

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Transvenous temporary phrenic nerve stimulator

Trade Name: AeroPace® System

Device Procode: SDL

Applicant's Name and Address: Lungpacer Medical USA, Inc.
260 Sierra Drive, Suite 116
Exton, PA 19341

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P240012

Date of FDA Notice of Approval: December 4, 2024

Breakthrough Device: Granted breakthrough device designation status on May 4, 2016 for patients 18 years or older, who are not hypovolemic and who have failed at least two spontaneous breathing trials, because the device is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition. In addition, the device has met at least one criterion for addressing an unmet need: 1) The device may represent a breakthrough technology that provides a clinically meaningful advantage over existing legally marketed technology; 2) The availability of the device may be in the best interest of patients (e.g. addresses an unmet medical need).

II. INDICATIONS FOR USE

The AeroPace System is indicated to improve weaning success – increase weaning, reduce ventilator days, and reduce reintubation - in patients ages 18 years or older on mechanical ventilation $\geq$ 96 hours and who have not weaned.

III. CONTRAINDICATIONS

Do not use the AeroPace System with active implanted cardiac pacemakers, defibrillators, or other implantable electronics within proximity to the AeroPace Catheter. The AeroPace System has not been clinically evaluated for safety with implantable devices.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling for the AeroPace System User Guide and the AeroPace Catheter Instructions for Use.

V. DEVICE DESCRIPTION

The AeroPace System (a Temporary Transvenous Diaphragm Activation System) is intended for temporary stimulation of the phrenic nerve(s) to increase diaphragmatic strength in mechanically ventilated patients. The AeroPace System utilizes a temporarily placed, central venous neurostimulation catheter and an external control unit, designed to operate in conjunction with mechanical ventilation in any mode, to transvenously stimulate the left and/or right phrenic nerves to strengthen the diaphragm and facilitate weaning. After placement of the AeroPace Catheter, the

AeroPace System is used to deliver 60 stimulations to contract the diaphragm twice a day, a total of 120 stimulations or diaphragm contractions daily, for up to 30 days. The sterile single-use AeroPace Catheter also functions as a standard central venous catheter for use for up to 30 days. A diagram of the AeroPace System shown relative to a patient and mechanical ventilator is shown in **Figure 1**.

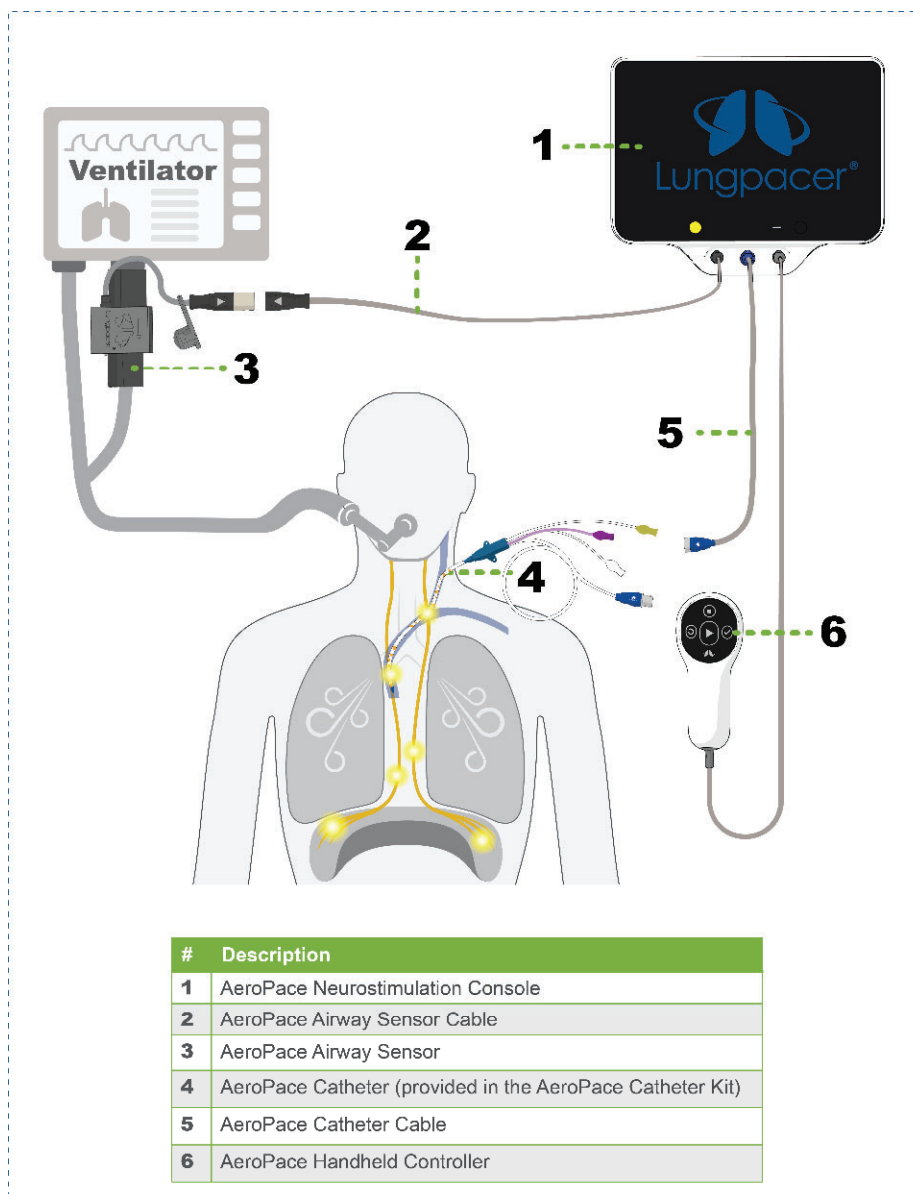


Figure 1: Diagram of AeroPace System

Shown relative to patient and mechanical ventilator, with the Catheter placed in the left jugular vein and Airway Sensor placed in the inspiratory limb of the ventilator airway circuit.

AeroPace Neurostimulation Console and Cart

The AeroPace Neurostimulation Console contains software-controlled electronics, housed in an enclosure, that generate stimulation output that is transmitted from the Console through the Catheter Cable to the electrodes on the AeroPace Catheter (**Table 1**). The Console is mounted on

the Cart containing cable and Handheld Controller storage. The Console includes a touchscreen monitor with a graphical user interface (GUI), allowing the operator to interact with and control the System. The Console can operate in either Manual or Automatic (Auto) mode. Auto modes for Placement, Mapping and Therapy are facilitated by the interface to the Airway Sensor. The Console is plugged into hospital-grade wall power.

Table 1: AeroPace System Stimulation Characteristics

Parameter	Specification
Waveform Type	Charge-balanced biphasic asymmetrical
Pulse Delivery Mode	Constant current stimulation pulses
Pulse Durations	200 μ s $\pm$ 5% to 300 μ s $\pm$ 5%
Pulse Repetition Frequencies	15 Hz (default), 20 Hz, 25 Hz, 30 Hz, and 40 Hz options in Therapy mode for each channel. Typically, 4 Hz in Mapping & Placement modes. Tolerance: $\pm$ 5%
Maximum Voltage	Current regulated 33V maximum
Maximum Current	27.0 mA $\pm$ 5% at 300 27.0 mA $\pm$ 5% at 500 27.0 mA $\pm$ 5% at 1000 (typical impedance) 13.0 mA $\pm$ 5% at 2000 6.0 mA $\pm$ 5% at 4500
Net DC Current (nA) at maximum pulse rate	$\leq$ 100 nA

Abbreviations: Hz=hertz; mA=milliampere; nA=nanoampere; V=volt

Handheld Controller

Certain controls on the GUI are duplicated on the AeroPace Handheld Controller, allowing specific Auto and Manual mode tasks to be performed by the operator without needing to be in arm's reach of the Console. The Handheld Controller has visual indicators for each of four procedural commands and for connection to the Console.

Airway Sensor and Cable

The Airway Sensor is a non-sterile, disposable, single-patient-use sensor that interfaces with the patient's ventilator airway circuit to measure the airway pressure and to communicate the data to the Console through the Airway Sensor Cable. The Airway Sensor is connected in the inspiration limb of the ventilator airway circuit. The Airway Sensor can also be connected to the patient's ventilator airway circuit and to the patient's tracheostomy/endotracheal tube. The Airway Sensor consists of an enclosure with integral patient airway connections and sensing electronics.

AeroPace Catheter and Cable

The AeroPace Catheter is intended for use as part of the AeroPace System for temporary transvenous diaphragm activation, and for short-term (< 30 days) central venous access for administering IV fluids, blood products, medications, and parenteral nutrition solutions, as well as blood withdrawal, central venous pressure monitoring, and power injection of contrast media.

The Catheter is provided sterile, for single-use, and can be inserted into either the left subclavian vein or the left jugular vein using an over-the-wire procedure and is marked with numerals to

indicate the distance from the tip of the Catheter. The Catheter is connected to the Console by way of the Catheter Cable. An intravascular electrogram (ECG) signal, acquired through electrodes on the catheter, can be visualized on the Console and can be used to assist the placement of the AeroPace Catheter tip in the distal superior vena cava (SVC). The Catheter contains one distal lumen for the guidewire, for over-the-wire insertion. After guidewire removal, three lumens are available for fluid and/or medication delivery. The distal lumen is rated for high-pressure injection. The Catheter's 30 integrated electrodes are activated via the AeroPace Neurostimulation Console to stimulate the left and right phrenic nerves, causing the diaphragm to contract.

AeroPace Catheter Kit

The AeroPace Catheter Kit contains one AeroPace Catheter and accessories that may be used for insertion of the Catheter (**Table 2**). The AeroPace Catheter Kit is sterilized by exposure to ethylene oxide (EO) gas. The AeroPace Catheter and accessories provided in the Catheter Kit are designed for single use only.

Table 2: AeroPace Catheter Kit Components

Catheter Kit Component	Qty	Catheter Kit Component	Qty
AeroPace Catheter, 8.5Fr. (2.8mm) x 23cm	1	Primary Cable Clamp	1
Over-the-Needle Catheter, 18G x 2.5in (1.3mm x 64mm)	1	Guidewire Tip Protector	1
Needle, 18G x 2.75in (1.3mm x 70mm)	1	Dressing, Tegaderm, 4in x 4.75in (10cm x 12cm)	1
Scalpel, #11	1	Gauze, 4in x 4in (10cm x 10cm)	5
Sharps Receptacle	1	Suture, 3-0 Silk, C7 Reverse Cutting Needle	1
Syringe, 3ml, Luer Lock with 25G x 1in (0.5mm x 25mm) Needle	1	Drape, 24in x 36in (60cm x 90cm), with 4in (10cm) Fenestration	1
Syringe, 5ml, Luer Slip	2	Catheter Clamp Fastener	1
Needle-Free Male Luer Lock Injection Site	3	Guidewire J-Tip, EHD 0.032in (0.81mm) x 70cm	1
Guidewire Dispenser	1	Dilator, 8Fr. x 4in (2.7mm x 10cm)	1
Guidewire J Straightener	1	Needle Holder, 5in (13cm)	1
Catheter Clamp	1		

Abbreviations: cm=centimeter; Fr=French; G=gauge; mm=millimeter; In=inch.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for weaning patients from mechanical ventilation (MV). Daily Ventilator Liberation Trials (also known as Spontaneous Breathing Trials, or SBTs) are used to facilitate weaning in adults on MV for more than 24 hours and are regarded as the standard of care (SoC) for weaning patients from MV (Girard, 2017, American Thoracic Society/American College of Chest Physicians “*Liberation from Mechanical Ventilation in Critically Ill Adults, Rehabilitation Protocols, Ventilator Liberation Protocols, and Cuff Leak Tests*”).

Ventilator settings using assisted breathing modes and devices that facilitate these ventilator modes are used to facilitate weaning patients from MV. Respiratory maneuvers using volitional

breathing against resistance are used to facilitate spontaneous breathing in MV patients. There are no alternatives that have a direct action on diaphragm strengthening to facilitate weaning from MV. 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.

VII. MARKETING HISTORY

The AeroPace System has not been previously marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The potential complications associated with diaphragm or phrenic nerve stimulation are:

- Arrhythmia
- Bradycardia
- Diaphragm injury
- Discomfort
- Hypercapnia / hypocapnia
- Hypoxia
- Liberation of lung mucus plugs/secretions
- Muscle fatigue or discomfort
- Nerve injury
- Pain or discomfort during stimulation
- Inappropriate stimulation
- Phrenic nerve damage or injury
- Syncope

The potential complications associated with central venous catheters are:

- Adverse tissue response
- Allergic reaction
- Arrhythmia
- Bleeding / Hemorrhage
- Bradycardia
- Bruising, swelling or seroma at insertion site
- Cardiac structure damage
- Central line-associated blood stream infection
- Cerebrovascular event
- Discomfort
- Embolism
- Hematoma
- Hemothorax
- Hypertension / hypotension
- Inadvertent arterial or venous puncture
- Infection
- Lung injury

- Lymphatic / thoracic duct injury
- Mediastinal injury
- Nerve injury
- Pain, tenderness, swelling, discomfort at access site
- Pneumohematoma
- Pneumomediastinum
- Pneumothorax
- Procedural complications
- Pseudo aneurysm or AV fistula at access site
- Sepsis
- Seroma
- Skin irritation
- Syncope
- Thrombosis / stenosis
- Tissue inflammation, fibrosis or damage
- Vessel occlusion
- Vessel wall damage / perforation
- Wound healing issues
- Wound infection / phlebitis

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

IX. SUMMARY OF NONCLINICAL STUDIES

Two preclinical animal model studies provided proof of principle for the AeroPace System for its intended use, and two animal model studies verified device safety and performance. Evaluations of biocompatibility, physical and mechanical testing, electrical safety, electromagnetic compatibility (EMC), sterilization, packaging and shelf life, software, human usability, and international standards compliance confirmed that the AeroPace System is acceptable for human use.

