A Protocol Comparing Temporary Transvenous Diaphragm Pacing to Standard of Care for Weaning from Mechanical Ventilation in ICU Patients (RESCUE 3)

A randomized, controlled, open-label, multi-center adaptive clinical trial to investigate the safe and effective performance of the Lungpacer Diaphragm Pacing Therapy System in patients who have failed to wean from mechanical ventilation.

Document No.: P-300
Revision: L-1US

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Sponsor

Name Lungpacer Medical, Inc.

Address Lungpacer Medical, Inc.
130-601 W Cordova Street
Vancouver, BC V6B 1G1
Canada

Contact Name and Title Nawzer Mehta, PhD
Senior Vice President, Clinical Affairs

Phone +1 484-480-9667

email nmehta@lungpacer.com

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Rev	DCO No.	Description of Change	Effective Date
A	2018-218	Introduction to QMS.	2018 Nov 15
B	2018-246	Add step-wise instructions for maximizing Stim Intensity, add primary safety outcome and conditional power information to statistical section, clarify AE/SAE collection for all subjects, remove "state of the art". Add updated safety data from RESCUE 2 study. Revise indication statement to add "inspiratory muscle strength". Clarified assumptions for sample size re-estimation. Change monitoring responsibility from CRO to Lungpacer.	2018 Dec 12
C	2019-021	Add stopping rules per FDA request. Minor clarifications.	2019 Jan 24
D	2019-121	Clarify that AEs and SAEs are collected until withdrawal or death, until completion of placement attempt or until LIVE Catheter removal, transfer, successful weaning, or unsuccessful weaning by Day 30; this is followed by only SAE collection during safety follow-up evaluation. Change investigational treatment exclusion to subjects enrolled in an investigational study. Add secondary endpoint for days on MV; add secondary endpoint analyses for MIP/RSBI; add secondary outcomes based on the added secondary endpoints and analyses. Remove observational endpoint of time to first successful VLT. All other changes are clarifications consistent with the protocol, or grammatical and formatting corrections.	2019 May 24
E	2019-166	Adds changes requested by FDA to add back observational endpoint of "time to first successful VLT" and add collection of observational endpoints to Section 1.8.1.4.1 for clarity. Adds collection of observational endpoints to Section 1.10.9.1 for clarity.	2019 Jul 11
F	2019-255	Changes SAE definition to meet MDR 2017/74; adds the German MPSV SAE definition. Adds reference to the RESCUE 3 Safety Plan for national reporting procedures.	2019 Oct 14
G	DCO-2020-0054	Changes exclusion from subjects on MV >45 days to >90 days, and for subjects with 6-month life expectancy to subjects for whom care/life support is expected to be withdrawn. Adds RR and FiO_2 as observational outcomes. Increases number of US sites from 32 to 55 and total number of sites to 80. Adds pleural effusion as an example of risk of lung injury. Changes timeframe to reinsert LIVE Catheter in case of infection from 48 hours to when clinically possible. Revises time of VLT for tracheotomized subjects from 12 hours to 12-18 hours. Adds additional Roll-In subjects based on site training needs. Adds recommendation to remove catheter for MRI as determined by physician. Adds minor clarifications to study processes to be consistent with site practices, and revises terminology to be consistent throughout protocol and with RESCUE 3 SAP.	2020 Apr 03
H	DCO-2020-0450	Changes exclusion for BMI from ≥40 kg/m^2 to >45 kg/m^2, adds make-up DPT session for missed session due to scheduled procedure or long VLT, updates Lungpacer anticipated risks based on literature review and RESCUE 2 and 3 safety data.	2020 Dec 15
I	DCO-2021-0441	Change proportion of randomized subjects enrolled in US from 50% to at least 20% at the end of Phase 2 of the study. Revise study design to Frequentist and Bayesian group sequential design using data from	2021 Nov 04

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		the RESCUE 2 RCT for some objectives (see RESCUE 3 SAP, CLN-0050, Rev B).	
J	DCO-2021-0437	Adds alternative device (AeroPace™ System). Adds AeroPace Catheter left jugular vein placement. Clarifies SAEs potentially related to protocol specific procedures are to be captured immediately upon obtaining informed consent. Clarifies imaging as part of medical records. Corrects statistical section per SAP to include both geography and device model for subgroup analyses where omitted.	2021 Nov 07
K-1US	DCO-2022-0183	Revision of study stopping criteria. Clarification and addition of further risk mitigation measures to reduce the risk of hemothorax/pneumothorax.	2022 Jun 24
L-1US	DCO-2022-0240	Revision of study stopping criteria to replace two stopping rule events with incidences pre-specified in the DSMB Charter. Revision of maximum per site randomization limit to 25%. Minor administrative clarifications.	2022 Oct 25

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Clinical Investigation Plan approval:

The Investigator and Sponsor agree to conduct the clinical investigation which is the subject of this protocol in accordance with the Clinical Study Agreement, this protocol, all applicable laws and regulations including Medical Device Regulation 2017/745, EN ISO 14155 and 21 CFR Parts 11, 50, 54, 56, and 812 including 812.28(a)(1).

Agreed to by Investigator:

Investigator (signature)	Date
Investigator (print)	Name of Institution

Agreed to by Sponsor:

Sponsor (signature)	Date
Sponsor (print), Lungpacer Medical, Inc.	

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Overall Synopsis of the Clinical Investigation

Protocol Element	Details
Title	A Protocol Comparing Temporary Transvenous Diaphragm Pacing to Standard of Care for Weaning from Mechanical Ventilation in ICU Patients (**RESCUE 3**) A randomized, controlled, open-label, multi-center adaptive clinical trial to investigate the safe and effective performance of the Lungpacer Diaphragm Pacing Therapy System in patients who have failed to wean from mechanical ventilation.
Protocol Number	P-300
Protocol Revision	L-1US
Investigational Device	The Lungpacer Diaphragm Pacing Therapy System (DPTS) consists of two models: the Keystone System, and the AeroPace™ System. The models are designed to deliver equivalent Lungpacer Diaphragm Pacing Therapy (DPT).
Sponsor	Lungpacer Medical, Inc. 130-601 W Cordova Street Vancouver, BC V6B 1G1 Canada
Principal Investigator	TBD
Overall Study Design	Randomized, controlled, open-label, multi-center adaptive clinical trial (RCT) with 1:1 randomization to Treatment with the Lungpacer Diaphragm Pacing Therapy System (plus Standard of Care) as compared to Control (Standard of Care).
Good Clinical Practice	This study is conducted in accordance with GCP as described in EN ISO 14155 and 21 CFR Parts 11, 50, 54, 56, and 812 including 812.28(a)(1).
Structure	Open-label interventional RCT. Randomized (1:1) assignment to Treatment (Lungpacer DPTS) or Control groups.
Device Description	Lungpacer DPTS refers to either of the two models: The Keystone System consists of Lungpacer's IntraVenous Electrode (LIVE) Catheter (left subclavian vein access) with integrated electrodes for transvenous electrical phrenic nerve stimulation to invoke diaphragm stimulation, the Lungpacer Control Unit (LCU) which controls delivery of therapy, and the Intermediate Cable to connect the LIVE Catheter to the LCU. Other accessories needed for placement of the LIVE Catheter and to deliver therapy are supplied with the device. Refer to the Lungpacer DPTS (Keystone) System and LIVE Catheter IFUs. The AeroPace System consists of the AeroPace Catheter (left subclavian vein or left jugular vein access) with integrated electrodes for transvenous electrical phrenic nerve stimulation to invoke diaphragm stimulation, the Neurostimulation Console (Console) which controls delivery of therapy, the Airway Sensor and Sensor Cable for breath detection during automated use, and the Catheter Cable to connect the AeroPace Catheter to the Console. Other accessories needed for placement and use of the AeroPace Catheter and to deliver therapy are supplied with the device. Refer to the AeroPace System and AeroPace Catheter IFUs.

