SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Diaphragm Pacing System

Device Trade Name: NeuRx® Diaphragm Pacing System (NeuRx DPS®)

Device Procode: OIR

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200018

Date of FDA Notice of Approval: March 31, 2023

Priority Review: N/A

Breakthrough Device: N/A

II. INDICATIONS FOR USE

The NeuRx DPS® is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but who lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. For use only in patients 18 years of age or older.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the NeuRx Diaphragm Pacing System labeling.

V. DEVICE DESCRIPTION

The NeuRx Diaphragm Pacing System (NeuRx DPS®) is an intramuscular, percutaneous, motor point diaphragm stimulation system (Figure 1). The device intramuscular

electrodes are implanted using standard laparoscopic surgical techniques and are connected to a four-channel external pulse generator at a percutaneous exit site. The pulse generator provides a capacitively coupled, charge balanced, biphasic stimulation to each electrode with a common indifferent electrode that is placed subcutaneously. The pulse generator controls the charge delivered through clinician programmed parameters of pulse amplitude, pulse duration, pulse frequency, pulse ramp, inspiration time, and respiratory rate. The user connects the device and turns it on for use; no other controls are available or necessary for operation.

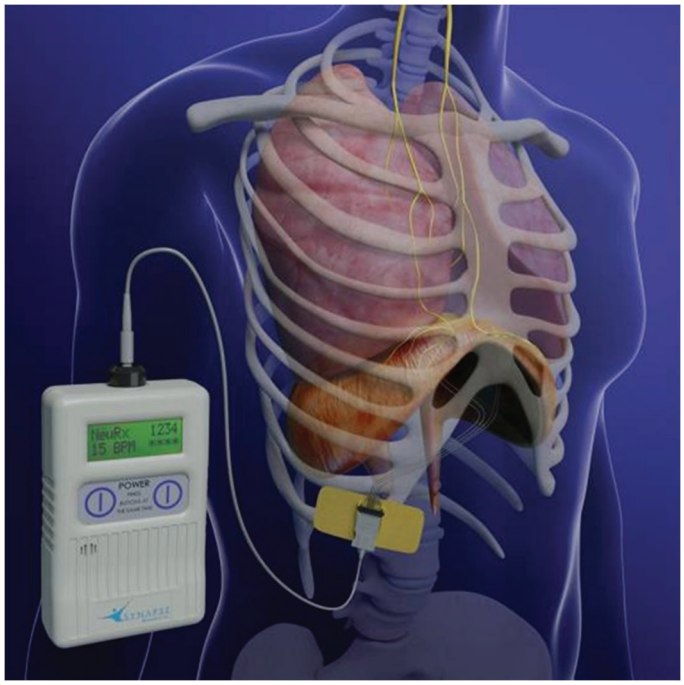

Figure 1: NeuRx DPS® System

The NeuRx DPS® System primary components include:

- Electrodes
  - Sterile PermaLoc Electrode
  - Sterile Indifferent Electrode
- External Components
  - External Pulse Generator
  - Patient Cable
  - Electrode connector, connector holder & strain relief boot
- Programmer and Accessories
  - Clinical station
  - Electrode delivery instrument, pressure sensor, pressure tube, cable set, surface anode, tunnelers, crimp tool, socket pusher, surface electrode and interconnect.

Device Operation

The NeuRx DPS® is a percutaneous, motor point, stimulation device that is implanted in the diaphragm during an outpatient laparoscopic procedure. The locations for implantation are identified by electrically mapping the inferior aspect of the diaphragm. Using the laparoscopic electrode delivery instrument, the PermaLoc intramuscular electrodes are surgically implanted in the diaphragm muscle in proximity to branches of the phrenic nerve without making contact or manipulating the nerve. The PermaLoc electrodes are tunneled, subcutaneously, to a percutaneous exit site on the lateral chest region. An indifferent return electrode (anode) is placed subcutaneously and exits at the same chest location. These electrodes are connected to an external pulse generator (EPG) (stimulator) that controls the timing and level of diaphragm pacing stimulation. Each electrode may be controlled individually in terms of charge (pulse duration and pulse amplitude) delivered and grouped together to recruit the diaphragm muscle to elicit the desired level of inspiratory effort.

Implantable Components

Stimulation is delivered to the phrenic nerve motor point through four intramuscular electrodes implanted into the diaphragm. Two electrodes are placed into each hemi-diaphragm at locations, found during surgical mapping, that elicit the greatest contraction of the diaphragm. This may be obtained by a single motor point, where the main trunk of the phrenic nerve enters the diaphragm, to produce a diffuse contraction or at two individual branches that recruit the anterior and posterior portions of the diaphragm. The electrodes are tunneled directly to the percutaneous exit site on the chest.

Intramuscular Electrode (PermaLoc® Electrode)

The PermaLoc intramuscular electrode is a double helix wound lead with exposed 316LVM stainless steel stimulating surface and polypropylene reinforced core. The PermaLoc also has a barb at the implanted end composed of 14 pieces of polypropylene suture fused together. The body of the lead is insulated with PFA (perfluoroalkoxy) fluoropolymer coating and terminated in a 316L stainless steel pin with a silicon reinforcing sleeve.

Indifferent Electrode (Anode)

The indifferent electrode provides a common return current path for all the electrodes implanted in the diaphragm. It is implanted in the subcutaneous tissue of the lateral chest region and is tunneled to the percutaneous exit site. The lead is fabricated of the same double helix wound 316LVM stainless steel as the intramuscular electrode and percutaneous extension lead.

External Components

NeuRx DPS® External Pulse Generator (EPG)

The patient external pulse generator (EPG) is an external four channel battery powered device that controls the stimulus output and respiratory timing. The four output channels are independently controlled, capacitively-coupled, biphasic outputs with a common return. The device is packaged in an impact resistant plastic enclosure with patient cable connector on the top, display, and power buttons on the front and replaceable battery compartment on the back. A programming connector is in the battery compartment for connection to the clinical station.

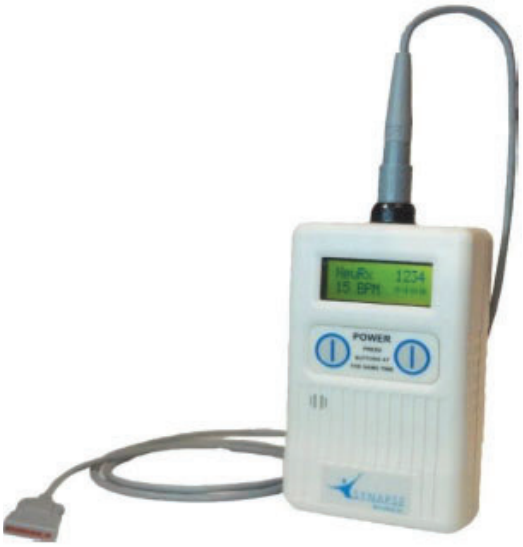

Figure 2: External Pulse Generator

The EPG has no controls that allow modification to any parameter settings. On-off power control consists of redundant switches that require actuation at the same time to provide protection from accidental actuation by incidental contact.

The device is powered from a user replaceable primary battery and a secondary rechargeable battery. The internal secondary battery recharges from the primary battery upon replacement. This configuration always allows a charged backup battery in the unit to allow sufficient time for the user to replace the primary battery. The display will indicate when the device is operating from the internal backup battery and provide an audio indicator when the internal backup battery reaches low charge remaining. A patient cable is provided that connects from the external pulse generator to the electrode connector socket. A disposable connector holder secures the electrode connector socket on the chest. The external portion of the electrode leads are protected at the connector by a strain-relief boot.

Surgical Instruments

Mapping Instrument

The initial step in the surgical implementation involves laparoscopic mapping of the diaphragm. This may be performed by introducing and connecting to an available laparoscopic dissector for stimulation or using the optional 5mm mapping instrument. Either instrument is used to stimulate the inferior surface of the diaphragm in a grid pattern to identify optimal implantation sites of the intramuscular electrodes. The connected laparoscopic dissector may be applied to sequential sites on the diaphragm by the surgeon and stimulated. Optionally, the mapping instrument may be applied to sequential sites on the diaphragm by the surgeon and secured by applying the operating room vacuum through the central lumen of the probe. Stimulation is applied in either a twitch or burst mode from the clinical station to elicit an abdominal pressure change.

Figure 3: Available Laparoscopic Dissector or Optional Mapping Probe

Transducer to Trocar Pressure Tube

A one-meter section of PVC tubing, with male Luer lock connectors on either end, is used to connect a Trocar port to the solid-state pressure sensor. The long length of the tube permits connection to the pressure sensor outside of the sterile field. The transducer to trocar pressure tube is packaged in Tyvek packaging and sterilized by ethylene oxide exposure.

Solid State Pressure Sensor

A differential, 1 PSI full scale, pressure sensor transduces the abdominal pressure changes to an electrical signal for the clinical station. It connects to the pressure tube with a female Luer lock and to the clinical station with a positive locking medical grade connector. The electrical signal provides an indication of relative pressure change.

Cable Set

A set of cables with touch-proof connectors are used to connect off the sterile field from the mapping instrument to the clinical station. A set of 3m meter cables connect to the mapping instrument or clip leads to test implanted electrodes. Another cable connects from the surface anode to the clinical station.

Surface Anode

The surface anode is an adhesive electrode that is placed on the skin during the intraoperative procedure. The anode is manufactured by Axelgaard and uses a proprietary hydrogel adhesive to adhere the surface anode to the skin.

Electrode Delivery Instrument

A single use, disposable laparoscopic electrode delivery instrument is used for implantation of the electrodes in the diaphragm. The barbed intramuscular electrode is loaded in the lumen of the instrument with the de-insulated barb extending out of the needle. The skirt of the polypropylene barb is loaded inside of the needle. When the needle is extended and inserted between the muscle fibers, parallel to the diaphragm surface, the de-insulated barb catches on the fibers and the lead is drawn out of the lumen as the instrument is withdrawn.

Tunnelers

The lead tunnelers are used intraoperatively to guide the electrode to the implantation site. They are thin-walled tubes of stainless steel (304SS). The material composition of the lead tunnelers is similar to the mapping probe cannula. The lead tunnelers are packaged in Tyvek packaging and sterilized by ethylene oxide exposure.

Clinical Station

The Clinical Station provides the following three primary aspects of the device implementation:

- intra-operative mapping functionality,
- incorporates NeuRx DPS® External Pulse Generator functionality, and
- NeuRx DPS® External Pulse Generator programming capability

Figure 4: Clinical Station

The Clinical Station provides intra-operative stimulation and sensing of stimulated response. This surgical mapping mode utilizes the surgical components listed above to provide twitch or burst stimulation to record and display the abdominal pressure response through the solid-state pressure sensor. A pulse generator mode is used to test the channels individually and in combination at the end of the surgery to make sure that all electrodes are intact and providing the anticipated response. The Clinical Station is also equipped with External Pulse Generator programming capability. The following parameters are adjustable by using the programmer:

Table 1: Stimulation Parameters

Parameter Description	Range	Resolution
ENABLE: Output Enable	Outputs 1 to 4	n/a
lc: Cathodic Current Amplitude	5 to 25 mA	1 mA
PW: Cathodic Current Pulsewidth	20 to 200 usec	10 usec
PER: Output Pulse Period	50 to 200 msec	1 msec
BPM: Breaths Per Minute	8 to 18	1
INSP: Inspiration Time	0.8 to 1.5 sec	0.1 sec
P_{MOD}: Pulse Modulation Count (First Pulsewidth = 20% PW)	0 to 10	1

The parameters listed below are programmable on a global output basis:

- Output Pulse Period (PER)
- Breaths Per Minute (BPM)
- Inspiration Time (INSP)
- Pulse Width Modulation Count (PMOD)

The following parameters are programmable on an individual output basis:

- Cathodic Current Amplitude (IC)
- Cathodic Current Pulsewidth (PW)
- Output Enable Control (ENABLE)

Clinician Crimp Tool

The electrode leads are terminated prior to installation into the connector socket block by using the Clinician Crimp Tool. The termination is of the electrode lead requires the crimping of a larger contact socket that is compatible with the connector socket block.

Socket Pusher

After the terminated electrode leads after terminated, the Socket Pusher is used to insert each terminated lead into the connector socket block

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of high spinal cord injury. The standard therapy for high spinal cord injured patients is mechanical ventilation via a tracheostomy. Other approved surgical and medical alternatives include Avery Laboratories Mark IV device, Non-Invasive Positive Pressure Ventilation (NIPPV), pneumobelt and Rocker beds. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

Mechanical ventilation via tracheostomy: These devices periodically force air, via positive pressure, directly into a patient's airway to inflate the lungs. Mechanical ventilation (MV) adversely effects quality of life and its use is associated with life-threatening complications including posterior lobe atelectasis, pneumonia, barotrauma and tracheomalacia. The associated issues with MV have led to the development of less invasive technologies to support respiration in SCI patients.

Avery Diaphragm Pacemaker System: An alternative to positive pressure mechanical ventilation, for a subset of patients, is the Avery Diaphragm Pacemaker System, also known as Avery Breathing Pacemaker. The original PMA (P860026) for the device was approved on the November 26: 1986 with indications for ventilatory support for treatment of central alveolar hypoventilation (CAH) and upper motor neuron respiratory muscle paralysis (RMP) (P860026) and whose remaining phrenic nerve, lung and diaphragm function are sufficient to accommodate electrical stimulation.

The Avery device is composed of four principal components: an external radio frequency (RF) transmitter, two external transmitter antenna coils, two RF receivers with a built-in coil and two nerve electrodes with insulated lead wires to connect the receiver to the electrode. Placement of each electrode is performed with meticulous dissection of the phrenic nerve in either the neck or thorax using an open thoracic procedure. The phrenic nerve is laid in the groove of the electrode and the electrode is sutured in place around the nerve. This is different from the Synapse device where the electrodes are implanted directly into the diaphragm muscle. The pacer operates on the principle of RF induction of energy and control through the intact skin. The transmitter and transmitting antenna are external to the body. The Synapse device is designed with a direct connection through a wire to the control mechanism. The Avery device uses an implanted RF receiver where none is required with the Synapse device.

Non-invasive positive pressure ventilation (NIPPV): Other alternatives to positive pressure mechanical ventilation consist of various forms of non-invasive ventilation. Non-invasive positive pressure ventilation (NIPPV) may be used for limited ventilatory support in some patients with spinal cord injury to provide periods of time off mechanical ventilation.