A. Laboratory Studies

Biocompatibility Testing

Biocompatibility testing was conducted for the AeroPace Catheter which is the only component of the AeroPace System with patient contact, and it was conducted for the AeroPace Airway Sensor which is the one component that has airway (gas pathway) contact. Patient-contacting components of the AeroPace Catheter Kit were subject to biocompatibility testing at the time of their 510(k) clearance.

AeroPace Catheter

Biocompatibility testing for the for the patient-contacting parts of the AeroPace Catheter was performed as required by ISO 10993-1, and FDA’s guidance document “*Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*” (issued September 4, 2020). All patient-contacting components of the Catheter were classified as contact duration Category B: prolonged contact, > 24 hours to 30 days, based on the intended use, per ISO 10993-1. Biocompatibility testing was completed according to Good Laboratory Practice (GLP) requirements 21 CFR 58.

Table 3 summarizes the results of testing performed on the AeroPace Catheter and demonstrates the catheter is biocompatible per its intended use per ISO 10993-1.

Table 3: Biocompatibility Testing – AeroPace Catheter

Biological Endpoint	Biocompatibility Test	Applied Standard	Results
Cytotoxicity	MEM Elution	ISO 10993-5: <i>Biological evaluation of medical devices - Part 5: Tests for In Vitro cytotoxicity</i>	Pass Non-cytotoxic
Irritation	Rabbit Intracutaneous Reactivity Assay	ISO 10993-10: <i>Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization</i>	Pass Non-irritating
Sensitization	Guinea Pig Magnusson-Kligman Maximization Assay	ISO 10993-10: <i>Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization</i>	Pass Non-sensitizing
Pyrogenicity	Rabbit Pyrogen Test (Material Mediated)	United States Pharmacopeia (USP) Pyrogen Test Procedure, Section <151>	Pass Non-pyrogenic
Hemocompatibility	Hemolysis (direct and indirect)	ISO 10993-4:2017: <i>Biological evaluation of medical devices Part 4: Tests for blood</i>	Pass Non-hemolytic
	Complement Activation		Pass Not a complement activator
	Dog Thrombogenicity (NAVI)		Pass Thromboresistant
Extractables and Leachables Testing	Chemical Characterization and Toxicological Risk Analysis	ISO 10993-18, <i>Biological evaluation of medical devices Part 18: Chemical characterization of materials within a risk management process</i>	Pass The AeroPace Catheter does not pose a significant systemic (acute, subacute/subchronic, or chronic), genotoxic, or carcinogenic toxicological safety risk to the patient when used as intended.
Acute, Subacute, Subchronic/Chronic Toxicity, Carcinogenicity, and Genotoxicity		ISO 10993-17, <i>Biological evaluation of medical devices Part 17: Toxicological risk assessment of medical device constituents</i>	Pass The AeroPace Catheter does not pose a significant systemic (acute, subacute/subchronic, or chronic), genotoxic, or carcinogenic toxicological safety risk to the patient when used as intended.

Abbreviations: ISO=International organizations for standardization; MEM=minimum essential medium; NAVI=non-anticoagulated venous implant model

AeroPace Airway Sensor

A Toxicological Risk Assessment examined potential toxicological hazards and demonstrated the overall biological safety of the AeroPace Airway Sensor per its intended use according to ISO 18562-1, “*Biocompatibility evaluation of breathing gas pathways in healthcare applications - Part 1: Evaluation and testing within a risk management process*” for the airway-contacting (i.e., gas pathway) parts of the Airway Sensor. Biological safety evaluation for the Airway Sensor was conducted in accordance with ISO 18562-2, “*Biocompatibility evaluation of breathing gas pathways in healthcare applications – Part 2: Tests for emissions of particulate matter*” and ISO 18562-3, “*Biocompatibility evaluation of breathing gas pathways in healthcare applications – Part 3: Tests for emissions of volatile organic compounds (VOCs) standards*”.

The evaluation of the results of the chemical characterization study per ISO 10993-18, and the risk assessment, indicate that there is no expected risk of acute, subacute/subchronic, and chronic toxicity, genotoxicity, and carcinogenicity from exposure to the extractables detected from potential condensate in the AeroPace Airway Sensor.

Physical and Mechanical Testing

Testing was conducted on the AeroPace System (Catheter, Neurostimulation Console, and accessories) according to test standards for active medical devices and to software verification/validation requirements following unique test protocols for the system. The AeroPace System, inclusive of the AeroPace Neurostimulation Console, AeroPace Catheter and all other system components passed all integrity and performance design verification testing. **Table 4** summarizes the testing that was performed on the AeroPace System. The completed testing verified that applicable material, function, system compatibility, and durability product specifications were met.

Testing related to sterilization, package integrity, shelf life and transport durability is summarized below.

Table 4: Summary of Verification Testing – AeroPace System

Test	Purpose	Acceptance Criteria	Results
Radio-detectability	To verify that the AeroPace Catheter can be visualized with x-ray imaging techniques	Detectable by x-ray or by other means per ISO 10555-1	Pass
Surface Condition and Distal Tip	To ensure the AeroPace Catheter is free from surface defects and extraneous matter	The external surface of the effective length of the catheter shall appear free from extraneous matter and free from process and surface defects which could cause trauma to vessels during use	Pass
Corrosion Resistance	To verify that the metallic components intended for fluid path contact show no signs of corrosion when tested as described in ISO 10555-1	Metallic components of the catheter intended for fluid path contact shall show no signs of corrosion per ISO 10555-1	Pass

Test	Purpose	Acceptance Criteria	Results
Peak Tensile Force	To verify that the AeroPace Catheter meets the requirements defined in ISO 10555-1 & ISO 10555-3 with respect to the peak tensile force for each tubular portion, and each junction between tubular portions	The AeroPace catheter tubular portions and joints shall withstand the pre-specified minimum tensile force requirements per ISO 10555-1 & ISO 10555-3	Pass
Freedom from Leakage	To verify that the AeroPace Catheter does not leak liquid under pressure or allow air to enter lumen under aspiration	- Air shall not enter the catheter under aspiration per ISO 10555-1 - The catheter shall not leak liquid under pressure per ISO 10555-1	Pass
Flow Rate	To verify that the AeroPace Catheter meets a minimum of 90% of its defined flow rate	For all lumens, the average flow rate is greater than 90% of recommended labeling flow rate as per ISO 10555-1	Pass
Burst Pressure	To verify that the AeroPace Catheter meets the burst pressure requirements of ISO 10555-1	The Catheter burst pressure shall exceed the peak pressure present in the catheter at maximum flow conditions per ISO 10555-1	Pass
Nominal Size	To ensure that the nominal outside diameter (crossing profile) and the nominal effective length are as designated on the labeling, and to perform dimensional	- The AeroPace Catheter crossing profile 8.5 French - The AeroPace Catheter's effective length 230 ± 5 mm - The AeroPace Catheter's inner diameter compatible with 0.032 in guidewires	Pass
Distance Markings	To verify that distance markings on the AeroPace Catheter meet the requirements defined in ISO 10555-3	Distance (depth) markers shall indicate the distance from the distal tip of the catheter per ISO 10555-3	Pass
Cleaning Agent Compatibility	To confirm that commonly used cleaning agents may be used to clean the AeroPace Catheter	At least one recommended cleaning agent is provided in labeling per ISO 10555-3	Pass
DC Resistance Test	To measure the DC resistance of each electrical conductor within the AeroPace Catheter	The DC resistance of each conductor shall meet the predetermined specification	Pass
Dielectric Strength Test	To ensure that there will not be crosstalk between conductors during normal operating conditions	Insulating parts that incorporate electrical conductors and are subject to electrical potential differences withstand pre-determined dielectric strength	Pass
Test for biphasic charge balanced waveform	To verify that the AeroPace System is not delivering residual charge into the body	The AeroPace System shall deliver biphasic, charge balanced waveforms	Pass

Test	Purpose	Acceptance Criteria	Results
Test for maximum pulse frequency	To verify the maximum pulse frequency delivered by AeroPace System	The maximum stimulation pulse rate delivered by the AeroPace System shall be less than 45 Hz (pulses per second) per side	Pass
Defibrillation protection	To verify the AeroPace System remains safe when subjected to energy applied during a patient defibrillation event	The System shall conform to applicable sections of 60601-1	Pass
Functional testing	To verify that the AeroPace Airway Sensor meets requirements	The AeroPace Airway Sensor shall conform to applicable sections of ISO 5356-1 for conical connectors	Pass
Electrical Safety	To determine the electrical safety of the AeroPace System	The AeroPace System shall conform to applicable sections of IEC 60601-1	Pass
AIM7351731 - Medical Electrical Equipment and System Electromagnetic Immunity Test for Exposure to Radio Frequency Identification Readers	To determine RFID compatibility of the AeroPace System	The AeroPace System shall conform to applicable sections of AIM7351731	Pass
Electromagnetic Compatibility (EMC)	To determine the Electromagnetic Compatibility (EMC) of the AeroPace System	The AeroPace System shall conform to applicable sections of IEC 60601-1-2	Pass
Human Factors (Usability) Testing	Formative and summative human factors testing to evaluate the usability of the AeroPace System	In accordance with applicable standards for medical device human factors engineering and risk management and in accordance with FDA's guidance, Applying Human Factors and Usability Engineering to Medical Devices (2016).	Pass

Abbreviations: AIM=Association for Automatic Identification and Mobility; DC=direct current; IEC=International electrotechnical commission; ISO=International organizations for standardization; MEM=minimum essential medium

Sterilization

The AeroPace Catheter Kit is the only subsystem of the AeroPace System that is supplied sterile. It is sterilized by ethylene oxide (EO). The EO sterilization process was successfully validated in accordance with ISO 11135. The test results from the sterilization testing confirmed that the product can be adequately sterilized to the desired level of sterility assurance of 10^{-6} . Additionally, routine testing of biological indicators is performed to confirm that the sterilization process is effective in eradicating viable microorganisms.

Packaging and Shelf Life

Packaging qualification testing (visual inspection, package integrity (bubble leak), and seal

strength testing) demonstrated the ability of the packaging to protect the product and maintain a sterile barrier following environmental conditioning and simulated distribution. A shelf life of two years was established for the AeroPace Catheter Kit based on product and package shelf-life testing.

B. Animal Studies

Two preclinical studies in a porcine model, verified proof of principle of the AeroPace System for activation of the diaphragm to retain diaphragmatic strength in mechanically ventilated subjects (Reynolds, 2017a; Rohrs, 2021). Two animal studies in the same porcine model validated safety and performance of the AeroPace System as summarized in **Table 5**.

Table 5: AeroPace System Pre-Clinical Animal Testing

Study	Functional Validation of the Lungpacer AeroPace System in an Acute Swine Model
Purpose	Validate the safety and functionality of the AeroPace System in an acute preclinical study.
Methods	• Anesthetized porcine subjects (3) on MV had an AeroPace Catheter placed into the left subclavian or left jugular vein • Evaluate functionality of AeroPace System components in both Pressure Support Mode and Volume Control Mode, with each of 3 ICU ventilators. ○ Auto and Manual Placement ○ Auto Mapping and Therapy ○ Manual Mapping and Therapy • The functionality of the AeroPace System was validated in an acute setting.
Results	All study objectives were met, and system functionality was validated in both Pressure Support Mode and Volume Control Mode, each with 3 different models of ventilators. Specifically, the following aspects of the AeroPace System functionality were validated: • Successful Catheter was insertion into the left jugular vein or left subclavian vein. • Intravascular electrogram assisted placement of the AeroPace Catheter. • AeroPace Catheter lumens were successfully used as central line lumens. • Placement of the left electrode array was successfully executed in Auto and Manual Modes. • Mapping of the left and right electrodes and Thresholds were successfully executed using Auto and Manual Modes. • Therapy was successfully executed using Auto and Manual Modes with the touchscreen or Handheld Controller. • The AeroPace Catheter was successfully removed. Transvenous stimulation of the phrenic nerves was well tolerated and did not cause clinically relevant changes in clinical parameters evaluated.
Purpose	Evaluate the effect of maximum charge stimulation on the left subclavian/jugular vein and cranial vena cava and the effect of stimulation on the phrenic nerves.
Methods	• Anesthetized porcine subjects (3) on MV with AeroPace Catheter placed into the left jugular vein. • Continuous charge using maximum intensity was delivered in the treatment mode for approximately 6 hours. • Post-study pathological and histological evaluations were conducted for the phrenic nerves and targeted vessels.
Results	• No adverse events related to the use of the AeroPace System were observed. • Maximum-charge transvenous stimulation was well tolerated and did not cause clinically relevant changes in clinical parameters evaluated. • No pathological or histopathological changes were found that indicated clinically adverse nerve or vessel damage.

Abbreviations: MV=mechanical ventilation

C. Additional Studies

Additional testing of the AeroPace System included electrical safety testing per IEC 60601-1, electromagnetic compatibility (EMC) testing per IEC 60601-1-2, formative and summative human factors (usability) testing and software testing, per FDA guidance and relevant standards. See **Table 4** above for information on electrical safety testing, EMC testing, usability testing.

Software documentation was provided in accordance with FDA's "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*" and the FDA-recognized software standard IEC 62304, "*Medical device software – Software life cycle processes*".

Lungpacer performed the following software verification and validation (V&V) activities:

- Code Reviews
- Static tool analysis used a Static Analysis tool to analyze the code for any coding errors or areas with potential errors
- Software unit verification
- Software Heavy Unit Testing (HUT) - developer-based testing to evaluate implementation of the software and confirm correct functionality. Heavy Unit testing evaluated the software itself and used fault injection and software demonstration to thoroughly test the most safety critical functions.

There is negligible cybersecurity risk for the AeroPace System. The AeroPace System does not have any electronics allowing for direct external contactless/wireless communications. The AeroPace System does not include any capability to connect to WiFi. The AeroPace System does not include RFID technology.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A. Feasibility Studies

The clinical program for the AeroPace System included six single-arm studies (total N=61) that evaluated the safety and feasibility of an early version of the AeroPace System in patients undergoing a diagnostic procedure or surgery and receiving short-term MV. These studies showed that stimulation of the phrenic nerves via the electrodes in the Catheter placed in the left subclavian vein (Reynolds, 2017b) or the left jugular vein (Gani, 2020), elicited contractions, and that bilateral or unilateral pacing in synchrony with MV resulted in airway pressure reductions (Reynolds, 2017b). No adverse events occurred in any patient. A summary of the feasibility studies is provided in **Table 6**.