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Protocol Element	Details
Patient Population	The Lungpacer Diaphragm Pacing Therapy System (DPTS) is indicated to improve inspiratory muscle strength and weaning success in patients ages 18 years or older who have failed to wean from mechanical ventilation. Patients will have failed two or more weaning attempts and required ≥96 hours (4 days) on mechanical ventilation.
Number of Subjects	Adaptive from N=200 to N=400 randomized subjects based on a Bayesian group sequential design. In addition to randomized subjects, one Roll-In subject is allowed per site; a second Roll-In subject is allowed if the first Roll-In has unsuccessful Catheter placement.
Number & Location of Investigational Sites	Maximum of 80 sites: Up to 55 centers in the United States and remaining sites in Europe and other Tier 1 countries.
Treatment (Lungpacer DPT)	Roll-In subjects or subjects randomized to Treatment will have Lungpacer DPT consisting of six (6) sets of ten (10) stimulations, twice daily for a total of 120 stimulations/day over a duration of up to 30 days from randomization or until study exit. The maximum number of stimulations that a subject could receive is expected to be 3600 delivered over the course of 30 days. Subjects will also receive Standard of Care.
Control	Subjects will receive Standard of Care.
Study Duration/Exit	Treatment Subjects: • Withdrawal or death • Unsuccessful placement of the Catheter – 48 hours after placement attempt or Catheter removal to maximum Day 32 • Successful wean/Unsuccessful wean/Transfer – to maximum Day 32 Control Subjects: • Withdrawal or death • Successful wean/Unsuccessful wean/Transfer – to maximum Day 32 Maximum study duration for any subject is 32 days. Successfully weaned is defined as passing the protocol-specific Ventilator Liberation Trial (VLT), or removed from MV, and not returned to MV *within 48 hours.*
Safety Evaluation and Follow-Up	Safety Evaluation (AE and SAE data collection during study *before* Safety Follow-up Evaluation): • 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 Evaluation (SAE data collection *after* completing study Safety Evaluation): 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 the 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*.

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Protocol Element	Details
Inclusion Criteria	Subjects who: 1. Are 18 years or older, and, 2. Have been mechanically ventilated for ≥96 hours (4 days), and, 3. Have satisfied the Readiness-to-Wean criteria, and, 4. Have failed at least 2 weaning attempts (of which one is a study-specific Ventilator Liberation Trial).
Exclusion Criteria	Subjects who satisfy one or more of the following: 1. MIP (absolute value) >50 cm H_2O. 2. Invasive mechanical ventilation >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 neurological, 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/m^2. 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. Prior bacteremia reported 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.
Blinding	Study personnel and subjects are not blinded to randomization arm (open-label design).
Primary Safety Endpoint	Adverse events for subjects randomized to Treatment (Lungpacer DPTS) as compared to subjects randomized to Control.
Primary Safety Outcome	A consistent risk profile is observed for subjects randomized to Treatment (Lungpacer DPTS) as compared to subjects randomized to Control.
Primary Effectiveness Endpoint(s)	• Proportion of subjects successfully weaned by Day 30. • Change in Maximal Inspiratory Pressure (MIP) from randomization (baseline) to last available measure.
Primary Effectiveness Outcome(s)	• The proportion of subjects who are successfully weaned will be statistically significantly greater for subjects randomized to Treatment (Lungpacer DPTS) compared to subjects randomized to Control.

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Protocol Element	Details
	• The MIP mean change from baseline will be statistically significantly greater for subjects randomized to Treatment compared to subjects randomized to Control.
Secondary Effectiveness Endpoints	To compare Treatment (Lungpacer DPTS) subjects to Control subjects for: • Days on mechanical ventilation from Day 1 to removal from MV associated with successful weaning or Day 30, whichever comes first. • Change in MIP over time from randomization (baseline). • Rate of MIP change per day from randomization (baseline) to last available measure. • Change in Rapid Shallow Breathing Index (RSBI) from randomization (baseline) to last available measure. • Change in RSBI over time from randomization (baseline). • Rate of RSBI change per day from randomization (baseline) to last available measure; • Day 30 mortality.
Observational Data Collection	• The time to first successful VLT after randomization. • Cessations and re-instatements of mechanical ventilation, to Day 30. • Proportion of subjects tracheotomized from randomization (baseline) to Day 30. • Ventilator settings (Pressure Support, Positive End Expiratory Pressure, Respiration Rate, Fraction of Inspired Oxygen, Ventilation Mode, Tidal Volume) daily, to last available measure. • ICU admissions and discharges to Day 30. • Hospital admissions and discharges to Day 30.

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LIST OF REFERENCE DOCUMENTS

Doc. No.	Document Name
650-0227	AeroPace System Instructions for Use (IFU)
650-0228	AeroPace System Instructions for Use, EU (IFU-EU)
650-0211	AeroPace Catheter Kit Instructions for Use (IFU)
650-0141	Lungpacer DPTS (Keystone System) Instructions for Use (IFU)
650-0045	LIVE Catheter Instructions for Use (IFU)
650-0065	Lungpacer Handheld Controller Instructions for Use (IFU)
650-0074	Lungpacer Intermediate Cable Instructions for Use (IFU)
650-0146-01	Lungpacer DPTS (Keystone System) Instructions for Use (IFU-EU)
650-0162-01	LIVE Catheter Instructions for Use (IFU-EU)
650-0153-01	Lungpacer Handheld Controller Instructions for Use (IFU-EU)
650-0155-01	Lungpacer Intermediate Cable Instructions for Use (IFU-EU)
CLN-0045	RESCUE 3 Patient Informed Consent Template
CLN-0084	RESCUE 3 Informed Consent Template (EU)
CLN-0142	RESCUE 3 Patient Data Protection Notification (EU)
CLN-0039	Readiness-to-Wean and VLT Protocol
CLN-0037	RSBI/RASS/MIP Protocol
CLN-0030	Stimulation Discomfort and Sensation Tool
CLN-0040	RESCUE 3 30-Day (Study Exit) Follow-Up Worksheet
CLN-0041	Treatment Subject Questionnaire
CLN-0046	Lungpacer DPTS RESCUE Investigator's Brochure

ABBREVIATIONS/ACRONYMS

NOTE: SI units are used throughout this document

Abbreviation/Acronym	Meaning
ADE	Adverse Device Effect
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ASADE	Anticipated Serious Adverse Device Effect
AV	Atrioventricular
AVNRT	Atrioventricular Nodal Re-entrant Tachycardia
AVRT	Atrioventricular Re-entrant Tachycardia
BMI	Body Mass Index

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Abbreviation/Acronym	Meaning
CA	Competent Authority
Ca	Calcium
CEC	Clinical Events Committee
CFR	Code of Federal Regulations (US)
CI	Cumulative Incidence (Proportion)
C-I	Confidence Interval
CIP	Clinical Investigation Plan
CLABSI	Central Line-Associated Blood Stream Infection
cm	Centimeter
COPD	Chronic Obstructive Pulmonary Disease
Cr	Creatinine
CRF	Case Report Form
CRO	Clinical Research Organization
CVC	Central Venous Catheter
DMP	Data Management Plan
DPT	Diaphragm Pacing Therapy
DPTS	Diaphragm Pacing Therapy System
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETT	Endotracheal Tube
FDA	Food and Drug Administration
FiH	First in Human
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HCO_3	Bicarbonate
ICU	Intensive Care Unit
IFU	Instructions for Use
IRB	Institutional Review Board
IMST	Inspiratory Muscle Strength Training
ITT	Intent-To-Treat
IV	Intravenous
K	Potassium
LAR	Legally Authorized Representative
LCU	Lungpacer Control Unit