NIPPV is delivered as:

- continuous positive pressure ventilation (CPAP) or
- bilevel positive pressure ventilation (BiPAP) via a mask, nasal occlusion device, or tracheostomy adapter.

Other forms of non-invasive ventilation include the pneumobelt and rocking bed.

Pneumobelt: inflates and deflates a bladder wrapped around the patient's abdomen and lower chest. Inflation of the bladder forces the abdominal contents to rise, compressing the lung allowing expiration of gas; deflation of the bladder allows the abdominal contents to move downward and the lung to expand. This device is used in the sitting position.

Rocker beds: used in the supine position and rely on the shifting of abdominal contents by positional changes in the patient.

VII. MARKETING HISTORY

NeuRx DPS® has been approved for distribution in the U.S. under Humanitarian Device Exemptions (HDE) H070003 for a spinal cord injury (SCI) indication and HDE H100006 for an amyotrophic lateral sclerosis (ALS) indication. The device has been distributed in Europe to treat diaphragm dysfunction which includes patients with spinal cord injury (SCI), amyotrophic lateral sclerosis (ALS), and other forms of diaphragm dysfunction under EC certificate number 518356. The device is also approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. In addition, the device has been approved and distributed in Canada, Australia, Brazil, Israel, Middle East, Scandinavian countries, South Africa, Switzerland, South America, and North Africa. To date, over 2,000 NeuRx DPS® devices have been implanted world-wide. The NeuRx DPS® has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A list of potential adverse effects associated with the placement and use of the device are provided below:

Implant Procedure Related

- Capnothorax
- Pneumothorax
- Bleeding /Hemothorax
- Nerve, tissue, or organ damage

Device Related

- Adverse biocompatibility reaction to the electrodes / leads
- Infection
- Skin sensitivity due to adhesive
- Skin erosion from leads
- Lead breakage, internal or external
- Lead dislodgement

Therapy Related

- Airway obstruction
- Aspiration
- Cardiac interaction
- Crosstalk with another implanted device
- Diaphragm fatigue
- Pain or discomfort due to stimulation
- Insufficient stimulation

Other Procedure, System or Therapy Related

- Autonomic dysreflexia
- Death
- Spasms

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The NeuRx DPS® System testing shown in Table 2 demonstrated compliance with specification requirements and performance. Evaluations of functional performance, EMC, environmental and mechanical robustness, electrical safety, and international standards compliance confirmed that the NeuRx DPS® System is acceptable for human use.

Table 2: Performance Testing

Test Name	Purpose	Result
Mechanical Random Vibration Test	To simulate a mechanical shock environment the NeuRx DPS EPG would be exposed to during typical use when tested per the requirements of IEC 60068-2-64:2008 Broad-Band Random Vibration 10-2,000Hz @ 30 minutes per axis	PASS

Test Name	Purpose	Result
Mechanical Impact Test	To simulate a mechanical impact environment the NeuRx DPS EPG would be exposed to during typical use when tested to the requirements of IEC 60601-1:2012 by conducting an impact test with a 50mm diameter steel ball weighing 500g falling from 1.3meters	PASS
Environmental - Cold Transport and Storage	To simulate temperature extremes the NeuRx DPS EPG would be exposed to during typical transport and or storage when tested per the requirements of IEC 60601-1 General Safety requirements at -20C for 6 hours minimum and 55C for 6 hours minimum	PASS
Battery Testing - Overload of battery at fuse rating	To mitigate the risk of a battery external short circuit, the NeuRx DPS EPG maximum surface temperatures were tested during an overloading event of the battery by operating at 110% of the maximum rated voltage per IEC 60601-1:2012 General Safety requirements	PASS
Battery Testing - Unintentional reverse charging	To mitigate the risk of a battery external short circuit, the NeuRx DPS EPG maximum surface temperatures were tested during potential reverse charging of battery per IEC 60601-1:2012 General Safety requirements for single fault conditions	PASS
Battery Life Testing - Battery life data	To verify NeuRx DPS EPG battery life meets expected user requirements and design specifications	PASS
Battery Testing (Primary Lithium) - Thermal abuse (cells) and short circuit	To mitigate the risk of NeuRx DPS EPG primary lithium-metal battery cells internal short circuit, certification from the manufacture to be compliant with IEC 60601-1:2012 General Safety requirements and specifically IEC 60086-4 Primary batteries - Safety of Lithium Batteries requirements has been obtained	PASS
Battery Testing (Secondary) - Thermal abuse (cells) and forced internal short	To mitigate the risk of NeuRx DPS EPG secondary lithium-ion battery cells internal short circuit, certification from the manufacture to be compliant with IEC 62133 has been obtained	PASS

Software:

The Software Level of Concern (LOC) is identified as MAJOR. Software documentation was provided in accordance with the Agency "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" Guidance document. Certain elements of the analysis were derived from the Agency recognized software standards IEC 62304:2006+A1:2015: Medical device software – Software life cycle processes.

The Sponsor has performed the following software V&V activities:

- Code Review – Examples of functions reviewed: Variable Allocation, Look-up tables (period and pulse modulation), Initialize Waveform Generator Shutdown, Display Breaths Per Minute, Message Process, Interrupt Service Routine, etc.
- Software Unit Testing - The code for the software units was verified through white box testing using the software development environment known as MPLAB IDE. Preconditions or pre-requirements for testing were also verified.
- Software Integration Testing - Evaluated that all software units, hardware items, and user interfaces, were properly integrated into the software system. Testing results successfully met the predefined specifications.

- Validation Testing - The system conforms to user needs and intended use.

An evaluation of alarms Alarm testing test Report was performed in accordance with IEC 60601-1-8 during software verification and validation in accordance with the Software Integration Test Procedure. The EPG has temporal audio alarm patterns for high, medium, and low priority error conditions. The alarm harmonics were established based on the specific requirements of the IEC 60601-1-8 standard for a variety of use environments which includes the EPG environment (home and professional healthcare).

The Sponsor has verified that the NeuRx DPS® System Cybersecurity Assessment was conducted in accordance with the current FDA guidance and draft guidance documents, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" regarding cybersecurity in medical devices.

EMC:

The sponsor provided detailed descriptions of the essential performance and the pass/fail criteria of the immunity testing performed. EMC testing was performed and passed for the NeuRx DPS® System including EPG and Clinical Station.

Essential Performance

Clinical Station

- Delivery of stimulation to the cable set (surgical) per the test evaluation parameters and verified by:
- LCD displayed stimulus parameters remain unchanged during continuous operation.
- Stimulus output is evident on LCD display with electrode continuity or test plug.
- Monitoring of stimulus waveforms using test-load resistors.

EPG

- Delivery of stimulation to the Patient Cable per the test evaluation parameters and verified by:
- Stimulus data array parameters remain unchanged during continuous operation when no changes are received from the Clinical Station.
- Stimulus output is evident on display with electrode continuity or test plug.
- Monitoring of stimulus waveforms using test-load resistors.

The essential performance of the device and the acceptance range of device operation are reasonable.

The device configuration and pass/fail criteria for the EMC immunity testing performed are listed below:

IMMUNITY PASS/FAIL CRITERIA (Per Synapse Biomedical Inc.)

Clinical Station

Delivery of stimulation to the cable set (surgical) per the test evaluation parameters and verified by:

- LCD displayed stimulus parameters remain unchanged during continuous operation.
- Stimulus output is evident on LCD display with electrode continuity or test plug
- Monitoring of stimulus waveforms using fixed test-load resistors.

EPG

Delivery of stimulation to the Patient cable per the test evaluation parameters and verified by:

- Stimulus data array parameters remain unchanged during continuous operation when no changes are received from the Clinical Station.
  - Stimulus output is evident on display with electrode continuity or test plug.
  - Monitoring of stimulus waveforms using fixed test-load resistors

Table 3: Stimulus parameters

	Range	Test Value	Tolerance
I_C: Cathodic Current Amplitude	5 to 25 mA	25 mA	+/-1 mA
PW: Cathodic Current Pulsewidth	20 to 200 usec	100 usec	+/-5 usec
PER: Output Pulse Period	20 to 250 msec	50 msec	+/-5 msec
BPM: Breaths per Minute	8 to 18	12 (5.0 sec)	+/-100 msec
INSP: Inspiration Interval (Time)	0.8 to 1.5 sec	1.1 sec	+/-50 msec
P_{MOD}: Pulse Modulation Count	0 to 10	10	Discrete Values

The device operation in the commercial aircraft environment has been verified with EMC immunity testing per RTCA DO-160 as category R.

Applicable Standards:

- AIM 7351731 – Medical Electrical Equipment and System Electromagnetic Immunity Test for Exposure to Radio Frequency Identification Readers
- FDA Guidance – Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices

- FDA Guidance – Immunity to exposure to known sources of EMI: Electrosurgical devices, Electrocautery devices, diathermy, and electromagnetic security systems (e.g., metal detectors and Electronic Article Surveillance system (EAS or anti-theft).

Table 4: EMI Test

EMI Source	Test Level	Results	Anomalies/Degradations
Diathermy (1.7 MHz to 2.3 MHz)	50 V/m	Pass	None
Electronic Article Surveillance (7.7 MHz to 8.7 MHz)	40 V/m	Pass	None
Electrosurgical Cut (1.7 MHz)	500 V/m Pulsed	Pass	None
Electrosurgical Coagulate (1.7 MHz)	400 V/m Pulsed	Pass	None
X-ray (30kHz)	10 V/m	Pass	None

Appropriate test levels specified for the home environment were utilized for the EPG and provided the following setting and the acceptance criteria.

Table 5: Test acceptance parameter values

Parameter	Value	Acceptance
Breaths per minute	15	+/- 0.1 sec
Inspiration Interval	1.2 Sec	+/- 50 msec
Pulse Frequency	20 Hz	+/- 5 msec
Pulse Amplitudes (Outputs 1 to 4)	20 mA	+/- 1 mA
Pulse Widths (Outputs 1 to 4)	100 usec	+/-5 usec
All Outputs	Active	Yes
Impedance Display	*	*

A. Laboratory Studies

The NeuRx DPS® includes several device components with patient-contact: 1) PermaLoc Electrode, 2) Indifferent Electrode, 3) Connector Holder, 4) Patient Cable, 5) Surface Anode, 6) Mapping Probe, 7) Electrode Delivery Instrument, and 8) Lead Tunneler Set. Device materials and categorization was carried out according to ISO 10993-1 and Table A.1 of the FDA's Biocompatibility Guidance document According to "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'".

Table 6: Patient-Contacting Device Components

Component	Body Contact	Material	Duration
Indifferent and PermaLoc Electrodes			
Insulated electrode wire	implanted	316LVM stainless steel & Perfluoroalkoxy fluoropolymer (PFA)	Long-term
Anchoring suture		Polypropylene	
Reinforcing sleeve		NuSil MED-4750 silicone rubber	
Adhesive		NuSil MED-2000 silicone adhesive	
Connector Holder			
Spun lace tape	Surface	MED5322 ● spunlace polyester cloth ● acrylic pressure-sensitive adhesive ● paper backing	Long-term
Patient cable			
Cable cover	Surface	C6-265 Silicone	Long-term
Surgical Components Surface Anode			
Cloth top neurostimulation rectangular electrode	Surface	Proprietary hydrogel	Limited
Surgical Components Mapping probe			
Cannula (6 G)	Externally Communicating	304SS	Limited
Ferrule (16 G)		304SS	
Silicone Tubing		NuSil MED-4750 silicone rubber	
Heat shrink Tubing		3527 polyolefin (PO) acrylate	
PVC Tubing		Clearflo® Tygon® polyvinyl chloride (PVC)	
Mapping probe tip (10 G)		304SS	
PFA Insulated Wire		316LVM stainless steel & Perfluoroalkoxy fluoropolymer (PFA)	
Electrode delivery instrument			
Tube tip w/main	Externally Communicating	304SS	Limited
Rack, actuator		303SS	
Needle (16 G)		304SS	
Chromium coating		MEDCOAT 2000™	
Lead Tunneler Set			
Lead tunneler (15 G)	Externally Communicating	15 GA 304SS	Limited

The PermaLoc Electrode and Indifferent Electrode are implant devices in contact with tissue for long-term contact duration (>30 days). Biocompatibility testing on the

final finished PermaLoc Electrode was performed and biocompatibility test reports for the PermaLoc electrode, included cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, material-mediated pyrogenicity, muscle implantation (30 day and 26 week), and genotoxicity (bacterial reverse mutation assay and in vitro mouse lymphoma assay) following the appropriate standards and the results support that the device is non-sensitizing, non-irritating, and non-toxic (acute).

Biocompatibility testing, including Cytotoxicity testing with MEM elution, was performed on the Connector Holder in its final form. A review of the Connector Holder categorization per ISO 10993-1:2018 determined the component to be long-term (>30 days) surface contact on intact skin. Test results support that the device is non-cytotoxic, non-sensitizing, and non-irritating.

The Disposable Electrode Delivery Tool is categorized as an Externally Communicating Device which contacts tissue/bone for a limited duration (< 24 hours).

Patient Cable categorization per ISO 10993-1:2018 determined the component to be long-term (>30 days) surface contact on intact skin. results support that the device is non-cytotoxic, non-sensitizing, and non-irritating.

The Mapping Probe is an external communicating device in contact with tissue for limited contact duration (<24 h). The biocompatibility testing provided on the Mapping Probe is adequate to support that the device is non-cytotoxic, non-sensitizing, non-irritating, non-pyrogenic, and non-toxic (acute).

The Lead Tunneler is an external communicating device in contact with tissue for limited contact duration (<24 h). The biocompatibility data is leveraged from the Mapping Probe for the Lead Tunneler and deemed acceptable based on the same materials/manufacturing and patient contact.

The sponsor has leveraged biocompatibility for the Surface Electrodes of the NeuRx DPS® proposed for the IDE as they are identical to a U.S. marketed device (ValuTrode® Neurostimulation Electrodes, K970426 and K130987, Axelgaard Manufacturing Co, Ltd.) with the same type and duration of patient contact.