Table 6. Feasibility Studies Applicable to the AeroPace System

Protocol No. Study Type (access) Year(s)	Study Design	Study Objectives	Study Population	No. Subjects Locations
First-in-Human (subclavian) 2015	Prospective, single-center, single treatment group	Catheter placement, Mapping	Non-MV patients undergoing a diagnostic procedure or surgery	N=4 Paraguay (one site)
First-in-Human (subclavian) 2015		Catheter placement, Mapping, Diaphragm pacing	Short-term MV patients undergoing a diagnostic procedure or surgery	N=13 Paraguay (one site)
Next-in-Human (subclavian) 2016 (Reynolds, 2017b)		Catheter placement, Mapping, Diaphragm pacing, heart rate data capture, multipolar stimulation		N=11 Paraguay (one site)
Jugular Access Feasibility (jugular) 2018 (Gani, 2019)	Prospective, multi-center, single treatment group	Catheter placement from left jugular vein, mapping, diaphragm pacing; heart rate data capture, multipolar stimulation, tidal volume generation	Short-term MV patients undergoing a diagnostic procedure or surgery	N=13 Paraguay (one site)
Jugular Access Feasibility (jugular) 2019 (Gani, 2020)		Catheter placement from left jugular vein, mapping, diaphragm packing; heart rate data capture, multipolar stimulation		N=20 Paraguay (one site)
P-100 RESCUE 1 Feasibility Study (subclavian) 2017-2018 (Ataya, 2020)	Prospective, multi-center, single treatment group	Safety & feasibility for up to 30 days - Catheter placement, phrenic nerve capture and activation, delivery of Lungpacer DPT up to 30 days. - Observational outcomes for weaning, MIP, RSBI, diaphragm thickening fraction.	Patients who failed ≥2 weaning trials and received ≥7 days MV	N=11 U.S. (three sites)

Abbreviations: FiH=first in human; MIP=maximal inspiratory pressure; MV=mechanical ventilation; N=number; NiH=next in human; RSBI=Rapid Shallow Breathing Index; US=United States.

RESCUE 1 was an open-label single-arm feasibility study conducted in 2018 at three (3) US sites in 11 patients who received MV for ≥7 days and who had failed ≥2 weaning attempts (IDE G170057). RESCUE 1 evaluated an early model of the AeroPace System using two to three sessions per day of 120 stimulations daily for up to 30 days. The study evaluated the safety and

feasibility of catheter placement/removal, phrenic nerve capture and therapy delivery for up to 30 days. Nine of the 11 patients formed the modified Intent-to-Treat (mITT) population which included all patients for whom the Catheter entered a blood vessel. Patients received the Catheter in the left subclavian vein for a median duration of 10 days, and all patients (mITT) met the feasibility outcomes.

Observational outcomes were collected for the mITT population. Of the nine patients, seven patients (77.8%) successfully weaned. Rapid shallow breathing index (RSBI) improved by 44% with a mean change of -627 ± 60.4 (mITT, N=8) and -63.5 ± 64.4 (mITT, weaned, N=6). Maximal inspiratory pressure (MIP) improved 64% to 105% with a mean change of $13.9 \text{ cm H}_2\text{O} \pm 20.6$ (mITT, N=9) and $19.7 \text{ cm H}_2\text{O} \pm 17.9$ (mITT, weaned, N=7). Maximal inspiratory pressure (MIP) improvement had a significant dose-response relationship with the number of stimulations delivered (mITT). The median increase in B-Mode diaphragm thickening fraction (right hemidiaphragm) was 28%, while the mean increase was $36.8\% \pm 51.8\%$ (N=7, mITT).

Adverse events collected for the ITT population were as expected for ICU patients on MV. A serious adverse event of bronchial mucus plug was associated with the procedure of Trendelenburg positioning used for left subclavian vein access (Ataya, 2020). There were no deaths in the study.

RESCUE 1 demonstrated the safety and feasibility of the AeroPace System (equivalent model) for use up to 30 days in patients on MV ≥ 7 days and who had failed to wean. Two independent indicators of diaphragm strengthening, MIP and diaphragm thickening fraction, improved. Both MIP and RSBI were significantly improved in the subjects who successfully weaned. The study results were published in Ataya (2020).

B. Randomized Controlled Trials

The applicant performed a clinical study, RESCUE 3, to establish a reasonable assurance of safety and effectiveness of the AeroPace System to improve weaning success of patients who have been on MV ≥ 96 hours in the US and EU under IDE G180237. Data from this clinical study were the basis for the PMA decision. A summary of the clinical study is presented below.

Two randomized controlled trials (RCT) were conducted to evaluate the safety and effectiveness of the AeroPace System or equivalent device models (with SoC) compared with SoC alone to increase diaphragmatic strength and improve weaning success in patients on MV ≥ 96 hours and who failed ≥ 2 weaning trials. This population had a high likelihood of diaphragm atrophy after 96 hours on MV, as was verified by mean baseline MIP values. Two weaning trials were utilized; the first weaning trial excluded patients who were able to wean with SoC alone, while the second weaning trial was used to implement a protocol-specific ventilator-liberation trial (VLT) to standardize the declaration of weaning failure across all sites.

RESCUE 2 (N=112) was a pilot RCT that enrolled subjects at 20 sites in Germany and France (Dres, 2022). The primary endpoint was the proportion of subjects successfully weaned through 30 days. Additional endpoints were days on MV, MIP and RSBI changes from baseline to last available measurement, diaphragm thickening fraction, mortality, incidences of reintubation and tracheostomy, and ICU and hospital discharge.

RESCUE 3 (N=223) was the main RCT to support the PMA decision that enrolled a similar

patient population, had a similar study design, and evaluated similar study endpoints as RESCUE 2. RESCUE 3 enrolled subjects at 48 sites in the US, France, Germany, and Spain. The study used a group sequential design. The designs and objectives of these studies are summarized in Table 7.

Table 7: Randomized Controlled Trials - AeroPace System

Protocol No. Study Type (access) Year(s)	Study Design	Study Objectives	Study Population	No. Subjects Locations
RESCUE 2 (P-200) Safety & effectiveness Pilot RCT (subclavian) 2019-2020 (Dres, 2022)	Pilot randomized (1:1), controlled, open-label, multicenter clinical trial of Lungpacer therapy with Standard of Care vs. Standard of Care alone.	Safety, effectiveness & performance of the AeroPace System (equivalent model) for up to 30 days. - Primary endpoint: successful weaning. - Secondary endpoints: days on MV, MIP, RSBI, mortality. - Observational endpoints: reintubation, tracheostomy, ventilator settings, ICU and hospital discharge.	Patients on MV ≥ 96 hours and who failed ≥ 2 weaning trials	N=112 randomized, N=12 roll-in Europe (France & Germany) (20 sites)
RESCUE 3 (P-300) Safety & effectiveness main RCT (subclavian & jugular) 2019-2022	Randomized (1:1), controlled, open-label, multicenter group sequential design clinical trial of Lungpacer therapy with Standard of Care vs. Standard of Care alone	Safety & effectiveness of the AeroPace System and equivalent model for up to 30 days. - Primary endpoint: successful weaning - Secondary endpoints: days on MV, MIP, RSBI, mortality - Observational endpoints: reintubation, tracheostomy, ventilator settings, ICU and hospital discharge.	Patients on MV ≥ 96 hours and who failed ≥ 2 weaning trials	N=223 randomized N=33 roll-in US & Europe (France, Germany, Spain) (48 sites)

Abbreviations: MIP=maximal inspiratory pressure; MV=mechanical ventilation; N=number; RSBI=Rapid Shallow Breathing Index; RCT=randomized controlled trial; US=United States.

RESCUE 2

1. Study Design and Population

RESCUE 2 was a randomized, controlled, open-label, multicenter clinical trial to investigate the safe and effective performance of an equivalent model of the AeroPace System in subjects on MV ≥ 96 hours and who had failed ≥ 2 weaning trials. Subjects were randomized 1:1 to Treatment with the Lungpacer system (plus SoC) compared with Control (SoC alone). One to two Roll-In

subjects were allowed per site. The duration of the study was 30 days with follow-up to Day 32 or study exit. The study enrolled subjects at 20 clinical centers in the EU and was completed in 2020.

One-hundred and twelve (112) randomized subjects (ITT population), 57 subjects in the Treatment group and 55 subjects in the Control group, and 12 non-randomized Roll-In subjects were enrolled. The overall study population was 57.1% (64/112) male, with a mean age of 64.6 years. The most common reason for MV was ARDS/ARF (37.5% (42/112)), followed by pneumonia, surgery, COPD and “other” that ranged from 18.8% to 12.8%. The mean duration of MV at enrollment was 28 days. More than half of the subjects (54.5% (61/112)) were tracheotomized at enrollment.

In the Treatment group, 43 subjects formed the mITT population for whom the Catheter could be placed (seven subjects excluded), stimulation delivered to at least one phrenic nerve (seven subjects excluded) and the diaphragm contracted. The Catheter placement was in the left subclavian vein with a median duration of 10 days. Catheters were used for infusion for 52% (35/67) of inserted catheters (some subjects had multiple catheters inserted and removed).

Lungpacer therapy was delivered in 4-6 sets of 10 stimulations, 2-3 times daily for a total of 120 stimulations/day, intensity maximized based on subject comfort, for up to 30 days or until study exit. A Treatment/Roll-In subject could receive a maximum of 3600 stimulations during the study. The maximum study duration for subjects was 32 days. Of all subjects, 62.8% (27/43) of required stimulations were delivered and 79% (34/43) of subjects received $\geq 50\%$ of the protocol required stimulations (which defined the Per Protocol group (PP)).

2. Effectiveness Results

The primary effectiveness outcome was the difference in the proportion of subjects successfully weaned by Day 30 in the Treatment group compared with the Control group, which, in this pilot RCT, was not statistically powered. “Successfully weaned” was defined as passing a protocol-specific VLT, and not returned to MV within 48 hours. Weaning success was 81.5% and 74.1% in the Treatment and Control groups, respectively, for 7.4% greater weaning success for Treatment subjects ($p=0.586$, mITT).

There were fewer days on MV in the Treatment group compared with the Control group (1.4 days, mean, mITT). MIP mean change from baseline was 16.6 cm H₂O and 4.8 cm H₂O in the Treatment and Control groups, respectively, for a mean difference between groups of 11.8 cm H₂O (mITT), representing a 245% MIP improvement with Treatment compared to Control. There was a dose-response relationship between MIP improvement and number of stimulations (mITT). Ultrasound was performed in 34 subjects at eight sites to assess diaphragm changes from baseline to last available measure. The change in right side diaphragm thickening fraction (DTf) with M-mode ultrasound was higher in the Treatment group (16.6%, mITT) compared with a decrease in DTf in the Control group (-13.6%, mITT). RSBI improved 127% in the Treatment group compared with the Control group for a difference between groups of 23 breaths/min/L (mITT).

3. Safety Results

Safety was assessed by documentation of AEs and SAEs during the study. AEs were reported in 57.9% of subjects in the Treatment group (96 AEs/33 subjects) and in 69.1% of the Control group (88 AE/38 subjects). SAEs were equally distributed between the randomized groups: 47.4% in the Treatment group (47 SAEs/27 subjects) and 49.1% in the Control group (39 SAEs/27 subjects).

AEs and SAEs by System Organ Class (SOC) with an incidence >10% in the Treatment group are shown in **Table 8**. The highest incidences were for respiratory / thoracic / mediastinal disorders and infections. The AEs and SAEs were typical for patients in an intensive care setting and using a central venous catheter (CVC). There were no unanticipated adverse device effects.

Table 8: Adverse and Serious Adverse Events by Randomized Group – System Organ Class (ITT)

System Organ Class	Adverse Events				Serious Adverse Events			
	Treatment		Control		Treatment		Control	
	# of events	# (%) of subjects	# of events	# (%) of subjects	# of events	# (%) of subjects	# of events	# (%) of subjects
Cardiac disorders	9	8 (14.0%)	6	6 (10.9%)	4	4 (7.0%)	4	4 (7.3%)
General disorders and administration site conditions	10	7 (12.3%)	5	5 (9.1%)	3	3 (5.3%)	3	3 (5.5%)
Infections and infestations	16	13 (22.8%)	22	18 (32.7%)	8	8 (14.0%)	7	7 (12.7%)
Investigations	6	6 (10.5%)	0	0	2	2 (3.5%)	0	0
Nervous system disorders	7	7 (12.3%)	4	4 (7.3%)	0	0	3	3 (5.5%)
Respiratory, thoracic and mediastinal disorders	17	13 (22.8%)	14	11 (20.0%)	15	13 (22.8%)	8	8 (14.5%)

Device- or procedure-related AEs, as determined by the investigator, by SOC for the Treatment group were most commonly for infections (14.5%), respiratory / thoracic / mediastinal disorders (14.0%), cardiac disorders (10.5%), and general disorders and administration site conditions (8.8%). Cardiac AEs included temporary arrhythmias related to transvenous electrical stimulation that were addressed by repositioning of the catheter without sequelae. All other AEs were related to the catheter or catheter placement.

There were no differences between Treatment and Control groups in the overall incidence of 28.1% vs. 29.1%, respectively, in device- or procedure-related SAEs. Device- or procedure-related SAEs were higher for the Treatment group compared with the Control group for respiratory / thoracic / mediastinal disorders (14%, Treatment; 5.5%, Control), mostly for pleural effusion and pneumothorax, and for infections (8.8%, Treatment; 5.5%, Control).

Pain was assessed in Treatment and Roll-In subjects using the 10-point Wong-Baker FACES[®] Pain Rating Scale (Wong-Baker FACES Foundation (2018)) at the beginning and end of each therapy session. Pain scores were collected in 84% (36/43) of subjects during at least one therapy session resulting in a mean pain score of 0 (interquartile range = 0, 3). Pain was reported in 9% of the sessions during which pain was assessed. For the subjects who reported pain in at least one session (44%, 16/36), the highest pain score reported per subject was 3.8 ± 3.5 (“hurts a little more”) on the 10-point rating scale.