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Abbreviation/Acronym	Meaning
LIVE	Lungpacer® IntraVenous Electrode
Lungpacer	Lungpacer Medical, Inc.
µg	Microgram
Min	Minute
MIP	Maximal Inspiratory Pressure
mITT	Modified Intent-To-Treat
MR	Magnetic Resonance
MV	Mechanical Ventilation
n/a	Not Applicable
Na	Sodium
NIV	Non-Invasive Ventilation
PEEP	Positive End-Expiratory Pressure
PI	Principal Investigator
PP	Per Protocol
PS	Pressure Support
RASS	Richmond Agitation-Sedation Scale
RCT	Randomized Controlled Trial
RSBI	Rapid Shallow Breathing Index
RR	Respiration Rate
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SBT	Spontaneous Breathing Trial
SD	Standard Deviation
s	Second
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SpO_2	Peripheral Capillary Oxygen Saturation
SVC	Superior Vena Cava
TT	Tracheostomy Tube
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VIDD	Ventilator-Induced Diaphragm Dysfunction
VILI	Ventilator-Induced Lung Injury
VLT	Ventilator Liberation Trial
V_T	Tidal Volume

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DEFINITIONS

Term	Cross-Reference	Definition
In Screening	Section 1.10.1	A subject is in screening if: • he/she or his/her legally authorized representative signed the informed consent form, and, • he/she failed at least one weaning attempt.
Enrolled	Section 1.10.1	A subject in screening (i.e., informed consent form has been signed and subject has failed at least one weaning attempt) is enrolled and can be randomized if: • he/she meets the Readiness-to-Wean criteria, and, • he/she fails a protocol-specific VLT (conducted after informed consent and on a different calendar day than the previous failed weaning attempt[s]), and, • he/she meets all inclusion criteria, and, • he/she does not satisfy any exclusion criteria, and, • he/she is not a Roll-In subject who is enrolled, but not randomized.
Mechanical Ventilation	Section 1.10.7	Administration of ventilatory support using an invasive artificial airway such as an endotracheal tube or tracheostomy tube.
Readiness-to-Wean screen	Section 1.10.10.1	The Readiness-to-Wean screen determines the readiness of a subject to participate in a Ventilator Liberation Trial (VLT). The subject must satisfy the criteria of this screen prior to conducting a VLT.
Roll-In Subject	Section 1.4.8	A study subject who is **not** randomized, is specified to receive Treatment (Lungpacer DPTS plus Standard of Care), and whose data will not be included in the endpoint evaluation. Roll-In subjects are not counted as part of the randomized population.
Successful VLT	Section 1.10.7	A Ventilator Liberation Trial (VLT) is conducted to determine whether the subject can breathe on his/her own over a defined period of time. If the subject remains off MV for the defined period of time, he/she has had a "Successful VLT".
Screening Failure	Section 1.10.1	A subject who is "in screening" is a screening failure if he/she: • fails the initial Readiness-to-Wean screen, or, • satisfies the initial Readiness-to-Wean criteria and passes the protocol-specific Ventilation Liberation Trial (VLT), or, • fails to meet inclusion criteria, or, • meets one or more exclusion criteria.
Standard of Care	Section 1.4.1.5	Standard of Care for weaning from MV • The protocol-specific VLT replaces the daily physician-directed weaning trial; no more than one additional weaning trial can be conducted each day for both study groups. • Institutions should follow current institutional practices for limb movement and exercise for MV patients. • Inspiratory Muscle Strength Training (IMST) protocols are ***prohibited***.

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Term	Cross-Reference	Definition
		• Physicians should minimize sedation for patients on MV >24 hours if possible. • Non-Invasive Ventilation (NIV) or high flow oxygen can be used to prevent post-extubation respiratory failure for subjects who pass a VLT or who were removed from MV.
Successful Placement	Section 1.4.8	The Catheter was successfully inserted in accordance with the Catheter Instructions for Use, and the diaphragm was stimulated.
Successfully Weaned	Section 1.10.7.3	Successfully weaned is defined as passing the *protocol-specific* Ventilator Liberation Trial (VLT), or removed from MV, and not returned to MV *within 48 hours*. Note: "Removed from MV" includes removal from mechanical ventilation support without being physically removed from MV.
Time 0	Section 1.10.7.3	The time the subject has a successful Ventilator Liberation Trial (VLT), or is removed from MV, and begins the 48-hour period to evaluate him/her for being successfully weaned.
Unsuccessful Placement	Section 1.4.8	Unsuccessful placement is defined as (i) the Catheter never entered the intended thoracic vein on the left side, or, (ii) the Catheter **entered** the intended thoracic vein, but the diaphragm could not be stimulated, or, (iii) the Catheter positioning is not in accordance with its associated Catheter IFU.
Ventilator Liberation Trial (VLT)	Section 1.10.10.2	The VLT provides a standardized protocol-specific procedure that ***replaces*** the institution's daily weaning trial to ensure a common method is used to determine weaning across all study sites.

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1 GENERAL

1.1 Sponsor

The Sponsor of this clinical investigation is:

Lungpacer Medical, Inc.
130-601 W Cordova Street
Vancouver, BC V6B 1G1
Canada

The Sponsor's legal representative in the European Union is:

Clinlogix Europe GmbH
Taunusstraße 57
55118 Mainz, Germany

1.2 Principal Investigator, Coordinating Investigator and Investigational Sites

A Principal Investigator (PI) will be selected for each RESCUE 3 study site. Information about participating PI(s), co- or sub-investigators, investigational site(s), and test laboratories is maintained by Lungpacer in the Trial Master File. The roles and responsibilities of the Sponsor and of the PI are defined in a contract between Lungpacer Medical, Inc. and the study site.

1.3 Financial Disclosure

All clinical investigators must disclose to the Sponsor any proprietary or financial interests they might hold in the investigational product or the Sponsor's company as outlined in the Sponsor's financial disclosure form that is maintained as part of the Trial Master File.

1.4 Identification and Description of the Investigational Device

1.4.1 Summary Description of the Investigational Device and Intended Purpose

1.4.1.1 *Lungpacer DPTS Breakthrough Device*

The Lungpacer Diaphragm Pacing Therapy System (DPTS) is an FDA-designated breakthrough device that is intended to treat a patient population with an *unmet medical need*. This population includes mechanically-ventilated patients who are difficult to wean or have been on prolonged mechanical ventilation (MV). In addition to high rates of ventilation-associated co-morbidities, the 30-day mortality ranges from 23% to 49% for this patient population (Lungpacer Literature review, 2018). The unmet need is further underscored by the studies of Huttman (2018) and Rubin (2016) that found that 32% to 50% of patients would have elected to die, in hindsight, rather than remain on prolonged invasive mechanical ventilation.

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1.4.1.2 *Intended Use and Rationale*

The Lungpacer Diaphragm Pacing Therapy System (DPTS) is a temporary, percutaneously-placed, transvenous, phrenic nerve-stimulating medical device intended to stimulate the diaphragm to improve inspiratory muscle strength in mechanically ventilated patients.

The indicated use is to improve inspiratory muscle strength and weaning success in patients ages 18 years or older who have failed to wean from mechanical ventilation. Patients will have failed two or more weaning attempts and required ≥96 hours (4 days) on mechanical ventilation.

1.4.1.3 *Intended Population and Rationale*

The patients for whom Lungpacer DPT is intended are difficult to wean from mechanical ventilation or may be dependent on prolonged MV. The rate of weaning failure after even a single failed weaning attempt is reported to be 26 to 42% (Boles, 2007; Béduneau, 2017). Although mechanical ventilation can be a life-saving intervention for patients suffering from respiratory failure, it can quickly (<72 hours) promote diaphragmatic atrophy and contractile dysfunction, leading to difficulty to wean (Powers, 2013; Jaber, 2011; Dres, 2017; Ferrari, 2014; Supinski, 2016). Patients who are difficult to wean from MV or have had prolonged mechanical ventilation have an increased risk of critical illness including myopathy and polyneuropathy, ventilator-associated pneumonia, decubitus ulcers, delirium and tracheotomy (Power, 2013; Zhou, 2014; Hui, 2013; Chastre, 2012; Apostolopoulou, 2014; Salluha, 2015; Kollef, 1999), and increased risk of death as high as 49% (Chastre, 2012; Esteban, 2002; Medrinal, 2016; Damuth, 2015).

