DE NOVO CLASSIFICATION REQUEST FOR PHAGENYX SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Oropharyngeal Electrical Stimulator. An oropharyngeal electrical stimulator is a device that stimulates afferent nerve fibers of oropharyngeal mucosa. The device is intended to treat swallowing dysfunction. The device may incorporate a feeding tube.

NEW REGULATION NUMBER: 21 CFR 874.5950

CLASSIFICATION: Class II

PRODUCT CODE: QQG

BACKGROUND

DEVICE NAME: Phagenyx System

SUBMISSION NUMBER: DEN220025

DATE DE NOVO RECEIVED: April 19, 2022

SPONSOR INFORMATION:

Phagenesis Limited
Enterprise House
Manchester Science Park
Manchester, UK, M15 65E

INDICATIONS FOR USE

The Phagenyx System is indicated as follows:

The Phagenyx System is a neurostimulation device delivering electrical stimulation to the oropharynx, to be used in addition to standard dysphagia care, as an aid to improve swallowing in patients with severe dysphagia post stroke.

LIMITATIONS

The sale, distribution, and use of the Phagenyx System are restricted to prescription use in accordance with 21 CFR 801.109.

The device is intended to be used in addition to standard dysphagia care.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Phagenyx System comprises; a sterile single-patient use catheter (PNX-1000) and a Base Station (EPSB3). The catheter is a two-part fine bore flexible tube that is introduced nasally and extends down as far as the patients' stomach. It incorporates two bipolar ring electrodes on its outer surface to deliver the electrical stimulation. It also incorporates a feeding tube to facilitate delivery of nutrition or hydration. The Base Station has a touch screen user interface that facilitates the optimization of stimulation levels for treatment and stores patient and treatment information.

Figure 1. Phagenyx System

Output parameters and other electrical specifications for the Phagenyx System are presented below in Table 1.

Table 1. Phagenyx System Specification

Parameter	Specification
Stimulation output (mA)	1 mA – 50 mA variable, controlled by user
Frequency	5 Hz fixed
Pulse width	200 µS fixed
Waveform	Monophasic square fixed
Current density at maximum output	4.4 mA/cm^2
Peak stimulation voltage	240V
Peak energy per pulse	2.4 mJ
Stimulation duration	10 minutes fixed
Indication Display – On/Off	 – Power button LED

– Active electrical output – Access control – Data input – Simulation optimization – Current level – Treatment timer – Electrode contact quality – Patient records	– Yellow LED hardware driven – Secure password access for authorized users – Touchscreen display/full qwerty keyboard – Stepwise graphic illustration/guide – mA display on screen – 10 minute countdown timer – Good/poor contact real time icon display – Patient ID and treatment information searchable database
Wireless connectivity	No
Data transfer	Via USB port in encrypted password controlled zipped files

SUMMARY OF NONCLINICAL/BENCH STUDIES

Non-clinical/bench studies were conducted on the Phagenyx System to demonstrate a reasonable assurance of safety and effectiveness.

BIOCOMPATIBILITY/MATERIALS

The Phagenyx System has been assessed and tested for biocompatibility as per FDA guidance Use of International Standard ISO 10993-1, "Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process" and ISO 10993 standards. The catheter part of the Phagenyx System is in contact with patient tissues for up to a maximum of 30 days and testing performed reflects this and the fact that the device is placed in a non-sterile environment via a natural bodily orifice. The materials in contact with internal patient tissues are known to be safe (stainless steel electrodes and polyurethane tubing) and have been used in the same types of body areas in other medical device products (e.g., fine bore nasogastric feeding tubes). Biocompatibility testing carried out on the PNX-1000 catheter is summarized in Table 2.

Table 2. Biocompatibility testing on the Phagenyx System catheter

Tests performed	**Acceptance criteria**	**Outcome**
Cytotoxicity (ISO 10993-5)	A reactivity score of 2 or less using the MEM Elution test	Pass
Sensitization (ISO 10993-10)	No macroscopic cutaneous reactions attributed to allergy on inspection post challenge	Pass
Irritation (ISO 10993-10)	Levels of irritation/edema within standard specified limits	Pass
Acute Systemic Toxicity (ISO 10993-11)	Equivalent biological reactivity levels in test and control sample animals	Pass
Ethylene Oxide (EO) residual (ISO 10993-7)	EO residuals within allowable limits	Pass

SHELF LIFE/STERILITY

The shelf life for the catheter component of the Phagenyx System is 3 years.

The catheter and catheter packaging have been tested for function and integrity (seal integrity per ASTM F1886, gross leaks per ASTM F2096 and seal strength per ASTM F88) after accelerated aging (ASTM F1980), real time aging and transportation simulation (ASTM D7386). All requirements were met.

The catheter is provided sterile for single patient use. It is sterilized with ethylene oxide (EO). The sterilization validation was performed to achieve a sterility assurance level (SAL) of 10^{-6} in accordance with ISO 11135-1:2014 Sterilization of health care products - Ethylene Oxide Requirements for development, validation, and routine control of a sterilization process for medical devices.

The base station of the Phagenyx System does not make direct patient contact and is provided non-sterile. Cleaning and disinfection instructions are included in the labeling.