Eleven deaths were reported in the study, 3 deaths (7%) in the mITT Treatment group and 8 deaths (15%) in the Control groups, which is within the expected 30-day mortality rates for patients on MV (Boles, 2007; Damuth, 2015; Béduneau, 2017).

4. Conclusions

The results of the RESCUE 2 study demonstrated that therapy using an early model of the

AeroPace System was well tolerated and had a safety profile as expected for CVCs and for temporary transvenous electrical stimulation. SAEs of infection, and pleural effusion and pneumothorax following misplacement of a CVC, occurred in the study at incidences consistent with the medical literature (Rai, 2023; Smit, 2018). AeroPace therapy with SoC compared with SoC alone improved diaphragmatic strength in MV patients as evaluated by two independent indicators of diaphragm strength: MIP and diaphragm thickening fraction. MIP and diaphragm thickening fraction are associated with weaning success in MV patients (Supinski, 2016; Martin, 2014; Goligher, 2018; Ferrari, 2014; Jung, 2016). Consistent with literature expectations, improvements with the AeroPace System compared to SoC were observed for RSBI, weaning success, and days on MV (Dres, 2022).

RESCUE 3

RESCUE 3 data were the main basis for the PMA approval decision.

1. Study Design and Population

The study was a randomized, controlled, open-label, international multi-center trial using a group sequential design to determine the safety and effectiveness of the AeroPace System or an equivalent model plus SoC (Treatment) compared to SoC (Control) to improve diaphragmatic strength and weaning success in patients on MV. Patients were ≥ 18 years of age and had received MV for ≥ 96 hours and had failed ≥ 2 weaning trials. The study duration was 30 days with follow-up to Day 32 or study exit.

The study enrolled 223 randomized subjects and 33 Roll-In subjects between June 14, 2019 and January 27, 2023. There were 48 investigational sites (27 US; 21 EU) that enrolled at least one subject.

Up to two Roll-In subjects could be enrolled at each site to obtain experience with the investigational device. All Roll-In subjects received Treatment and SoC. Data for Roll-In subjects were collected in the same manner as for randomized Treatment subjects but were analyzed separately from the randomized study population. Study results for Roll-In subjects and randomized Treatment group subjects were similar.

The AeroPace System was used to deliver six sets of 10 stimulations, twice daily for a total of 120 stimulations/day (stimulation intensity was maximized based on subject comfort) for up to 30 days or until study exit. A Treatment/Roll-In subject could receive a maximum of 3600 stimulations delivered over 30 days. Treatment and Control subjects received SoC for weaning, which included one daily protocol-specific weaning trial (maximum of two weaning trials daily). The maximum study duration for subjects was 32 days.

Standard of care included a daily protocol-specific physician-directed VLT, and no more than one additional weaning trial daily. Sedation for patients on MV > 24 hours was minimized, if possible, and institutional practices were followed for limb movement and exercise. Non-invasive ventilation or high flow oxygen was used, if needed, to prevent post-extubation respiratory failure for subjects who passed a VLT or who were removed from MV. Inspiratory muscle strength training (IMST) protocols were prohibited.

Statistical Design

The study was designed to randomize 200 to 400 subjects 1:1 blocked by investigational site to Treatment or Control and using a group sequential design borrowing data from the RESCUE 2 trial for subjects who met RESCUE 3 inclusion/exclusion criteria and furthermore were propensity matched.

Bayesian analyses and frequentist analyses were used for the primary endpoint of successful weaning and the related secondary endpoints of days on MV and mortality. All other endpoints were evaluated using frequentist analyses using RESCUE 3 data only.

Propensity score adjustment was used to account for potential residual differences between subjects in the two studies and were calculated based on various pre-specified demographic, clinical and medical history characteristics. The propensity score adjustment included rescaling weights (discounting) that resulted in an equivalent of 64 subjects from RESCUE 2 borrowed in a power prior approach. Sensitivity analyses were performed to demonstrate the robustness of the RESCUE 2 borrowing based on different possible weighting schemes.

The group sequential design allowed for interim analyses, limited to unblinded review only by the study DSMB, of aggregate data for the primary effectiveness and safety outcomes while study enrollment continued without interruption. Interim analyses with the potential for stopping occurred at 150 subjects and every 50 subjects thereafter, up to the maximal sample size of 400 subjects. This range of sample sizes provided 86% power in the anticipated scenario. The sample size included a 15% expected study attrition rate. No more than 25% of subjects were to be randomized at any given investigational site. At least 20% of subjects were to be randomized in the US.

Safety Monitoring

An unblinded Clinical Events Committee (CEC) operated independently from the study Sponsor and study sites according to the study CEC Charter to adjudicate individual SAEs meeting certain criteria for relatedness to the device or procedure and was empowered to make judgements regarding the safety data and safety endpoints. All SAEs were adjudicated for verification as an SAE, and all deaths were adjudicated. SAEs and UADEs were adjudicated for Treatment and Roll-in subjects including determining the relationship to the device or procedure.

A Data Safety Monitoring Board (DSMB) conducted safety assessments and planned interim analyses according to the study DSMB Charter.

Study stopping rules were for the occurrence of two incidences of death or massive hemothorax / pneumohemothorax, defined as rapid blood loss of more than 30% of blood volume (1500-2000 mL), that were device-related or procedure-related.

2. Clinical Inclusion and Exclusion Criteria

Enrollment in the RESCUE 3 study were limited to patients who met the following inclusion criteria:

- 1) 18 years or older, and,
- 2) Mechanically ventilated for ≥ 96 hours (4 days) and,
- 3) Satisfied the Readiness-to-Wean criteria, and,

- 4) Failed ≥ 2 weaning attempts*:
 - That were conducted ≥ 48 hours after initiation of MV, and,
 - That were conducted on different calendar days, and,
 - ≥ 1 of which was the protocol-specific VLT.

*Self-extubation from MV with subsequent re-intubation within 48 hours was considered a failed weaning attempt. Institutional weaning attempt was in accordance with the institution's defined standard of practice and weaning attempt was to be documented in the subject's medical records.

Patients were not permitted to enroll in RESCUE 3 if they met any of the following exclusion criteria:

- 1) MIP (absolute value) > 50 cm H₂O;
- 2) Invasive MV > 90 days;
- 3) Currently on ECMO;
- 4) Weaning failure due to hypervolemia;
- 5) Medical history (including imaging) or known anatomy that prevents percutaneous insertion of the Catheter into the intended thoracic vein on the left side;
- 6) Clinically overt congestive heart failure that is preventing weaning;
- 7) Currently being treated with neuromuscular blockade;
- 8) Pre-existing neurologic, neuromuscular, or muscular disorder that could affect the respiratory muscles;
- 9) Pre-existing severe chronic pulmonary fibrosis;
- 10) Pleural effusions occupying greater than one-third of the pleural space on either side;
- 11) BMI > 45 kg/m²;
- 12) Known or suspected phrenic nerve paralysis;
- 13) Any electrical device (implanted or external) that may be prone to interaction with or interference from the Lungpacer DPTS, including neurological pacing/stimulator devices, cardiac pacemakers, and defibrillators;
- 14) Current hemodynamic instability, sepsis, or septic shock;
- 15) Bacteremia within the last 48 hours;
- 16) Anticipating withdrawal of life support and/or shift to palliation as the goal of care;
- 17) Known or suspected to be pregnant or lactating;
- 18) Currently being treated in another clinical trial studying an experimental treatment that could affect the study primary outcome.

3. *Follow-up Schedule and Assessments*

The following study evaluations and follow-up were conducted:

- After consent and prior to randomization
 - Qualifying protocol-specific Ventilator Liberation Trial
 - RSBI/RASS/MIP
 - SOFA
 - Laboratory tests
- Daily up until the day of MV removal, transfer to a facility outside of the enrolling institution, or study completion, whichever comes first:

- Ventilator Settings (PS, PEEP, RR, FiO₂, Ventilation Mode, VT),
 - Protocol-specific Ventilator Liberation Trial
- For Treatment subjects only:
 - Wong-Baker 10-point Pain Visual Analogue Scale (at the beginning and end of each therapy session)
 - Stimulation Discomfort and Sensation Tool (at the end of each therapy session)
- Baseline, Day 7 ± 1, 14 ± 1, 21 ± 1, 28 ± 1 or Day 30 while on MV, as well as the day of removal from MV (Day 1 is the *anticipated placement date*) until removal from MV associated with successful weaning, prior to transfer to a facility outside of the enrolling institution or study completion, whichever comes first:
 - Rapid Shallow Breathing Index (RSBI)
 - Richmond Agitation-Sedation Scale (RASS)
 - Maximal Inspiratory Pressure (MIP)
- Following Catheter Removal (for Treatment subjects only):
 - Treatment Subject Questionnaire (completed at study exit or before transfer, whichever comes first)
- Other data evaluations to Day 30 and follow-up:
 - The time to first successful VLT after randomization;
 - Cessation and re-instatement of mechanical ventilation;
 - Date of tracheotomy, if applicable;
 - ICU admissions and discharges;
 - Hospital admission and discharges, and
 - Mortality

The following safety evaluations and follow-up were conducted:

- Safety Evaluations (AE and SAE data collection during study before Safety Evaluation Follow-up):
 - All Subjects: all AEs and SAEs until withdrawal or death, until completion of placement attempt, or until Catheter removal, transfer, successful weaning, or unsuccessful weaning by Day 30.
- Safety Follow-up Evaluations (SAE-only data collection after study Safety Evaluation completed):
 - Treatment Subjects:
 - Withdrawal or death – no follow-up;
 - Unsuccessful placement of the Catheter – SAEs for 48 hours after placement attempt or Catheter removal;
 - Successful wean/Unsuccessful wean/Transfer – SAEs to Day 30, or 48 hours after Catheter removal, or 48 hours after successful VLT or removal from MV, whichever is latest.
 - Control Subjects:
 - Withdrawal or death – no follow-up;

- Successful wean/Unsuccessful wean/Transfer – SAEs to Day 30, or 48 hours after successful VLT, or removal from MV, whichever is latest.

4. *Clinical Endpoints*

Primary Endpoint

With regards to effectiveness, the primary endpoint was the cumulative incidence (proportion) of subjects “successfully weaned” by Day 30. “Successfully weaned” was defined as passing the protocol-specific VLT, or removed from MV, and not returned to MV within 48 hours. A protocol-specific VLT was used to standardize weaning trials and all study sites were trained on its use. The primary effectiveness outcome was superiority for Treatment subjects compared with Control subjects for successful weaning within the 30-day study period.

The primary null and alternative hypotheses are:

H₀: The hazard ratio for successful weaning is the same in subjects randomized to Treatment as compared to those randomized to Control, HR=1.

H₁: The hazard ratio for successful weaning is greater than 1, indicating subjects wean faster on the Lungpacer device, HR>1.

The primary analysis was performed on the mITT population. As a sensitivity analysis, the model was repeated for the Per Protocol (PP) population.

A 10% improvement in weaning success for Treatment compared with Control was defined as a minimal clinically important difference (MCID) for RESCUE 3 based on a large RCT evaluation of 3 weaning strategies (VENISE Trial, Girault, 2011) using rate of extubation, i.e., successful weaning, as the primary outcome.

With regards to safety, the primary endpoint was assessment of AEs for subjects randomized to Treatment (Lungpacer DPTS plus SoC) compared with subjects randomized to Control (SoC) over the study period and follow-up. The study’s primary safety outcome was the expected safety profile for Treatments subjects compared with Control subjects.

Secondary Endpoints

Secondary effectiveness endpoints in priority order were:

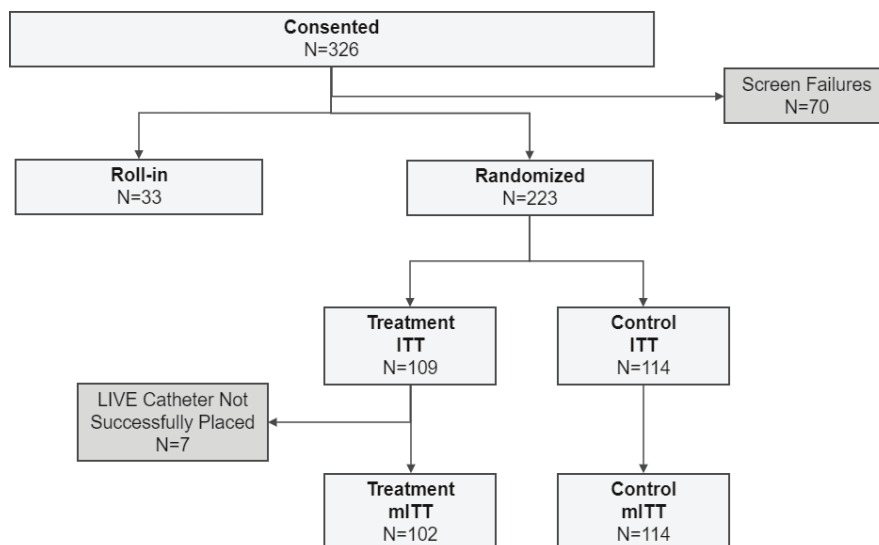
- Days on mechanical ventilation from Day 1 to removal from MV associated with successful weaning or Day 30, whichever comes first. Days on MV had a pre-specified MCID of 0.5 days.
- Change in MIP from randomization (baseline) to last available measure. MIP is an indirect measurement of diaphragmatic strength.
- Change in RSBI from randomization (baseline) to last available measure. RSBI measures the ratio of the Respiratory Rate to Tidal Volume (breaths/min/L) and is an index for weaning success.
- Day 30 mortality/survival.

C. Accountability of PMA Cohort

There were 326 subjects consented, 70 screen fail subjects, 33 Roll-In subjects, and 223 randomized subjects (109 Treatment; 114 Control) in the RESCUE 3 study (**Figure 2**). For

randomized Treatment subjects, 102 subjects had successful catheter placement, and comprised the mITT Treatment population.