By delivering electrical stimulation to the phrenic nerves, which in turn causes the diaphragm muscle to contract, Lungpacer DPT is intended to strengthen the diaphragm sufficiently to allow patients to wean successfully from mechanical ventilation and regain the ability to breathe independently. Lungpacer DPT is expected to allow more patients who are difficult-to-wean or are on prolonged ventilation to recover from dependency on MV, and patients may wean more quickly, as compared to standard of care. Lungpacer DPT is temporary; once a patient is weaned from mechanical ventilation, the LIVE Catheter is removed.

1.4.1.4 *Mechanism of Action*

It was first described by Pavlovic (2003) that intermittent direct electrical or magnetic stimulation of the diaphragm while the lungs are still being mechanically ventilated may be beneficial. Based on his experience with the rehabilitation of skeletal muscles during long-term immobilization following trauma or surgery, and on experience with diaphragm pacing in quadriplegics, he proposed that the result of such stimulation would be to preserve the diaphragm from atrophy and thus reduce long-term dependence on MV, the risk of complications and length of stay in the ICU. Posluszny (2014) demonstrated that direct diaphragm pacing can successfully wean traumatic cervical spinal cord injury patients from ventilator support even when pacing was initiated several weeks to several months after the initial injury. His study found that 18 of 22 (81%) patients with

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stimulable diaphragms were weaned from MV and 8 (36%) regained complete independent recovery of respiration.

Case studies have reported that *phrenic nerve* pacing which stimulates the diaphragm to contract, can condition the diaphragm after prolonged disuse (Nochomovitz M, 1984) and that diaphragmatic strength and endurance can be significantly increased with this approach (Wilcox, P, 1988).

The feasibility of diaphragm pacing by *transvenous phrenic nerve stimulation* using the Lungpacer DPTS was observed in a study of 28 patients on short-term mechanical ventilation (Reynolds, 2017). A feasibility study (RESCUE 1, N=11) confirmed the safety and feasibility of diaphragm pacing using the Lungpacer DPTS in patients difficult to wean from prolonged mechanical ventilation (Ataya, 2019; Ataya, 2020). More recently, a randomized controlled trial (RESCUE 2, N = 112) conducted in Europe in difficult to wean patients on MV for ≥96 hours, showed that Lungpacer DPTS and standard of care, as compared to standard of care alone, was safe, and significantly improved diaphragm strength. Lungpacer DPTS as compared to standard of care was also shown to weaned more patients from MV, and more quickly, although these results were not statistically significant (Dres, 2020).

1.4.1.5 *Treatment Options for Patients on Mechanical Ventilation*

Refer to the *Lungpacer DPTS RESCUE Investigator's Brochure (CLN-0046)*, for an assessment of standard of care treatments for patients on mechanical ventilation.

Standard of care for patients on mechanical ventilation, after resolution of the reason for MV, endeavors to increase patient muscular strength, particularly in the respiratory system, to promote weaning. Exercise of the respiratory system is conducted using breathing trials that are intended to improve inspiratory muscle strength, particularly of the diaphragm.

Inspiratory Muscle Strength Training (IMST), which uses sequences of breathing trials to strengthen the diaphragm and respiratory muscles, has been shown to accelerate weaning from mechanical ventilation in difficult-to-wean patients. However, there is no standardized IMST protocol, and it is not an accepted standard of care. IMST, like all ventilator liberation trials, requires participation of the patient and, therefore, presents challenges for use in patients who are sedated or critically ill.

Surgically implanted diaphragmatic/phrenic nerve stimulators have been used since the 1970s to contract the diaphragm rhythmically, however, use of this surgical intervention is intended for long-term use and is often not feasible or appropriate for critical care patients.

Magnetic stimulation has been proposed but is cumbersome (Adler, 2011) and not applicable in a standard ICU setting.

The Lungpacer DPTS provides a technological solution to achieve temporary transvenous phrenic nerve stimulation to invoke diaphragm stimulation in ICU patients in a minimally invasive manner

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at the bedside. It consists of a proprietary intravenous multi-electrode stimulating catheter which can also deliver fluids. It is inserted percutaneously in the same way as a standard central venous catheter, and provides transvenous delivery of electrical stimulation via the electrodes to the phrenic nerves, which in turn, results in stimulation of the diaphragm.

Lungpacer DPT has an advantage to breathing trials conducted as standard of care to wean patients from MV in that it delivers diaphragm stimulation without the need for active patient participation and therefore can be used for patients with greater respiratory weakness, who are sedated or critically ill. Lungpacer DPT delivers more diaphragm contractions than IMST, which may allow some patients to wean from MV more quickly. Such outcomes are highly clinically meaningful given the increased morbidity and mortality associated with increased duration of mechanical ventilation.

1.4.2 Manufacturer of the Investigational Device

The Lungpacer DPTS (Keystone System and AeroPace System) is manufactured by Lungpacer Medical, Inc., and its contract manufacturers.

1.4.3 Model Name and Number including Software Version and Accessories

The names, model numbers and versions of the components of the Lungpacer DPTS to be used in this study are provided in Appendix 1 (AeroPace System) and Appendix 2 (Keystone System).

1.4.4 Device Traceability During and after the Clinical Investigation

All components of the Lungpacer DPTS are identifiable by lot number, equipment number, or serial number. Component lot numbers and reference numbers are tracked by Lungpacer using a device accountability log. Return of investigational product will be confirmed at the site close out visit and will be reconciled against clinical study shipping logs.

In accordance with federal regulations, all investigators are required to keep accurate records showing final disposition of all investigational materials. The PI or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices. Dispositions of all investigational devices are maintained in the investigator's file.

The stimulation console is installed at each site by service personnel who are trained on the device installation and set-up. The device meets product specifications at shipment, and the set-up process confirms proper operation upon installation. Device maintenance is managed by Lungpacer. The Catheter Kits will remain within the expiry date for the duration of the clinical study; as a sterile, disposable product, no maintenance is required. Catheter Kits will be replaced in study site inventory and returned to the Sponsor prior to their expiry date. Replacement Catheter Kits will be provided as necessary.

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1.4.5 Intended Purpose of the Investigational Device in the Clinical Investigation

The Lungpacer Diaphragm Pacing Therapy System (DPTS) is a temporary, percutaneously-placed, transvenous, phrenic nerve-stimulating device intended to stimulate the diaphragm in conjunction with a mechanical ventilator to improve diaphragm muscle strength in mechanically-ventilated patients.

The Lungpacer DPTS is intended for use in hospitals and hospital-type facilities which provide care for patients requiring mechanical ventilation. The device is intended to be used by appropriately trained, personnel under the direction of a physician.

1.4.6 Populations and Indications for which the Investigational Device is Intended

The indicated use is to improve inspiratory muscle strength and weaning success in patients ages 18 years or older who have failed to wean from mechanical ventilation. Patients will have failed two or more weaning attempts and required ≥96 hours (4 days) on mechanical ventilation.

1.4.6.1 *Indicated Population*

Weaning from MV is often classified as simple, difficult, or prolonged weaning based on the number, timing and results of weaning attempts and extubation outcomes as given below.