Standards Followed for Component Testing for Biocompatibility:

ISO 10993-1 and Table A.1 of the FDA guidance "Use of International Standard, ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'",

NeuRx RA/4 Diaphragm Pacing System Peterson-Type Electrodes and Leads, NeuRx RA/4 Diaphragm Pacing System Mapping Probe, Electrode Delivery Instrument (MEDCOAT 2000) -ISO 10993-5:2009, "Biological evaluation of

medical devices — Part 5: Tests for in vitro cytotoxicity”- Cytotoxicity MEM Elution

NeuRx RA/4 Diaphragm Pacing System Peterson-Type Electrodes and Leads, “NeuRx RA/4 Diaphragm Pacing System Mapping Probe”, patient Cable, Electrode Delivery Instrument (MEDCOAT 2000) - ISO 10993-10 2002. Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization- Guinea Pig Maximization test

NeuRx RA/4 Diaphragm Pacing System Peterson-Type Electrodes and Leads, “NeuRx RA/4 Diaphragm Pacing System Mapping Probe, Electrode Delivery Instrument (MEDCOAT 2000) -” ISO 10993-10 2002. Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization Intracutaneous Reactivity in rabbits

NeuRx RA/4 Diaphragm Pacing System Peterson-Type Electrodes and Leads”: ISO 10993-11 “Biological evaluation of medical devices – Part 11: Tests for systemic toxicity”,

NeuRx RA/4 Diaphragm Pacing System Mapping Probe, Electrode Delivery Instrument (MEDCOAT 2000)- Acute Systemic Toxicity

ISO 10993-11:2017Biological evaluation of medical devices — Part 11: Tests for systemic toxicity

NeuRx RA/4 Diaphragm Pacing System Peterson-Type Electrodes and Leads, NeuRx RA/4 Diaphragm Pacing System Mapping Probe, Electrode Delivery Instrument (MEDCOAT 2000):” ISO 10993-11:1993 “Material-Mediated Pyrogenicity”-Rabbit Pyrogen Test (Material-Mediated)

NeuRx RA/4 Diaphragm Pacing System Peterson-Type Electrodes and Leads “SO 10993-6: 1994 “Implantation”-Intramuscular Implantation in Rabbits– 30 days and 26 weeks

NeuRx RA/4 Diaphragm Pacing System Peterson-Type Electrodes and Leads:

ISO 10993-3:2003 “Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity”- Bacterial Reverse Mutation- Bacterial Mutagenicity Test (Ames) Assay

Sterile PermaLoc Electrode:

ISO 10993-3:2003 “Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity”- Bacterial Reverse Mutation- In Vitro Mouse Lymphoma Assay

Genotoxicity testing in accordance with ISO 10993-3:2014 and ISO/TR 10993-33:2015 has been conducted and included two in vitro assays, one in bacterial cells (Ames) and one in mammalian cells (MLA). It should be noted that genotoxicity potential as determined from biological testing of device extracts may not be leveraged to waive the need to demonstrate acceptable genotoxicity risk of extractables identified by exhaustive chemical characterization analyses (conducted in accordance with ISO 10993-18) to be potential leachables that may be released from the subject implant device under worst case clinical use conditions.

The Sponsor's toxicological risk assessment of NeuRX Diaphragm Pacing System may support acceptable toxicological risk of exposure to potential device leachables that may be released from the subject device during its intended use under worst-case clinical-use conditions provided chemical characterization did not underestimate exposure (as determined by the chemical characterization review).

Table 7: NeuRx DPS® Biocompatibility 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.

B. Animal Studies

Pre-clinical animal testing of the NeuRx device was performed to support IDE approval (G920162). Proof of Concept, assessment of tissue encapsulation and surgical procedure testing was conducted as noted in Table 8. These pre-clinical studies followed standard university research laboratory protocols accepted by a peer review panel of the Case Western Reserve University School of Medicine.

Table 8: NeuRx DPS® Pre-Clinical Animal Testing

Purpose	Animal	Number	Results
Demonstration that this procedure could produce the same maximum tidal volumes as phrenic nerve cuff electrodes	Dogs	7 dogs, 32 intramuscular electrodes	The tidal volume induced 167% of the ventilation required for basal metabolic needs without fatiguing the diaphragm.
To study the nature of tissue encapsulation surrounding the implanted electrode	Rats	4 electrodes in each Rat. 3 rats to a group	No encapsulation of the implanted electrode was observed.
Test new vacuum probing device	Dogs	2 dogs, device placed in multiple diaphragmatic locations for 1 to 5 minutes	Exposure damage at 5 minutes is minimal and limited to area of application.

C. Additional Studies

Electrical:

- Classification information against electric shock is provided as the Stimulation Module is classified as internally powered and Clinical Station as Class II.
- The Clinical Station is disabled and can't be used on the patient when it is connected to the live power for battery charging.
- Applied parts of this device are classified as BF.
- Subject device water leak protection has been evaluated. The Clinical Station is rated IP20 (no ingress protection), and Pulse Generator is rated IPX4 per the IEC 60601-1 test report and IP24 per IEC 60601-1-11.
- Stimulation Module intended to operate in home environment. IEC60601-1-11 test report

Compliance with basic electrical safety required by IEC 60601-1-11 (Stimulation Module only):

Sufficient information is provided to demonstrate that the subject Pulse Generator Module meets the electrical safety related requirements for home use collateral standard.

For the electrical safety in home use environment, manufacturer has provided test report showing that the subject pulse generator meets following IEC 60601-1-11 clauses.

Table 9: Essential Performance

List of ESSENTIAL PERFORMANCE functions	MANUFACTURER'S document number reference or reference from this standard or collateral or particular standard(s)	Remarks
Stimulus data array parameters remain unchanged	Within NeuRx DPS® Risk Management Plan 20-0000-6.1 Rev 10 there is a section titled "Essential Performance". The Essential Performance items are evaluated in the NeuRx DPS® Risk Management Detail 20-0000-05 Rev A19.	P
Stimulus output is evident on display with electrode continuity or test plug.		P
Delivery of stimulation to the Patient cable at the stimulus data array settings.		P
Parameter Data Ranges for the NeuRx External Pulse Generator		P
Supplementary Information: ESSENTIAL PERFORMANCE is performance, the absence or degradation of which, would result in an unacceptable risk.		

Battery safety summary:

The subject stimulator utilizing two alkaline primary and two lithium-ion rechargeable batteries. The alkaline batteries are the main power source for the Stimulation Module. They are rated to provide proximately 96 hours of power to this module. Rechargeable lithium-ion batteries are serving as backup power source and can provide power to this module for approximately 8 hours for device normal operation. These batteries connecting to the device power input when the primary batteries fail to provide powered to the device. Lithium-ion batteries are charged from primary alkaline batteries. The surface temperature of Tadiran battery has been measured under its maximum discharge load (i.e., loaded with 300 Ω resistor).

Stimulation module battery safety:

The risk of battery premature failure is mitigated by backup batteries, visual and audio alarm

- Lithium-ion battery pack that is utilized with the stimulation module, includes overcharge, over discharge and over current protection circuit. The manufacturer claims that this battery follows IEC62133. The compliance with this standard and the imbedded battery pack safety circuit, provides adequate means to prevent internal short circuit.

- IEC60601-1 test report includes information demonstrating adequate venting for alkaline batteries.
- Information is provided to demonstrate that the reverse charge of nonchargeable batteries is mitigated by design.
- Switch polarity of Primary Battery and Short circuit of rechargeable battery has been tested per the requirements of IEC60601-1:2005 MOD.

Documentation provided supports subject device's compliance with applicable electrical safety sections of IEC60601-1:2005 MOD. In addition, risk hazard analysis provided demonstrates that the hazards risk associated with the device essential performance are adequately mitigated per ISO 14971.The rechargeable battery in compliance with both IEC 60086-4 and IEC62133.

Sterilization/Shelf Life and Packaging:

Table 10: Shelf Life and Packaging:

Test	Acceptance Criteria	Results	Analysis Type
Sterilization			
One year Aging Study-Packaging	No Test Method Acceptance Criteria-Sponsor specified: sponsor seal must withhold a minimum of 1.0 pounds of pressure.	Passed	From 3 boxes (60 samples), a one-inch segment of the seal was cut to connect sufficient material on each side of the seal to the instrument. Standard Method Based On: ASTM: F1980 and ISO 11607
X-Ray Energy Dispersion Spectroscopy (EDS) from samples in Scanning Electron Microscope (SEM)	None Stated	debris materials from the package snap and the shaft to the base package film. white residues identified as PET polyester.	2 test articles disposable medical tool in blister package; tested per ASTM E1252-98(13)e1
Transportation and Distribution Tests	No test method acceptance criteria	Passed	test articles (10 boxes) were dropped from a Longmont PDT80 drop tester. Per ASTM D4169 (DC13 Assurance Level II) distribution cycle.

The implantable portions of the device are sterilized by ethylene oxide (EO). The EO Sterilization process was revalidated most frequently in 2018 and has not been altered, although additional electrodes have been added using product adoption evaluation and procedures. Sterility met the assurance level of 10^{-6} and all sterilized components were demonstrated to have a useful shelf life of two years from the date of sterilization. The Shelf life, 2 years, for the EO sterilized products (all use the same sterile barrier system) was initially validated based on accelerated aging of

product; shelf life was confirmed in 2010 with the results of testing after real time aging of packaged product. The EO sterilization validation, revalidation, and shelf life/packaging validation for the electrodes and other components that are provided sterile was provided and is acceptable.

The single patient use, disposable instrument is provided sterile to the hospital (gamma sterilization) and has a useful shelf life of one year from the date of sterilization. The VDmax method was selected for determining the the average bioburden of the device and sterilization dose for this disposable device. This method requires determination of which was performed. The sterility assurance level (SAL) established was 10-6. Documentation supporting the sterilization validation of the single-patient use electrode delivery system was provided and is acceptable.

PermaLocThese electrodes are provided sterile and single use only.

Visual inspection for debris at 1X and at 10X magnification of all packages on hand was performed and noted no dislodgement or debris. Additional ASTM 4169 distribution and transportation testing on 30 device packages in the 2-pack boxes is has been performed.

Human Factors:

All applicable standards including guidance, Applying Human Factors and Usability Engineering to Medical Devices documents were taken into consideration when developing the Synapse Human Factors and Usability Engineering process. Regarding the Agency's 2016 guidance, Applying Human Factors. The Human Factors and Usability Engineering processes used a Formative and Summative evaluation with 4 user test groups with 15 participants in each test group. The survey results are summarized in the following tables.

Table 11: Usability Tasks

USER GROUPS	Surgeons (15)	Surgical Nurses (15)	Technicians (15)	Caregivers (15)	Totals (60)
Formative Evaluation	180 tasks	105 tasks	330 tasks	195 tasks	810 tasks
Summative Evaluation	150 tasks	45 tasks	375 tasks	255 tasks	825 tasks
Totals	330 tasks	150 tasks	705 tasks	450 tasks	1,635 tasks

Table 12: Usability Response

USER GROUPS	Surgeons (15)	Surgical Nurses (15)	Technicians (15)	Caregivers (15)	Totals (60)

Response	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Formative Evaluation	169	8	3	94	9	2	326	4	0	189	5	1	778	26	6
Summative Evaluation	141	4	5	42	2	0	370	5	0	254	1	0	807	13	5
Totals	310	12	8	136	11	2	696	9	0	443	6	1	1,585	39	11

Note: A-Acceptable B-Acceptable with feedback C-Could be Improved

In addition, the alarm harmonics for the EPG comply based with the specific requirements of the IEC 60601-1-8 standard for a variety of use environments which includes the EPG environment (home and professional healthcare). The EPG alarms were compliant to this standard as evidenced by the validation report, results analysis, and test report.

Based on these real-world observations of task performance and occurrences of use errors, close calls, and use problems including the feedback from interviews with test participants regarding device use, critical tasks, use errors, and problems, it was determined that the device is safe and effective for the intended users, uses and use environments. All USE associated residual risk hazards have an acceptable risk rating and acceptable mitigations to make the device to be safe and effective for the intended users, uses and use environments.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Summary IDE G920162 and data from patients implanted with the NeuRx device after HDE approval.

The applicant performed a one-armed pivotal clinical study to establish a reasonable assurance of safety and effectiveness of NeuRx DPS® implanted via a laparoscopic surgical procedure. The NeuRx Diaphragm Pacing System is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but who lack control of their diaphragms (G920162). The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. It is indicated for use only in patients 18 years of age or older in the US.

This clinical study summary describes data collected in IDE G920162 as well as data from patients implanted with the NeuRx device after HDE approval.

To support this PMA, the sponsor presents the data analysis of 3 cohorts:

1. The primary cohort of 53 patients in the IDE trial (G920162)

2. A 106-patient cohort– comprised of 53 patients from the primary cohort pooled with 53 HDE patients in the secondary cohort (Onders et. al where the total n= 92, 39 of which were included in the IDE primary cohort)
3. A 196-patient cohort – 106 pooled patients plus 90 patients from 3 tertiary studies (the tertiary cohorts are comprised of additional HDE patients (n=40, n=31 and n=29).

These 5 groups of patients comprise the clinical population used in the statistical analyses for this PMA. Of note, the clinical protocol notes that "p-values are provided for comparative purposes only, to update the original study report results, and not for labeling purposes per the Statistical Analysis Plan".

Effectiveness Data:

Primary Endpoint

Proportion of patients not requiring MV 4hrs/day. FDA agreed that this is a clinically meaningful endpoint. The performance goal was 45% and was based on the efficacy results of the Avery diaphragm pacing system.

Cohort 1

Table 13: Primary Endpoint, Primary Analysis Cohort (n=53)

Event	% (n/N)	95% confidence interval	p-value*
Primary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day)	96.2% (51/53)	(87.0%, 99.5%)	<0.001

* Exact two-sided binomial test against performance goal of 45% (0.45)

The survival endpoint of the primary cohort was not identified as feasible to be analyzed in the original one-year follow-up at the time of the study. The survival analysis was added based on the follow-up at the time of Onders et al. 2018 publication, which was 18 years after the first patient was implanted in the primary analysis cohort. Thus, survival also appears to be improved with DPS although this was not a pre-specified endpoint.