At the time of database lock, of 223 patients enrolled in the PMA study, 83% (184) patients are available for analysis at the completion of the study, 30 days after device placement.



Abbreviations: ITT=Intent to treat, mITT=modified intent to treat; N=number. Source: RESCUE 3 Frequentist Final Report_2023_06_26, Figure 1

Figure 2: RESCUE 3 Subject Disposition

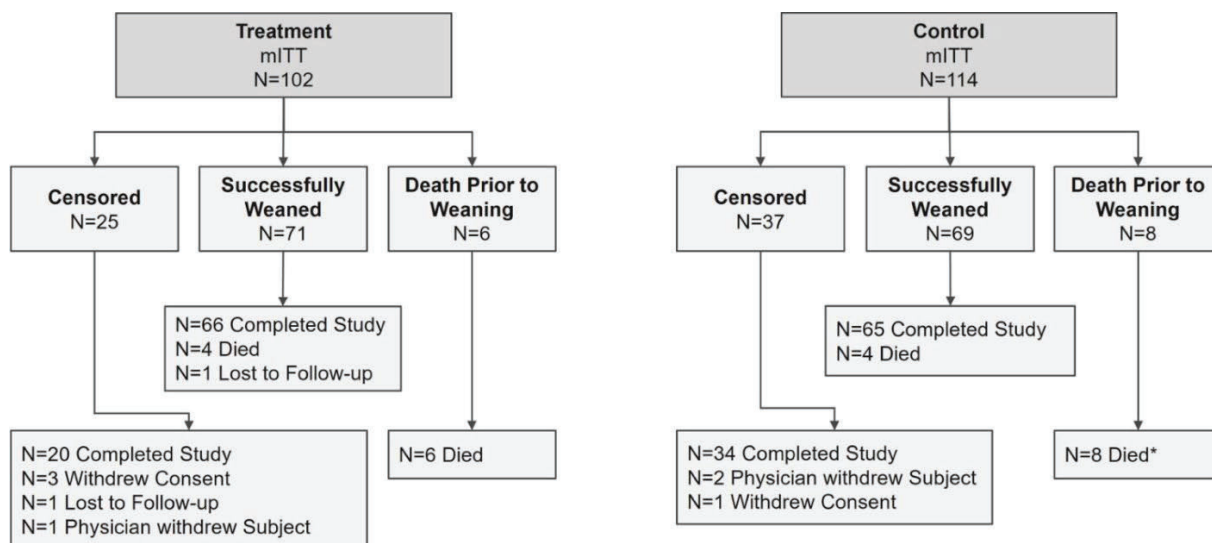
The Keystone System/LIVE Catheter was used in 67.6% (69/102) of randomized mITT Treatment subjects, and the AeroPace System/AeroPace Catheter was used in 32.4% (33/102) of randomized mITT Treatment subjects. Catheters were used for infusion for 64% of (65/102) subjects.

The analyses utilized the mITT and PP Treatment populations except for 30-day mortality which used the ITT population, as defined below:

- **Intent-to-treat (ITT) population:** all subjects who were randomized, with study group defined by the randomization. There were 109 Treatment subjects and 114 Control subjects in the ITT group.
- **Modified Intent-to-Treat (mITT) population:** a subset of the ITT population for the Treatment group consisting of 102 subjects that had successful placement of the Catheter defined as entering the vein, at least one phrenic nerve captured, and the diaphragm stimulated. The mITT and ITT groups were the same for Control subjects.
- **Per Protocol (PP) population:** a subset of the mITT population for Treatment subjects, consisting of 90 subjects defined by completion of $\geq 50\%$ of the protocol-required number of stimulations (Stims) in ≥ 1 phrenic nerve, without a major protocol deviation that precluded effectiveness evaluation (no subjects met this criteria), and who had observed data for evaluation of the primary effectiveness endpoint. The PP, mITT and ITT groups

were the same for Control subjects.

Subject completion in the randomized groups is summarized in **Figure 3**. For randomized Treatment subjects, 102 subjects had successful catheter placement, and comprised the mITT Treatment population. Eighty-four percent (84%, 86/102) of the mITT Treatment group and 86% (98/114) of the Control group completed the study to Day 30.



Abbreviations: ITT=Intent to treat, mITT=modified intent to treat;
N=number. Source: RESCUE 3 Frequentist Final
Report_2023_06_26, Figure 2

Figure 3: Randomized mITT, Primary Endpoint and Study Completion

D. Study Population Demographics and Baseline Parameters

The demographics (age, sex, race/ethnicity) of the study population were typical for a population of mechanically ventilated patients in a randomized study performed in the US and EU.

Baseline demographics for randomized subjects are provided in **Table 9**. The average age of subjects was 64 years. Subjects were primarily male (65% (145/223)), with mean BMI of 28.5 kg/m², and 65% (145/223) were previous or current smokers. Subjects were randomized in the US (36.3% (81/223)) and EU (63.7% (142/223)). Subjects from the US had race collected and were Caucasian (34.5% (28/81)), Black (7.6% (6/81)) and Asian (2.7% (2/81)). There were no statistical differences in the baseline demographics between study groups.

Table 9: Baseline Demographics

Parameter	% (n/N) or Mean ± SD (N) (Min, Median, Max)				
	Randomized			ITT	mITT
	Treatment (ITT=109)	Treatment (mITT=102)	Control (ITT=mITT=114)	p-value ¹	p-value ¹
Age (years)*	64.9 ± 12.0 (30.0, 66.0, 87.0)	64.6 ± 12.1 (30.0, 66.0, 87.0)	63.8 ± 11.5 (27.0, 65.0, 87.0)	0.4943	0.6119

Male*	65.1% (71)	67.6% (69)	66.7% (76)	0.8878	0.8858
BMI* (kg/m²)	28.4 ± 6.2 (106)	28.3 ± 6.1 (99)	28.7 ± 6.7 (113)	0.7987	0.7263
Smoking					
Current	17.4% (19/109)	17.6% (18/102)	17.5% (20/114)	0.6287	0.7097
Previous	44.0% (48/109)	45.1% (46/102)	50.0% (57/114)		
Never	38.5% (42/109)	37.3% (38/102)	32.5% (37/114)		
Race					
American Indian or Alaska Native	1.8% (2)	2.0% (2)	0.9% (1)	0.6852	0.6004
Asian	2.8% (3)	2.0% (2)	2.6% (3)		
Black or African American	9.2% (10)	8.8% (9)	6.1% (7)		
Caucasian	32.1% (35)	30.4% (31)	36.8% (42)		
Not Reported	47.7% (52)	50.0% (51)	50.0% (57)		
Other	0.0% (0)	0.0% (0)	0.9% (1)		
Unknown	6.4% (7)	6.9% (7)	2.6% (3)		
Ethnicity					
Hispanic or Latino	5.5% (6)	4.9% (5)	3.5% (4)	0.8861	0.8868
Not Hispanic or Latino	37.6% (41)	35.3% (36)	38.6% (44)		
Not Reported	48.6% (53)	51.0% (52)	50.9% (58)		
Unknown	8.3% (9)	8.8% (9)	7.0% (8)		

Abbreviations: BMI=body mass index; ITT=Intent-to-Treat; mITT=Modified Intent-to-Treat; SD=standard deviation

¹Wilcoxon Rank Sum Test or Fisher's Exact Test.

* Pre-specified factors to compare between randomized groups at baseline.

Baseline clinical characteristics for randomized subjects are provided in **Table 10**. Subjects had received a mean 29.1 days of MV at enrollment. More than half of the subjects (65% (145/223)) were tracheostomized at enrollment consistent with their duration on MV. Mean baseline MIP was 28.8 cm H₂O indicating the presence of diaphragm atrophy. Mean baseline RSBI was 112.5 breaths/min/L. The baseline values for MIP and RSBI were below the values known to be predictive for successful weaning.

One-half of subjects required MV due to acute respiratory stress disorder (ARDS) or acute respiratory failure (ARF), followed by surgical, pneumonia (independent of chronic obstructive pulmonary disease (COPD), ARDS/ARF or surgery), and COPD each in 12% to 16% of subjects. Fewer than 10% of subjects were on MV for trauma or "other" reasons. The heterogeneity of the underlying causes for respiratory failure and the higher incidence of ARDS/ARF was consistent with an ICU population requiring extended durations of MV. Baseline clinical characteristics were not statistically different between study groups.

Table 10: Baseline Clinical Characteristics

Parameter	% (n/N) or Mean ± SD (N) (Min, Median, Max)				
	Randomized			ITT	mITT
	Treatment (ITT=109)	Treatment (mITT=102)	Control (ITT=mITT=114)	p-value ¹	p-value ¹
Tracheostomy Prior to Enrollment*	61.5% (67)	61.8% (63)	67.3% (76/113)	0.4018	0.4752
	27.9 ± 19.0	27.8 ± 19.1	30.3 ± 19.5 (113)	0.2656	0.2544

Days on MV at Randomization*	(5.0, 23.0, 85.0)	(5.0, 22.5, 85.0)	(5.0, 27.0, 86.0)		
Absolute Value of Baseline MIP*	29.0 ± 11.2 (109) (2.4, 29.8, 48.9)	29.9 ± 10.7 (102) (4.9, 30.3, 48.9)	28.7 ± 11.0 (114) (0.2, 27.8, 49.4)	0.6636	0.3506
Baseline RSBI*	122.0 ± 116.0 (106) (14.8, 91.8, 891.3)	120.0 ± 113.4 (99) (14.8, 90.5, 891.3)	103.4 ± 79.8 (110) (17.9, 83.1, 676.5)	0.2914	0.3535
Baseline SOFA Score*	4.0 ± 2.2 (108) (0.0, 3.0, 10.0)	4.0 ± 2.3 (101) (0.0, 3.0, 10.0)	3.9 ± 2.5 (111) (0.0, 3.0, 12.0)	0.4534	0.6444
Reason for Mechanical Ventilation					
ARDS/ARF	45.9% (50)	46.1% (47)	53.1% (60)	0.6652	0.6028
COPD	11.9% (13)	12.7% (13)	11.5% (13)		
Pneumonia**	15.6% (17)	14.7% (15)	9.7% (11)		
Surgical	16.5% (18)	16.7% (17)	14.2% (16)		
Trauma	2.8% (3)	2.0% (2)	5.3% (6)		
Other***	7.3% (8)	7.8% (8)	6.2% (7)		

Abbreviations: ARDS=acute respiratory distress syndrome; ARF=acute respiratory failure;
COPD=Chronic Obstructive Pulmonary Disease; ITT=Intent-to-Treat; mITT=Modified Intent-to-Treat;
MIP=maximal inspiratory pressure; MV=mechanical ventilation; RSBI=Rapid Shallow Breathing Index;
SD=standard deviation; SOFA=Sequential Organ Failure Assessment

¹ Wilcoxon Rank Sum Test or Fisher's Exact Test.

* Pre-specified factors to compare between randomized groups at baseline.

** Pneumonia independent of COPD, ARDS/ARF or Surgery

*** Others were recategorized into existing categories by Lungpacer.

Baseline medical history was as expected for patients on MV and was not statistically different between randomized groups except for a prior history of ARF and Type II Diabetes. Subgroup analyses evaluating the presence or absence of ARF on successful weaning outcomes showed no statistical difference between groups. Similar analyses for Type II Diabetes found no difference in successful weaning between the Treatment and Control groups for the subgroup *with* Type II Diabetes but found a significantly higher rate of successful weaning in the subgroup *without* Type II Diabetes (p=0.0185). A prior medical history of Type II Diabetes, associated with worse outcomes, was present in 39% (43/109) of Treatment subjects compared with 26% (29/112) of Control subjects, a difference unlikely to impact study outcomes.

Overall, the randomization was successful, resulting in balanced baseline characteristics between the Treatment and Control groups.

E. Safety and Effectiveness Results

Safety Results

The analysis of safety was based on the ITT cohort of 223 subjects (109 Treatment subjects and 114 Control subjects). The study's primary safety outcome, that the safety data would show the expected safety profile for Treatment subjects compared with Control subjects, was met.

1. Adverse effects that occurred in the PMA clinical study:

Adverse events (AEs) and serious adverse events (SAEs) were collected through Day 30 unless the patient was withdrawn from the study or died. Patients in the Treatment group with an unsuccessful Catheter placement were followed for 48 hours for post-procedural complications and then exited from the study. Patients who did not wean by Day 30, had their Catheter removed on Day 30 and were then followed for 48 hours (Day 32) for safety events. AEs and SAEs were

categorized by MedDRA System Organ Class (SOC) and lower-level term (LLT).

There were 189 AEs in 74 Treatment subjects (67.9%) and 152 AEs in 60 Control subjects (52.6%). Among all AEs, 70 events in 39 Treatment subjects (35.8%) and 46 events in 27 Control subjects (23.7%) were SAEs. The number and types of AEs reported were consistent with an expected safety profile of critically ill, mechanically ventilated patients. The higher incidence of catheter-related events in Treatment subjects reflect higher (100%) catheter usage compared with Control subjects (typically 50%-80%, Climo, 2003).

AE and SAEs, by SOC, that occurred in >10% of Treatment group subjects are shown in **Table 11**. There were no AEs or SAEs of ventilator dyssynchrony with stimulation or reports of diaphragm injury. The Catheter was used for fluid delivery in 63.8% (65/102) of mITT Treatment subjects and there were no AEs reported related to use of the Catheter for fluid delivery.

Table 11: AEs and SAEs in Treatment Group (ITT) with > 10% Incidence

Body System Organ Class	Adverse Events				Serious Adverse Events*			
	Treatment N=109		Control N=114		Treatment N=109		Control N=114	
	# of events	# (%) of Subjects	# of events	# (%) of Subjects	# of events	# (%) of subjects	# of events	# (%) of subjects
Infections	44	34 (31.2%)	37	27 (23.7%)	22	19 (17.4%)	16	12 (10.5%)
Respiratory, thoracic and mediastinal disorders	33	27 (24.8%)	32	24 (21.1%)	15	14 (12.8%)	16	13 (11.4%)
Cardiac disorders	21	17 (15.6%)	15	11 (9.6%)	13	12 (11.0%)	2	2 (1.8%)
Vascular disorders	17	15 (13.8%)	8	8 (7.0%)	1	1 (0.9%)	2	2 (1.8%)
Gastrointestinal disorders	16	11 (10.1%)	11	9 (7.9%)	6	4 (3.7%)	3	3 (2.6%)

Abbreviations: ITT=Intent-to-Treat; N=Number

*SAE relationship and seriousness were adjudicated by the study Clinical Events Committee. AE relationship and seriousness were determined by the investigator.

