NeuRx DPS® Post-Approval Clinical Study Summary

NeuRx Diaphragm Pacing System (DPS)

HUMANITARIAN USE DEVICE

Humanitarian Device. Authorized by Federal law for use in the treatment of chronic hypoventilation in ALS patients. The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

INTENDED USE

The NeuRx Diaphragm Pacing System (DPS)® is a percutaneous, intramuscular, diaphragm motor point stimulating device intended for use in amyotrophic lateral sclerosis (ALS) patients with a stimulatable diaphragm (both right and left portions) as demonstrated by voluntary contraction or phrenic nerve conduction studies, and who are experiencing chronic hypoventilation (CH), but not progressed to an FVC less than 45% predicted. For use only in patients 21 years of age or older.

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INTRODUCTION

The purpose of this document is to provide a summary of the results of the post-approval study (PAS) of the NeuRx Diaphragm Pacing System (DPS)® approved under Humanitarian Device Exemption (HDE) H100006 for use in amyotrophic lateral sclerosis (ALS) patients.

INDICATIONS FOR USE

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

- FVC less than 50% predicted
- MIP less than 60 cm H_2O
- PCO_2 greater than or equal to 45 mm Hg
- SaO_2 less than 88% for 5 consecutive minutes during sleep

CONTRAINDICATIONS

None known

WARNINGS AND PRECAUTIONS

See the NeuRx Diaphragm Pacing System (DPS)® Clinician's Manual - Procedure & Technique Guide (Part Number 77-0057) for warnings and precautions.

DEVICE DESCRIPTION

The NeuRx DPS® is a percutaneous, intramuscular, diaphragm motor point stimulation system. It is implanted using standard laparoscopic surgical techniques in an outpatient procedure. The implanted intramuscular diaphragm electrodes are connected to a four channel external stimulator at a percutaneous exit site. The stimulator provides a capacitively coupled, charge balanced, biphasic stimulation to each electrode with a common indifferent electrode that is placed

subcutaneously. The stimulator controls the charge delivered through clinician programmed parameters of pulse amplitude, pulse duration, pulse frequency, pulse ramp, inspiration time, and respiratory rate. The clinician uses a clinical station to characterize electrode response to stimulation and program the external stimulator with the patient specific parameters. The user connects the stimulator and turns it on for use; no other controls are available or necessary for operation.

HDE POST-APPROVAL STUDY (PAS)

Summary of the Study Methods

This study was conducted as an open-label, post-approval study of the NeuRx DPS in subjects with ALS. For subjects to be considered for enrollment, they had to meet the HDE device indications. Most notably subjects were required to have bilateral phrenic nerve function and chronic hypoventilation as described below under Study Population. The study was required to enroll 60 subjects. The primary study outcome measure was to evaluate device safety (types and frequency of major device-related adverse events). The study further evaluated the relationship of NeuRx DPS treatment to survival. Survival was defined as time to (a) death or (b) permanent tracheostomy mechanical ventilation (PTV) with discontinuation of pacing.

Subjects that met the screening criteria, where scheduled for electrode implant. Those subjects that did not have a stimulatable diaphragm during the intra-operative mapping procedure were not implanted and were considered to be screen failures. Subjects not receiving implants were followed for at least 30 days to evaluate for the occurrence of adverse events associated with the procedure. Subjects that received implants were followed every 3 months until the last enrolled subject until the last enrolled subject reached the 2-year follow-up visit, as long as the participant continued to survive and had not reached the PTV endpoint.

Study Objectives

The study objectives and outcome measures are defined in the protocol as follows:

Primary Objective

1. *Safety:* Characterize the types and frequency of major device-related adverse events (AEs) over the time of device use.

Secondary Objectives

2. *Safety:* Determine whether the frequency of major device-related AEs increases dramatically toward end of life.
3. *Probable Benefit:* Determine whether there is a relationship between survival time and onset type (bulbar and limb), time from onset to treatment, and use of noninvasive ventilation (NIV), Riluzole, or percutaneous endoscopic gastrostomy (PEG) in subjects treated with the device.

Study Design

This study was conducted as an open-label, multi-center, post-approval study of the NeuRx DPS system in subjects that met the HDE device indications for use.

Study Population

This study enrolled ALS subjects who met the HDE device indications for use and had undergone the surgical implantation procedure to receive the NeuRx DPS System. Key eligibility criteria were:

- age 21 or older
- familial or sporadic ALS diagnosed as laboratory-supported probable, probable
- bilateral phrenic nerve function clinically acceptable as demonstrated by bilateral diaphragm movement with fluoroscopic sniff test or with EMG recordings and nerve conduction times
- chronic hypoventilation documented by at least one of the following:
    - FVC less than 50% predicted (but not less than 45% predicted), or
    - |MIP| less than 60 cmH_2O, or
    - $PaCO_2$ greater than or equal to 45 mmHg, or
    - nocturnal SaO_2 less than or equal to 88% for at least five continuous minutes

Data Source

Data were collected prospectively under a post-approval study protocol approved by FDA under HDE H100006 (NCT01605006).