ELECTRICAL SAFETY & ELECTROMAGNETIC COMPATIBILITY (EMC)

The Base Station and the integrated use of Base Station and PNX-1000 catheter as the Phagenyx System have been independently tested to demonstrate compliance with the following standards. All requirements were met.

- IEC 60601-1:2005 + COR1:2006 + COR2:2007 + A1:2012, Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

- EN 60601-1-2:2015 Medical electrical equipment. Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests

- EN60601-2-10:2015+A1:2016. Medical electrical equipment Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators

SOFTWARE

The software used in the Phagenyx Base Station was developed in accordance with IEC 62304:2006/A1:2016 Medical device software - Software life cycle processes. The software is considered to be a moderate level of concern. The submission contains all the elements of software documentation as recommended in the FDA guidance "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices."

Cybersecurity information for the USB flash drive was provided in accordance with the FDA Guidance Document, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices"

USABILITY

Critical tasks associated with the correct insertion, positioning and use of the catheter for feeding and stimulation were identified through the usability hazard analysis and a US usability study was conducted per the FDA's guidance "Applying Human Factors and Usability Engineering to Medical Devices." Following the training and competency assessment the representative users demonstrated correct and safe use of the device at the intended environment.

PERFORMANCE TESTING - BENCH

Design verification testing were performed for the PNX-1000 Catheter and EPSB3 Base Station component of the system and summarized below.

Table 3. Design Verification of the PNX-1000 Catheter

Category	Description
Mechanical	A range of tensile and actuation tests were performed to assess physical integrity of materials and robustness of manufacturing processes to produce finished parts. These tests were repeated after transport conditioning and 3-year real time aging to ensure integrity was not compromised under a range of environmental conditions or due to the passage of time. All tests were passed.
Nutritional	Tensile, pressure, flow, and corrosion tests were performed to ensure the nasogastric tubing part of the catheter met obligatory performance requirements for feeding tubes. A subset of these tests were repeated after transport conditioning and 3-year real time aging to ensure integrity was not compromised under a range of environmental conditions or due to the passage of time. All tests were passed.
Electrical	Functional tests to ensure pulse characteristics were within specification and temperature change testing to ensure safe performance at maximum output over time. Electrical integrity and continued function were assessed post transport conditioning and aging. All tests were passed.
Visual/dimensional	Measurements and inspections to verify design output drawings match physical parts. Visual appearance/integrity was repeated after aging studies to ensure no degradation over time. All tests were passed.

Table 4. Design Verification of the EPSB3 Base Station

Category	Description
Electronics Tests	These tests verified the electronic design of the EPSB3 Base Station by checking that the electronics operate correctly. All tests were passed.
System Tests	These tests verified the overall design of the EPSB3 Base Station by checking that the complete Base Station operates correctly. All tests were passed.

User Interface (UI) Software Tests	These tests verify the UI software design of the EPSB3 Base Station. These tests verify that the software can successfully perform the user interface functional operations as specified in the User Requirements Specification. All tests were passed and requirements met.
Unit Tests	These tests verify the design of key software functions/modules/units by checking that they work independently and correctly for EPSB3. All tests were passed.
Mechanical/ dimensional	These tests ensure that design outputs in the form of drawings, dimensions and physical features match the physical aspects of the finished product. All tests were passed and requirements met.

SUMMARY OF CLINICAL INFORMATION

Data from three studies, STEPS, PHAST-TRAC and PHADER involving a total of 298 subjects in 38 hospital sites and 7 countries are provided to evaluate the safety of the Phagenyx System. Five studies involving a total of 317 subjects in 26 hospital sites and 5 countries are provided in support of Phagenyx treatment effectiveness.
All of the studies relevant to the use of the device in severe dysphagia post-stroke are summarized below.

A. Clinical Studies Overview

Table 5. Clinical Studies Overview

Company Sponsored		**Independent**	
Name	Type and Design	Name	Type and Design
PHAST TRAC	• RCT • 9 sites/3 countries (DE, AT, IT) • Dysphagic tracheotomized post stroke patients • Warnecke primary endpoint • DSRS secondary endpoint • (n=69)	YOUSSEF	• Independent • RCT • Single site (UAE) • Dysphagic acute stroke • PAS, FOIS endpoints • (n=18)
PHADER	• Single arm PM registry • 14 sites/3 countries (DE, AT, UK) • Post stroke dysphagia • DSRS primary endpoint • (n=177)	SUNTRUP	• Independent • RCT • Single site (DE) • Dysphagic tracheotomized post stroke patients • Warnecke primary endpoint • (n=30)
STEPS*	• RCT • 16 sites/5 countries (UK, DE, FR, ES, DK) • Dysphagia post stroke • (n=52)	MUHLE	• Independent • Single arm observational • Single site (DE) • Dysphagic tracheotomized post stroke patients • Warnecke primary endpoint

			• (n=23)

* The STEPS study had a neutral outcome. The primary reason for this is that overall the patients in STEPS were undertreated. The key metric in identifying whether a patient has been given sufficient optimized stimulation, is not the absolute value of the stimulation level but the delta between the Threshold mA and the Stimulation mA (i.e., the intensity of stimulation above the sensory threshold for that patient). This must be individually determined for each patient and for every treatment. Only 5% of the STEPS subgroup with severe dysphagia received delta stimulation levels comparable to those used in PHAST TRAC. In PHAST TRAC, the delta between the Stimulation Level and Threshold had a mean value of 18mA. In PHADER the mean of the delta was over 13mA. By contrast, in STEPS the mean delta was 40-66% lower, at less than 6mA, with many of the patients receiving stimulation at, or just above, the sensory threshold.