AEs and SAEs determined to be possibly, probably, or definitely related to the study device and/or procedure are shown by SOC in **Table 12**. There were no unanticipated adverse device events.

The overall incidence of device- or procedure-related AEs in the Treatment group was 21.1% (36 events in 23 subjects). The most frequent device- or procedure-related AEs by SOC were infections (9.2%), cardiac disorders (6.4%), and vascular disorders (3.7%). Other less frequent related AEs were procedural or catheter placement complications.

AEs for infection were mostly related to the device rather than the procedure and were associated with catheter insertion and use. AEs for cardiac disorders were mainly due to inadvertent cardiac stimulation associated with the device for transvenous stimulation. Vascular AEs were mostly related to the device and were associated with catheter placement (hemothorax/pneumothorax).

Table 12: Procedure/Device-Related AEs and SAEs in Treatment Subjects System (ITT)

Body System Organ Class	Procedure or Device-Related Adverse Events		Procedure or Device-Related Serious Adverse Events	
	# of events	# (%) of subjects	# of events	# (%) of Subjects
Blood and lymphatic system disorders	1	1 (0.9%)	0	0
Cardiac disorders	10	7 (6.4%)	4	3 (2.6%)
General disorders and administration site conditions	3	3 (2.8%)	0	0
Infections and infestations	11	10 (9.2%)	7	7 (6.1%)
Injury, poisoning and procedural complications	6	3 (2.8%)	0	0
Surgical and medical procedures	1	1 (0.9%)	0	0
Vascular disorders	4	4 (3.7%)	1	1 (0.9%)
Total	36	23 (21.1%)	12	11 (9.6%)

Abbreviations: ITT=Intent-to-Treat; N=Number

*SAE relationship and seriousness were adjudicated by the study Clinical Events Committee. AE relationship and seriousness were determined by the investigator.

The overall incidence of device- or procedure-related SAEs was 9.6% (12 events in 11 subjects). The most frequently reported related SAEs by SOC were infections (6.1%) and cardiac disorders (2.6%).

Infection and cardiac disorder device- or procedure-related SAEs were predominantly related to the device rather than the procedure. Cardiac SAEs were associated with inadvertent cardiac stimulation due to transvenous stimulation during electrode mapping (1.8%) or were related to catheter misplacement (0.9%). These AEs were temporary, were resolved by stopping stimulation with no further sequelae, and did not occur in subsequent sessions. Acute coronary syndrome in one (1) subject who died was possibly related to the procedure due to possible undetected tension pneumothorax. There was one vascular SAE of hypovolemic shock in one (1) subject who died that was possibly related to the device due to hemothorax / pneumohemothorax.

Deaths occurred in 9.2% (10/109) of ITT subjects in the Treatment group and 10.5% (12/114) of ITT subjects in the Control group due to cardiac/cardiopulmonary shock, organ failure, respiratory failure, or ARDS/pneumonia. Mortality was at the lower end of the expected range of 10% to 30% for this critically ill population.

Discomfort and pain assessment was conducted using a 10-point visual analogue pain rating scale before and after each therapy session. The mean pain scale rating before and after all therapy sessions for mITT Treatment subjects was negligible with an increase of 0.2 points (2% of the 10-point scale). The percentage of sessions in which subjects perceived any pain after therapy was approximately 8% (8/102) indicating therapy was well tolerated even with stimulation delivered at maximum intensity in 83% (85/102) of subjects.

In summary, safety events in the RESCUE 3 trial were as expected for a patient population on MV. Safety events related to the AeroPace System, or its procedures, were those expected for a CVC delivering transvenous electrical stimulation. Transvenous stimulation may cause inadvertent cardiac stimulation during electrode mapping or therapy. These expected cardiac events were temporary, occurred at a low incidence (2.6%), and were resolved without sequelae.

Effectiveness Results

The effectiveness of the AeroPace System was evaluated based on data from 223 subjects randomized in RESCUE 3 study.

The trial was prematurely terminated due to the difficulty in enrollment and the final population consists of 223 randomized subjects. Given the unplanned deviation from the study design, the study results are reported descriptively.

Successful weaning was numerically superior in the Treatment group compared with the Control group for RESCUE 3 subjects. There were 10.4% (mITT) to 14.1% (PP) more patients in the Treatment group who were successfully weaned compared with the Control group. These results exceeded a pre-specified minimal clinically important difference (MCID) of $\geq 10\%$, with a relative risk reduction of remaining on MV by day 30 of up to 37% (RR=0.629). RESCUE 3 patients in the Treatment group required 1.9 (mITT) to 2.432 (PP) fewer days on MV compared with the Control group, for up to a 5-fold greater reduction than the pre-specified MCID of 0.5 MV days. Mortality at day 30 was lower by 1.3% for patients in the Treatment group (ITT) compared with the Control group.

Re-intubation rates were 2.4 to 2.6 times lower for patients in the Treatment group (5.6% mITT,; 6.1% PP), compared with the Control group (14.5%), for a relative risk reduction for reintubation within 30 days of 60% (RR=0.386, mITT). MIP change from baseline to last available measurement for patients in the Treatment group compared with the Control group was greater by 4.1 cmH₂O (mITT) to 5.1 cmH₂O (PP), a 50% comparatively greater improvement. RSBI was numerically improved from baseline for patients in the Treatment group (mITT: -35.0 breaths/min/L; PP: -37.0 breaths/min/L) compared to the Control group (-19.9 breaths/ min/L).

Patients in the Treatment group had numerically fewer tracheostomies over 30 days (mITT: 12.8%; PP: 11.4%) compared with the Control group (18.8%). Patients in the Treatment group also required reduced ventilator requirements from Day 1 to last available measurement for pressure support (mITT: -1.9 ± 5.0 cmH₂O; PP: -2.0 ± 4.9 cmH₂O) compared with the Control group (-0.1 ± 4.5 cmH₂O) and for fraction of inspired oxygen (mITT:

$-2.7\% \pm 8.6$; PP: $-3.0\% \pm 8.7$), compared with the Control group ($0.1\% \pm 10.9$). The effectiveness outcomes are summarized in Table 13.

Table 13: RESCUE 3 Effectiveness Outcomes

Effectiveness Endpoint	Analysis Population	Treatment (95% CI ¹) [min, med, max]	Control (95% CI) [min, med, max]	Treatment Minus Control (95%CI)
Successful Weaning (%)	mITT	72.4% (62.1, 80.3)	62.0% (52.2, 70.4)	10.4%
	PP	76.1% (65.4, 83.9)	62.0% (52.2, 70.4)	14.1%
Days on MV (Days)	mITT	15.4 $\pm$ 10.2 [0.0, 13.0, 29.0]	17.3 $\pm$ 10.9 [1.0, 18.0, 29.0]	-1.9 (-4.8, 1.0)
	PP	14.9 $\pm$ 9.9 [0.0, 12.5, 29.0]	17.3 $\pm$ 10.9 [1.0, 18.0, 29.0]	-2.43 (-5.3, 0.5)
Mortality (%)	ITT	9.2% (3.8, 14.6)	10.5% (4.9, 16.2)	-1.3%
Reintubation (%)	mITT	5.6% (2.7, 11.0)	14.5% (6.2, 22.8)	-8.9% (-18.7, 1.0)
	PP	6.1% (3.0, 11.8)	14.5% (6.2, 22.8)	-8.4% (-18.5, 1.7)
	mITT	13.9 $\pm$ 19.3 [-32.7, 12.8, 81.9]	9.8 $\pm$ 15.2 [-32.5, 7.7, 48.4]	4.1 (-0.6, 8.8)

MIP (cm H ₂ O, absolute)	PP	14.9 ± 19.9 [-32.7, 13.7, 81.9]	9.8 ± 15.2 [-32.5, 7.7, 48.4]	5.1 (0.1, 10.1)
RSBI (breaths/min/L)	mITT	-35.0 ± 107.9 [-819.9, -12.2, 258.6]	-19.8 ± 78.2 [-611.7, -8.6, 225.0]	-15.1 (-41.1, 10.8)
	PP	-37.0 ± 106.4 [-819.9, -12.4, 71.4]	-19.8 ± 78.2 [-611.7, -8.6, 225.0]	-17.2 (-44.1, 9.7)

Abbreviations: CI=confidence interval; ITT=Intent-to-Treat; mITT=Modified Intent-to-Treat; MIP=maximal inspiratory pressure; MV=mechanical ventilation; RSBI=Rapid Shallow Breathing Index.

Note: All confidence intervals are nominal without adjustment of multiplicity

¹ Two-sided 95% confidence interval

In summary, statistical success criteria were not pre-specified for the 223 randomized subject population such that statistical success could not be declared. Pre-specified MCIDs between the Treatment group compared with the Control group were exceeded for the primary endpoint of successful weaning and for the secondary endpoint of days on MV indicating clinically significant outcomes, which along with superior outcomes across multiple study endpoints established evidence of device effectiveness.

1. Subgroup Analyses

For the successful weaning primary effectiveness endpoint, sensitivity analyses were performed to assess interaction by geography, study site, device model and catheter insertion site. Additional sensitivity analyses were conducted to summarize the data based on age, sex, race/ethnicity, and tracheostomy versus endotracheal tube at study entry. The device was not powered for any of these subgroups.

For all subgroups, the posterior summaries and probabilities of superiority for each population favored treatment, indicating consistency of the results across subgroups. The borrowing utilized for the Bayesian analysis resulted in more power and these results were consistent across a variety of weighting schemes, providing confidence in the robustness of the chosen weighting scheme.

Pooling analysis was conducted for MIP based on an analysis of variance model with terms for the factor of interest (geography, investigational center, and device model; there was insufficient data available for catheter insertion site), randomized treatment group, and their interaction for the RESCUE 3 mITT Treatment and Control populations. There was no significant interaction ($\alpha > 0.15$) for any of these factors indicating no evidence that the treatment effect for MIP varied significantly as a function of these factors.

2. Pediatric Extrapolation

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

XI. 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 352 investigators of which none were full-time or part-time employees of the sponsor. Two investigators 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: 0
- Significant payment of other sorts: 2
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Emergency Use Authorization

An earlier and equivalent model of the AeroPace System, the Keystone System, was granted Emergency Use Authorization (EUA 200178) for the treatment of mechanically ventilated patients at high risk of weaning failure during the COVID-19 pandemic.

EUA results from a benefit/risk analysis based on the totality of the scientific evidence available, by virtue of which it is reasonable to believe that the product may be effective for the specified purpose and that its benefits outweigh the inherent risks.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to an FDA advisory committee for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The AeroPace System uses transvenous phrenic nerve stimulation to improve diaphragmatic strength and weaning success in mechanically ventilated (MV) patients. A series of preclinical and clinical studies have demonstrated that this mode of diaphragm strengthening is safe and feasible, mitigates ventilator-induced diaphragm atrophy, and improves weaning success in MV patients.

Preclinical studies in a porcine model showed that bilateral phrenic nerve stimulation prevented declines in diaphragmatic thickness and mitigated reductions in diaphragm muscle fiber cross-sectional area after 50 to 60 hours of MV in a dose-dependent manner while preserving diaphragm myofiber type proportions necessary for weaning from MV (Reynolds, 2017a; Rohrs, 2021; Fernandez, 2023). First-in-human studies demonstrated the safety and feasibility of phrenic nerve stimulation in 61 patients on short-term MV (Reynolds, 2017b; Gani, 2020). The RESCUE 1 trial provided data from 11 subjects on MV ≥ 7 days and who had failed ≥ 2 weaning trials, indicating that early AeroPace models were safe and feasible for phrenic nerve stimulation and diaphragm

activation for up to 30 days (Ataya, 2020). This study also found a significant dose-response relationship between diaphragm strength (MIP improvement) and the number of stimulations delivered. A second measurement of diaphragm strength (B-Mode diaphragm thickening fraction) also improved. This data provided evidence that phrenic nerve stimulation by the AeroPace System builds diaphragmatic strength in patients on prolonged MV who have failed to wean.

Two subsequent RCTs, RESCUE 2 and RESCUE 3, evaluated the safety and effectiveness of the AeroPace System or equivalent models (and SoC), compared with SoC, in patients on MV ≥ 96 hours and who failed ≥ 2 weaning trials.

RESCUE 2 in 112 patients confirmed the RESCUE 1 findings on diaphragm strengthening; AeroPace therapy significantly improved MIP and diaphragm thickening fraction changes from baseline measurements compared with SoC (Dres, 2022). As in RESCUE 1, MIP improved in a significant dose- response relationship with the number of stimulations delivered. Weaning success was numerically improved and patients had fewer days on MV with AeroPace therapy compared with SoC.

RESCUE 3 study was a randomized, controlled, open-label, international multi-center clinical trial using a two-phase group sequential design. RESCUE 3 was the main trial conducted to determine the safety and effectiveness of the AeroPace System (and SoC) compared with Control (SoC only) on improving diaphragm strength and weaning success in a population similar to patients enrolled in RESCUE 2. A Bayesian analysis, borrowing data from the equivalent of 64 patients in RESCUE 2, was used for the primary endpoint of successful weaning.

The study enrolled a critically ill, heterogeneous patient population on MV (one-half due to ARDS/AHF, and the remainder included COPD, pneumonia, surgery or trauma). Patients had experienced a prolonged duration of MV (mean, 29 days) and by baseline MIP and RSBI measurements had low diaphragmatic strength and endurance and were unlikely to wean with SoC alone.