Key Study Endpoints

Safety Outcome Measure

The safety outcome measure for this study was the occurrence of major device-related (including procedure-related) adverse events as defined as:

- Serious capnothorax requiring invasive intervention (such as chest tube placement).
- Mechanical ventilation for 24 hours or longer post-procedure.
- Post-procedure extubation failure resulting in permanent tracheostomy ventilation (PTV).
- Perioperative complication which delays the initiation of NeuRx DPS therapy.
- Severe discomfort due to stimulation which is unable to be tolerated or resolved and results in interruption or discontinuation of NeuRx DPS therapy.
- Device malfunction (e.g., broken wire or stimulator) which interrupts or causes an undesired diminution of NeuRx DPS therapy (e.g., no stimulation in one hemi-diaphragm).
- Electrode dislodgement from the diaphragm.
- Wire infection.

- Any other device- or procedure-related serious adverse event (SAE) that is fatal, life threatening, requires or prolongs hospitalization, or requires intervention to prevent permanent impairment or damage.

Probable Benefit Outcome Measure

The probable benefit outcome measure for this study was:
Survival, defined as time to (a) death or (b) permanent tracheostomy mechanical ventilation (PTV) with discontinuation of pacing. (All deaths and PTV events will be reported regardless of relationship to the device or procedure.)

Total Number of Enrolled Study Sites and Subjects, Follow-up Rate

Twelve (12) clinical sites received IRB approval for the study, had an executed clinical trial agreement with Synapse (the study sponsor) and were considered enrolled. Ten (10) of these sites initiated the study and enrolled at least one participant. The minimum enrollment target of 60 participants was met on August 11, 2014. The demographics of the enrolled subjects are summarized in Table 1 and Table 2.

Table 1: Summary of demographic characteristics of the enrolled participants (Part 1)

Demographic Characteristic	All Subjects			Ongoing			Endpoint			Fail-to-Stim			Withdrew*		
Gender	n	N	%-age	n	N	%-age	n	N	%-age	n	N	%-age	N	N	%-age
Male	37	60	61.7%	5	8	62.5%	21	33	63.6%	3	6	50.0%	8	13	61.5%
Female	23	60	38.3%	3	8	37.5%	12	33	36.4%	3	6	50.0%	5	13	38.5%
ALS diagnosis															
laboratory-supported probable	0	60	0.0%	0	8	0.0%	0	33	0.0%	0	6	0.0%	0	13	0.0%
probable	19	60	31.7%	4	8	50.0%	13	33	39.4%	1	6	16.7%	1	13	7.7%
definite	41	60	68.3%	4	8	50.0%	20	33	60.6%	5	6	83.3%	12	13	92.3%
ALS onset location															
limb	40	60	66.7%	6	8	75.0%	19	33	57.6%	4	6	66.7%	11	13	84.6%
bulbar	20	60	33.3%	2	8	25.0%	14	33	42.4%	2	6	33.3%	2	13	15.4%
limb and bulbar	0	60	0.0%	0	8	0.0%	0	33	0.0%	0	6	0.0%	0	13	0.0%
Chronic hypoventilation established with															
|MIP|	50	60	83.3%	6	8	75.0%	29	33	87.9%	5	6	83.3%	10	13	76.9%
FVC	8	60	13.3%	1	8	12.5%	4	33	12.1%	0	6	0.0%	3	13	23.1%
PaCO2	3	60	5.0%	1	8	12.5%	2	33	6.1%	0	6	0.0%	0	13	0.0%
SaO2	4	60	6.7%	2	8	25.0%	0	33	0.0%	1	6	16.7%	1	13	7.7%
Stimulatable diaphragm established with															
sniff test under flouroscopy	37	60	61.7%	7	8	87.5%	18	33	54.5%	4	6	66.7%	8	13	61.5%
phrenic nerve conduction study (PNCS)	43	60	71.7%	5	8	62.5%	27	33	81.8%	4	6	66.7%	7	13	53.8%
Baseline concomitant treatments															
baseline NIV	42	60	70.0%	7	8	87.5%	25	33	75.8%	4	6	66.7%	6	13	46.2%
baseline PEG	9	60	15.0%	2	8	25.0%	6	33	18.2%	0	6	0.0%	1	13	7.7%
baseline cough assist	16	60	26.7%	1	8	12.5%	12	33	36.4%	1	6	16.7%	2	13	15.4%
baseline Riluzole	37	60	61.7%	6	8	75.0%	21	33	63.6%	4	6	66.7%	6	13	46.2%

*Withdrew: N=13 is inclusive of 11 withdrawals and 2 lost to follow up participants.

** Note: Some participants qualified with more than one of the chronic hypoventilation tests (at least one is required).

***Note: Some participants qualified with both sniff test and PNCS (at least one is required). One participant did not have either test done (protocol deviation) but was stimulatable during mapping at surgery.