Table 6. Patient Demographics

Study Name	**Patient Age**	**Patient Race/Ethnicity**
PHAST TRAC	Inclusion: > 18 years old. No upper age limit. ***Actual recruited*** Mean age years and (SD) Treated: 61.7 (13.0) Mean age years and (SD) Sham: 66.8 (10.3)	Not recorded.
PHADER	Inclusion: > 18 years old. No upper age limit. ***Actual recruited*** Mean age years and (SD): 68.2 (14.2)	Not recorded.
STEPS	Inclusion: > or = 18 years old. No upper age limit. ***Actual recruited (whole study)*** Mean age years and (SD): 74.4 (11.2) ***Actual recruited (n=52 subgroup)*** Mean age years: 74.9	Information on ethnicity was recorded. Distribution as follows: Asian (9%), Black (3%), White (86%), Other (3%)
YOUSSEF	Inclusion criteria relating to age unknown ***Actual recruited*** Mean age years and (SD) Treated: 64.3 (11.3) Mean age years and (SD) Sham: 66.7 (8.5)	100% Middle Eastern/Non-white
SUNTRUP	Inclusion criteria relating to age unknown ***Actual recruited*** Mean age years and (SD) Treated: 63.0 (14.5) Mean age years and (SD) Sham: 66·7 (14.5)	Not recorded.
MUHLE	Inclusion criteria relating to age unknown ***Actual recruited*** Mean age years and (SD) Treated: 64.4 (11.7)	Not recorded.

1. SUNTRUP

Study summary - The Suntrup study was an independent sham controlled single blinded randomized controlled trial (RCT) in post stroke patients with severe persistent dysphagia that were tracheotomized, where the dysphagia was the only remaining impediment to safe removal of the tracheostomy tube. Patients were considered suitable for inclusion if they were fully weaned from mechanical ventilation and were able to stay alert for at least 15 minutes. Dysphagia severity was assessed both at screening and for the primary endpoint by endoscopic exam using the Warnecke endpoint. This measures management of secretions, spontaneous swallow frequency and laryngeal sensitivity. Patients that passed Warnecke were eligible for decannulation of their tracheostomy tube based on the observed improvement in swallowing. All subjects received standard of care and the treatment group received the standard 3 x 10 minutes of Phagenyx System treatment over 3 consecutive days.

Subject accountability – 51 subjects were screened and 30 randomized 2:1 to the treatment or sham arm. Post intervention or sham all 30 subjects were assessed with 72 hours using the Warnecke endpoint. 8 sham subjects that were Warnecke negative after primary endpoint assessment were offered treatment in an unblinded crossover but one of these was lost to discharge prior to treatment.

Safety Results – The authors reported that there were no device or treatment related adverse events.

Effectiveness Results – For the primary endpoint 75% of treated subjects passed the Warnecke assessment by comparison with 20% of the sham subjects ($p<0.01$). In the unblinded crossover phase 71% of subjects that received treatment passed the Warnecke assessment. None of the subjects subsequently decannulated on passing Warnecke from either phase required recannulation on follow up to the point of discharge.

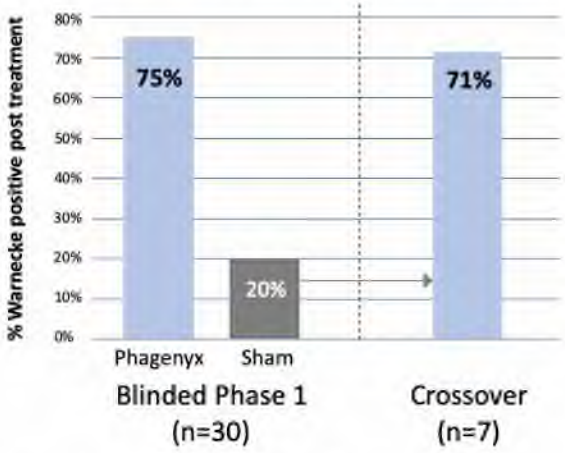

Figure 2. Suntrup Study Outcomes

Study Conclusions – Phagenyx treatment appears to be both safe and effective in improving swallow function and secretion management in patients with persistent severe dysphagia post stroke. Treatment outcomes in the blinded phase 1 of the study were replicated in the unblinded crossover phase suggesting that treatment effects are reproducible in this patient population.

Treatment effects appear durable on the basis that no recannulations due to dysphagia were required for the duration of follow up.

Publication - Suntrup et al., "Electrical pharyngeal stimulation for dysphagia treatment in tracheotomized stroke patients: a randomized controlled trial" *Intensive Care Med* (2015) 41:1629–1637

2. STEPS

Study summary - STEPS was a randomized sham controlled single blinded study to assess the effectiveness and safety of the Phagenyx System in treating patients with dysphagia post ischemic or hemorrhagic stroke in hospital sites in the UK, Germany, Denmark, Spain and France. All patients received standard of care and in the treatment group, additionally received Phagenyx System treatment. STEPS used the Penetration Aspiration Score (PAS) at 2-weeks post treatment as the primary endpoint measure.

