning on sleep. It was hypothesized that a positive effect of DPS on diaphragm function could improve the sleep of ALS patients.

The sleep study patients had sleep assessments at month 3 and after 4 months of diaphragm stimulation (month 7). Sleep assessments included evaluation of the Epworth score and full-night laboratory polysomnographic recordings (PSG). The sleep assessments were performed with the patients breathing spontaneously or under non-invasive ventilation depending on their current clinical status, but always with DPS off.

The results of this study show that after 4 months of DPS conditioning, patients with ALS exhibit significant sleep improvements. These include an increased sleep efficiency (median 9%), with a reduction in arousal index driving a decrease of wake after sleep onset (median 69 minutes). The magnitude of this effect is important. For reference, widely prescribed drugs for the treatment of primary insomnia increase sleep efficiency by 6-7% and reduce wake after sleep onset by 15-20 minutes[29, 30]. The sleep improvements occurred despite a continuing deterioration in vital capacity and respiratory pressures, in line with progression of ALS and a worsening ALSFRS-R score.

Conclusion

DPS implantation surgery was safe (infrequent serious adverse effects); DPS use was safe and well tolerated (no serious adverse effects). Evidence of probable benefit includes:

(1) a significant improvement in survival from diagnosis (by 16 months) and from the start of NIV (by 9 months) compared to standard-of-care NIV;
(2) a remarkable 100% 30-day survival rate of patients with simultaneous PEG and DPS compared to 30-day mortality expectations of 2% - 25% with continued long term improvement in survival;
(3) a 16 month survival from implant for patients with no other respiratory options that are intolerant or unable to use NIV;
(4) significant sleep improvement after just 4 months of DPS conditioning: an increased sleep efficiency (median 9%), with a reduction in arousal index driving a decrease of wake after sleep onset (median 69 minutes) which is also clinically significant given that widely prescribed drugs for the treatment of primary insomnia increase sleep efficiency by 6-7% and reduce wake after sleep onset by 15-20 minutes.

XI. RISK/PROBABLE BENEFIT ANALYSIS

Diaphragm pacing has been implanted in over 350 patients to date with over 150 in controlled clinical trials for spinal cord injury (SCI) and ALS. The first SCI patient was implanted in March 2000 in an approved investigational device exemption (IDE) study. This patient has the longest history of use with over ten years of continuous pacing to meet his full time (24 hours per day, 7 days per week) ventilatory needs. There were a total of 50 patients in the SCI IDE, now approved as HDE 070003. They have now been using the device for over three years on average. This population of pure upper motor neuron dysfunction provides the baseline from which the ALS population can potentially benefit. While the treatment in ALS is not intended to provide complete ventilatory support, as it is in SCI, it is based on the same initial effects. In the SCI patients we initially see weakened diaphragms from disuse atrophy that must be strengthened to achieve the level of pacing to support their ventilatory needs. In addition to disuse atrophy the conversion of muscle to Type II glycolytic fibers can be initially seen in SCI patients with the response to low frequency stimulation. With conditioning, these fibers are converted to Type I oxidative fibers as demonstrated in response to frequency of stimulation.[31]

Although direct phrenic pacing, by placing electrodes bilaterally on the phrenic nerves in the thoracic region, has been available for many years it is not a suitable alternative to the $NeuR_X$ DPS™ intramuscular approach to diaphragm pacing. To place a direct phrenic pacing system the phrenic nerves must be mobilized for electrode positioning. While this can usually be safely performed in spinal cord injured patients, it does have risks and complications.[32] Unfortunately, this technique is further complicated by potential for recurrent "occasional axonal degeneration and scattered foci of mild to moderate demyelinization" as was found in post-mortem study of a long-term direct phrenic pacing patient.[33] While this is not immediately detrimental to a chronic ventilator dependent spinal cord injured patient, it would be essentially fatal to an ALS patient.

Given the long history in spinal cord injured patients and the absence of contact with the phrenic nerve, the risks associated with the $NeuR_X$ DPS™ are minimal. While any surgical procedure has inherent risks, especially in a compromised ALS patient, the minimally invasive laparoscopic procedure to implant the DPS has demonstrated to have few adverse events and has had no peri-operative mortality in the targeted population. Further, the techniques that have been developed for surgical implantation have led to improvements in the overall use of surgery in the ALS patient population.[23]

In this devastating disease it is well published that the expected median survival from first onset of symptoms is three years.[6, 34-39] From ALS diagnosis, the median survival is down to two years.[36, 37, 39] Pulmonary complications and respiratory failure are reported to be responsible for 77% - 84% of deaths in ALS.[35, 40-42]

There is certainly a dearth of treatment options available for ALS patients. The only approved drug to slow the progression of ALS, riluzole, is a glutamate inhibitor which adversely affects the function of the central respiratory center response to hypoxia [4] and offers a modest survival benefit of approximately three months.[1, 2] Non-invasive ventilation (NIV) is currently the first line treatment for patients experiencing symptoms of respiratory insufficiency. A number of recent publications[5-11] have identified the probable benefit of NIV in advancing survival and improving quality of life in patients with ALS. In recent studies[5-7, 9, 11] of NIV, the median survival has ranged from 0.7 years to 1.5 years from intervention. Finally, in many of those same studies the median survival of patients, intolerant of NIV and thus receiving no intervention upon diagnosis of chronic hypoventilation, was much worse, at 0.4 years. While beneficial to ventilation, the literature[16, 43] suggests that NIV may have deconditioning effects on the diaphragm and subsequently increase dependence on NIV.

The combination of DPS with NIV provides a combination therapy for the respiratory neuromuscular system (with DPS) and with gas exchange for respiration (with NIV) and allows the patient more flexibility in amount of NIV use and perhaps even in the pressure settings required to promote greater tolerance. Finally, for patients that are intolerant of NIV or otherwise choose not to use NIV, DPS presents a treatment option where nothing else exists.

The risks of the surgical implementation are low, with a repeatable minimally invasive implantation and relatively few perioperative serious adverse effects. Beyond the perioperative period, the risks of device use are low, with no serious adverse device effects reported. Device use was well tolerated with nearly all discomfort from stimulation able to be resolved. Quality of life was maintained. Evidence of probable benefit includes a significant improvement in survival from diagnosis (by 16 months) and from the start of NIV (by 9 months) compared to standard-of-care NIV; a remarkable 100% 30-day survival rate of patients with simultaneous PEG and DPS compared to 30-day mortality expectations of 2% - 25% with continued long term improvement in survival; a 16 month survival from implant for patients with no other respiratory options that are intolerant or unable to use NIV; and statistically and clinically significant improvement in sleep.

Taking into account the probable risks and benefits of currently available devices or alternative forms of treatment (principally riluzole and NIV), in our view NeuRx Diaphragm Pacing System (DPS)™ meets the criteria for Humanitarian Device Exemption in ALS, i.e., that the probable benefit to health (principally delaying respiratory failure, MV, and death) from the use of the device outweighs the minimal risk of injury or illness from its use.

XII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Neurological Devices Advisory Panel Because it was determined that the preclinical and clinical issues raised by the HDE did not require panel review for the proposed indication.

XIII. CDRH DECISION

CDRH has determined that **,** based on the data submitted in the HDE**,** that the NeuRx DPS™, Diaphragm Pacing System will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on September 28, 2011.

XIV. APPROVAL SPECIFICATIONS

Directions for use: see physician's labeling.

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