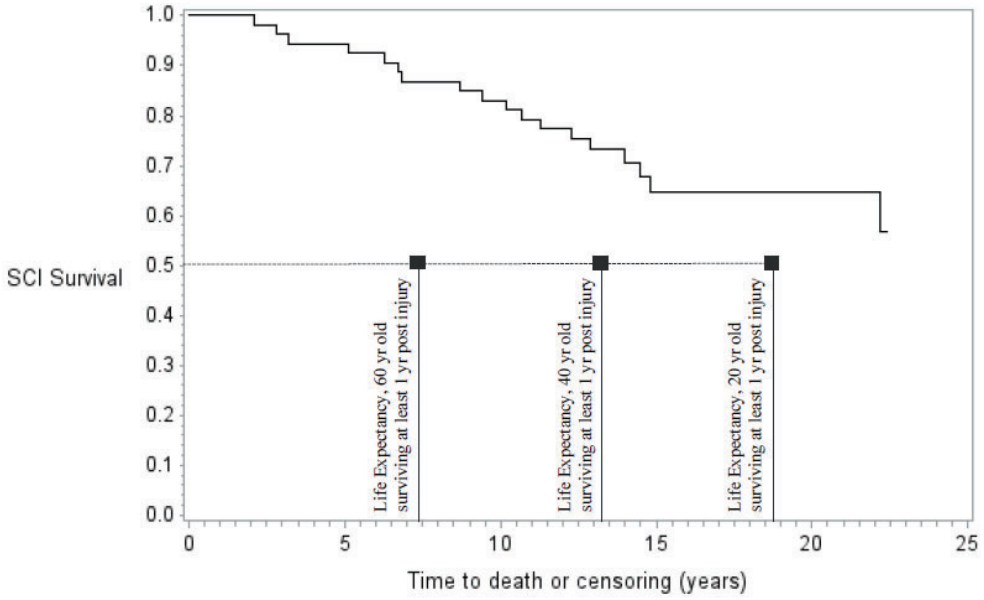

Figure 5: SCI Survival (years since injury for Primary Analysis Cohort n=53)

Cohort 2

Table 14: Primary Endpoint, Secondary Analysis Cohort (n=106)

Event	%(n/N)	95% confidence interval	p-value*
Primary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day)	89.6% (95/106)	(82.2%, 94.7%)	<0.001

* Exact two-sided binomial test against performance goal of 45% (0.45)

Cohort 3

Table 15: Primary Endpoint, Secondary Analysis Cohort(n=196)

Event	%(n/N)	95% confidence interval	p-value
Primary endpoint (Proportion of subjects using the NeuRx DPS® without the assistance of a mechanical ventilator 24 hours a day)	92.2%	82.6%, 96.7	<0.001

Secondary Endpoint = Tidal Volume in Chronic Use

Cohort 1

Table 16: Tidal Volume All Subjects

Characteristic	Mean ± SD (N) [Median] (IOR)	p-value (Vt vs basal requirements)

Basal requirement	**524.3 ± 146.1 (53) [518.01] (441.0,637.0)**	
Stimulated Vt	**745.6 + 217.7 (53) [700.0] (605.0,865.0)**	
Percentage of tidal volume over basal requirements (PTOVB)	**48.4 ±41.5 (53) [51.51] (26.1,68.1)**	**<0.001**

Cohort 2 = N/A

Cohort 3 = N/A

Secondary Endpoint = Use of NeuRx DPS® without MV 24hrs/day

An objective of the NeuRx therapy is to replace mechanical ventilation for patients on a chronic use basis; a surrogate secondary indicator of this objective is tidal volume (Vt) during chronic stimulation. Standard of care for ventilated patients indicates that the basal Vt requirements for an adult male are typically 7ml / kg of body weight and 6ml / kg for adult females. Due to ventilator circuit dead space, tracheotomy leakage, and duration/volume of speech concerns, spinal cord patients are typically mechanically ventilated at much higher settings than their basal Vt requirements.

The tables below display basal requirements, stimulated Vt, and the computed percentage of tidal volume over basal requirements (PTOVB) along with a hypothesis test against μ (PTOVB)=0 as provided in the original IDE Pivotal Study report; data are analyzed from the primary analysis cohort only (the IDE Pivotal Study) as this is the only source providing tidal volume data (Table 17). p-values are provided for comparative purposes only, to update the original study report results, and not for labeling purposes per the Statistical Analysis Plan.

Cohort 1

Table 17: Tidal Volume All Subjects

Characteristic	Mean ± SD (N) [Median] (IQR)	p-value (Vt vs basal requirements)
Basal requirement	524.3 ± 146.1 (53) [518.0] (441.0,637.0)	
Stimulated Vt	745.6 ± 217.7 (53) [700.0] (605.0.865.5.0)	
Percentage of tidal volume over basal requirements (PTOVB)	48.4 ± 41.5 (53) [51.5] (26.1,68.1)	<0.001

Further analysis by gender, an also performed in the pm or IDE Pivotal Study report, shown sufficient PTQYB performance in both males (Table 18) md females (Table 19).

Table 18: Tidal Volume Males

Characteristic	Mean ± SD (N) [Median] (IOR)	p-value (Vt vs. basal requirements)
Basal requirement	575.4 ± 119.1 (41) [556.0] (476.0,058.0)	
Stimulated Vt	793.9 ± 219.4 (41) [800.0] (660.0,900.0)	
Percentage of tidal volume over basal requirements (PTOVB)	42.0 ± 41.5 (41) [47.5] (11.8,61 9]	<0.001

Table 19: Tidal Volume Females

Characteristic	Mean ± SD (N) [Median] (IOR)	p-value (Vt vs basal requirements)
Basal requirement	349.8 ± 80.2 (12) [336.0] (300.0,373.5)	
Stimulated Vt	580.4 ± 102.5(12) [602.5] (507.5,650.0)	
Percentage of tidal volume over basal requirements (PTOVB)	70.1 ± 35.2 (12) [65.5] (47.1,84.7)	<0.001

Use of NeuRx DPS® to breathe without the assistance of a mechanical ventilator for 24 continuous hours a day

As with the primary endpoint, the primary analysis cohort for this secondary endpoint is defined to be data collected from the Primary Study, for which 58.5% (31/53) of subjects achieved at least 24 hours daily use (Table 20). A two-sided 95% confidence interval is provided for descriptive purposes, but no formal statistical test is conducted, in keeping with the Statistical Analysis Plan. Ultimately, this represents full independence from mechanical ventilation and ability to support natural negative pressure respiration for the 58.5% of patients that have reached this endpoint.

Table 20: 24 hour/daily use - Primary Analysis Cohort (n=53)

Event	%(n/N)	95% confidence interval
Secondary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator 24 hours a day)	58.5% (31/53)	(44.1%,74.9%)

Cohort 2

Table 21: Secondary Endpoint (24 hr/daily use), Secondary Analysis Cohort (n=106)

Event	%(n/N)	95% confidence interval
Secondary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator 24 hours a day)	56.6% (60/106)	(46.6%, 66.2%)

Cohort 3

Table 22: Secondary Endpoint (24hr/daily use), Secondary Analysis Cohort (n=196)

Event	%(n/N)	95% confidence interval
Secondary endpoint (Proportion of subjects using the NeuRx DPS® without the assistance of a mechanical ventilator 24 hours a day)	52.7%	(36.2, 68.6)

Safety Endpoints:

In no case was the patient required to return to the operating room for device repair. In the IDE Pivotal Trial, none of the commonly tracked peri-operative complications, including venous thrombosis, pulmonary embolus, wound infections, and pulmonary infections were reported. The most common peri-operative adverse event was a capnothorax, which is a common side- effect of laparoscopic surgery, was tracked and involved 21 out of 54 patients (39%).

In the IDE Pivotal Trial there were no perioperative deaths.

This device met the predefined primary endpoint by allow 90% of patients to breath without a ventilator for at least four hours per day. A secondary endpoint of breathing without a ventilator for 24 h per day was achieved in 50% - 60% of subjects.

A. Study Design

IDE Pivotal Study– G920162

The Pivotal Study of the NeuRx DPS® system was conducted at 5 investigational sites as a prospective, non-randomized, multi-center study to demonstrate the safety and effectiveness of the NeuRx device utilizing a patient as their own control. Patients were implanted between March 2000 and March 2008.

The primary effectiveness endpoint was defined as use of the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. It was reported that 96.2% (51/53) of patients achieved at least 4 continuous hours daily use compared to the performance goal (PG) of 45% ($p<0.001$). In addition, it is found that 58% of subjects achieved at least 24 hours daily use.

Safety: There was no specific safety hypothesis, but the sponsor provided a detailed summary of all adverse events (AEs). The sponsor claimed that safety of the NeuRx device was comparable to patients on mechanical ventilation with no apparent increase due to the device. Survival rates of patients using the NeuRx device were at least comparable if not better than patients on mechanical ventilation.

The clinical study data was collected and analyzed per the protocol. The clinical data were collected on the final design of the device except changes enumerated in Supplements since approval of H070003. The study population selected matches the device IFU and the endpoints are clinically relevant.

According to the study results described in this PMA (P200018), there is strong evidence that the NeuRx device can benefit SCI patients in terms of breathing without the assistance of a mechanical ventilator for at least 4 continuous hours a day.

Data Safety Monitoring

A Data and Safety Monitoring Board consisting of a pulmonologist, spinal cord rehabilitative specialist and surgeon was formed to regularly review study progress and adjudicate adverse events. Members of the DSMB were not employees or major shareholders of Synapse, Inc. and did not participate as investigators. The committee's purposes were to review and classify all serious adverse events including death occurring in treated patients, to determine if the rate of adverse events was acceptable, to evaluate data analysis results, and to provide related advice to Synapse, Inc., on study management and progress. Meetings were held on a basis determined appropriate for this study.

1. Clinical Inclusion and Exclusion Criteria

   Enrolment in the NeuRX -RA/4 Neuromuscular Stimulator study was limited to patients who met the following inclusion criteria

   Inclusion:

   - Age 18 years or older
   - Cervical spinal cord injury with dependence on mechanical ventilation
   - Clinically stable following acute spinal cord injury
   - Bilateral phrenic nerve function clinically acceptable as demonstrated with EMG recordings and nerve conduction times
   - Diaphragm movement with stimulation visible under fluoroscopy
   - Clinically acceptable oxygenation on room air (>90% 02 saturation)
   - Hemodynamically stable
   - No medical co-morbidities that would interfere with the proper placement or function of the device
   - Committed primary caregiver
   - Negative pregnancy test in females of child-bearing potential
   - Informed consent from patient or designated representative

Patients were not permitted to enroll in the NeuRX -RA/4 Neuromuscular Stimulator study if they met any of the following exclusion criteria:

- Co-morbid medical conditions that preclude surgery
- Active lung disease (obstructive, restrictive or membrane diseases)
- Active cardiovascular disease
- Active brain disease
- Hemodynamic instability or low oxygen levels on room air
- Hospitalization for, or a treated active infection, within the last 3 months
- Significant scoliosis or chest deformity
- Marked obesity
- Anticipated poor compliance with protocol by either patient or primary caregiver
- Currently breastfeeding

The study population matches the device intended use.

2. Follow-up Schedule

The 52 subjects, and their caregivers, agreed to a follow-up schedule that could last 12 months. Follow-up was scheduled on subjects who had not achieved steady state use of the system at 3 months, 6 months, and 12 months.

Once a subject achieved steady state use of the system, follow-up was performed on an as-requested basis or at the discretion of the Investigator Postoperatively, following the implant procedure, conditioning was started when patients were stable after surgery and when it was convenient for the patient's caregiver. Each electrode was characterized over the range of stimulus parameters using the Clinical Station. The objective parameters after initiation of stimulation measured during the study included tidal volumes which were recorded with a calibrated Wrights Spirometer and oxygen saturation was monitored with a pulse oximeter. It should be noted that the tidal volumes were measured with the patient's tracheotomy, which in many cases was a cuffless tracheal tube. This means that tidal volumes recorded (and subsequently reported in the results) with the Wrights Spirometer were lower than the actual inspired air volume due to air leaks around the patient's stoma and through their upper airway. An EKG rhythm strip was recorded at maximal stimulus parameters to assure that there was no capture of the cardiac waveform. Initial parameter settings were determined, and the external stimulator was programmed. Initial conditioning sessions were performed while the patient was at the hospital to assure the patient and their caregivers understood and were comfortable with the operation of the DPS. The patient returned home and logged his/her use of the NeuRx DPS® and the improvement in tidal volume as determined with the Wrights

Spirometer. Pulse oximetry and a rank scale indication of respiratory effort were recorded along with any comments with each use of the DPS.

All patients were scheduled to return for follow-up examinations during the initial weeks of DPS use, the clinical team assessed the patient's progress on a weekly basis by reviewing the log sheets and making any changes to parameters as necessary. Log sheets were maintained until the patient had reached, or was capable of, full time use. If the patient had not reached a steady-state plateau or full time use of the system by 3, 6, and 12-month intervals post-surgery, the electrodes were characterized again. Once the patient had achieved full time use of the DPS or was using it at a level that was consistent with their desired level of activity, they were free to use the system as desired.

Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Additional Supporting Studies

After ten years of real-world experience under the HDE, additional sources of evidence of effectiveness have been independently published which support the use of DPS. Each of these supporting studies, designated as studies #2 - #5 are summarized in Table 23. These studies were used to support the efficacy endpoints as described below.

Table 23: Published Supporting Data of NeuRx DPS®

Study ID	Study Population Study Type Subject Number Characteristics	Efficacy Results as Published	Safety Results as Published
Study #2 - Onders et al. (2018)	Single center, single arm, open label, retrospective review N=92 39 IDE and 53 HDE tetraplegic patients with viable phrenic nerves and diaphragm muscles; including pediatric pts. (15%). Mean time on MV = 47.5m (range 6d-25y)	• 88% (81/92) achieved 4 hours of DPS pacing • 60.8% (56/92) used DPS 24 h/d • 5 pts (5.4%) had full recovery of volitional breathing • Five patients (5.4%) were not successfully weaned from MV • Subgroup analysis showed a trend that earlier DPS implantation leads to a greater number of patients utilizing DPS for 24 hours.	• Median survival was 22.2 years (95% Cl 14.0 - not reached) with only 31 deaths. • 4/5 (80%) of patients unable to be weaned from MV died a mean of 9.9 months post-injury. • 17 patients with causes of death available, none were attributable to the device.