Subject accountability – A total of 52 subjects in STEPS presented with severe dysphagia (Dysphagia Severity Rating Scale (DSRS) baseline of 12). Overall, 84% of subjects were available for primary endpoint assessment at the first follow-up (FU1) dropping to 80% at the second follow up (FU2). Patient data was not available for a number of reasons including patient death, withdrawal of consent and loss to follow up as indicated.

Safety Results – The Phagenyx System was shown to be safe in this study based on extensive safety data collection and analysis. There were no device or treatment related serious adverse events or deaths. There were a small number of nonserious device related adverse events such as gagging or nausea linked to catheter insertion and one instance of hypersalivation. All events resolved without complications.

Effectiveness Results – The STEPS study was neutral for the primary endpoint. Post hoc analysis indicated the majority of subjects with severe dysphagia may have been sub-optimally stimulated and that the control group may have received some level of therapeutic stimulation unintentionally (Bath et al 2016).

Publication - Bath et al., Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke: A Randomized Controlled Trial *Stroke* 2016 Jun;47(6):1562-70.

3. YOUSSEF

Study summary - This was an independent randomized controlled trial in patients with dysphagia post stroke. Patients were included in the study within 10 days of a hemispheric stroke event where dysphagia was confirmed via endoscopic exam, i.e., Penetration Aspiration Score (PAS) of 3 or higher. Patients were randomized 1:1 into a treatment or sham control group. The sham group had the catheter inserted and went through a process of level optimization but did not receive the standard 3 x 10-minute optimized stimulation sessions over 3 days as per the treatment group. Both groups continued to receive standard of care. Treatment outcomes were

assessed 2 weeks post the last treatment using a number of swallow measures and a patient global satisfaction measure.

Subject accountability – 18 subjects were recruited. All 18 subjects were assessed at baseline for PAS, Functional Oral Intake Scale (FOIS), Pharyngeal Secretions and Pharyngeal Stasis and randomized to treatment or sham groups.

Safety Results – The authors reported that no serious adverse events occurred during the study.

Effectiveness Results – Study outcomes are summarized in Table 5-5. All measures other than pharyngeal stasis showed a statistically greater improvement in the treated group by comparison with the sham group. Seven subjects reported satisfaction in the treatment group by comparison with 3 patients in the sham group at 2 weeks.

Table 7. Youssef Study Outcomes

Outcome	Timing	PES group	Sham group	Difference p
PAS	Baseline	5.7 ± 1.1	5.1 ± 0.9	
	Post treatment	2.3 ± 0.37	3.58 ± 0.78	0.017
FOIS	Baseline	2.8 ± 1.54	2.58 ± 1.79	
	Post treatment	5.18 ± 1.7	4.33 ± 0.98	0.024
Pharyngeal secretions	Baseline	2.2 ± 0.35	2.3 ± 0.65	
	Post treatment	0.7 ± 0.47	1.52 ± 0.81	0.032
Pharyngeal stasis	Baseline	3.1 ± 0.6	2.9 ± 0.9	
	Post treatment	2.2 ± 0.69	2.1 ± 0.7	0.116
Patient satisfaction	At 2 weeks	2.6 ± 1.19	3.8 ± 1.71	0.046

Study conclusions – Phagenyx treatment appears to be safe and effective in the treatment of moderate to severe dysphagia post stroke. The improvement in mean PAS, FOIS and Pharyngeal Secretions scores were statistically greater in the treated group by comparison with the sham group.

Publication - Youssef et al., "The outcome of intraluminal electrical pharyngeal stimulation (EPS) on oropharyngeal dysphagia in acute stroke patients" *Al-Azhar Assuit Medical Journal* 2015 Vol 13 No.1 Jan, 67-72.

4. MUHLE

Study summary - This was an independent prospective single arm study in patients with severe persistent dysphagia post stroke fully weaned from ventilation with a tracheostomy tube still in place. The goals of the study were two-fold: a) To establish the effectiveness of Phagenyx System treatment in improving swallowing function as measured by Warnecke and; b) To

establish whether Phagenyx System treatment success correlated with an increase of a swallow related neurotransmitter 'Substance P' in the pharyngeal mucosa. Patients who could not be decannulated after the standard cycle of 3 treatments with Phagenyx were offered additional treatments in phase 2 and 3. Saliva samples were collected before and after each stimulation and Substance P concentration measured using and ELISA immunoassay.

Subject accountability – A total of 68 subjects were screened identifying 23 subjects suitable for treatment. All 23 subjects were given 3 Phagenyx System treatments over 3 days and assessed within 24-72 hours after the third treatment using the Warnecke endoscopic exam. A total of 9 subjects that remained Warnecke negative after phase 1 were eligible for a second cycle of treatment but 6 of these subjects were discharged at this time prior to treatment. Of the 3 subjects treated in phase 2, 1 was discharged after treatment. A single patient was given one further cycle of treatment. All subjects that were Warnecke positive had their tracheostomy tubes removed based on the observed improvement in swallowing and were monitored along with Warnecke negative patients until discharge (mean Length of Stay (LOS) 35 days ± 11 days).

Safety Results – The authors reported no device or treatment related adverse events occurred during the study.