Table 2: Summary of demographic characteristics of the enrolled participants (Part 2)

Demographic/Clinical Characteristic	Min.	Mean	Median	Max.	Std. Dev.	N
Age at Surgery						
All subjects	42.0	59.2	59.0	79.0	9.1	60
Ongoing (implanted, surviving)	42.0	55.3	54.5	76.0	11.1	8
Endpoint (death or PTV)	47.0	61.3	60.0	75.0	7.4	33
Fail-to-Stim (not implanted)	43.0	58.0	56.5	79.0	12.3	6
Withdrew (implanted, withdrew)	43.0	56.7	56.0	76.0	9.7	13
Time since ALS onset (months)						
All subjects (impute 15 for missing day and 7 for missing month)	6.4	32.4	25.3	129.3	24.6	60
All subjects (impute 15 for missing day)	6.4	27.5	22.1	86.7	16.7	52
Implanted subjects (observed data)	6.6	24.3	19.7	60.1	15.4	14
All subjects (observed data)	6.6	24.5	21.0	60.1	14.5	16
Time since ALS diagnosis (months)						
All subjects (impute 15 for missing day and 7 for missing month)	0.7	15.5	10.4	78.5	14.7	60
All subjects (impute 15 for missing day)	0.7	15.3	10.3	78.5	14.6	59
Implanted subjects (observed data)	0.7	14.5	9.1	78.5	16.2	44
All subjects (observed data)	0.7	14.0	8.6	78.5	15.7	48
Ongoing (implanted, surviving)	4.0	17.2	7.5	40.3	16.2	5
Endpoint (death or PTV)	0.7	9.5	6.2	42.4	9.7	29
Fail-to-Stim (not implanted)	1.1	7.6	6.1	17.3	7.1	4
Withdrew (implanted, withdrew)	3.6	27.8	21.1	78.5	23.8	10
Time from Implant to Last Follow-up or Endpoint (months)						
All subjects	0.2	16.1	14.4	37.5	9.5	54
Ongoing (implanted, surviving)	24.0	28.9	28.5	35.9	4.4	8
Endpoint (death or PTV)	0.2	13.2	10.8	28.1	8.4	33
Fail-to-Stim (not implanted)	N/R	N/R	N/R	N/R	N/R	0
Withdrew (implanted, withdrew)	6.8	15.8	15.4	37.5	8.0	13
Chronic hypoventilation qualification values						
|MIP|						
All subjects	8.0	40.1	40.0	64.0	12.7	51
Ongoing (implanted, surviving)	32.0	43.3	44.0	53.0	8.7	6
Endpoint (death or PTV)	8.0	40.1	41.0	59.0	13.0	29
Fail-to-Stim (not implanted)	21.0	36.0	36.0	57.0	13.5	5
Withdrew (implanted, withdrew)	21.0	40.3	35.0	64.0	14.5	11
FVC						
All subjects	30.0	61.8	60.0	104.0	13.5	45
Ongoing (implanted, surviving)	45.0	60.4	60.0	76.0	11.6	5

Demographic/Clinical Characteristic	Min.	Mean	Median	Max.	Std. Dev.	N
Endpoint (death or PTV)	30.0	62.3	63.0	104.0	14.8	27
Fail-to-Stim (not implanted)	63.0	66.3	63.0	73.0	5.8	3
Withdrew (implanted, withdrew)	47.6	60.0	54.0	81.0	13.7	10
$PaCO_2$						
All subjects	34.0	48.0	49.5	59.0	10.7	4
Ongoing (implanted, surviving)	34.0	43.5	43.5	53.0	13.4	2
Endpoint (death or PTV)	46.0	52.5	52.5	59.0	9.2	2
Fail-to-Stim (not implanted)	N/R	N/R	N/R	N/R	N/R	0
Withdrew (implanted, withdrew)	N/R	N/R	N/R	N/R	N/R	0
SaO_2						
All subjects	83.0	86.6	87.6	88.0	2.4	4
Ongoing (implanted, surviving)	87.2	87.6	87.6	88.0	0.6	2
Endpoint (death or PTV)	N/R	N/R	N/R	N/R	N/R	0
Fail-to-Stim (not implanted)	88.0	88.0	88.0	88.0	N/R	1
Withdrew (implanted, withdrew)	83.0	83.0	83.0	83.0	N/R	1
Baseline ALSFRSr total score						
All subjects	10.0	28.6	30.0	46.0	8.2	57
Ongoing (implanted, surviving)	14.0	28.8	31.0	36.0	7.3	8
Endpoint (death or PTV)	10.0	30.3	32.0	46.0	8.4	30
Fail-to-Stim (not implanted)	22.0	31.3	32.0	41.0	6.4	6
Withdrew (implanted, withdrew)	14.0	23.5	20.0	35.0	7.7	13
Baseline ALSFRSr respiratory subscore						
All subjects	4.0	8.7	9.0	12.0	2.2	58
Ongoing (implanted, surviving)	5.0	8.9	9.5	12.0	2.4	8
Endpoint (death or PTV)	4.0	8.6	9.0	12.0	2.2	31
Fail-to-Stim (not implanted)	8.0	9.0	8.0	12.0	1.7	6
Withdrew (implanted, withdrew)	5.0	8.4	8.0	12.0	2.2	13

Of the 60 participants enrolled, 54 subjects were successfully implanted with the NeuRx DPS electrodes. Six (6) participants had a negative diaphragm mapping procedure (i.e., did not have a stimulatable diaphragm at surgery) and were not implanted. All 6 of these subjects completed the study after being followed per the protocol for perioperative adverse events of which none were reported. Thirty-four (34) participants reached a study endpoint with 30 having died and 4 having discontinued diaphragm pacing after transitioning to permanent tracheostomy ventilation (PTV). Ten (10) participants withdrew from the study and 2 participants were lost to follow-up. Eight (8) subjects reached the 24-month follow-up visit and continued to use the device. Participant progression through the study is shown in Table 3 below.