Study ID	Study Population Study Type Subject Number Characteristics	Efficacy Results as Published	Safety Results as Published
Study #3 - Kerwin et al (2018)	Single center, single arm, retrospective matched cohort analysis (NeuRx DPS® vs MV). N=40 HDE patients with early DPS implants vs 61 matched pts w/o DPS implant. Mean time to implant=14d	● The DPS patients that developed VAP (26/40) had significantly shorter vent days as compared to the control patients that developed VAP (39/61): 24.5 ± 15.2d vs. 33.2 ± 23.3d; p=0.05	Mortality and length of hospital stay were significantly higher in the control group: ● Mortality significantly higher in the MV group (15% vs 3%; p=0.04) ● Length of hospital stay significantly higher in the MV group (65±61 vs 43±24d; p=0.03)

Study ID	Study Population Study Type Subject Number Characteristics	Efficacy Results as Published	Safety Results as Published
Study #4 - Larmmertse et al (2016)	6 centers, prospective experience report of SCI and implanted with DPS: N=31 patients, (predominantly commercial HDE); with follow-up data on 28 pts. Outcomes collected 2011-2016 on pts., 78% had C1 or C2 SCI, with implants 2007-2014, and mean implant time post-injury: 4.5y (<1 month to 28y)	● 24/26 pts. (86%) were still using DPS at the lime of the follow-up (mean 16h/d) ● 7/28 pts. (25%) were pacing 24h/d ● 4/28 pts. (14%) were not pacing due to: "medical issues", adverse reaction to pacing, shoulder pain, or need for pressure support via ventilator ● Patients (n =28) initiated DPS at mean of 2.5d and a median of 1d (range 0-7d) post-implant. Achieved pacing for 6h/d after a median of 7d (range 0-60d) and 24h/d after a median of 5d (range 0-30d). Mean follow-up: 3.2y (range 15d-7.4y)	Device-related adverse effects reported were. ● infection Issues at the electrode wire exit site (17%), ● pain with pacing (14%), and ● electrode wire issues involving hospitalization (13%)
Study #5 - Posluszny et al (2014)	10 centers, retrospective analysis of SCI pts. implanted with DPS. N=29 patients; 22 implanted, 7 nonresponsive diaphragms. Patients included at median 33d post injury (range 3-112d)	● 73% (16/22) implanted were free of MV at a mean of 10.2d after DPS ● 36% (8/22) had complete recovery of respiration and DPS wires were removed	● 1 patient, withdrawal of care and death ● 3 (14%) partial wean and/or use with MV

3. Clinical Endpoints

Safety Endpoints:

- Assessment of device-related adverse events in the NeuRx DPS® population, compared to a similar patient population without DPS use.
- All-cause mortality in the NeuRx DPS® population, compared to a similar patient population without DPS use.

Primary Effectiveness Endpoint:

The primary effectiveness endpoint was defined as use of the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. This endpoint is reported as the proportion of subjects achieving the endpoint and assessed using binomial methods for the primary cohort (IDE

population n=53), the secondary cohort of the pooled data between the Primary cohort and Onders HDE patients (n=106), and then using mixed models for the meta-analysis of all data sources (n=196).

The three hypothesis tests specified above are tested hierarchically in the order indicated, with the analysis of the primary cohort alone first, the pooled secondary cohort second, and the meta-analysis results from all data sources third. Each test is only performed if the prior test in the sequence meets statistical significance against the performance goal at the 0.05 two-sided level, thereby preserving overall Type I error at 0.0.

Secondary Effectiveness Endpoints:

- Tidal volume (VT) during chronic stimulation is a secondary indicator of the objective to replace mechanical ventilation for patients on a chronic use basis. Standard of care for ventilated patients indicates that the basal VT requirements for an adult male are typically 7ml / kg of body weight and 6ml / kg for adult females.
- Use of NeuRx DPS® to breathe without the assistance of a mechanical ventilator for 24 continuous hours a day.

B. Accountability of PMA Cohort

The IDE (G920162) that was in progress at the time of HDE submission, and used in support of the HDE approval, continued with enrollment up to the inclusion of 50 subjects enrolled at U.S. centers. Three additional subjects were implanted (all three included in the HDE analysis) at investigational sites outside of the U.S. and one subject was a compassionate use patient that was approved by FDA with instructions from FDA that "data from this patient should be clearly distinguished from the study data" and not combined. Thus, a total of 54 subjects gave informed consent and the analysis cohort has 53 subjects. One subject, in the analysis cohort, had an unresponsive diaphragm at implant and thus never actively used the device. The remaining 52 subjects, and their caregivers, agreed to a follow-up schedule that could last 12 months. Follow-up was scheduled on subjects who had not achieved steady state use of the system at 3 months, 6 months, and 12 months. Once a subject achieved steady state use of the system, follow-up was performed on an as-requested basis or at the discretion of the Investigator. All subjects were allowed to continue device use once HDE approval was received

Table 24: Primary Cohort Demographics and Injury History

Period	Analysis Cohort	Active During Period	Reached 4 continuous hour milestone	Exclusion or Withdrawal	
Enrolled	54	54	—	1	1 compassionate use excluded
Implanted	53	52	—	1	1 unresponsive diaphragm at surgery
3 months	53	52	36	0	
6 months	53	52	43	0	
12 months	53	50	50	2	Two deaths between 6 & 12 months

One subject suspended conditioning because of a malfunctioning baclofen pump. Conditioning resumed but the subject did not achieve 4 continuous hours by the date of HDE approval.

One subject achieved 4 hours of use after six months but died before 12 months.

Table 25: Deaths reported during the IDE study, prior to HDE approval

Subject	Age at Injury (years)	Date of Implant	Date of Death	Months After Implant	Months After Injury
01-03	42.7	2/28/03	10/10/04	19.3	112.4
01-15	20.3	2/16/05	8/28/05	6.4	167.9
01-17	69.7	5/18/05	3/24/06	10.2	38.5
01-20	14.6	1/23/06	10/10/07	20.6	73.3

The sponsor presents the data analysis of 3 cohorts:

1. the primary cohort of 53 patients in the IDE trial (G920162)
2. 106 patients – 53 from the primary cohort pooled with 53 HDE patients in the secondary cohort (Onders et. al where the total n= 92, 39 of which were included in the IDE primary cohort)
3. 196 patients – 106 pooled patients plus 90 patients from 3 tertiary studies (the tertiary cohorts are comprised of additional HDE patients (n=40, n=31 and n=29).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. Per the National Spinal Cord Injury Statistical Center (NSCISC), the average age at injury has increased from 29 years during the 1970s to 43 since 2015. About 78% of new SCI cases are male. Vehicle crashes are the most recent leading cause of injury, closely followed by falls. Acts of violence (primarily gunshot wounds) and sports/recreation activities are also relatively common causes for SCI.

About 24% of injuries have occurred among non-Hispanic blacks, which is higher than the proportion of non-Hispanic blacks in the general population (13%).

Table 26 provides the consolidated values for the demographics and injury history of the primary cohort (the IDE Pivotal Study). On average, 65.1 months had elapsed from injury to implant, and the mean age at the time of injury was 30.6 years. The most frequent causes of injury were motor vehicle accident and sporting activities, each occurring 37.7% (20/53) of the time. The most common level of injury was C2, with 45.3% (24/53) of cases, followed by C1/C2 with 30.2% (16/53).

Table 26: Primary Cohort Demographics and Injury History

Characteristic	Mean ± SD (N) [Median] (IQR) or % (n/N)
Age at implant	36.1 ± 16.9 (52) [28.4] (22.6,50.5)
Gender	
Female	22.6% (12/53)
Male	77.4% (41/53)
Age at injury	30.6 ± 18.6 (52) [23.2] (17.9,43.6)
Time from injury (months)	65.1 ± 81.0 (53) [28.3] (12.1,83.3)
Cause of injury	
Assault	1.9% (1/53)
Bicycle	1.9% (1/53)
Fall	13.2% (7/53)
Industrial	1.9% (1/53)
Meningitis	1.9% (1/53)
MVA	37.7% (20/53)
SP. Infarct	1.9% (1/53)
Sports	37.7% (20/53)
TM	1.9% (1/53)
Level of injury	
C1	7.5% (4/53)
C1/C2	30.2% (16/53)
C2	45.3% (24/53)
C2/C3	1.9% (1/53)
C3	5.7% (3/53)
C3/C4	5.7% (3/53)
C4	1.9% (1/53)
C4/C5	1.9% (1/53)

Table 27 displays subject demographics and injury history for the secondary cohort (Onders et al.). Of the 92 patients implanted, 39 were included in the IDE primary cohort; 53 HDE patients were analyzed as part of the pooled secondary cohort. Table 27 information is restricted to the 53 HDE patients.

Table 27: Onders et al. Demographics and Injury History

Characteristic	Mean ± SD (N) [Median] (IQR) or % (n/N)
Age at implant	29.1 ± 17.8 (53) [25.0] (17.0,40.0)
Gender Female Male	 24.5% (13/53) 75.5% (40/53)
Age at injury	26.3 ± 18.8 (53) [23.0] (16.0,38.0)
Time from injury (months)	35.9 ± 54.2 (53) [13.9] (4.3,49.6)
Cause of injury Crush Electrocution Fall Forceps Delivery GSW MVA Sports	 5.7% (3/53) 1.9% (1/53) 15.1% (8/53) 3.8% (2/53) 13.2% (7/53) 50.9% (27/53) 9.4% (5/53)
Level of injury C1 C1-2 C1-4 C2 C2-3 C2-4 C3 C3-4 C3-7 C4 C4-5 C5 C5-6 C5-7 C6 C6-7	 7.5% (4/53) 13.2% (7/53) 1.9% (1/53) 17.0% (9/53) 11.3% (6/53) 1.9% (1/53) 13.2% (7/53) 5.7% (3/53) 1.9% (1/53) 1.9% (1/53) 9.4% (5/53) 1.9% (1/53) 3.8% (2/53) 3.8% (2/53) 1.9% (1/53) 3.8% (2/53)

D. Safety and Effectiveness Results

1. Safety Results

Safety of the Primary Cohort

Adverse Events

There were 165 adverse events recorded during the study, from the first patient implant on 3/6/2000 until the study patients were converted to HDE patients with the approval of the HDE on 6/17/2008. Thirty-eight (38) of the 54 implanted patients (including the compassionate use patient that is excluded from the efficacy analysis) had adverse events recorded. Thus, 16 of the 54 patients had no adverse events recorded during the study. There were 72 device related adverse events reported in 35 patients. Thus, 19 of the 54 patients had no device related adverse events. Of the 72 device related events, 30 were due to equipment malfunctions (external lead breaks or stimulator malfunctions) and another 21 were due to procedure related capnothorax, which is a side-effect of laparoscopic surgery and discussed in more detail below.

Eliminating those categories, 11 patients had device related adverse events.

Table 28 lists the adverse events for patients in the primary cohort. Device related events are identified and placed into categories with respect to being device related, unanticipated or serious adverse events. There were four deaths during the study, none of them were device related. The full reports, as provided to the institutional review boards for the four deaths, are in Appendix 11.9. There was no device related serious adverse events (SAEs). There were 23 non-device related SAEs with several of them related to a root incident. With the exception of the deaths, the SAEs occurred in 5 patients. One patient had acute polynephritis that was reported with three additional SAEs at the same time, including elevated temperature, chest pain, and blood around the tracheostomy. Another patient had recurring pneumonia, reported six times over the course of eight months, also had an elevated temperature and UTI reported as SAEs at the same time. All of the SAEs had resolved by the end of the study.

There were 10 unanticipated adverse device events in 5 patients. The events were temporary spasms, elevated temperature, low VT O2, difficulty eating with device and interference with cardiac pacemakers.

Cohort 1 =

Table 28: Adverse Event Listing for Primary Cohort

Adverse Event (AE)	# Events	Anticipated Device Related AE	# Affected Patients	UADE	SAE	Device Related SAE	% of Patients (n=54)
Capnothorax	21	21	21	0	0	0	39%
Broken External Wire	12	12	7	0	0	0	13%
External Equipment Failure	10	10	8	0	0	0	15%
UTI	10	0	7	0	2	0	13%
Broken Anode	8	8	6	0	0	0	11%
Upper Respiratory Infection	9	0	5	0	0	0	9%
Temporary Spasms	5	0	5	2	0	0	9%
Elevated Temperature	8	0	5	1	2	0	9%
Pneumonia	11	0	4	0	10	0	7%
Pain Discomfort with device	4	4	3	0	0	0	6%
Pain/Discomfort no device use	3	0	3	0	0	0	6%
Aspiration	11	11	3	0	0	0	6%
Low V_T, O_2	5	0	3	5	0	0	6%
Pressure Sore	4	0	3	0	0	0	6%
Increased Secretions	3	1	3	0	0	0	6%
Airway Obstruction	2	2	2	0	0	0	4%
Localized Infection	3	3	2	0	0	0	4%
Redness or swelling	4	0	2	0	0	0	4%
Autonomic Dysreflexia	3	0	2	2	0	0	4%
Death (while device not in use)	2	0	2	0	2	0	4%
Death (with device in use)	2	0	2	0	2	0	4%

Device related SAE = 0

Deaths with device

Adverse events (AEs) or outcomes are generally related to the device itself, o the use of the device or procedure to use the device and to anesthesia or sedation to use the device. Events likely confounded by, and attributed to, other comorbidities or treatment modalities

Cohort 2 =

Median survival = 22.2 yrs. 4/5 not weaned died at mean 9.9 mos.

Device related deaths = 0

Safety information in the Secondary Cohort is limited to mortality as a listing of adverse Events was not part of the published information. Of the 53 patients implanted, there were 15 deaths (28%) which is not an unexpected rate for SCI patients who require mechanical ventilation.

Cohort 3 =

Adverse events not meta-analysed as data was incomplete. 1 study reports 17% wire infection rate, 14% pain with pacing, and 13% hospitalized due to wire issues.

There were 16 patients that had no adverse events reported. There were 84 device related adverse events recorded in 35 patients. The most frequently occurring adverse event recorded, in 21 patients, was a capnothorax at the time of implantation.

After the surgical related events of capnothorax and interference with cardiac pacemaker (which was programmed around with lower non-interfering settings), the adverse event of aspiration was the most frequent occurring.

There were 81 adverse events not related to the device or procedure recorded in 20 patients.

Complaints, post-approval of HDE (H070003):

Over the five years period of Sept 1, 2015, to August 31, 2020, there were a total of 547 patients implanted. During this period, there were ten MDR's filed with FDA related to patients implanted under H070003. There was a total of 182 total complaints from implanting sites or patients implanted during this period. In total 84% of the patients did not register any complaints over the five-year period, with 87% of SCI patients and 71% of off-label patients not having complaints. The majority of complaints occur in the first twelve months after implant. During the first year (day 0 – 360), there was a total of 67 complaints in 57 different patients. That represents 10.4% of the patient population with a complaint during the first year. Focusing on complaints that were deemed to be medical device reportable adverse events there were nine events in the five-year sample with an MDR for 1.6% of the patient population.

Thus, given the large sample of post-approval patients, there does not appear to be any indication of a discrepancy with the primary IDE cohort in terms of an increase in events in the first-year post-implant or in subsequent years. There also is no indication, in the complaint data, of a wear-out mechanism over time with use of the device.