Effectiveness Results – A total of 61% of subjects were Warnecke positive after a single cycle of 3 Phagenyx System treatments. This number increased to 65% of subjects after 2 cycles and 70% of subjects after 3 cycles (see Figure 3). All subjects decannulated on the basis of the improvement in swallow function and secretion management as measured by Warnecke were followed up to discharge and none required recannulation.

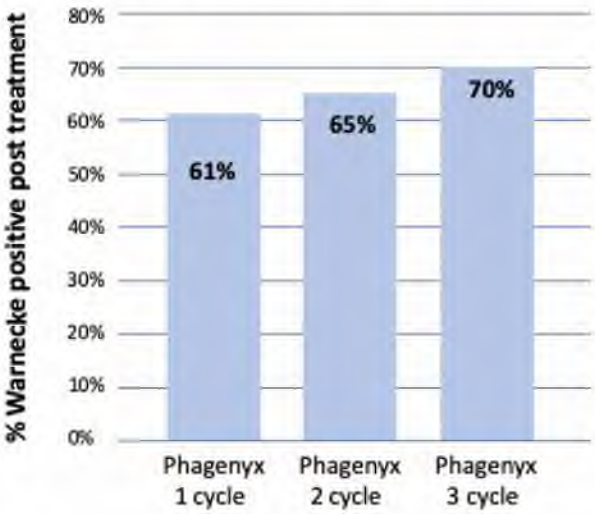

Figure 3. Warnecke Outcomes

Study conclusions – The Phagenyx System is safe and effective in the treatment of severe dysphagia post stroke. Certain patients may require a higher number of treatments to demonstrate improvement in swallowing.

Publication - Muhle et al., "Increase of Substance P Concentration in Saliva after Pharyngeal Electrical Stimulation in Severely Dysphagic Stroke Patients – an Indicator of Decannulation Success?" *Neurosignals* 2017; 25:74-87.

5. PHAST TRAC

Study summary - PHAST TRAC was a company sponsored prospective single-blind randomized controlled trial across 9 sites in Germany, Austria and Italy in tracheotomized patients with severe persistent dysphagia post stroke. Patients were randomized to receive 3 Phagenyx System treatments or sham treatments. The primary endpoint was an endoscopically captured measure of swallowing function and secretion management (Warnecke). After primary endpoint collection (phase 1) the study had a second, open-label phase where the subjects initially assigned to the sham arm were offered treatment. In addition, any patients in the phase 1 part that had not responded to the standard regimen of 3 treatments were allowed an additional 3 treatments. The Dysphagia Severity Rating Scale (DSRS) was one of a number of secondary endpoints also recorded in this study.

Subject accountability – A total of 97% of subjects were available for primary endpoint assessment in phase 1 of the study. Of expected subjects, 94% were available for the endpoint assessment in the open label crossover. Thereafter 93% of subjects were followed up to discharge and 74% at the last follow up at 60-120 days. Subjects were not available for a number of different reasons including inability to pass the catheter, death, withdrawal of consent or loss to follow up.

Safety Results – There were no treatment or device related serious adverse events or deaths. There were a number of non-serious device or treatment related events such as catheter insertion difficulty, gagging during insertion and throat pain during stimulation. All events were resolved without complications.

Effectiveness Results – A total of 49% subjects passed Warnecke following treatment by comparison with 9% of sham subjects. When sham subjects were offered treatment in the crossover phase of the study a similar % of subjects, 53%, passed Warnecke post treatment (see Figure 4). In addition, when those treated subjects from phase 1 that had not passed Warnecke were given additional treatments, the total % of treatment responders in that group increased from 49% to 60% (Figure 5). DSRS results also showed that Warnecke positive subjects post treatment were more likely to return to oral intake (see Figure 6).