- Simple Wean – Patients are considered to have undergone a simple wean when they pass their first weaning attempt. Approximately one-half to two-thirds of patients in intensive care units (ICUs) undergo simple weaning, many of whom will proceed with extubation.
- Difficult-to-Wean – Patients are considered difficult to wean if they fail their first weaning attempt and require up to three weaning attempts, or as long as seven days to pass a weaning attempt (Boles, 2007). The incidence ranges from 26 to 39 percent (Funk, 2010; Peñuelas, 2011). This population mostly includes patients intubated in the first few weeks of acute ICU admission.
- Prolonged Weaning – Patients are considered to have undergone prolonged weaning if they fail at least three weaning attempts or require more than seven days to pass a weaning attempt (Boles, 2007). The incidence ranges from 6 to 14 percent (Funk, 2010; Peñuelas, 2011). Patients who require more than seven days to wean are at increased risk for death (Peñuelas, 2011) and are also more likely to fail extubation compared with those who undergo simple weaning (Jeong, 2015). While in the ICU, many of these patients are managed similarly to patients who are difficult to wean, and many will require tracheostomy and be managed accordingly.

According to weaning classifications, the RESCUE 3 study population includes some patients who are difficult to wean and patients who have required prolonged MV (Boles, 2007; Béduneau, 2017). This population constitutes approximately one-third of all patients on mechanical ventilation and

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represents those patients most at risk of diaphragm atrophy and ventilator-induced diaphragm dysfunction (VIDD).

VIDD is highly prevalent in patients who fail to wean, likely proceeding from MV-associated diaphragmatic inactivity or unloading, and possibly aggravated by various ICU-related co-morbidities (e.g., sepsis). It is characterized by severe muscle fiber shrinkage (Powers, 2013). The onset of diaphragm atrophy under MV is rapid, with abnormalities being visible histologically and functionally after a few hours and shown to worsen over time (Jaber, 2011; Levine, 2008; Martin, 2014). Just 18-69 hours of controlled MV leads to more than a 50% reduction in the cross-sectional area of type I and II diaphragm fibers (Levine, 2008). Duration of mechanical ventilation is associated with a logarithmic decline in diaphragmatic force (Hermans, 2010; Jaber, 2011; Dres, 2017; Supinski, 2016). Patients ventilated at least 72 hours, have smaller diaphragmatic fiber sizes than patients on MV less than 24 hours, showing progressive reduction in trans-diaphragmatic pressure with a 32% drop in strength after 5 days of MV (Jaber, 2011).

In patients ventilated for more than 48 hours, diaphragm dysfunction was observed in 80% of the patients and over half of those patients failed to wean; half of the patients who failed the weaning process died during the ICU stay (Jung, 2016). Dres (2017) demonstrated that 63% of ICU MV patients had diaphragm dysfunction at the time of their first spontaneous breathing trial and that diaphragm dysfunction was associated with higher ICU and hospital mortality. Diaphragm dysfunction was present in almost all patients with at least one weaning failure; 92% of the difficult-to-wean patients and 100% of the prolonged-wean patients demonstrated diaphragm dysfunction. Béduneau (2017) found across large ICU populations of MV patients, mortality increases with each additional day spent on the ventilator. Mortality for MV patients increases from 5% for those who pass their first weaning trial to 25% for those patients who fail their first weaning trial (Boles, 2007).

The RESCUE 3 protocol inclusion criteria select subjects who have failed two weaning attempts and have received mechanical ventilation for ≥96 hours (4 days), thereby selecting difficult-to-wean patients or patients on prolonged MV, all of whom are at the highest risk of ventilator-induced diaphragm dysfunction (VIDD). Based on a literature review of randomized controlled trials for patients on MV for ≥96 hours, 30-day mortality for this population ranges from 23% to 49% (Lungpacer Literature Review, Data on File, 2020).

The rationale for selecting subjects receiving mechanical ventilation for ≥96 hours is based on (i) ≥72 hours of mechanical ventilation results in maximum decline in diaphragm muscle strength (Schepens, 2015) and a high probability of diaphragm dysfunction (Dres, 2017; Jung, 2016; Supinski, 2016), and (ii) the morbidity and mortality in this patient population increases with each day spent on mechanical ventilation (Boles, 2007; Jung, 2016; Béduneau, 2017, Dres, 2017; Supinski, 2016). This significant unmet need justifies the minimal risk of receiving temporary treatment with the Lungpacer DPTS. In addition, the Diagnosis-Related Group (DRG) system for

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US Medicare and Medicaid payments for mechanical ventilation, groups patients into a tiered system based ≤96 hours MV or >96 hours MV (Centers for Medicare & Medicaid Services (CMS), 2017) consistent with the RESCUE 3 patient population. Similarly, payment groups are specified according to the length of time for MV, starting with a minimum of 96 hours (Bittner, 2013), in European countries.

The RESCUE 3 study exclusion criteria are designed to prevent the enrollment of subjects for whom treatable diaphragm weakness is not the primary cause for mechanical ventilation (e.g., inability to protect the airway, massive parenchymal lung damage, hypervolemia, end stage heart disease and neuromuscular diseases involving the diaphragm muscle, phrenic nerve and other nerves) and therefore may be less likely to benefit from Lungpacer DPT. An exclusion of absolute MIP >50 cm H_2O also excludes MV patients with sufficient remaining inspiratory muscle strength (ATS/ERS, 2002; Hermans, 2010; Jaber, 2011; Demoule; 2013; Jung, 2016; Supinski, 2016; Dres, 2017). An exclusion of subjects receiving more than 90 days of mechanical ventilation also excludes subjects less likely to benefit over the course of the 30-day treatment period (MacIntyre, 2005; White, 2012).

1.4.7 Description of the Investigational Device and Materials in Contact with Tissues or Body Fluids

The Lungpacer DPTS consists of a sterile, single-use, disposable intravenous electrode catheter that is connected by a cable to a bedside control unit, and includes a Handheld Controller.

The Catheter is similar in appearance, composition, and functionality to commonly-used catheters for central venous access. It includes two sets of integral electrode arrays which are designed to transvenously and selectively stimulate the left and right phrenic nerves thereby activating the diaphragm. The Catheter is placed using aseptic technique and the standard Seldinger technique. The Catheter is designed to be placed with its tip in the superior vena cava (SVC) above its junction with the right atrium and parallel to the vessel wall, and its distal tip positioned at a level above either the azygous vein or the carina of the trachea. The Catheter has a vacant lumen for insertion over a guidewire; this lumen may be used for fluid delivery and blood sampling after the guidewire has been removed.

The bedside control unit is an external console and a user interface to control stimulation settings and to provide a workflow for electrode mapping and delivery of Lungpacer DPT. Once the Catheter is placed, a mapping process is conducted via the external console, which identifies the electrodes that are adjacent to the left or right phrenic nerves. The console controls the delivery of a series of low-level stimulations (6 sets of 10 stimulations) that are delivered via the identified Catheter electrodes. Without directly contacting the nerves, this “transvenous stimulation” of the left and right phrenic nerves causes contraction of each respective hemidiaphragm providing a contribution to the work of breathing. Lungpacer DPT is delivered in concert with the patient’s MV support. Lungpacer DPT

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consists of 6 sets of 10 stimulations delivered twice daily for a total daily delivery of 120 stimulations. A typical therapy session lasts about 15 to 30 minutes. The therapy is expected to require no more than 30 days of stimulation, and a maximum expected delivery of 3600 stimulations.

The Lungpacer DPTS is available as two investigational models that are designed to deliver equivalent Lungpacer DPT. Both models deliver Lungpacer DPT using the same critical stimulation characteristics. They differ in the user interface and other features designed to simplify the workflow and improve the user experience.

The Keystone System/LIVE Catheter utilizes the Lungpacer Control Unit attached to the Catheter by the Intermediate Cable. The LIVE Catheter is a single lumen catheter with 18 electrodes and can be inserted using the left subclavian vein. Other accessories needed for placement and use of the LIVE Catheter and to deliver therapy are supplied with the device. Additional information on the Keystone System/LIVE Catheter is provided in Appendix 2 and in the instructions for use.