The RESCUE 3 trial pre-specified statistical success criteria for successful weaning of 150 randomized subjects and every 50 randomized subjects thereafter, but none was pre-specified for the final analysis population of 223 randomized subjects such that statistical success could not be declared. Successful weaning for the 223 randomized subjects was numerically greater for the Treatment group compared with the Control group for all analysis populations (mITT, PP, and with and without Bayesian borrowing). The Per Protocol, but not the mITT, population exceeded the statistical success criteria for successful weaning that was established for the interim analyses from 200 to 400 randomized subjects. Successful weaning with the AeroPace System compared with SoC exceeded the pre-specified MCID for the Per Protocol population, indicating a clinically significant treatment effect. These results for successful weaning were not influenced by demographic or clinical subgroups, or devices utilized, and the Bayesian analyses were robust.

Clinically significant improvements were also obtained across multiple effectiveness endpoints in RESCUE 3 as summarized below. Reasonable assurance of the effectiveness of the AeroPace System for successful weaning - weaning success, fewer days on MV, and fewer re-intubations - was substantiated by the numerical and clinically significant superiority of the AeroPace System (plus SoC) compared with SoC alone for these endpoints and was further supported by the totality of favorable data across RESCUE 3 endpoints.

Furthermore, supporting evidence that the AeroPace System is effective for weaning outcomes comes from the numerical superiority of the AeroPace System (and SoC) compared with SoC alone in the two RCTs alone, RESCUE 2 and RESCUE 3, using frequentist analysis.

Weaning Success

- The hazard ratio, estimating the probability of weaning with the AeroPace System versus SoC, was >1 (HR=1.27, mITT; HR=1.36, PP), showing improved weaning. Successful weaning was numerically superior for the AeroPace System compared with SoC with posterior probabilities of superiority of 91.6% (mITT) to 96.5% (PP). Using the Bayesian model and posterior distribution, the proportion of subjects successfully weaned was numerically superior in subjects treated with the AeroPace System with 8.3% (mITT) to 11.1% (PP) more subjects weaned compared with SoC. Subjects treated with the AeroPace System had a relative risk reduction of remaining on MV by day 30 of 35% (RR=0.647) compared with SoC.
- Weaning success was not affected by geographic region (US/EU), pooling by study site, device model, catheter insertion site or by the method of borrowing data from the RESCUE 2 study.

Days on MV

- There were 1.9 fewer days on MV (mITT) and 2.5 fewer days on MV (PP) with the AeroPace System compared with SoC. Days on MV was numerically superior for the AeroPace System compared with SoC with posterior probabilities of superiority between 89.8% (mITT) to 94.8% (PP). These days on MV benefits with the AeroPace System are ≥ 5 times than the pre-specified MCID of 0.5 days on MV savings.

Maximal Inspiratory Pressure (MIP)

- Change in MIP, from baseline to last available measurement was numerically greater in RESCUE 3 subjects (non-Bayesian) treated with the AeroPace System compared with SoC by 4.1 cmH₂O (mITT, $p=0.087$) to 5.1 cm H₂O (PP, $p=0.046$), a 50% comparatively greater improvement. MIP improvement was significantly correlated with the number of AeroPace System stimulations delivered ($p=0.021$), consistent with the mechanism of action of the device of diaphragm strengthening. MIP improvement is correlated with weaning success and improved patient outcomes (Ferrari, 2014; Supinski, 2016; Jung, 2016; Medrinal, 2016; Goligher, 2018; Dres, 2017, Vorona, 2018; including survival 1 year after MV (Medrinal, 2016).

Rapid Shallow Breathing Index (RSBI)

- RSBI, an index of respiratory endurance associated with weaning success was numerically superior in RESCUE 3 subjects (non-Bayesian) for a 46% greater improvement with the AeroPace System compared with SoC, but this difference was not statistically significant (mITT, -15.1 breaths/min/L, $p=0.2518$; PP, -17.2, breaths/min/L, $p=0.2089$).

Reintubation

- The percentage of RESCUE 3 subjects (non-Bayesian) requiring reintubation within 30 days was 14.5% with SoC compared with 5.6% ($p=0.096$, mITT) with the AeroPace

System for a 60% relative risk reduction ($RR=0.386$, mITT) for reintubation within 30 days. Lower rates of reintubation indicate that successful weaning attributable to the AeroPace System is durable. Reintubation is associated with a greater risk of complications, longer intensive care unit stays, and a 5-fold increased risk of death (Rothaar, 2003; Frutos-Vivar, 2011; Thille, 2013; Thille, 2021), making this outcome clinically meaningful.

B. Safety Conclusions

The risks of the AeroPace System were based on nonclinical laboratory studies, animal studies as well as data collected in clinical studies conducted to support PMA approval. Several analyses established the equivalence of the AeroPace System with prior devices such that safety and effectiveness data from these studies are applicable to the AeroPace System.

Cumulative safety data was available from 166 patients on $MV \geq 4$ days and who failed ≥ 2 weaning trials. Safety of the AeroPace Catheter was also established across 269 patients evaluated in the various clinical studies. Safety data across all clinical studies showed the same pattern of safety indicative of a CVC delivering transvenous electrical stimulation.

Safety was assessed in RESCUE 3 by documentation of AEs and SAEs during the study. AEs and SAEs occurring more often in the Treatment group compared with the Control group ($<10\%$ difference) were for infections, cardiac disorders, and vascular disorders (AEs only) that are events known to occur with CVCs. This difference was a consequence of all Treatment group patients having a CVC placed (i.e., all had an AeroPace Catheter placed) while Control group patients did not. A reasonable estimate of CVC usage in Control subjects was 63%, which was the usage prior to randomization (collected for Treatment group only) and consistent with 50%-80% CVC usage typical for ICU patients (Climo, 2003).

There were no unanticipated adverse device events. Device- or procedure-related AEs and SAEs by SOC occurred in $< 10\%$ of Treatment group subjects and were for infections, cardiac disorders, and vascular disorders (AEs only). Related infection AEs and SAEs were more often associated with the device (Catheter) than the procedure and were bacteremia, catheter infection and sepsis. Related cardiac SAEs were inadvertent cardiac stimulation due to transvenous stimulation during therapy (1.8%) or were related to CVC misplacement (0.9%) and were resolved by catheter repositioning. There were no AEs or SAEs of ventilator dyssynchrony with stimulation or reports of diaphragm injury. The Catheter was also used safely for fluid delivery.

There were 9.2% (10/109) deaths in the ITT Treatment group and 10.5% (12/114) deaths in the IIT Control group. Two SAEs in patients who died in the Treatment group were possibly related to the device (hypovolemic shock and hemothorax/pneumothorax) or procedure (acute coronary syndrome and tension pneumothorax).

Discomfort and pain assessment conducted using a 10-point visual analogue pain rating scale before and after each Lungpacer therapy session showed a negligible increase of 0.2 points (2% of the 10-point scale). Pain was perceived in only 8% of assessed sessions even with stimulation delivered at maximum intensity in 83% of subjects.

In summary, safety events in the RESCUE 3 trial were as expected for a patient population on MV. The AeroPace System was well tolerated. AEs and SAEs during use of the AeroPace System were anticipated catheter-related events (i.e., infection) and events associated with catheter misplacement (i.e., hemothorax/pneumothorax). These events were within incidences reported in

the medical literature (Rai, 2023; Hodzic, 2014). There was a low incidence (1.8%) of inadvertent cardiac stimulation due to transvenous stimulation during therapy or due to catheter misplacement (0.9%). Cardiac arrhythmias were temporary, occurred at low incidence and resolved without sequelae. The study's primary safety outcome, that the safety data would show the expected safety profile for Treatment subjects compared with Control subjects, was met.

Safety data from RESCUE 2 and RESCUE 3 RCTs across 166 treated subjects were comparable. Data from other Lungpacer clinical trials and preclinical studies using comparable device models did not identify any additional risks. Sufficient safety data are available to characterize the risks for the AeroPace System in the indicated patient population.

C. Benefit-Risk Determination

The probable benefits of the AeroPace System are based on data collected in preclinical and clinical studies conducted to support PMA approval for this breakthrough device as described above.

The AeroPace System provides dose-responsive diaphragmatic strengthening over 30 days in patients on MV $\geq$ 96 hours and who have failed to wean with SoC (RESCUE 2, MIP and diaphragm thickening fraction; RESCUE 3, MIP). The clinical benefits of the AeroPace System (and SoC) compared with SoC alone are 3 fewer days on MV, 30% risk reduction for remaining on MV by 30 days, and a 60% risk reduction of reintubation by 30 days (RESCUE 3). Other measures supporting clinical benefit in this otherwise critically ill population are fewer tracheotomies, a reduced need for ventilator support, and nominally greater 30-day survival (RESCUE 3). The totality of these clinical outcomes provides reasonable assurance of the effectiveness of the AeroPace System to improve weaning success in the indicated population. The importance of these clinical outcomes with the AeroPace System is amplified by the lack of therapeutic options to address the fundamental reason for failure to wean – diaphragmatic atrophy.

The probable risks of the device are also based on data collected in a clinical study (RESCUE 3) conducted to support PMA approval as described above. The treatment group experienced higher rates of serious adverse events (SAEs) compared to the control group in two categories: cardiac disorders and infections. For the 13 cardiac events in the treatment group (in 12 subjects, compared to two events in two subjects in the control group), four of them were adjudicated to be device-related. One subject had acute coronary syndrome and died, possibly related to the procedure due to a possible undetected tension pneumothorax. This event met study criteria for a stopping rule event. The other three device-related events were bradycardia and extrasystoles. For the 22 infection events (in 19 subjects, compared to 16 events in 12 subjects in the control group), seven were adjudicated to be device-related. All of the events were catheter-related infections, including bacteremia, catheter infection, catheter sepsis, and post-procedural sepsis. The total SAE incidence of catheter-related events was 4.6 events/1000 catheter days, which is consistent with the event rate for catheter infections of 4.8 events/1000 catheter days (Teja, 2024).

Sufficient safety data are available to characterize the benefit-risk for the AeroPace System in the proposed indication. The safety profile of the AeroPace System is predictable, and AEs/SAEs related to its function as a CVC delivering temporary transvenous stimulation present minimal risk. Physicians treating patients in critical care settings are familiar with monitoring and managing the AEs associated with CVCs that are commonly used in ICU patients. Because the AeroPace Catheter can replace a traditional CVC for fluid delivery while also providing therapy, *it*

does not add to the risks of CVC use which are already part of standard of care.

AEs due to transvenous stimulation are temporary and occur at low incidence, and instructions to prevent or mitigate them are provided in the device labeling. The use of the AeroPace System's electrode exclusion feature can also be utilized to exclude use of electrodes causing unintended stimulation. The AeroPace System's ECG-guided catheter placement assists in preventing inadvertent cardiac stimulation during catheter insertion procedures.

In conclusion, given the available information above, the clinical benefits and acceptable minimal risks of the AeroPace System support its clinical use in the indicated patient population that faces increasingly lower chances of weaning and concomitantly higher risks of death with no other options to facilitate weaning.

2. Patient Perspectives

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

D. Overall Conclusions

Mechanical ventilation is a life-saving treatment but every day on MV increases the risk of morbidity and mortality while the likelihood of successful weaning decreases (Ruan, 2020). Daily weaning trials and adjustments to ventilator parameters are effective for weaning many patients but one-third of patients do not wean. There are no treatment options to wean patients on MV ≥ 4 days and who have not weaned. These patients may have failed weaning trials, are unable to tolerate SBTs, or they are under heavy sedation.

These patients lack a viable treatment option to target the underlying reason for failure to wean – diaphragmatic atrophy.

The AeroPace System is intended to increase diaphragmatic strength and is clinically indicated to improve weaning success in patients on MV ≥ 96 hours and who have not weaned. The AeroPace System significantly improved diaphragmatic strength in a dose-responsive manner in two RCTs in this patient population. More patients (10.5% to 12.9%) treated with the AeroPace System were able to wean within 30 days, a clinically meaningful improvement compared with SoC.

Successful weaning was consistent across all populations requiring MV including ARDS/ARF, COPD, surgical, and pneumonia. Weaning success occurred within a mean of 14 days with patients treated with the AeroPace System, weaning up to 3 days faster than SoC, a clinically meaningful outcome. Successful weaning was durable with 3-fold fewer patients requiring reintubation over 30 days than with SoC.

Improvements in the respiratory measures of MIP, an indicator of diaphragmatic strength, and RSBI, for patients treated with the AeroPace System compared with Control corroborated the positive clinical effects. These outcomes are consistent with the medical literature in which improved diaphragmatic strength results in improved weaning outcomes (Ferrari, 2014; Supinski, 2016; Jung, 2016; Medrinal, 2016; Goligher, 2018; Dres, 2017; Vorona, 2018).

Significant improvements in ventilator parameters also showed a reduced need for ventilator support in patients treated with the AeroPace System compared with SoC. Other measures supporting clinical benefit in this critically ill population included fewer tracheotomies and numerically greater survival over 30 days.

Statistical success was not pre-specified for the final analysis population of 223 randomized subjects in RESCUE 3 such that statistical success could not be declared. However, the benefits of the AeroPace System compared with SoC of weaning 3 days faster, reducing the relative risk over 30 days of remaining on MV by 35% and of requiring reintubation by 60%, provides reasonable assurance of the effectiveness of the AeroPace System. This data is further supported by the consistent safety and effectiveness data available separately for the RESCUE 2 and RESCUE 3 RCTs.

The safety of the AeroPace System has been evaluated in a sufficiently large population to adequately assess its risk profile. The AeroPace System has demonstrated a predictable and manageable safety profile consistent with its use as a CVC delivering transvenous electrical stimulation, where it can replace traditional standard of care CVC use with only minimal additional risk.

In conclusion, healthcare providers and patients are seeking options to reduce the time on MV and prevent the negative clinical and mental health impact of prolonged MV. Given the available information above, the data support that for the AeroPace System the benefits outweigh the probable risks. 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.

XV. CDRH DECISION

CDRH issued an approval order on December 4, 2024. The final clinical conditions of approval cited in the approval order are described below.