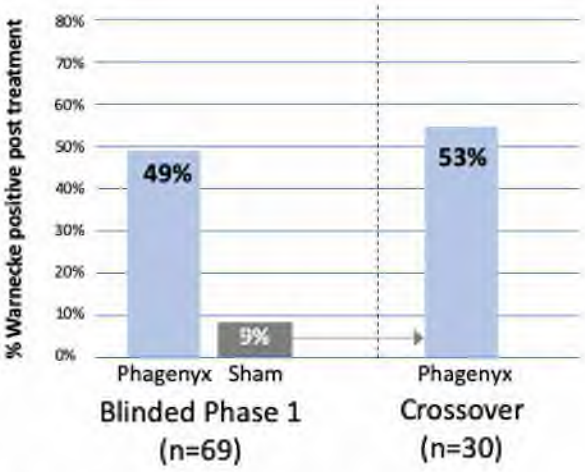

Figure 4. Warnecke Outcomes

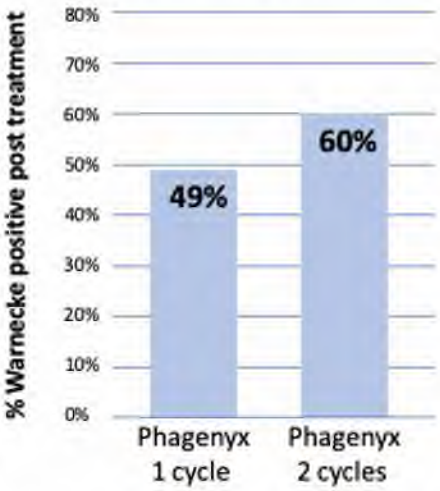

Figure 5. Effect of Additional Treatments

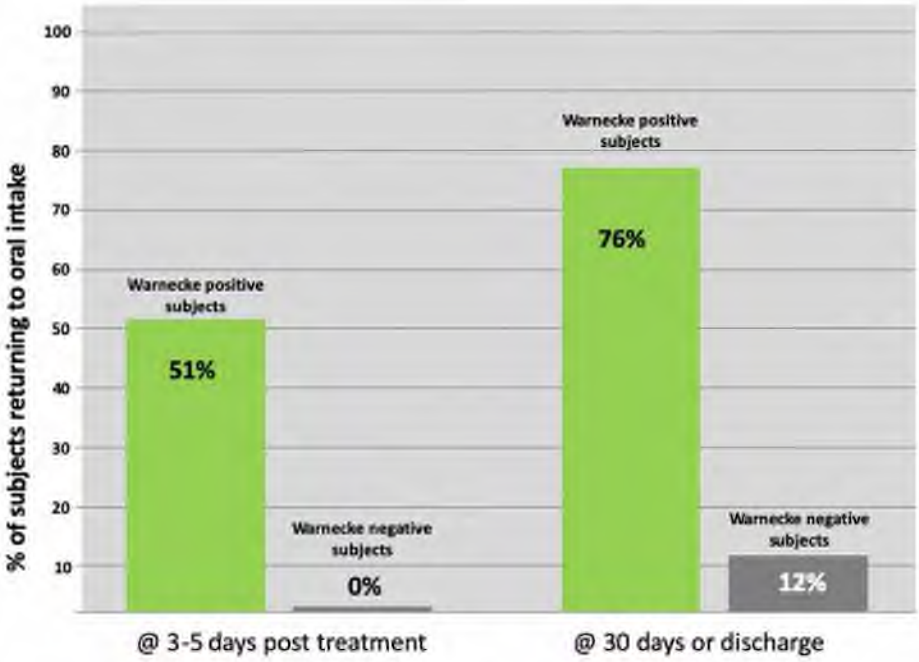

Figure 6. Comparison of Return to Oral Intake of Warnecke (+) and (-) Subjects

Study conclusions – Phagenyx is safe and effective in the treatment of severe dysphagia post stroke. Treatment outcomes in the blinded phase 1 of the study were replicated in the unblinded crossover phase suggesting that treatment effects are reproducible in this patient population. Certain patients may require a higher number of treatments to demonstrate improvement in swallowing. Treatment responders (Warnecke positive) are more likely to return to oral intake in the days and weeks following treatment than treatment non-responders.

Publication - Dziewas et al., Pharyngeal electrical stimulation for early decannulation in tracheotomized patients with neurogenic dysphagia after stroke (PHAST-TRAC): a prospective, single-blinded, randomized trial. *Lancet Neurol* 2018;17: 849–59.

6. PHADER

Study summary - PHADER was a company sponsored prospective single-arm observational post market registry study. It was designed to capture safety and effectiveness data in a broad range of patients with neurogenic dysphagia categorized into 5 different groups. PHADER Group A – Patients with dysphagia post stroke and PHADER Group B - Patients with dysphagia post stroke that also required ventilation and had been extubated, were two of the groups studied. The primary endpoint used in PHADER was the Dysphagia Severity Rating Scale (DSRS). DSRS data was recorded at baseline prior to treatment, at follow up 1 which was 2-3 days post last PES treatment, follow up 2 which was 7-21 days post last PES treatment and follow up 3 at 60-120 days post last PES treatment. Secondary endpoints included FOIS, PAS and hospital LOS. All patients in the study received standard dysphagia care and additionally received Phagenyx System treatment.

Subject accountability – Of the 188 subjects screened, 177 eligible subjects were identified and given at least one Phagenyx treatment session. A total of 170 subjects received all three treatments and 173 subjects were assessed at follow up 1 (FU1) (98% expected). For follow up 2 (FU2) there were 86% of expected subjects and at follow up 3 (FU3) 77% of expected subjects. There were a number of deaths, consent withdrawals and losses to follow up over the course of the study.

Safety Results – There was one serious adverse event recorded as 'possibly device related' in this study where a difficult catheter insertion with coughing and copious secretions was followed within 24 hours by a chest infection. It was resolved without complications. There were a small number of non-serious device or treatment related adverse events such as temporary headache, pain during treatment and jaw chattering. All events resolved without complication.

Effectiveness Results – Subjects showed significant improvements in DSRS, FOIS and PAS from baseline over the course of the study. The majority of subjects were *nil per os* (NPO) (DSRS 12) at baseline with mean onset to treatment time of 50 days where they showed no response to standard dysphagia care. Following Phagenyx System treatment 22% of these persistently dysphagic NPO patients unresponsive to standard dysphagia care for 7 weeks returned to oral intake (DSRS 10) within 3 days. This % increased to 47% by follow up 2 (7-21 days) and to 74% of those assessed at follow up 3 (60-120 days). Those that responded to treatment (i.e., change from DSRS 12) showed a large improvement in their DSRS scores (mean of >4 DSRS at follow up 1, >6 DSRS at follow up 2 and >9 DSRS at follow up 3). This is illustrated in Figure 7.