Adverse effects that occurred in the PMA clinical study:

The table below provides the data comparison of a Standard of Care surgical procedure population with the primary cohort in the DPS study. The literature reference for the Standard of Care population is identified in the Source column of the table. The Comparative Population column provides the data for the identified Adverse Event from the Source literature. In all cases, the incidence rate of the adverse event is lower for the DPS Primary Cohort than that published for the Comparative Population.

Table 29: Adverse events, primary cohort to comparative populations

Adverse Event	DPS Primary Cohort	Comparative Population	Source
Capnothorax	21 / 53 (39.6%)	21 / 45 (47%)	Clements, 2000
Pneumonia	4 / 53 (7.5%)	1,968 / 3,019 (65.2%)[2]	2018 NSCISC Annual Report
		146 / 180 (81%)	Jaja, 2019
Aspiration	3 / 53 (5.7%)	15 / 46 (33%)	Ihalainen, 2017
Operative Mortality	0	2% - 7%	Johnson, 2007
Perioperative Complications			
Venous thromboembolism (VTE)[3]	0	21,630 / 4,107,430 (0.53%)	Stein, 2014
Pulmonary embolism (PE)	0	5,960 / 4,107,430 (0.15%)	Stein, 2014
Deep Vein Thrombosis (DVT)	0	16,610 / 4,107,430 (0.40%)	Stein, 2014
Wound infections	2 / 53 (3.8%)	1,579 / 9655 (16.3%)	Kagawa, 2019
Pulmonary infections	5 / 53 (9.4%)	430 / 3,084 (13.9%)[1] 3,019 / 14,094 (21.4%)[2]	2018 NSCISC Annual Report
Catheter/wire complications	5 / 53 (9.4%)	9 / 57 (16%)	Saval, 2010

[1] Reported as Diseases of the Respiratory System as cause of re-hospitalization during the first-year post-injury (Table 102)

[2] Reported as Diseases of the Respiratory System as the primary cause of death (Table 10)

[3] Venous Thromboembolism is PE and/or DVT

The laparoscopic approach described by Clements is very similar to that used by surgeons to implant the Permaloc electrodes. The procedures discussed in this article involve dissecting the phrenoesophageal ligament, which can create a path for pressurized carbon dioxide to pass from the abdomen into the mediastinum. Similarly, the insertion of the Permaloc electrode can create a potential track for pressurized carbon dioxide from the abdomen to enter the chest.

Pneumonia & Pulmonary Infections –NSCISC Annual Report, 2018

The National Spinal Cord Injury Statistical Center (NSCISC) at University of Alabama, Birmingham (UAB) supervises and directs the collection, management, and analysis of the world's largest spinal cord injury database. The Center is at the hub of a network of 14 federally sponsored regional Spinal Cord Injury Model Systems located at major medical centers throughout the United States. The NSCISC has developed extensive quality control procedures that further enhance the reliability and validity of the database.

Pneumonia – Jaja, 2019

The authors examined acute spinal cord injury (SCI) patients from two comprehensive databases. This prospective study reported high rates of pneumonia in acute SCI patients and concluded there is a relationship between pneumonia, wound infection, and sepsis occurring during acute admission and poorer functional outcomes following SCI.

Aspiration – Ihalainen,2017

Dysphasia commonly occurs in cervically injured SCI patients. Dysphagia is a contributor to poor outcomes, such as pneumonia and other respiratory complications as well as malnutrition, dehydration, and reduced quality of life. The authors observed a high percentage of traumatic cervical spinal cord injury patients experienced aspiration.

Operative Mortality – Johnson, 2007

The authors utilized National Department of Veteran Affairs datasets to select patients with SCI and subsequent surgical conditions. Their findings revealed the operative mortality rates ranged from 2% to 7%.

Perioperative Complications – Stein, 2014

The authors reported a low prevalence of in-hospital deep venous thrombosis (DVT), pulmonary embolism (PE), and venous thromboembolism (PE and/or

DVT) following laparoscopic cholecystectomy. This procedure is very similar to the laparoscopic approach for Permaloc electrode placement.

Wound Infections – Kagawa, 2019

Minimally invasive laparoscopic techniques, similar to those used for Permaloc electrode placement, coupled with improved post-operative care continue to reduce the rate of surgical site infections.

Catheter/Wire Complications – Saval, 2010

This article reports on a retrospective chart review of 57 individuals (SCI and non-SCI patients) requiring an intrathecal baclofen pump. With respect to complications, the authors reported a complication prevalence of 16% over 3 years.

A measure of "durability" of the NeuRx DPS® to stimulate the diaphragm at levels that would produce the indicated endpoint of at least 4 continuous hours of stimulation was not specifically recorded for the primary cohort. Prior to human clinical studies, Peterson et al. (1994) looked specifically at long term use and impedance of the electrodes in an animal model. Peterson (1994) Safety: showed that all electrodes were below 1KΩ impedance in animals implanted up to six months. Note: that impedance was reported in the original HDE submission (Vol I Appendix G, page 10) as 615 } 92Ω and as stable over time. Also, impedance is measured with each stimulated "breath" and alarms if the device measures an impedance over 2.4KΩ. Thus, there is no evidence of electrode impedance changes over time that would affect the treatment.

Onders reported that 88% (81/92) achieved 4 consecutive hours of pacing, that 76% (70/92) of patients used the NeuRx DPS® for at least 12 hours per day and 60.8% (56/92) of patients achieved 24 hours of device use per day.

Onders, et.al., submitted a further analysis of all patients using DPS 24 hours a day for a minimum of 48 months as of 2020. A total of 17 patients were identified. Range of continuous DPS use was 48 months to 203 months with an average of 150 months. Conclusion is that DP has long term continuous durability.

Assessment of most common device-related adverse events in the NeuRx DPS® population, compared to a similar patient population without DPS use:

The most common occurrence of device-related adverse event in the study was a result of air tracking into the pleural cavity from the CO2 used to inflate the

abdomen during surgery, e.g., a capnothorax. One patient experienced a capnothorax that was determined to be serious. Patient 4 sustained a capnothorax during implantation that required an extended hospitalization. In most of the cases, the capnothorax which is just the CO2 from the laparoscopic surgery is rapidly absorbed by the body and quickly resolves after the laparoscopic part of the surgical procedure. One infection occurred local to the in-line connectors in patient 3, which was subsequently externalized and treated with antibiotics. Other incidents of aspiration (3) and upper airway obstruction during sleep (3) occurred and they were reminded to use a Passy-Muir valve on their tracheotomy during eating and sleep to eliminate that risk.

The largest, and one of the best, databases for spinal cord injured patients is maintained by the National Spinal Cord Injury Statistical Center in Birmingham, Alabama and can be accessed through www.spinalcord.uab.edu. The number one cause of death in this database for all spinal cord injured patients is diseases of the respiratory system (22% of deaths) with pneumonia accounting for 71% of these. In the experience of high tetraplegics implanted with the NeuRx DPS® there were no respiratory deaths.

A review of surgery in patients with spinal cord injury can also be compared to diaphragm pacing surgery. The large Department of Veterans Affairs computer dataset was analyzed for spinal cord injured patients who underwent surgery (ranging from aneurysm repair to appendectomy) and found operative mortality rates ranging from 2% to 7%. There were no peri-operative deaths in the IDE Pivotal trial. The reported complication rate in the VA dataset ranged from 23% (for appendectomy) to 57% (for aneurysm repair). In the IDE Pivotal Trial, none of the commonly tracked peri-operative complications, including venous thrombosis, pulmonary embolus, wound infections, and pulmonary infections were reported. The most common peri-operative adverse event was a capnothorax, which is a common side-effect of laparoscopic surgery, was tracked and involved 21 out of 54 patients (39%).

One report (Chiodo, 2007) of the use of intrathecal baclofen pumps for spasticity showed that 5 out of 44 patients (11.4%) had catheter complications. This is comparable to our reported external wire break rate of 5 out of 48 patients (10.4%). A main difference is that when there is a complication with a Baclofen intrathecal catheter it requires a surgical procedure to correct. The NeuRx DPS® still works even with an isolated broken external wire because of the redundancy of 4 wires implanted. All of the external wire breaks are able to be fixed with an office visit.

Although surgery is not done in patients with spinal cord injury, placement of a gastric electrical stimulator (Enterra-Medtronic) does involve placement of

electrodes in the abdominal cavity either through laparoscopy or open surgery. This allows comparison of adverse events between a transabdominal electrical stimulation procedure and the NeuRx surgical procedure. In one large trial of 55 patients, implanted there was one immediate peri-operative death, in the IDE Pivotal Trial there were no perioperative deaths. In Forster's report, three devices and wires had to be surgically removed for infection while no NeuRx wires needed to be surgically removed for infection. In addition, three patients had surgical revision of the gastric pacemaker while only our first patient in the IDE Pivotal Trial had to have additional wires placed to obtain successful diaphragm recruitment. Since that initial change in mapping technique, no DPS patients required revision surgery.

All-cause mortality in the NeuRx DPS® population, compared to a similar patient population without DPS use:

The graphics below display overall survival (that is, freedom from all-cause mortality) in Kaplan Meier format for both time since injury ("SCI survival," Figure 1) and time since DPS implant ("DPS survival," Figure 2). Data displayed are for the primary analysis cohort, that is, the IDE Pivotal Study.

The results indicate a majority of patients surviving at least 22 years, measured from time of injury and at least 19 years after their DPS implant (with a median time between injury and DPS implant of 28.3 months). This compares numerically (without formal hypothesis testing) to values published by the National Spinal Cord Injury Statistical Center, which reported survival among a ventilator-dependent population as 11.2 years for 20-year-olds down to 3.7 years for 60-year-olds (NSCISC Annual Report 2018, Table 14A). Even using the more conservative NSCISC data for those surviving at least one-year post-injury, the relevant numbers are 18.7 years for 20-year-olds, 13.3 years for 40-year-olds, and 7.9 years for 60-year-olds as referenced on Figure 16.

The results below, therefore, indicate that patients treated with DPS had survival rates that were comparable or better to those reported in the literature in a non-DPS population (NSCISC Annual Report 2018, Table 14A).

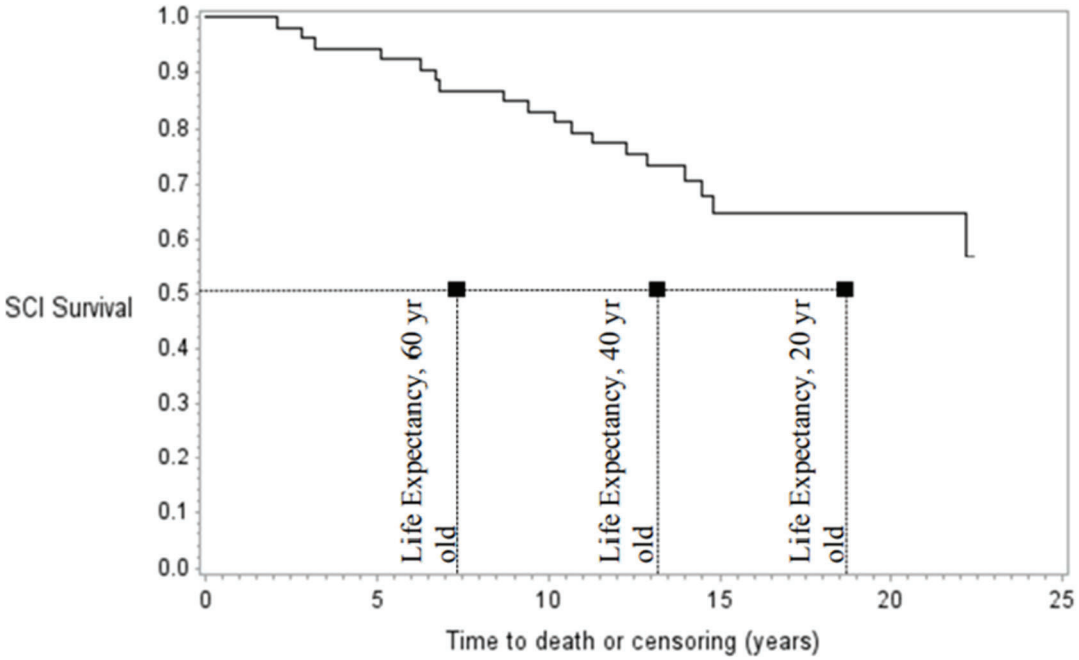

Figure 6: SCI Survival (years since injury)

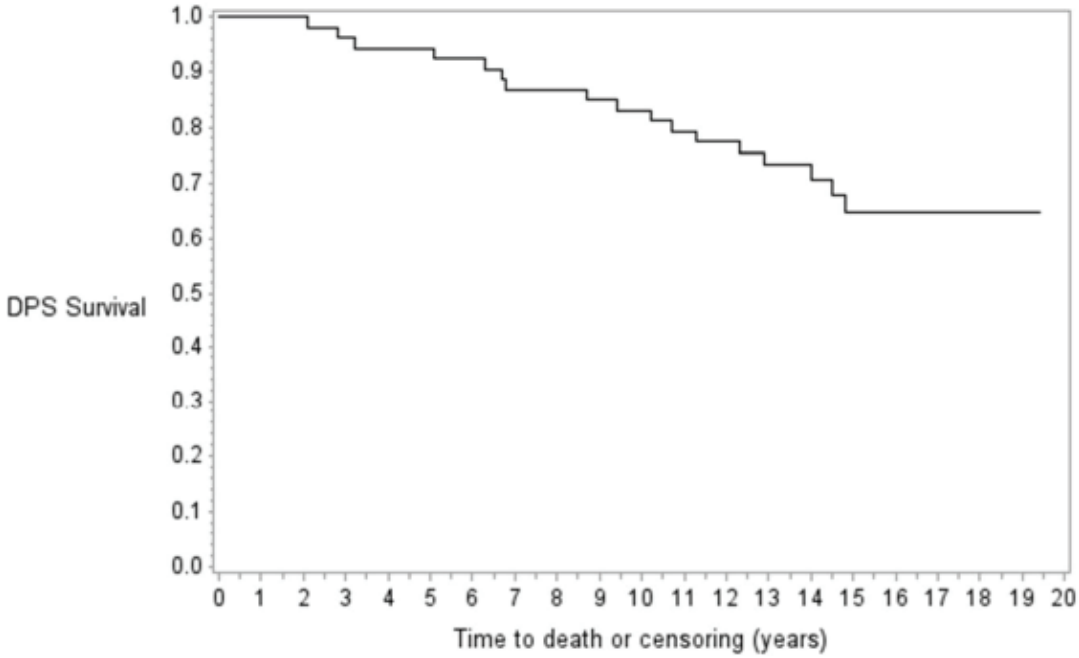

Figure 7: DPS Survival (years since implant

2. Effectiveness Results

Efficacy Analysis of the Primary Cohort

For analyses of the Primary analysis cohort, an exact two-sided 95% confidence interval was constructed for the proportion p of subjects meeting the primary endpoint, and the resulting lower confidence bound compared to the PG. This estimate has been summarized with its corresponding 95% confidence interval and compared to a performance goal (PG) representing meaningful clinical benefit.