The AeroPace System utilizes the Neurostimulation Console (Console) with a simplified user interface. The Console is attached to the AeroPace Catheter by the Catheter Cable. The AeroPace Catheter is a triple-lumen catheter with 30 electrodes and can be inserted using either the left subclavian vein or the left jugular vein. An intravascular electrogram display is provided to assist with Catheter placement. The AeroPace System also contains the Airway Sensor and Sensor Cable for breath detection that is used for automated placement, mapping and therapy. Stimulation settings relative to the Stimulation Threshold are adjusted manually by the operator. Other accessories needed for placement and use of the AeroPace Catheter and to deliver therapy are supplied with the device. Additional information on the AeroPace System is provided in Appendix 1 and in the instructions for use.

Lungpacer DPT will be delivered to RESCUE 3 Roll-in subjects or subjects randomized to Treatment using either the Keystone System/LIVE Catheter or the AeroPace System/Catheter for up to 30 days. The same system must be used for the entire study period for a given subject.

1.4.8 Summary of Training and Experience Needed to Use the Investigational Device

The Lungpacer DPTS is intended for use in hospitals and hospital-type facilities which provide care for patients requiring respiratory support. The device is intended for use by appropriately trained personnel under the direction of a study physician. Investigational sites and participating study personnel will meet these requirements.

Prior to study participation, physicians, study coordinators, respiratory therapists, and additional support staff will be trained on the study protocol, Instructions for Use (IFUs), case report forms, and electronic data entry processes according to their roles and responsibilities for the trial. Study investigators and other medical personnel responsible for insertion of the Catheter will receive didactic training on proper Catheter insertion, placement, removal, and potential risks and mitigations. Device training will be conducted for all study staff who will be responsible for the delivery of therapy and

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will include instruction on the set up and use of system components and for placement, mapping and delivery of therapy.

Lungpacer's clinical representatives will be present for the first subject Catheter placement, initial mapping, and Lungpacer DPT sessions at each study site to provide protocol-related clinical and technical support. Additional Lungpacer support will be available to sites for Catheter placement and DPT sessions, as deemed necessary by Lungpacer, for the duration of the study.

One Roll-In subject is allowed for each investigational site to allow for additional training on the investigational device. A second Roll-In subject is allowed if the first Roll-In subject has an unsuccessful Catheter placement or at the discretion of the Sponsor for additional training on the investigational device.

English language Instructions for Use (IFUs), listed below, are packaged with the investigational device. Versions of the IFUs in other languages can be accessed on Lungpacer Medical Inc.'s website at www.lungpacer.com under the Clinicians/Physicians tabs, using a username and password, or can be obtained upon request.

- AeroPace System
    - *AeroPace Catheter Kit IFU*: Step by step instructions for insertion, placement, and removal of the AeroPace Catheter.
    - *AeroPace System IFU*: Instructions for device set up including connections and disconnections between cables and components, Neurostimulation Console functions, Airway Sensor use, stepwise mapping and delivery of DPT using the Handheld Controller, use of intravascular electrogram, troubleshooting, and disinfection of the Console, Handheld Controller, Airway Sensor and cables.
- Keystone System
    - *Lungpacer LIVE Catheter Kit IFU*: Step by step instructions for insertion, placement, and removal of the LIVE Catheter.
    - *Lungpacer DPTS (Keystone System) IFU*: Instructions for device set up including connections and disconnections between cables and components, LCU functions, stepwise mapping and delivery of Lungpacer DPT using the Handheld Controller, troubleshooting, and disinfection of the LCU.
    - *Intermediate Cable IFU*: Instructions on disinfection of the Intermediate Cable.
    - *Handheld Controller IFU*: Instructions on disinfection of the Handheld Controller.

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1.4.9 Specific Medical or Surgical Procedures Involved in the Use of the Investigational Device

Lungpacer DPT includes the use of the Catheter that is placed percutaneously in the intended thoracic vein on the left side using the Seldinger technique, which is the most common method used when placing a central intravenous (IV) line. The Catheter is used for Lungpacer DPT and can be used for fluid delivery and blood sampling as for standard central venous catheters.

Lungpacer DPT uses temporary, low energy stimulation of the left and right phrenic nerves using electrodes integrated in the Catheter. The stimulation is intended to induce contractions of the diaphragm for strengthening. Other devices that utilize implanted electrodes for stimulation of the phrenic nerves for the purposes of diaphragm contraction and strengthening are approved in both the US and Europe.

1.5 Justification for the Design of the Clinical Investigation

1.5.1 Summary of Pre-Clinical Studies

Preclinical testing conducted for the Lungpacer DPTS is described in *Lungpacer DPTS RESCUE Investigator's Brochure (CLN-0046)*.

Bench testing for the Lungpacer DPTS was performed in accordance with applicable standards for central venous catheters and medical devices containing software. *In vivo* preclinical studies evaluated the Lungpacer DPTS models (Keystone System and AeroPace System) for maximum charge, thrombogenicity, biocompatibility, simulated use testing, and *in vivo* functionality and charge delivery.

The results of these studies indicate that the design is safe for human use, the system functions as intended, and no unwanted side-effects were observed.

1.5.2 Summary of Clinical Studies

Clinical testing conducted for the Lungpacer DPTS is described in *Lungpacer DPTS RESCUE Investigator's Brochure (CLN-0046)*.

1.5.2.1 *First-in-Human Studies*

Three First-in-Human clinical studies were conducted by Lungpacer in Paraguay in October and November 2015, and April 2016 to test the feasibility of transvenous phrenic nerve stimulation to stimulate the diaphragm muscle using the LIVE Catheter and an early prototype Lungpacer DPTS.

The LIVE Catheter was placed via the left subclavian vein temporarily in 28 subjects on short-term mechanical ventilation, and stimulation energy was delivered to 27 of them. Results from the evaluation showed that stimulation, via the electrodes in the catheter, elicited diaphragm contractions in most subjects, and that bilateral or unilateral pacing in synchrony with mechanical ventilation resulted in airway pressure reduction. No adverse events occurred in the paced subjects.

The results of these studies were published in Reynolds (2017).

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1.5.2.2 *Jugular Access Feasibility Study*

In Paraguay in 2018 and 2019, Lungpacer conducted two feasibility studies of LIVE Catheter insertion and delivery of Lungpacer DPT using venous access via the internal or external left jugular vein rather than via the left subclavian vein.

The primary feasibility endpoints assessed were: 1) phrenic nerve engagement as defined by contraction of one side or both sides of the diaphragm upon stimulation; and 2) delivery of Lungpacer DPT as shown by contraction of one side or both sides of the diaphragm upon delivery of stimulation to the phrenic nerve(s) as confirmed by cinefluoroscopy. One study also assessed generation of tidal volume upon delivery of stimulation to the phrenic nerve(s) without spontaneous or ventilator support, as measured by the ventilator.

In the 2018 study, 13 subjects were consented and enrolled and, while on short-term mechanical ventilation, had the LIVE Catheter temporarily placed either via the left external jugular vein (N=4) or the left internal jugular vein (N=9). Stimulation of the phrenic nerve(s) via the LIVE Catheter electrodes elicited diaphragmatic contractions in all subjects. Of the 13 subjects, 11 had bilateral phrenic nerve capture and 2 subjects had unilateral phrenic nerve capture. Adequate tidal volume was generated without spontaneous or ventilator support in 7 of 8 subjects evaluated.