The applicant must conduct a post-approval study. The post-approval study is a single-arm, prospective, multicenter cohort study to assess the 30-day safety and effectiveness of the AeroPace System in patients on mechanical ventilation (MV) at least 96 hours and who have not weaned. The AeroPace System will be used as intended and in accordance with FDA-approved labeling. All subjects will undergo standard of care for weaning including at least once daily spontaneous breathing trials (SBT). Safety and clinical effectiveness outcomes will be compared to data from the RESCUE 3 pivotal IDE study control group. The study will meet the following requirements:

- 100 subjects at up to 20 sites
- Primary Safety Endpoint: Incidence of device/procedure-related SAEs including, but not limited to, vascular, infection, and cardiac events.
- Primary Effectiveness Endpoint: Proportion of subjects successfully weaned by Day 30.
- Secondary Outcomes:
 - Days on mechanical ventilation
 - Incidence of reintubation
 - 30-day mortality
 - ICU/hospital days from enrollment to Day 32
- Baseline assessments will be age, sex, BMI, smoker/non-smoker, race, reason for MV (ARDS/ARF/COPD, pneumonia, surgical, trauma, other), presence of tracheostomy, days on MV at the time of enrollment.
- Assessments over 32 days will be SAEs, SBTs, need for tracheostomy, weaning, reintubation, mortality, ICU and hospital discharge.
- Registry enrollment milestones:

- First subject enrolled within 18 months
- 20% of subjects enrolled within 24 months
- 50% of subjects enrolled within 30 months
- 100% of subjects enrolled within 36 months

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

XVI. 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.

XVII. REFERENCES

- Ataya, A., Silverman, E. P., Bagchi, A., et al. (2020). Temporary Transvenous Diaphragmatic Neurostimulation in Prolonged Mechanically Ventilated Patients: A Feasibility Trial (RESCUE 1). *Crit Care Explor* 2(4): e0106. PMID: 32426748 PMCID: PMC7188416 DOI: 10.1097/CCE.0000000000000106.
- Béduneau, G., Pham, T., Schortgen, F., et al. (2017). Epidemiology of Weaning Outcome according to a New Definition. The WIND Study. *Am J Respir Crit Care Med* 195(6): 772-783. PMID: 27626706 DOI: 10.1164/rccm.201602-0320OC.
- Boles, J. M., Bion, J., Connors, A., et al. (2007). Weaning from mechanical ventilation. *Eur Respir J* 29(5): 1033- 1056. PMID: 17470624 DOI: 10.1183/09031936.00010206.
- Chahraoui, K. (2015) Psychological experience of patients 3 months after a stay in the intensive care unit: A descriptive and qualitative study. *J Critical Care*, 30 (3) 599-605. ISSN 0883-9441. <https://doi.org/10.1016/j.jcrc.2015.02.016>.
- Climo, M., Diekema, D., Warren, D. K., et al. (2003). Prevalence of the Use of Central Venous Access Devices Within and Outside of the Intensive Care Unit: Results of a Survey Among Hospitals in the Prevention Epicenter Program of the Centers for Disease Control and Prevention. *Infection Control & Hospital Epidemiology* 24(12): 942-945. DOI: 10.1086/502163.
- Damuth, E., Mitchell, J. A., Bartock, J. L., et al. (2015). Long-term survival of critically ill patients treated with prolonged mechanical ventilation: a systematic review and meta-analysis. *Lancet Respir Med* 3(7): 544-553. PMID: 26003390 DOI: 10.1016/S2213-2600(15)00150-2.
- Demoule, A., Similowski, T. (2019). Respiratory Suffering in the ICU: Time for Our Next Great Cause. *Am J Respir Crit Care Med* 199(11): 1302-1304. PMID: 30562045 PMCID: PMC6543714 DOI: 10.1164/rccm.201812- 2248ED.
- Demoule, A., Hajage, D., Messika, J., et al. (2022). Prevalence, Intensity, and Clinical Impact of Dyspnea in Critically Ill Patients Receiving Invasive Ventilation. *Am J Respir Crit Care Med* 205(8): 917-926. PMID: 35061577 DOI: 10.1164/rccm.202108-1857OC.

- Dres, M., Dube, B. P., Mayaux, J., et al. (2017). Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. *Am J Respir Crit Care Med* **195**(1): 57-66. PMID: 27310484 DOI: 10.1164/rccm.201602-0367OC.
- Dres, M., de Abreu, M. G., Merdji, H., et al. (2022). Randomized Clinical Study of Temporary Transvenous Phrenic Nerve Stimulation in Difficult-to-Wean Patients. *Am J Respir Crit Care Med* **205**(10): 1169-1178. PMID: 35108175 PMCID: PMC9872796 DOI: 10.1164/rccm.202107-1709OC.
- Fernandez, K. C., Rohrs, E. C., Bassi, T. G., et al. (2023). Transvenous stimulation yields exposure-dependent protection from ventilator-induced diaphragm atrophy. *J Appl Physiol (1985)* **135**(1): 15-25. PMID: 37227182 DOI: 10.1152/jappphysiol.00547.2022.
- Ferrari, G., De Filippi, G., Elia, F., et al. (2014). Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. *Critical Ultrasound Journal* **6**(1): 8. DOI: 10.1186/2036-7902-6-8.
- Frutos-Vivar, F., Esteban, A., Apezteguia, C., et al. (2011). Outcome of reintubated patients after scheduled extubation. *Journal of Critical Care* **26**(5): 502-509. DOI: <https://doi.org/10.1016/j.jcrc.2010.12.015>.
- Gani, M. (2019) Transvascular stimulation of left and right phrenic nerves using a single catheter via jugular access - a feasibility study. ATS 2019 (Poster)
- Gani, M. (2020) Transvenous stimulation of left and right phrenic nerves using a single catheter via jugular access – a second feasibility study in a larger population. ATS 2020 Virtual (ePoster)
- Girard, T. D., Alhazzani, W., Kress, J. P., et al. (2017). An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults. Rehabilitation Protocols, Ventilator Liberation Protocols, and Cuff Leak Tests. *Am J Respir Crit Care Med* **195**(1): 120-133. PMID: 27762595 DOI: 10.1164/rccm.201610-2075ST.
- Girault, C., Bubenheim, M., Abroug, F., et al. (2011). Noninvasive Ventilation and Weaning in Patients with Chronic Hypercapnic Respiratory Failure. *American Journal of Respiratory and Critical Care Medicine* **184**(6): 672-679. DOI: 10.1164/rccm.201101-0035OC.
- Goligher, E. C., Dres, M., Fan, E., et al. (2018). Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. *Am J Respir Crit Care Med* **197**(2): 204-213. PMID: 28930478 DOI: 10.1164/rccm.201703-0536OC.
- Hajiabadi, F., Heydari, A., Manzari, Z. S. (2018). Enclosed in the synergistic rings of suffering: The experience of conscious patients under mechanical ventilation in the intensive care unit of the causes of suffering. *Electronic Physician* **10**(4): 6697-6706. DOI: 10.19082/6697.
- Herridge, M. S., Tansey, C. M., Matté, A., et al. (2011). Functional Disability 5 Years after Acute Respiratory Distress Syndrome. *New England Journal of Medicine* **364**(14): 1293-1304. DOI: 10.1056/nejmoa1011802.
- Hodzic, S., Golic, D., Smajic, J., et al. (2014). Complications Related to Insertion and Use of Central Venous Catheters (CVC). *Med Arch* **68**(5): 300-303. PMID: 25568558 PMCID: PMC4276017 DOI: 10.5455/medarh.2014.68.300-303.

Jung, B., Moury, P. H., Mahul, M., et al. (2016). Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. *Intensive Care Medicine* 42(5): 853-861. DOI: 10.1007/s00134-015-4125-2.

Huttmann, S. E., Magnet, F. S., Karagiannidis, C., et al. (2018). Quality of life and life satisfaction are severely impaired in patients with long-term invasive ventilation following ICU treatment and unsuccessful weaning.

Annals of Intensive Care 8(1). DOI: 10.1186/s13613-018-0384-8.

Kahn, J. M. (2010). Long-term Acute Care Hospital Utilization After Critical Illness. *JAMA* 303(22): 2253. DOI: 10.1001/jama.2010.761.

Karlsson, V., Bergbom, I., Forsberg, A. (2012). The lived experiences of adult intensive care patients who were conscious during mechanical ventilation: a phenomenological-hermeneutic study. *Intensive Crit Care Nurs* 28(1): 6-15. PMID: 22172747 DOI: 10.1016/j.iccn.2011.11.002.7.

Khalaila, R., Zbidat, W., Anwar, K., et al. (2011). Communication difficulties and psychoemotional distress in patients receiving mechanical ventilation. *Am J Crit Care* 20(6): 470-479. PMID: 22045144 DOI: 10.4037/ajcc.2011.9894.

Martin, A. D., Joseph, A.-M., Beaver, T. M., et al. (2014). Effect of Intermittent Phrenic Nerve Stimulation During Cardiothoracic Surgery on Mitochondrial Respiration in the Human Diaphragm*. *Critical Care Medicine* 42(2): e152-e156. DOI: 10.1097/ccm.0b013e3182a63fdf.

Merchán-Tahvanainen, M. E., Romero-Belmonte, C., Cundín-Laguna, M., et al. (2017). Patients' experience during weaning of invasive mechanical ventilation: A review of the literature. *Enferm Intensiva* 28(2): 64-79. PMID: 28131790 DOI: 10.1016/j.enfi.2016.11.003.

Rai, D., Kumar, P., Gupta, P., Verma, P. K. (2023). Surveillance of central line associated bloodstream infection (CLABSI) - comparison of current (CDC/NHSN) and modified criteria: A prospective study. *J Anaesthesiol Clin Pharmacol* 39(3): 349-354. PMID: 38025573 PMCID: PMC10661645 DOI: 10.4103/joacp.joacp_393_21.

Reynolds, S., Ebner, A., Meffen, T., et al. (2017a). Diaphragm Activation in Ventilated Patients Using a Novel Transvenous Phrenic Nerve Pacing Catheter. *Crit Care Med* 45(7): e691-e694. PMID: 28441238 DOI: 10.1097/CCM.0000000000002366.

Reynolds, S. C., Meyyappan, R., Thakkar, V., et al. (2017b). Mitigation of Ventilator-induced Diaphragm Atrophy by Transvenous Phrenic Nerve Stimulation. *Am J Respir Crit Care Med* 195(3): 339-348. PMID: 27500981 DOI: 10.1164/rccm.201502-0363OC.

Rohrs, E. C., Bassi, T. G., Fernandez, K. C., et al. (2021). Diaphragm neurostimulation during mechanical ventilation reduces atelectasis and transpulmonary plateau pressure, preserving lung homogeneity and PaO₂/FiO₂. *J Appl Physiol* (1985) 131(1): 290-301. PMID: 34110233 DOI: 10.1152/jappphysiol.00119.2021.

Rothaar, R. C., Epstein, S. K., (2003). Extubation failure: magnitude of the problem, impact on outcomes, and prevention. *Current Opinion in Critical Care* 9(1): 59-66. PMID: 00075198-200302000-00011, https://journals.lww.com/cocriticalcare/fulltext/2003/02000/extubation_failure__magnitude_of_the_problem,.11.aspx.

Rotondi, A. J., Chelluri, L., Sirio, C., et al. (2002). Patients' recollections of stressful experiences

while receiving prolonged mechanical ventilation in an intensive care unit*. *Critical Care Medicine* 30(4): 746-752. PMID: 00003246-200204000-00004, https://journals.lww.com/ccmjournal/fulltext/2002/04000/patients_recollections_of_stressful_experiences.4.aspx.

Ruan, S. Y., Teng, N. C., Huang, C. T., et al. (2020). Dynamic Changes in Prognosis with Elapsed Time on Ventilators among Mechanically Ventilated Patients. *Ann Am Thorac Soc* 17(6): 729-735. PMID: 32011907 PMCID: PMC7258420 DOI: 10.1513/AnnalsATS.201908-646OC.

Rubin, E. B., Buehler, A. E., Halpern, S. D. (2016). States Worse Than Death Among Hospitalized Patients With Serious Illnesses. *JAMA Intern Med* 176(10): 1557-1559. PMID: 27479808 PMCID: PMC6848972 DOI:10.1001/jamainternmed.2016.4362.

Smit, J. M., Raadsen, R., Blans, M. J., et al. (2018). Bedside ultrasound to detect central venous catheter misplacement and associated iatrogenic complications: a systematic review and meta-analysis. *Crit Care* 22(1): 65. PMID: 29534732 PMCID: PMC5851097 DOI: 10.1186/s13054-018-1989-x.

Supinski, G. S., Westgate, P., Callahan, L. A. (2016). Correlation of maximal inspiratory pressure to transdiaphragmatic twitch pressure in intensive care unit patients. *Critical Care* 20(1). DOI: 10.1186/s13054-016-1247-z.

Teja, B., Bosch, N. A., Diep, C., et al. (2024). Complication rates of central venous catheters: A systematic review and meta-analysis. *JAMA Internal Medicine*, 184(5), 474–482. <https://doi.org/10.1001/jamainternmed.2023.8232>

Thille, A. W., Richard, J.-C. M., Brochard, L. (2013). The Decision to Extubate in the Intensive Care Unit. *American Journal of Respiratory and Critical Care Medicine* 187(12): 1294-1302. DOI: 10.1164/rccm.201208-1523CI.

Thille, A. W., Wairy, M., Pape, S. L., Frat, J. P. (2021). Oxygenation strategies after extubation of critically ill and postoperative patients. *J Intensive Med* 1(2): 65-70. PMID: 36788799 PMCID: PMC9923965 DOI: 10.1016/j.jointm.2021.05.003.

Vorona, S., Sabatini, U., Al-Maqbali, S., et al. (2018). Inspiratory Muscle Rehabilitation in Critically Ill Adults. A Systematic Review and Meta-Analysis. *Annals of the American Thoracic Society* 15(6): 735-744. DOI: 10.1513/annalsats.201712-961oc.

Wong-Baker FACES Foundation. (2018). "Wong-Baker FACES® Pain Rating Scale." Retrieved 26 April 2018 with permission, from <http://www.WongBakerFACES.org>. Originally published in Whaley & Wong's Nursing Care of Infants and Children.