Table 3: Summary of participant progression through the study

Study Milestone / Follow-Up / Event	Milestone / Follow-Up Completed	Missed Follow-up	Follow-up (Awaiting Report)	Lost to Follow-up	Withdrawn	Death or PTV Endpoint
Enrolled	60	-	-	-	-	-
Implanted	54	-	-	-	-	0
Not Implanted	6	-	-	-	-	0
30 - 45 Day No-Implant Follow-up	6	0	0	0	0	0
3-Mon. Follow-up	51	0	0	0	0	3
6-Mon. Follow-up	47	1	0	0	0	3
9-Mon. Follow-up	36	3	0	0	1	8
12-Mon. Follow-up	31	0	0	0	2	6
15-Mon. Follow-up	25	1	0	0	3	2
18-Mon. Follow-up	19	4	0	0	2	1
21-Mon. Follow-up	15	3	0	0	1	4
24-Mon. Follow-up	14	2	0	1	0	1
27-Mon. Follow-up	6	1	0	1	0	4
30-Mon. Follow-up	5	0	0	0	1	1
33-Mon. Follow-up	2	1	0	0	0	0
36-Mon. Follow-up	1	0	1	0	0	0
39-Mon. Follow-up	0	0	0	0	1	0

Study Visits and Length of Follow-up

Follow-up assessments were performed every three months following NeuRx DPS implantation until the last enrolled subject reached the 2-year follow-up visit, as long as the participant continued to survive and had not reached the PTV endpoint. Any participant who went to surgery but was not ultimately implanted with the device (e.g., due to complications) was followed under the PAS protocol for at least 30 days. At least one post-operative follow-up assessment was conducted 30-45 days following the date of the surgical procedure.

Summary of the Study Results

Primary Objective – Types and Frequency of Major Device-related Adverse Events

The "major device-related adverse events" (MDRAEs) which have been reported to date are summarized in Table 4 below. Of the 41 MDRAEs, 5 were classified by the investigator as serious:

- 2 reports of capnothoraces requiring invasive intervention with a chest tube; all resolved in 1-2 days. (1 additional report of capnothorax treated with a pigtail catheter was classified as non-serious and resolved within 1 day.)
- 1 report of history of poor pain control precluding the ability to program and use the DPS device.
- 1 report of pulmonary embolism peri-operatively requiring hospitalization and having fatal resolution.
- 1 report of post-operative spasticity and development of bilateral lung infiltrates requiring 2 bronchoscopies, one with removal of a mucous plug.

The most commonly occurring MDRAEs were due to skin infection at the percutaneous wire exit site. These 22 events classified under "wire infection" occurred in 12 study participants. All have been classified as not serious. All signs and symptoms of wire infection have been localized to the skin and surface area and reports have included tenderness, redness, discomfort, irritation, swelling, pain and in a few accounts a small amount of drainage. These infections are typically the result of normal skin flora and in some cases due to improper site care. In each case there have been no reports of the development of signs and symptoms of systemic inflammatory response syndrome (SIRS). No subject has reported fever, chills, tachycardia, hypotension or other signs of sepsis in connection with the reported wire infections. There have been no reported cases of the infection progressing to down the electrode wires to the diaphragm, sepsis which may have been directly or indirectly linked to an electrode wire (line) infection, or bacteremia in any subject. No treating physician has elected to perform blood cultures for these subjects.

Table 4: Occurrence of major device-related (including procedure-related) adverse events (MDRAEs)

Major device-related (including procedure related) adverse event (MDRAE)	Number of Reports	Number of Participants	Percentage of Participants
Serious capnothorax requiring invasive intervention (such as chest tube placement).	3	3	1.8%
Mechanical ventilation for 24 hours or longer post-procedure.	0	0	0%
Post-procedure extubation failure resulting in permanent tracheostomy ventilation (PTV).	0	0	0%
Perioperative complication which delays the initiation of NeuRx DPS therapy.	2	2	1.2%
Severe discomfort due to stimulation which is unable to be tolerated or resolved and results in interruption or discontinuation of NeuRx DPS therapy.	1	1	0.6%
Device malfunction (e.g., broken wire or stimulator) which interrupts or causes an undesired diminution of NeuRx DPS™ therapy (e.g., no stimulation in one hemi-diaphragm).	11	10	6%
Electrode dislodgement from the diaphragm.	0	0	0%
Wire infection (skin infection at the percutaneous wire exit site).	22	12	7.2%
Any other device- or procedure-related serious adverse event (SAE) that is fatal, life threatening, requires or prolongs hospitalization, or requires intervention to prevent permanent impairment or damage.	2	2	1.2%

Table 5 presents a cumulative incidence of any MDRAE at 9 months and 21 months. The highest incidence rate of MDRAEs at 9 and 21 months was due to skin infection at the percutaneous wire exit site [21.7% (95%CI: 12.7, 35.8)] at 9 months and [21.7% (95%CI: 12.7, 35.8)] at 21 months followed by device malfunction which interrupts or causes an undesired diminution of NeuRx DPS therapy being [18.3% (95%CI: 9.9, 32.4)] at 9 months and [21.9% (95%CI: 12.2, 37.6)] at 21 months.