Primary Endpoint – DPS Use

The primary endpoint was defined as use of the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. This endpoint is reported as the proportion of subjects achieving the endpoint and assessed using binomial methods for the primary analysis.

For this purpose, the Avery diaphragm pacer (PMA P860026) reported a 45% success rate, where "success" was defined as "consistent, adequate ventilatory support from diaphragm pacing for some part of a day." To provide reasonable assurance of meaningful clinical benefit from the NeuRx DPS®, the PG is defined as the reported Avery success rate for a PG of 45%; meeting the accompanying hypothesis test then constitutes statistical evidence that the success rate with the NeuRx DPS® is greater than the 45% reported by Avery.

The primary analysis cohort is defined to be data collected from the IDE Pivotal Study, for which 96.2% (51/53) of subjects achieved at least 4 continuous hours daily use (Table 30). The primary endpoint was met on the primary analysis cohort with $p<0.001$.

Table 30: Primary Endpoint, Primary Analysis Cohort (n=53)

Event	% (n/N)	95% confidence interval	p-value*
Primary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day)	96.2% (51/53)	(87.0%, 99.5%)	<0.001

* Exact two-sided binomial test against performance goal of 35% (0.35)

Thus, the primary endpoint was met on the primary analysis cohort with $p<0.001$.

The second test of the primary endpoint is then specified to be based on the pooled IDE Pivotal Study and secondary cohort data (n=106 total). Results are summarized in table 31. Thus, the primary endpoint was met on the secondary (pooled IDE Pivotal Study and Onders) analysis cohort with p<0.001.

Table 31: Primary Endpoint, Secondary Analysis Cohort (n=106)

Event	% (n/N)	95% confidence interval	p-value*
Primary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day)	89.6% (95/106)	(82.2%, 94.7%)	<0.001

* Exact two-sided binomial test against performance goal of 35% (0.35).

Thus, the primary endpoint was met on the secondary (pooled Primary and Secondary cohorts) analysis cohort with p<0.001.

The third and final test of the primary endpoint is then specified to be based on all available sources (n=196 across five studies including the ones cited above), using meta-analytic methods. The results, summarized in Figure 8, indicate each of the individual studies reaching the 35% performance goal based on exact binomial inference (although this was not a requirement of the success criterion definition) and furthermore that the meta-analytic summary showing success of 92.2% with a two-sided 95% confidence interval of (82.6%, 96.7%), p<0.001 versus the performance goal. The heterogeneity between studies is moderate, with I^2=0.64 indicating some differences between studies in the primary endpoint. The random-effects model used for the meta-analysis incorporates this disparity and appropriately weights the study results, resulting in a lower confidence bound of 82.6% which is less than that derived from pure pooling (95% two-sided lower bound of 85.9% on 178/196 successes). Based on these considerations, the endpoint is met under this analysis as well.

The Primary Effectiveness Endpoint was easily met in the original IDE cohort and in subsequent reported analyzed cohorts.

Meta-Analysis of all Cohorts

The third and final test of the primary endpoint was based on all available sources using meta-analytic methods as stated in the Statistical Analysis Plan. There was a combined n=206 in the five studies, however, 7 patients were not implanted, and 3 patients did not undergo pacing initiation in two of the tertiary sources. Therefore, 10 patients are excluded from this analytic cohort where n=196. The results, summarized in Figure 8, indicate each of the individual

studies reaching the 45% performance goal based on exact binomial inference (although this was not a requirement of the success criterion definition) and, furthermore, that the meta-analytic summary showing success of 92.2% with a two-sided 95% confidence interval of (82.6%, 96.7%), p<0.001 versus the performance goal. In Figure 8, the data presented for Onders is the data analyzed for only the Secondary cohort of HDE patients where n=53.

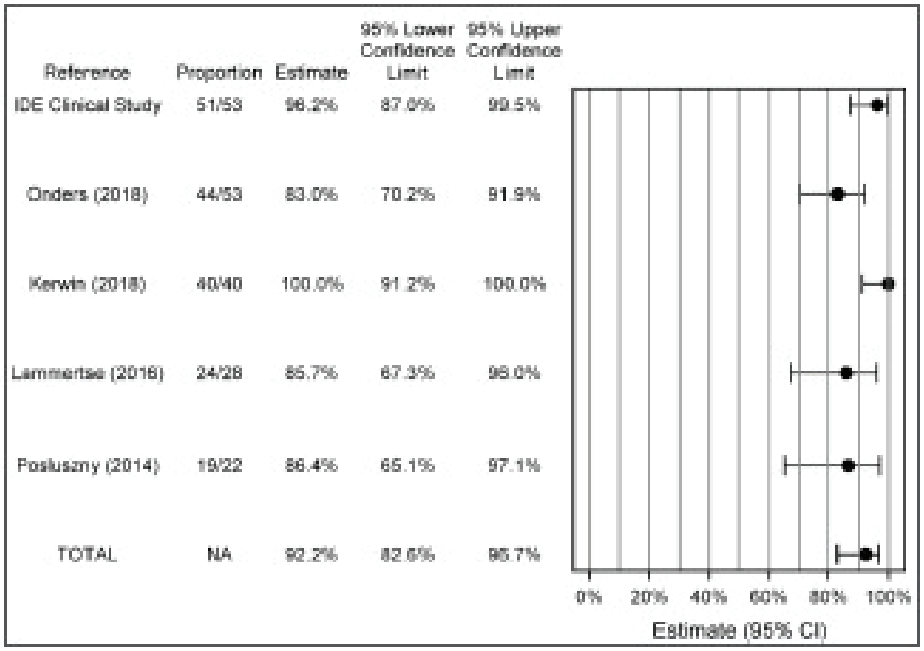

Figure 8: Forest Plot of NeuRx Success

The heterogeneity between studies was moderate, with I2=0.64 indicating some differences between studies in the primary endpoint. The random-effects model used for the meta-analysis incorporates this disparity and appropriately weights the study results, resulting in a lower confidence bound of 82.6% which is less than that derived from pure pooling (95% two-sided lower bound of 85.9% on 178/196 successes).

Thus, the endpoint was met under this analysis as well.

For the third cohort, four studies among the five cited in this report provided data on 24- hour use (n=156 across four studies including the ones cited above). The meta-analytic summary (Figure 9) shows success on 24-hour use of 52.7% with a two-sided 95% confidence interval of (36.2%, 68.6%).

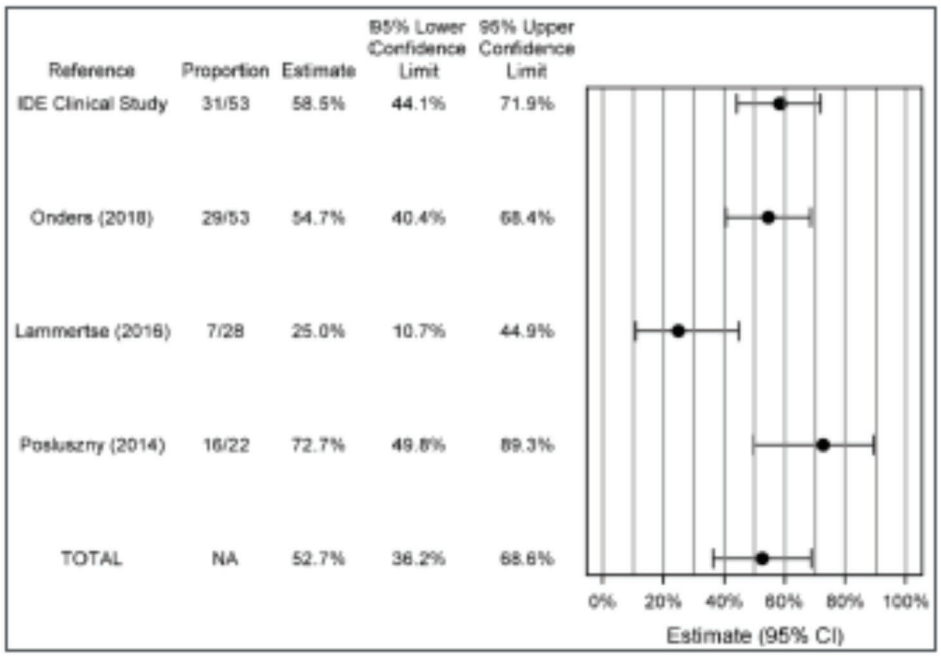

Figure 9: Forest Plot All Cohorts – Secondary Endpoint (24 hr/daily use)

3. Subgroup Analyses

The following preoperative characteristics e.g., sex/gender, site, age were evaluated for potential association with outcomes and are consistent with national statistics available in 2020 Annual Statistical Report for the National Spinal Cord Injury Statistical Center, University of Alabama at Birmingham, which lists the most common age at injury as19 years. Their data shows that nearly a quarter (23.7%) of all injuries occurred between the ages of 17 and 22 years, nearly half (47.0%) of all injuries occurred between the ages of 16 and 30, and 12.2% of all injuries occurred at age 60 or older.

Table 32: pre-operative characteristics, primary cohort

Characteristic	Mean ± SD (N) [Median] (IQR) or % (n/N)
Age at implant	36.1 ± 16.9 (52) [28.4] (22.6,50.5)
Gender Female Male	 22.6% (12/53) 77.4% (41/53)
Age at injury	30.6 ± 18.6 (52) [23.2] (17.9,43.6)
Time from injury (months)	65.1 ± 81.0 (53) [28.3] (12.1,83.3)

Overall, 80.3% of all reported SCIs occurred among males. There was very little variability among Systems with regard to the composition of the participant populations by sex. Among Systems, the proportion of male participants ranged from a low of 70.2% to a high of 86.8%.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 16 investigators. 15 of the clinical investigators did not have disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

The pivotal clinical study included 1 investigator of who was full-time or part-time employees of the sponsor and] had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 of investigators
- Significant payment of other sorts: 1 of investigators
- Proprietary interest in the product tested held by the investigator: 1 of investigators
- Significant equity interest held by investigator in sponsor of covered study: 1 of investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A total of 791 SCI patients have been implanted under IDE and HDE through the date of the PMA submission, March 11, 2020. As of the PMA submission date (March 2020),

there have been an additional 132 patients implanted and recorded as off-label use, for a total of 923 patients implanted in the U.S. for the IDE and HDE, from March 6, 2000, to March 11, 2020.

During a five-year period from Sept 2015 to Aug 2020, there were 547 patients implanted under H070003. There were 455 identified as SCI patients and 92 as off-label. There was a total of nine adverse events reported as MDRs filed on the 547 patients.

Special Population:

Implanted pacemakers: Ten patients enrolled in the study also had implanted pacemakers. In one instance, an electrode was found to have device-device interaction but was left in the diaphragm to determine if the interaction would subsequently cease. The device-device interaction persisted in subsequent testing and the electrode remained disabled.

Pediatric: Onders reports on 92 subjects, 14 of whom are under the age of 18 years. All pediatric patients were implanted with the HDE approved device under an IRB approved protocol for compassionate use in pediatric patients. There was one death among the 14 pediatric patients which occurred 1.6 years after implant. There were 13 of the 14 (93%) pediatric patients that achieved greater than four continuous hours on DPS. Eight of the 14 (57%) achieved 24 hour per day use of DPS.

Compassionate Use

A female Subject a female with transverse myelitis at her C2 level resulting in ventilator dependence was implanted as a compassionate use patient. Subject was implanted on July 11, 2007. On April 5, 2008, subject was able to achieve 4 hours of continuous use of DPS and subsequently, on the next day, used DPS 24 hours per day.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

Device did not go to Panel

A. Panel Meeting Recommendation

Not Applicable.

B. FDA's Post-Panel Action

Not Applicable.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In prospectively defined statistical analysis, the data from the NeuRx IDE Pivotal Trial, and data from real world use of the device implanted under the HDE was analyzed for the ability of the NeuRx DPS® to provide respiratory support without the assistance of a mechanical ventilator for at least four continuous hours per day. A performance goal (PG) of 45% was defined, and the analysis of the PG was conducted in a sequential manner by evaluating:

1. the primary cohort of 53 patients in the IDE trial.
2. a second cohort of 106 patients – 53 from the primary cohort pooled with 53 patients treated by Onders et al.; and
3. a third cohort of 196 patients – 106 pooled patients plus 90 patients from 3 tertiary studies.

The percentage of patients that were able to use NeuRx DPS® for at least four hours a day was 96.2%, 89.6%, and 92.2% in the respective cohorts. These results met the PG of 45% as determined by the statistical significance achieved ($p < 0.001$). NeuRx patients achieved nearly 90% ventilator independence, in all cohort analyses, for at least 4 hours/day which almost doubles the success rate for the efficacy endpoint.

The study also evaluated two un-powered secondary endpoints. The first was the ability of the NeuRx DPS® to provide tidal volume to meet basal metabolic requirements. This analysis showed that the mean percentage of tidal volume over basal metabolic requirements was 48.4% ± 41.5% ($p<0.001$).

The second analysis was the evaluation of the number of patients that could use NeuRx DPS® for 24 hours a day (i.e., completely replace mechanical ventilation for respiratory support). In the meta-analysis cohort, four of the five studies cited provided data on 24-hour use. In the three analysis cohorts -primary: 31/53 (58.5%), pooled - 60/106 (56.6%), and meta-analysis - 82/156 (52.7%) the percentage achieving 24 hours of continuous device use is unprecedented in this population, resulting in a sizeable percentage of high-level SCI patients having the ability to gain full-time independence from positive pressure mechanical ventilation.

Effectiveness of the NeuRx device as measured by the proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day was statistically met with $p < 0.001$. Therefore, it is reasonable to conclude that the probable benefit and meaningful outcome to health from using the device for the target population regardless of differences by age, sex/gender, race, and ethnicity outweighs the risk of illness or injury without impacting the effectiveness or safety of the device, taking into account the probable

risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use and that effectiveness outcomes of the PMA clinical studies and outcomes met acceptance criteria for a significant portion of the target patient population.