In the 2019 study, 20 subjects were consented and enrolled and, while on short-term mechanical ventilation, had the LIVE Catheter temporarily placed via the left internal jugular vein. Stimulation of the phrenic nerve(s) via the LIVE Catheter electrodes elicited diaphragmatic contractions in all subjects. Of the 20 subjects, 19 had bilateral phrenic nerve capture and 1 subject had unilateral phrenic nerve capture.

No adverse events occurred in any of the enrolled subjects in either study. In summary, these studies show that LIVE Catheter access can be achieved by internal or external jugular vein access, and that Lungpacer DPT can be delivered using a jugular insertion method. The results of the 2018 jugular clinical study were reported at the American Thoracic Society 2019 (Gani, 2019), and at the European Respiratory Society 2019 (Gani, 2019). The results of the 2019 jugular clinical study were reported at the American Thoracic Society 2020 Virtual Congress (Gani, 2020).

1.5.2.3 *RESCUE 1 Study*

The RESCUE 1 study was an open-label feasibility study conducted in 3 US sites in 2018 in subjects who had failed ≥2 weaning attempts and received mechanical ventilation for ≥7 days. The RESCUE 1 study was conducted using the Lungpacer DPTS (Keystone System/LIVE Catheter) and evaluated device safety and feasibility over 30 days.

The study evaluated the safety and feasibility of left subclavian vein placement of the LIVE Catheter, mapping using the Lungpacer DPTS, delivery of Lungpacer DPT, and removal of the LIVE Catheter. Of 14 subjects conditionally enrolled, 11 were fully enrolled and 9 received the

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LIVE Catheter. Subjects were followed over 30 days or until study exit for safety evaluation. Two subjects did not receive the LIVE Catheter due to the inability to insert the guidewire.

All 9 subjects who received the LIVE Catheter met all 4 feasibility outcomes. For the 11 subjects (N=11), adverse events were as expected for ICU patients on mechanical ventilation. There were no deaths reported. One procedure-related serious adverse event, bronchial mucus plug, was associated with the Trendelenburg technique used for subclavian vein access. Liberation of mucus plugs or secretions is a known risk of diaphragm stimulation. An additional histological evaluation of 11 LIVE Catheters used for treatments in this study indicated no evidence of thrombogenicity.

This study demonstrates that Lungpacer DPT is feasible in patients who are difficult to wean or have received prolonged mechanical ventilation. This study data was published in Ataya, et al. (2019; 2020).

1.5.2.4 *RESCUE 2 Study*

RESCUE 2 was a randomized, controlled, open-label, multi-center clinical trial to investigate the safe and effective performance of the Lungpacer Diaphragm Pacing Therapy System (Keystone System/LIVE Catheter left subclavian vein placement) in patients who failed to wean from mechanical ventilation. Study subjects had failed two or more weaning attempts and required ≥96 hours (4 days) on mechanical ventilation. Subjects were randomized 1:1 to Treatment with the Lungpacer DPTS (plus standard of care) as compared to Control (standard of care); 1-2 Roll-in subjects were allowed per site. The study was for 30 days with follow-up to Day 32 or study exit. The study enrolled subjects at 20 clinical centers in Europe and was completed in January 2020.

One-hundred and twelve (112) randomized subjects and 12 non-randomized Roll-In subjects were enrolled. The overall study population was 57.1% male, with a mean age of 64.6 years. The most common reason for mechanical ventilation was ARDS/ARF (37.5%), followed by pneumonia (18.8%), surgical (15.2%), COPD (14.3%) and Other (12.75%). More than half of patients (54.5%) were tracheotomized at enrollment.

The primary efficacy outcome was the difference in the proportion of subjects successfully weaned by Day 30 for the Treatment group as compared to the Control group. “Successfully weaned” was defined as passing a Ventilator Liberation Trial (VLT) and not reintubated (subjects with an oral or nasal endotracheal tube) or returned to MV within 48 hours. Weaning success was 81.5% and 74.1% in the Treatment and Control groups, respectively, for a 7.4% greater weaning success for Treatment patients (p=0.586, mITT). While this outcome was not statistically significant, the study was not powered to reach statistical significance for this outcome measure.

Secondary outcomes included duration of mechanical ventilation, and improvements from baseline for maximal inspiratory pressure (MIP) and rapid shallow breathing index (RSBI). Mean days on mechanical ventilation showed a trend for the Treatment group to be weaned earlier, by 1.4 days

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compared to the Control group (p=0.498, mITT). Mean change in MIP showed statistically significant improvements for the Treatment group of 12 cm H_2O when compared to the Control group (p=0.001, mITT). Mean change in RSBI showed a trend of greater improvement for the Treatment group of 23 breaths/sec/liter when compared to the Control group (p=0.1016, mITT).

Safety was assessed by documentation of adverse events collected throughout the study. There were 96 adverse events reported in 33 (57.9%) Treatment group subjects and 88 adverse events in 38 (69.1%) Control group subjects. Ten adverse events were reported in 7 (58.3%) Roll-In subjects. There were no unanticipated adverse device effects noted in the study. There were 47 serious adverse events (SAEs) reported in 27 (47.4%) Treatment group subjects and 39 SAEs in 27 (49.1%) Control group subjects. All SAEs occurred at an incidence of less than 10%, except for respiratory/thoracic/mediastinal disorders, which were 22.8% and 14.5% in the Treatment and Control groups, respectively, and infections and infestations (14.0% Treatment; 12.7% Control). The most frequently reported SAEs were septic shock (Treatment 7.0%; Control 7.3%), and pneumothorax (Treatment 7.0%; Control 5.4%), with one of the pneumothorax events adjudicated as procedure-related.

The incidences of septic shock and pneumothorax reported in the RESCUE 2 study are within the expected incidence rates for these events in critically ill patients in European ICUs (Sakr, 2018; Yarmus, 2012). The SAE for pneumothorax that was considered to be related to the study procedure was the result of vessel wall perforation. This SAE occurred in a subject who presented with atypical anatomy of the superior vena cava, likely due to right lung resection, which precluded optimal placement of the tip of the LIVE Catheter. Vessel perforation was likely due to the location of the LIVE Catheter tip within the atypical anatomy of the patient's subclavian-superior vena cava. Vessel wall perforation is a known adverse event that can occur with central venous catheters (Vesely, 2003; Stonelake, 2006).

Of the 47 SAEs in the Treatment group, 20 events in 16 subjects (28.1%) were deemed by the blinded Clinical Events Committee to be related to the device or procedure. The most frequent device/procedure--related SAEs were respiratory, thoracic and mediastinal disorders (14%) and infections/infestations (8.8%).

Eleven deaths were reported in the study, three (7%) and eight (15%) in the Treatment and Control groups, respectively, which are within the expected 30-day mortality rates for ICU patients on mechanical ventilation (Boles, 2007; Damuth, 2015; Béduneau, 2017).The overall safety profile of the Lungpacer DPTS is as expected for similar devices, such as central venous catheters, and the adverse events reported in the RESCUE 2 study are representative of ICU patients receiving mechanical ventilation.

This study demonstrates that Lungpacer DPT statistically significantly improves inspiratory muscle strength, as shown by improvements in MIP as compared to Control, and shows a trend

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for improved weaning success and reduction in days on MV in patients who are difficult to wean from mechanical ventilation. This study data was reported at the 2020 European Respiratory Society Virtual Congress and will be published in a peer reviewed journal.

1.6 Risks and Benefits of the Investigational Device and Clinical Investigation

1.6.1 Anticipated Clinical Benefits

Participation in this study may allow patients to be weaned more quickly from MV by increasing the strength and endurance of the diaphragm muscle enough to sustain spontaneous breathing without the assistance of a mechanical ventilator.

Knowledge gained from this investigation may enable future patients to benefit from this technology.