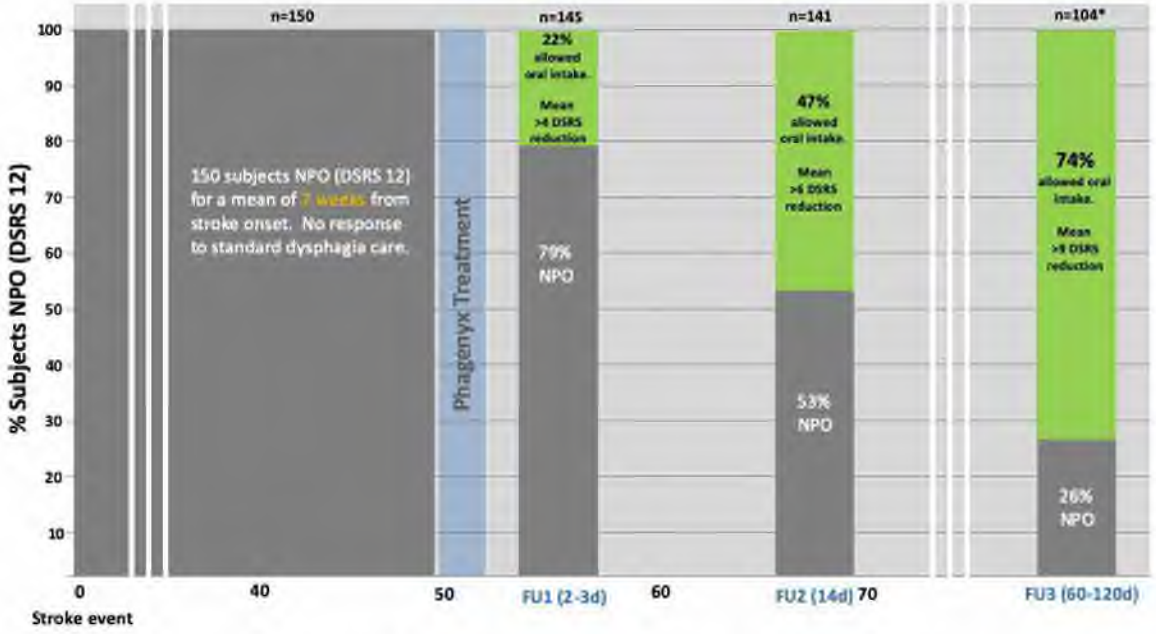

Figure 7. DSRS Outcomes for 150 Subjects with Baseline DSRS of 12

Study conclusions – Phagenyx is safe and potentially effective in the treatment of severe dysphagia post stroke in patients that do not respond to standard dysphagia care. Although this was a single arm study, the timing and size of improvement in DSRS seen in a significant % of

subjects that had not responded to standard dysphagia care for many weeks strongly suggests a treatment effect. The single device related serious adverse event seen in this study was resolved without complication and was only possibly related to catheter insertion and not to treatment.

Publication - Bath et al., Pharyngeal electrical stimulation for neurogenic dysphagia following stroke, traumatic brain injury or other causes: main results from the PHADER cohort study, *EClinicalMedicine* 28 (2020) 100608.

B. Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

TRAINING

Prior to the usability assessment a standard training program was provided the participants. The training program included three parts:

- Classroom training 1 – Theory (understand the science and clinical evidence)
- Classroom training 2 – Practical (understand how to optimally use and care for the Phagenyx System)
- Hands on training and competency assessment

Training was performed on site with participants and the results of their performance were documented and signed off if appropriate by a qualified Phagenesis trainer. Usability studies conducted in Europe and U.S. validated that the training program is equally effective when delivered to U.S. healthcare users.

LABELING

The labeling is sufficient and meets the requirements of 21 CFR 801.109 Prescription devices.

Labeling includes PNX-1000 instructions for use for adjustment and insertion of the catheter component of the system, its use for feeding purposes and maintenance and care of the device. It also includes a list of contraindications and warnings and shelf life.

Labeling additionally includes the Phagenyx System User Guide which presents detailed information on the use of the overall system for treatment optimization and delivery, contraindications, warnings and anticipated adverse events and cleaning and disinfection instructions. The User Guide also includes a summary of clinical studies.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the oropharyngeal electrical stimulator and measures necessary to mitigate these risks.

Table 8. Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Incorrect stimulation output leading to discomfort or delayed treatment, or incorrect location of stimuli leading to jaw chattering or facial/ear pain	Non-clinical performance testing Software verification, validation and hazard analysis Usability testing Training
Off target neurostimulation due to patient specific injury resulting in harmful neurological activity	Usability testing Training
Tissue damage due to mechanical stress, electrical effects, or heating effects	Usability testing Training Electrical safety testing
Electrical shock from electrical component malfunction	Non-clinical performance testing Electrical safety testing
Interference with other devices leading to malfunction or injury	Electromagnetic compatibility (EMC) testing
Adverse tissue reaction	Biocompatibility evaluation
Infection	Sterilization validation Reprocessing validation Shelf life testing Labeling
Software failure leading to delayed treatment or discomfort	Software verification, validation and hazard analysis
Fire hazard in the presence of supplementary oxygen	Non-clinical performance testing Training
For devices with feeding tubes, leakage and misplacement of feeding tube leading to feeding-related complications (e.g., temporary suboptimal nutrition, reflux aspiration, respiratory distress)	Non-clinical performance testing Training Usability testing