B. Safety Conclusions

The NeuRx DPS® device has never been the subject of any recall or field action. The risks of the device are based on nonclinical laboratory and/or data collected in the clinical study conducted to support PMA approval as described above.

The primary analysis results from the prospective, non-randomized pivotal trail demonstrate the safety and effectiveness of the NeuRx device. The study met the success criterion for the primary effectiveness endpoint statistically. It provides strong evidence that the NeuRX device can successfully achieve the performance goal of providing respiratory support without the assistance of a mechanical ventilator for at least four hours/day. In addition, the result of secondary effectiveness endpoint provides the evidence that more than 50% of the enrolled patients can be fully independently from mechanical ventilation. There was no specific safety hypothesis, but the sponsor provided a detailed summary of all adverse events (AEs). AE associated with the device are typically not serious in nature and in most cases can have quick resolution.

The sponsor also provided safety and effectiveness analyses combining the primary cohort and real-world data. The combined results provide supportive evidence of safety and effectiveness of the device.

Table below regarding MDRs support that the adverse responses are infrequent and do not present a significant biocompatibility risk. The device has been implanted in over 1800 patients in the US and the rarity of these events suggest no systemic problems

Table 33: Potential incidents related to biocompatibility
(n = number of parents in year reporting on event)

	2009	2010	2011	2012	2013	2014	2015	2016	2017	201S	2019	Total
HDE H070003 (SC I)												
Electrode wires have tunneled through the epigastric port					1							1
Skin erosion							1					1
Skin sensitivity to connecter holder adhesive	1				]							2
HDE HI00006 (ALS)												
Skin erosion	n/a	n/a	n/a					2				2
Skin irritation at percutaneous electrode wire site	n/a	n/a	n/a		1							i

n/a – not approved

The three events of skin erosion exposing the electrode wires were associated with tunnelling the electrodes too close to the skin surface at the time of implantation. The one event of wires emerging through the skin at the epigastric port was due to not pushing the electrode wires far enough into the port at the completion of surgery allowing them to re-emerge before the wound was healed over.

Lammertse et al reported infection issues at the electrode wire exit site of 17% while patient cohort 1 in the study experienced 4% infection rate only. The apparent disparity is reported due to self-reporting by patients vs. reporting by physicians who confirmed the presence of an infection as opposed to normal skin reactions to percutaneous wires.

In no case was the patient required to return to the operating room for device repair. In the IDE Pivotal Trial there were no perioperative deaths. In the IDE Pivotal Trial, none of the commonly tracked peri-operative complications, including venous thrombosis, pulmonary embolus, wound infections, and pulmonary infections were reported. The most common peri-operative adverse event was a capnothorax, which is a common side- effect of laparoscopic surgery, was tracked and involved 21 out of 54 patients (39%).

Audio alarms and messaging provides the user with cues to replace the primary battery. An interconnect assembly is provided that allows the temporary connection of a surface indifferent electrode. With redundancy in all other components, this assembly provides redundancy for the implanted anode.

In conclusion, Safety of the NeuRx device, based on rates and types of adverse events, is comparable to patients on mechanical ventilation with no apparent increase due to the device. Survival rates of patients using the NeuRx device were at least comparable if not better than patients on mechanical ventilation. The safety outcomes of the PMA clinical study(ies) support safety profile of the NeuRx DPS® including determination of clinical significance of endpoint outcomes and evidence that outcomes met acceptance criteria.

C. Benefit-Risk Determination

The NeuRx DPS® is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but who lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. It is intended for use only in patients 18 years of age or older

As a catastrophic, life changing event, spinal cord injury continues to present risks throughout the patient's life. Predominant among the risks is that of pulmonary dysfunction, which has the greatest impact on reduced life expectancy in spinal cord

injury. The National Spinal Cord Injury Statistical Center 2017 annual report notes recent estimate showed that the annual incidence of spinal cord injury (SCI) is approximately 54 cases per one million people in the United States, or about 17,810 new SCI cases each year. It further notes that "life expectancies for persons with SCI remain substantially below normal, particularly for persons with tetraplegia and ventilator dependency." Depending on patient age, those that survive at least 24 hours post-injury and require mechanical ventilatory support have a 59 to 83% reduction in life expectancy when compared to the patients with high spinal cord injury (levels C1-C4) that do not require mechanical ventilation. Diseases of the respiratory system constitute 22% of the deaths, which is the leading cause in individuals with spinal cord injury. Further, 65% of those deaths are caused by pneumonia.

The inability to independently breathe is compromised in SCI patients due to disruption of the signaling pathway, the spinal cord, from the respiratory center in the brain to the diaphragm. In patients with an intact phrenic nerve, the signaling pathway can be bypassed by implanting permanent electrodes to provide direct electrical stimulation to the diaphragm, which is the mechanism of action of the NeuRx DPS®.

NeuRx DPS® is implanted via a laparoscopic surgical procedure, by placing electrodes into each hemidiaphragm near the phrenic nerve motor point. Each electrode percutaneously exits the body and is connected to a four-channel external stimulator.

In ventilator-dependent SCI patients, NeuRx DPS® effectively functions initially as a powered muscle stimulator for treating disuse atrophy and then, once the diaphragm has been sufficiently reconditioned, as a functional electrical stimulator (or breathing pacemaker) to drive respiration

Even with the device's favorable benefit-risk profile, relatively few clinical sites are willing to go through the IRB approval process given the paucity of patients who meet the indications. Thus, patients with new injuries at centers without an existing IRB-approved program or in geographical areas without one of the IRB-approved centers do not have access to the treatment. Occasionally, patients of means travel across the country to IRB-approved centers to obtain the device. However, when they return home, they cannot receive local device maintenance such as reprogramming because only IRB-approved centers may administer the HUD. This means that device reprogramming, for remote patients who cannot make the trip, must be done by shipping external pulse generators back and forth between center and patient.

PMA approval would remove significant barriers for patient access to the device and improve the ability to support long-term maintenance in implanted patients.

Alternative systems and procedures for people with high spinal cord injury include mechanical ventilation, phrenic nerve stimulators, and non-invasive ventilatory assistance devices including non-invasive positive-pressure ventilation (NIPPV) in the form of continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), pneumobelt, and a rocker bed.

Mechanical ventilation, the Standard of Care for spinal cord injury patients requires the patient to be connected (usually through a tracheostomy tube) to a ventilator which supplies positive pressure to inflate the lungs and allows for respiration. Ventilators are connected to external power sources and in many cases have internal battery back-up for transportation, outside activities and for use in the event of power failure. While they can be used outside the home, they are cumbersome and require that the patient be connected to the device at all times. Furthermore, patients on prolonged mechanical ventilation have higher incidences of morbidity and mortality when compared to SCI patients that do not require mechanical ventilation in large part due to the adverse events associated with mechanical ventilation. Patients on full-time mechanical ventilation may still tolerate some time off from mechanical ventilation with support of some form of non-invasive ventilation.

NIPPV in the form of CPAP or BiPAP requires a mask or nasal occlusion device and is variably tolerated. The devices can cause skin and nasal mucosal irritation. A pneumobelt requires the patient remain in the sitting position, while the rocker bed requires the supine position, limiting mobility. All the devices for non-invasive ventilation require either a battery operated or electrical power source; NIPPV and the pneumobelt potentially provide more mobility than mechanical ventilation.

In the pivotal clinical study conducted to support PMA approval, performance goal (PG) of 45% was defined, and the analysis of the PG was conducted in a sequential manner by evaluating:

- the primary cohort of 53 patients in the IDE trial,
- 106 patients – 53 from the primary cohort pooled with 53 patients treated by Onders et al.,
- 196 patients – 106 pooled patients plus 90 patients from 3 tertiary studies.

The percentage of patients that were able to use NeuRx DPS® for at least four hours a day was 96.2%, 89.6%, and 92.2% in the respective cohorts. The results met the PG of 45% as determined by the statistical significance achieved ($p < 0.001$). NeuRx patients achieved nearly 90% ventilator independence, in all cohort analyses, for at least 4 hours/day which almost doubles the success rate for the efficacy endpoint.

The study also evaluated two un-powered secondary endpoints. The first was the ability of the NeuRx DPS® to provide tidal volume to meet basal metabolic

requirements. This analysis showed that the mean percentage of tidal volume over basal metabolic requirements was 48.4% ± 41.5% ($p<0.001$).

The second analysis was the evaluation of the number of patients that could use NeuRx DPS® for 24 hours a day (i.e., completely replace mechanical ventilation for respiratory support). In the meta-analysis cohort, four of the five studies cited provided data on 24-hour use. In the three analysis cohorts --- primary: 31/53

(58.5%); pooled - 60/106 (56.6%); and meta-analysis - 82/156 (52.7%) the percentage achieving 24 hours of continuous device use is unprecedented in this population, resulting in a sizeable percentage of high-level SCI patients having the ability to gain full-time independence from positive pressure mechanical ventilation.

The primary analysis results from the prospective, non-randomized pivotal trail demonstrate the safety and effectiveness of the NeuRx device. The study met the success criterion for the primary effectiveness endpoint statistically. It provides strong evidence that the NeuRx device can successfully achieve the performance goal of providing respiratory support without the assistance of a mechanical ventilator for at least four hours/day. In addition, the result of secondary effectiveness endpoint provides the evidence that more than 50% of the enrolled patients can be fully independently from mechanical ventilation.

The sponsor also provided safety and effectiveness analyses combining the primary cohort and real-world data. The combined results provide supportive evidence of safety and effectiveness of the device.

The probable risks of the device are also based on data collected in the pivotal clinical study. There was no specific safety hypothesis, but the sponsor provided a detailed summary of all adverse events (AEs). AE associated with the device are typically not serious in nature and in most cases can have quick resolution. Adverse events (AEs) or outcomes are related to the device itself, use of the device or procedure to use the device and to anesthesia or sedation to use the device. Events are likely confounded by, and attributed to, other comorbidities or treatment modalities There were 0 devices related SAEs in the primary cohort. The most common AEs were capnothorax in 39% of the primary cohort which is common in laparoscopic procedures and almost always resolves without intervention, external equipment failure in 15%, and broken external wires in 13% for which repair methods are established and specified; and these are consistent with the anticipated AEs for such a procedure.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, considering the probable risks and benefits of currently available devices or

alternative forms of treatment when used as indicated in accordance with the directions for use.

Improved activities seen in a multicenter study in 57% with overall satisfaction in 79% and 96% happy with decision to undergo implantation. There appears to be a survival benefit for the primary cohort, particularly over age 40, compared to published similar reference cohorts. Thus, device benefit is substantial, and risks appear to be low.

1. Patient perspectives considered during the review included:

   Posluszny (2014) reports the findings of a multicenter experience with diaphragm assessment and pacing in the initial hospitalization after traumatic cervical SCI. The objectives were to report the present-day real-time use of DP in SCI patients early

   in their disease course, to review the reported surgical findings, and to discuss success at weaning from mechanical ventilation with regard to diagnostic laparoscopic diaphragm evaluation. A total of 16 sites of implantation were identified. Each site had the same database for data collection including age, sex, mechanism and level of injury, date of injury, date of DP surgery, surgical findings, and outcome of patient in respect to DP. Of the 16 sites identified, 14 responded with patient information.

   Ten of these 14 sites supplied sufficient patient data to be included. All patients with stimulatable diaphragms (22) had electrodes implanted. Sixteen (72.7%) were completely weaned from mechanical ventilation in a mean time standard error of the mean (T SE) of 10.2 T 13.1 days (range, 1Y45 days). Of the remaining six patients, two were eventually weaned of mechanical ventilation but are considered delayed weans because their ultimate follow-up occurred after transfer to a ventilator facility (180 days following implantation). Two other patients had partial weans, using DP for part of the day (4 and 12 hours, respectively) and the ventilator for the remainder. While DP provided adequate ventilation, these patients choose to use both therapies. One patient used DP with simultaneous mechanical ventilation by preference. The final patient was successfully implanted and discharged to a long-term acute care (LTAC) hospital but subsequently had life prolonging measures withdrawn.

   Of the 18 patients who were able to be weaned from mechanical ventilation, 12 (67%) did not require LTAC placement. These patients were weaned from mechanical ventilation in an average of 5.7 days. Interestingly, these patients had earlier than average implantation at 11.1 days after trauma. In addition, eight patients (36%) had complete recovery of respiration, DP was no longer needed, and their percutaneous electrodes were removed.

DP can successfully wean traumatic cervical SCI patients as evidenced by 73% of the implanted patients being completely weaned from ventilators and 44% with complete recovery and DP removal. For those patients with stimulatable diaphragms, remarkably, 73%were completely weaned from mechanical ventilation. If the two patients with delayed weaning from ventilator facilities at 180 days after implantation are included, 82% of all patients with DP were completely weaned. Of these, 63% did not require LTAC placement. This reduction in time spent weaning and avoidance of LTAC placement are obviously significant improvements in care that should allow SCI patients earlier access to acute rehabilitation for sooner reintegration into their family and community.

The study evaluated psychosocial issues regarding patient and caregiver response to diaphragm pacing via assessment of quality of life, functional recovery and caregiver strain. Using logs that the patients and caregivers will maintain, information regarding device use was collected such as the patients full-time use of the device, the preference to use it for either day or night-time assist instead of a mechanical ventilator, or partial use to accomplish some activity or achieve independence that would otherwise be difficult or unable to be accomplished on mechanical

In conclusion, given the available information above, the data support that for NeuRx Diaphragm Pacing System is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. For use only in patients 18 years of age or older. The probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

Device benefit is demonstrated by the ability of 90% of subjects in the study to breath without a ventilator for at least 4 hour/day and 50-60% of subjects to breath without a ventilator for 24 hours/day. There were 0 device-related SAEs in the primary cohort. The most common AEs were capnothorax in 39% of the primary cohort which is common in laparoscopic procedures and almost always resolves without intervention, external equipment failure in 15%, and broken external wires in 13% for which repair methods are established and specified; and these are consistent with the anticipated AEs for such a procedure. Improved daily activities was observed in 57% of subjects from a multicenter study; 79% of subjects expressed overall satisfaction and 96% were happy with their decision to undergo implantation.

There appears to be a survival benefit for the primary cohort, particularly in subjects over age 40, compared to published similar reference cohorts. Thus, device benefit is substantial, and risks appear to be low. The benefits of using the device outweigh the risks and the data support that a significant portion of the patient population will achieve clinically significant results.

XIV. CDRH DECISION

CDRH issued an approval order on March 31, 2023.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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