Table 5: Cumulative Incidence for Any MDRAE (n=54 implanted subjects)

Major device-related adverse events (MDRAEs)	Incidence at 9 months (270 days)		Incidence at 21 months (630 days)	
	Rate (%)[1,2]	95% CI[1,2,3]	Rate (%)[1,2]	95% CI[1,2]
Serious capnothorax requiring invasive intervention (such as chest tube placement).	5.6%[1]	(1.8, 16.2)[1]	5.6%[1]	(1.8, 16.2)[1]
Mechanical ventilation for 24 hours or longer post-procedure.	0%[2]	(0.0, 9.2)[2]	0%[2]	(0.0, 17.6)[2]
Post-procedure extubation failure resulting in permanent tracheostomy ventilation (PTV).	0%[2]	(0.0, 9.2)[2]	0%[2]	(0.0, 17.6)[2]
Perioperative complication which delays the initiation of NeuRx DPS therapy.	3.7%[1]	(0.9, 14.0)[1]	3.7%[1]	(0.9, 14.0)[1]
Severe discomfort due to stimulation which is unable to be tolerated or resolved and results in interruption or discontinuation of NeuRx DPS therapy.	0%[2]	(0.0, 9.2)[2]	4.2%[1]	(0.6, 26.1)[1]
Device malfunction (e.g., broken wire or stimulator) which interrupts or causes an undesired diminution of NeuRx DPS™ therapy (e.g., no stimulation in one hemi-diaphragm).	18.3%[1]	(9.9, 32.4)[1]	21.9%[1]	(12.2, 37.6)[1]
Electrode dislodgement from the diaphragm.	0%[2]	(0.0, 9.2)[2]	0%[2]	(0.0, 17.6)[2]
Wire infection (skin infection at the percutaneous wire exit site).	21.7%[1]	(12.7, 35.8)[1]	21.7%[1]	(12.7, 35.8)[1]
Any other device- or procedure-related serious adverse event (SAE) that is fatal, life threatening, requires or prolongs hospitalization, or requires intervention to prevent permanent impairment or damage.	3.7%[1]	(0.9, 14.0)[1]	3.7%[1]	(0.9, 14.0)[1]
At least one MDRAE	42.7%[1]	(30.4, 57.6)[1] (, 55.1%)[3]	47.9%[1]	(33.6, 64.7)[1] (, 61.9%)[3]

[1] Estimates are made using the Kaplan-Meier Product Limit method. Two-sided 95% confidence interval.

[2] A proportion was calculated with 0 events and N=38 subjects alive without a tracheostomy past 270 days/9 months and N=18 followed past 630 days/21 months with a Wilson's 95% confidence interval.

[3] Estimates are made using the Kaplan-Meier Product Limit method. One-sided 95% confidence interval.

Secondary Objectives

Safety Objective - Frequency of MDRAE at End of Life

A secondary safety objective was to determine whether the frequency of MDRAEs increased dramatically toward end of life. A corresponding probable benefit outcome measure was participant survival, defined as time to (a) death or (b) permanent tracheostomy mechanical ventilation (PTV) with discontinuation of pacing. A total of 34 subjects experienced either death (30 subjects) or PTV (4 subjects) during the follow-up period. Of the 30 deaths and 4 PTV:

- Relationship to the surgical implant procedure
    - 29 deaths and 4 PTVs were classified by the investigator as not related to the surgical implant procedure
    - One (1) death (following pulmonary embolism in participant 12-002) was classified as having a highly probable relationship.
- Relationship to the device
    - 27 deaths and 4 PTVs were classified as not related to the device.
    - Three (3) deaths were classified as unlikely related to the device
        - Participant 01-002 experienced respiratory failure and required use of a ventilator.
        - Participant 01-003 experienced respiratory failure while using NIV and DPS pacer, resuscitated but found to have extensive brain damage and treatment stopped.
        - Participant 12-003 entered hospice and died due to progression of ALS.

Probable Benefit Objective – Survival Time and Relationship to Subject Characteristics

The Kaplan-Meier curve for time to first endpoint event from time of implant surgery is provided in Figure 1. The median survival time is estimated at 583 days or 19.4 months with lower 95% confidence limit of 373 days or 12.4 months and the upper confidence limit of 823 days and 27.4 months. The Kaplan-Meier curve for time to first endpoint from time of ALS diagnosis is provided in Figure 2. The median survival time from diagnosis is 959 days or 32.0 months with lower 95% confidence limit of 842 days or 28.1 months and the upper confidence limit of 991 days or 32.0 months in 53 subjects (with day imputed if missing). The Kaplan-Meier curve for time to first endpoint from time of onset of ALS symptoms is provided in Figure 3. The median survival time from diagnosis is 1348 days or 44.9 months with lower 95% confidence limit of 1088 days or 36.3 months and the upper confidence limit of 1877 days or 62.6 months in 48 subjects (with day imputed if missing).