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the oropharyngeal electrical stimulator is subject to the following special controls:

(1) Non-clinical performance testing must demonstrate the device performs as intended under anticipated conditions of use, including the following:

- (i) Electrical output testing;
- (ii) Mechanical integrity testing of electrical components;
- (iii) Testing to verify safe use of the electrical stimulator component in the presence of supplementary oxygen; and
- (iv) If the device incorporates a feeding tube, feeding tube functionality testing, including mechanical integrity, liquid leakage, flow rate and connector compatibility.

(2) The patient-contacting components of the device must be demonstrated to be biocompatible.

(3) Performance testing must demonstrate the sterility of the components intended to be provided sterile.

(4) Performance data must validate the reprocessing instructions for any reusable components of the device.

(5) Performance testing must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the labeled shelf life.

(6) Software verification, validation and hazard analysis must be performed for any software components of the device.

(7) Performance testing must demonstrate the electromagnetic compatibility (EMC) and electrical safety of any electrical components.

(8) A training program must be included with sufficient educational elements so that upon completion of the training program, the users can correctly operate the device.

(9) Usability testing must demonstrate that the device can be correctly used as per training and labeling.

(10) The labeling must include a shelf life for any sterile components.

BENEFIT-RISK DETERMINATION

The benefits associated with use of the Phagenyx System have been established through assessment of data derived from 4 randomized controlled trials, a single arm observational study, and a postmarket registry study. These 6 studies included 369 subjects across 8 countries to assess Phagenyx for its intended use.

Benefits were demonstrated in multiple aspects of swallowing function, including spontaneous swallows, secretion management, and laryngeal sensibility. The magnitude of effect compared to controls was generally large in the controlled studies, with meaningful improvements in swallowing function that were demonstrated to correlate with return to oral intake even after prolonged periods of no response to standard of care. Overall, these results demonstrate that device provides a treatment benefit for different aspects of nutritional intake including fluids, diet and level of supervision/independence.

The risks associated with the Phagenyx System are low as evidenced by the safety data gathered in the randomized controlled studies as well as the post-market data gathered. Although there was 1 SAE reported and a number of nonserious device or treatment related events reported across the different studies assessing the device, these events were reported as resolved without

complications. Furthermore, the risk of respiratory AEs and SAEs, such as aspiration pneumonia and respiratory infection is consistent with the rates reported in the literature and, overall, there were no significant differences in these AEs and SAEs between the treatment and control groups in the studies assessing the safety the Phagenyx System.

In summary, the Phagenyx System offers a benefit to patients with severe dysphagia post stroke with relatively few risks. The data on safety and effectiveness for the Phagenyx System support a clinically meaningful degree of benefit that outweighs the low risk of serious, device-related adverse events.

PATIENT PERSPECTIVES

Patient reported outcome data were collected in PHADER, STEPS and YOUSSEF clinical studies and summarized below:

Table 9. Patient Reported Outcomes

Study Name	Patient Reported Outcomes
PHAST TRAC	Patients in the study were critically ill and, in most cases, not suited to partaking in patient reported outcome measures where a baseline data set was needed as a comparison. As a result these types of endpoints were not included in the study design.
PHADER	The PHADER post market registry study included EQ5D, Dysphagia Handicap Index and EAT-10 as secondary endpoint patient centric measures. However, for the same reasons as indicated in PHAST TRAC, SUNTRUP and MUHLE (i.e., inability of the subjects to comply) less than 20% of these patients could have an EQ5D measure taken at baseline for example and less than 1% had a full set of EQ5D results over all the timepoints. Meaningful statistical analysis of the patient reported outcome data was therefore not possible. *EQ5D: EuroQol-5D scale for measuring quality of life*
STEPS	EQ5D, HADS and LOT-R information was gathered in this study, but for reasons previously explained, this study was neutral overall for both primary and secondary endpoints. No significant difference was seen therefore between treated and sham patients using any of these measures. *HADS: Hospital Anxiety and Depression Score* *LOT-R: Life Orientation Test-Revised*
YOUSSEF	7-point categorical scale. Statistically greater patient satisfaction was shown in the treated group versus the control group.
SUNTRUP	Patients in the study were critically ill and, in most cases, not suited to partaking in patient reported outcome measures where a baseline data set was needed as a comparison. As a result these types of endpoints were not included in the study design.
MUHLE	Patients in the study were critically ill and, in most cases, not suited to partaking in patient reported outcome measures where a baseline data set was needed as a comparison. As a result these types of endpoints were not included in the study design.

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

> The Phagenyx System is a neurostimulation device delivering electrical stimulation to the oropharynx, to be used in addition to standard dysphagia care, as an aid to improve swallowing in patients with severe dysphagia post stroke.

The probable benefits outweigh the probable risks for the Phagenyx System. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Phagenyx System is granted and the device is classified as follows:

> Product Code: QQG
> Device Type: Oropharyngeal electrical stimulator
> Regulation Number: 21 CFR.874.5950
> Class: II