Figure 1: Kaplan-Meier Curve for Freedom from Death or Permanent Tracheostomy Mechanical Ventilation with Discontinuation of Pacing from Implant Surgery for Subjects Implanted with DPS (N=54)

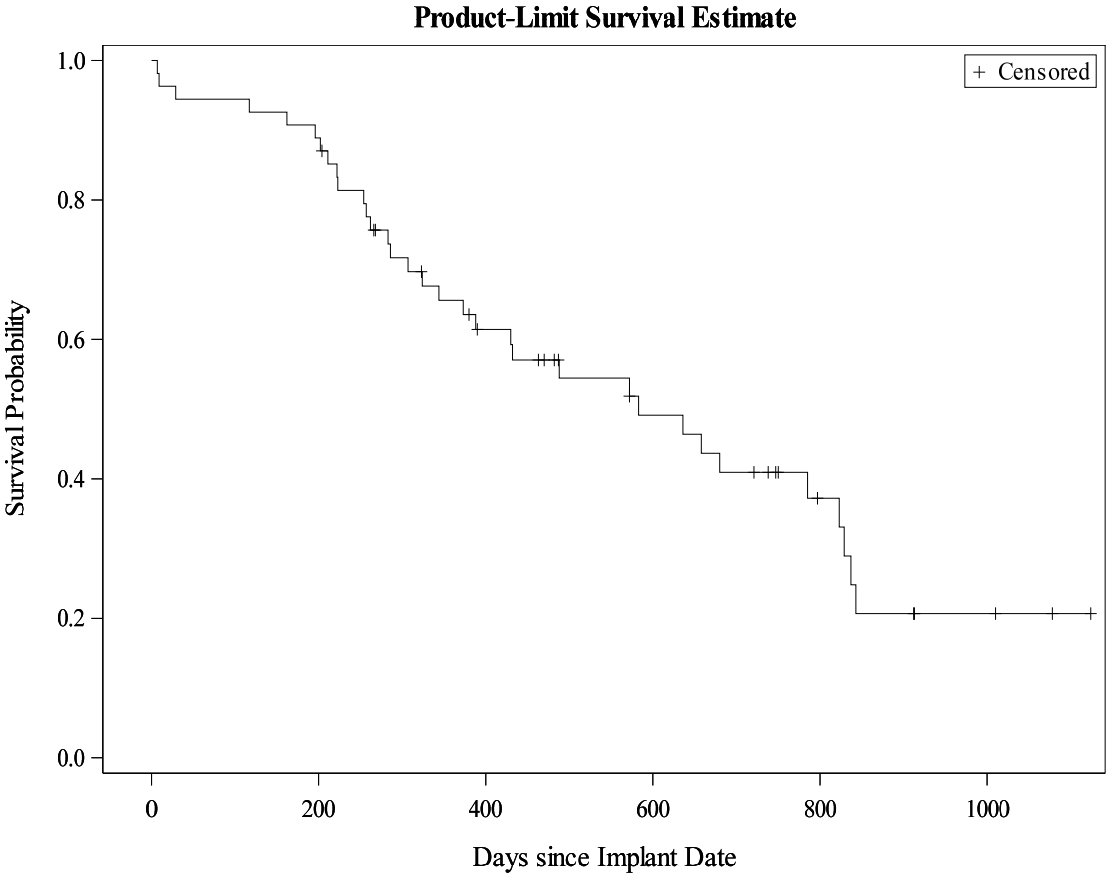


Figure 2: Kaplan-Meier Curve Tracheostomy Free Survival from ALS Diagnosis in Implanted Subjects with Diagnosis Date (N=53)

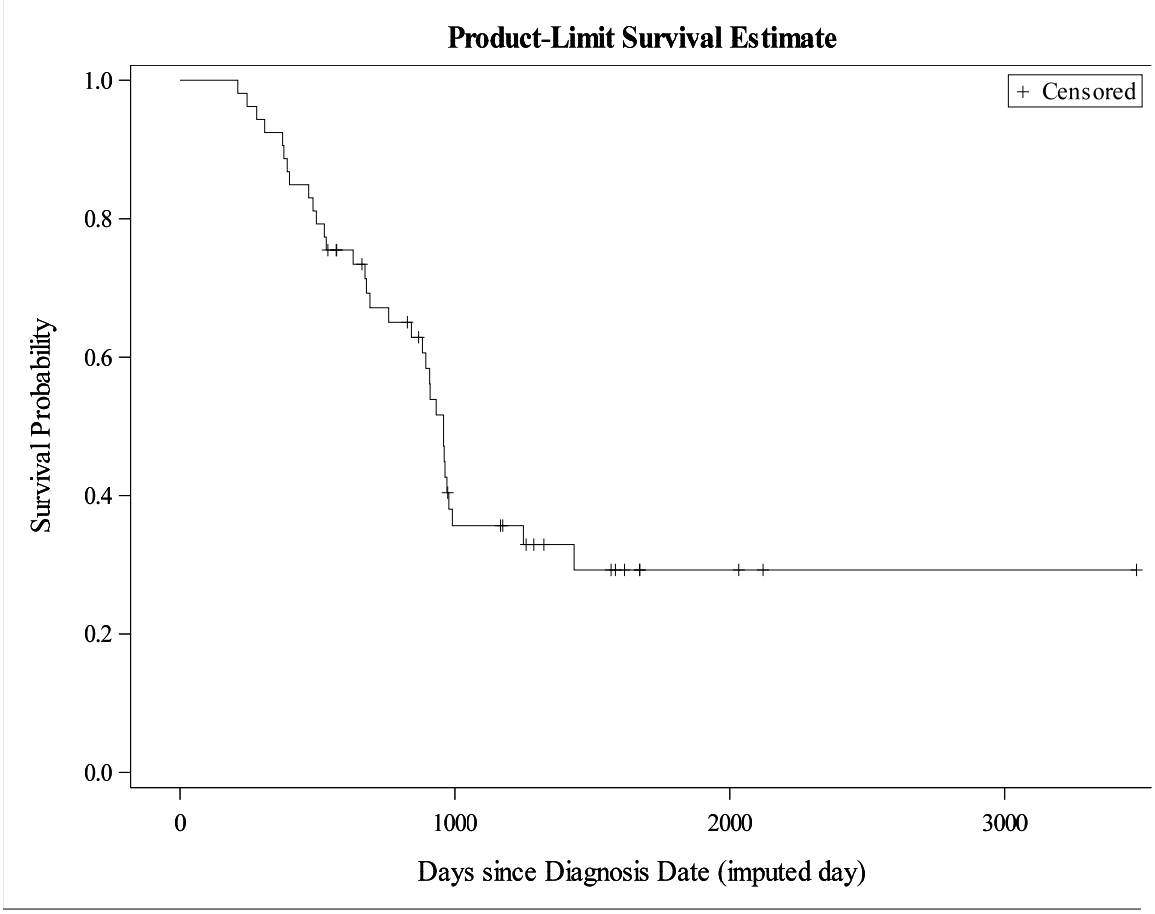
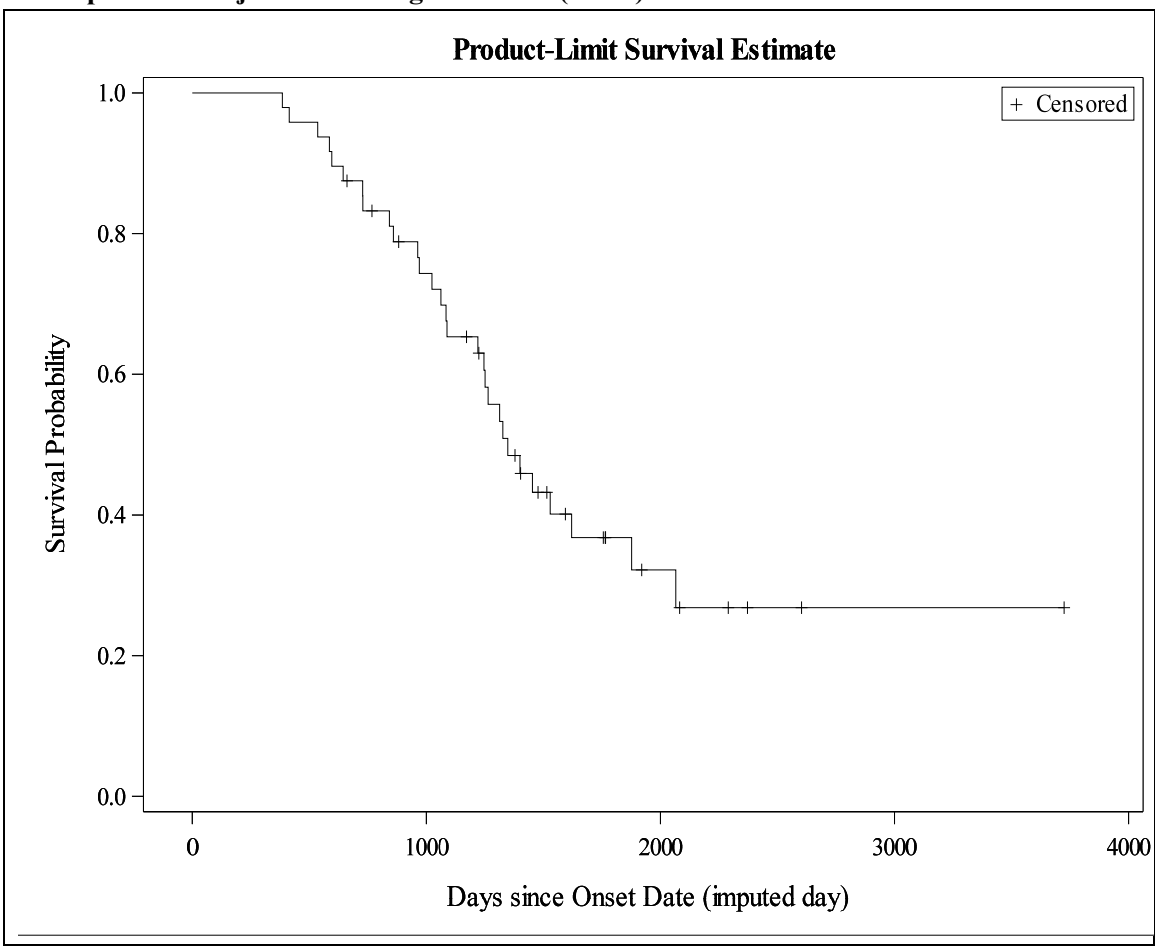


Figure 3: Kaplan-Meier Curve Tracheostomy Free Survival from ALS Onset in Implanted Subjects with Diagnosis Date (N=48)



An additional secondary endpoint focused on determining if there was a relationship between survival time and a set of defined criteria: onset type (bulbar and limb), time from onset to treatment, and use of NIV, riluzole or PEG in subjects treated with the device. No relationship was identified between these elements using the Log Rank Test and Kaplan Meier Analysis (
Table **6**).

Table 6: Relationship between survival time and defined criteria

Covariate	Log Rank P-value from Single Variable Model*
Onset Type (Bulbar vs. Limb)	0.3520 N=54
Time from Onset to Treatment (impute 15 for missing day)	0.0719 N=48
Time since ALS Diagnosis (impute 15 for missing day)	0.1955 N=44
Use of NIV (y/n) as recorded at baseline	0.5451 N=53
Use of Riluzole (y/n) as recorded at baseline	0.8672 N=54
Use of PEG (y/n) as recorded at baseline	0.9107 N=54

Final Safety Findings (Key Endpoints)

A total of 41 MDRAEs were reported over the cumulative device implant time of 1,013.6 months. The rate of event occurrence was 0.04 per month or 0.68 events per subject during the course of the study.

Wire infections accounted for 54% of these events and occurred in only 20% of the study participants (some participants experience more than one event). As noted above, these events were not serious and treatable with one course of antibiotic except in one case which required a second course of medication. Device malfunctions (e.g., broken wire or stimulator) accounted for 26.8% and occurred in 16.7% of the study participants. None of these events were classified by the investigators as serious. Serious MDRAEs occurred in 8.3% of the subjects and included 2 capnothoraces requiring intervention, one instance of severe discomfort and 2 instances of post-operative lung complications.

Analysis of the secondary safety endpoint shows no indication of an increased frequency of MDRAEs toward the end of life.

Final Probable Benefits Findings (Key Endpoints)

Additionally, the secondary endpoint looking at survival as defined by time to (a) death or (b) PTV with discontinuation of pacing indicated probable benefit from device use. Median survival was 19.4 months from DPS implant which is comparable to the median survival of 18.9 months from DPS implant previously reported for the HUD Group (N=84) in the HDE H100006.

An additional secondary endpoint focused on determining if there was a relationship between survival time and a set of defined criteria: onset type (bulbar and limb), time from onset to treatment, and use of NIV, riluzole or PEG in subjects treated with the device. No relationship was identified between these elements using the Log Rank Test and Kaplan Meier Analysis.

Study Strength and Weaknesses

The strength of this study is that enrolled subjects were consistent with the HDE criteria for treating subjects with this device. The results are similar to the results from the HDE trial. The weakness of this study is that there is no control group with which to compare the results.

OTHER STUDIES

HDE Pre-Approval Study (IDE G040142)

Prior to HDE approval NeuRx DPS, an investigational device exemption (IDE) study was conducted. The results of that study are summarized in the Summary of Safety and Probable Benefit (SSPB) which is available on the FDA website at https://www.accessdata.fda.gov/cdrh_docs/pdf10/H100006B.pdf

DiPALS UK Study

McDermott et al., 2015, in the UK, undertook an open-label, randomized controlled trial of NeuRx DPS in ALS patients with respiratory insufficiency. Their published report concluded that addition of diaphragm pacing to standard care with non-invasive ventilation (NIV) was associated with decreased survival in patients with ALS, and that diaphragmatic pacing should not be used as a routine treatment for patients with ALS in respiratory failure[1]. In a published letter in response, Miller and Lewis[2] stated that the shorter survival was significant in a post-hoc analysis only when comparing patients who did not use NIV (were intolerant or non-compliant) and asked for a per-protocol analysis. The response by McDermott indicates that, in the per-protocol analysis, the survival difference was not statistically significant.

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[1] DiPALS Writing Committee; DiPALS Study Group Collaborators. Safety and efficacy of diaphragm pacing in patients with respiratory insufficiency due to amyotrophic lateral sclerosis (DiPALS): a multicentre, open-label, randomised controlled trial. Lancet Neurol. 2015 Sep;14(9):883-892. doi: 10.1016/S1474-4422(15)00152-0. Epub 2015 Jul 30. PubMed PMID: 26234554.

[2] Miller RG, Lewis RA. Diaphragm pacing in patients with amyotrophic lateral sclerosis. Lancet Neurol. 2016 May;15(6):542. doi: 10.1016/S1474-4422(16)30012-6. Epub 2016 Apr 11. PubMed PMID: 27302114.