1.6.2 Anticipated Adverse Device Effects

Anticipated adverse device effects potentially associated with the Lungpacer DPTS (Keystone and AeroPace Systems) including the Catheter are based on the known risks of similar devices and clinical experience with the Lungpacer DPTS. **Table 1** lists anticipated adverse events for central venous catheters. **Table 2** lists anticipated adverse events for delivery of stimulation energy from a temporary stimulation device, (e.g., nerve stimulation). **Table 3** lists anticipated adverse events associated with diaphragm stimulation.

Table 1: Risks Associated with Central Venous Catheters

- Adverse tissue response
- Allergic reaction
- Arrhythmia[1]
- Bleeding / Hemorrhage
- Bradycardia
- Bruising, swelling or seroma at insertion site
- Cardiac structure damage (e.g. atrial or ventricular perforation, tricuspid valve injury, cardiac tamponade)
- Central Line-Associated Blood Stream Infection (CLABSI)
- Cerebrovascular event
- Discomfort
- Embolism (device, air or thrombus, including pulmonary embolism due to blood vessel blockage)
- Hematoma
- Hemothorax
- Hypertension / hypotension
- Inadvertent arterial or venous puncture
- Infection (including endocarditis)
- Lung injury (including pleural effusion)
- Lymphatic / thoracic duct injury (including chylothorax, chylopericardium, lymphocutaneous fistula)

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- Mediastinal injury
- Nerve injury (e.g. cervical / brachial plexus, vagus, recurrent laryngeal nerves, phrenic nerve, and sympathetic chain [Horner Syndrome])
- Pain, tenderness, swelling, discomfort at access site
- Pneumohematoma
- Pneumomediastinum
- Pneumothorax
- Pseudo aneurysm or AV fistula at access site
- Sepsis
- Skin irritation
- Syncope
- Thrombosis / stenosis
- Tissue damage
- Vessel occlusion
- Vessel wall damage / perforation
- Wound healing issues
- Wound infection / phlebitis

[1] Arrhythmia including, but not limited to, asystole (cardiac arrest), atrial extrasystole(s), atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular (AV) block, atrioventricular nodal re-entrant tachycardia (AVNRT), atrioventricular re-entrant tachycardia (AVRT), pulseless electrical activity, supraventricular extra systole(s), transient atrial arrhythmia lasting less than 2 seconds, transient ventricular arrhythmia lasting less than 2 seconds, ventricular extrasystole(s), ventricular fibrillation, ventricular flutter, and ventricular tachycardia.

Table 2: Risks Associated with Stimulation Energy from a Temporary Stimulation Device

- Arrhythmia[1]
- Bradycardia
- Discomfort
- Hypertension / hypotension
- Inappropriate stimulation
- Pain or discomfort during stimulation
- Phrenic nerve damage or injury
- Syncope

[1]Arrhythmia including, but not limited to, asystole (cardiac arrest), atrial extrasystole(s), atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular (AV) block, atrioventricular nodal re-entrant tachycardia (AVNRT), atrioventricular re-entrant tachycardia (AVRT), pulseless electrical activity, supraventricular extra systole(s), transient atrial arrhythmia lasting less than 2 seconds, transient ventricular arrhythmia lasting less than 2 seconds, ventricular extrasystole(s), ventricular fibrillation, ventricular flutter, and ventricular tachycardia**.**

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Table 3: Risks Associated with Diaphragm Stimulation

• Diaphragm injury • Discomfort • Hypercapnia / hypocapnia • Hypoxia • Liberation of lung mucus plugs/secretions • Muscle fatigue or discomfort • Pain or discomfort during stimulation

1.6.3 Risk Mitigation Measures

Risks associated with the Lungpacer DPTS have been minimized by design.

RESCUE 3 procedure risks are further mitigated by:

- Stopping systemic anticoagulation prior to central venous catheter insertion. Cessation and reinitiation of subtherapeutic anticoagulation before procedures should be governed by either local hospital guidelines or published medical society guidelines.
- Use of ultrasound guidance for placement of the study catheter.
- Considering reducing ventilator parameters of positive end-expiratory pressure (PEEP) at the time of study catheter insertion within parameters of the physician's experience, hospital and association guidelines to reduce risk of pneumothorax.
- Administering a questionnaire at the end of each therapy session for those subjects who receive Lungpacer DPT to assess subject sensations and comfort with the treatment.

RESCUE 3 study risks are further mitigated by:

- Adverse events monitoring throughout the study.
- Use of an independent Clinical Events Committee (CEC) for adverse event adjudication and a Data and Safety Monitoring Board for overall assessment of the study and device risk-to-benefit profile.
- Selecting experienced investigators and by conducting training on the use of the Lungpacer DPTS and Catheter for investigators and research staff designated by the PI to use the device.
- Site selection procedures confirming that participating ICUs have appropriate back-up equipment (e.g., for defibrillation), and that standard hospital procedures for handling medical conditions (e.g., oxygenation levels, airway occlusions) or emergencies are available.

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1.6.4 Residual Risks Associated with the Investigational Device

The residual risks associated with the use of the Lungpacer DPTS are defined here as potential harms that do not have a Negligible Risk after implementation of design risk control measures. None of the hazards identified are significant risks after implementation of risk control measures. The residual risk is considered acceptable.

1.6.5 Other Complications and Risks in Clinical Use

Pregnant subjects are not eligible to participate in this study and a pregnancy screen is conducted prior to enrollment, if not available during hospital admission. The risks of Lungpacer DPTS to pregnant or lactating patients or to the fetus is unknown at this time.

Concomitant medical treatments with which Lungpacer DPT may interact include those listed in **Table 4.** Subjects using these medical treatments are excluded from the study or may be withdrawn. There may be interactions between the Lungpacer DPT and other concomitant medical treatments that have not been identified.

Table 4: Excluded Concomitant Medical Treatments with Lungpacer DPT

Concomitant Medical Treatment	Pre-Enrollment	Post-Enrollment
Neuromuscular blockade	Excluded	DPT temporarily suspended (Treatment) until neuromuscular blockade is discontinued
ECMO	Excluded	Subject withdrawn from the study
Neurological pacing/stimulator devices	Excluded	Subject withdrawn from the study
Cardiac pacemakers and defibrillators	Excluded	Subject withdrawn from the study

For information on the safety and compatibility of the Catheter in the Magnetic Resonance (MR) environment, refer to Appendices 1 and 2 for the AeroPace Catheter and LIVE Catheter, respectively. Information on MRI compatibility is also provided in the respective Catheter Instructions for Use.

1.6.6 Risk-to-Benefit Rationale

It is not expected that subjects enrolled into this study will be exposed to risks beyond those normally associated with other temporarily inserted devices such as central venous catheters, temporary pacemaker leads, and neurostimulation devices.

Lungpacer DPT may strengthen the diaphragm, which may help difficult-to-wean MV patients or patients on prolonged MV to wean sooner from MV. Given the significant morbidity and mortality associated with prolonged MV, even a small reduction in MV time may be beneficial to study subjects.

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However, this benefit remains to be proven at this time. Knowledge gained from this investigation may enable future patients to benefit from this technology.

Based on the risk-reduction measures taken, both with regard to the device and the protocol, and the potential benefit to study subjects (or to future study subjects and patients), the risk/benefit profile of the Lungpacer DPTS is considered acceptable and the study is justified.

1.7 Endpoints of the Clinical Investigation

1.7.1 Primary and Secondary Endpoints

1.7.1.1 *Primary Effectiveness Endpoints*

- Proportion of subjects "successfully weaned" by Day 30;
- Change in Maximal Inspiratory Pressure (MIP) from randomization (baseline) to last available measure.

"**Successfully weaned**" is defined as passing the protocol-specific Ventilator Liberation Trial (VLT), or removed from MV, and not returned to MV **within 48 hours**.

Additional information on the primary effectiveness endpoint(s) is provided in a statistical analysis plan that will not be provided to study personnel in order to protect the study from observational bias.

1.7.1.2 *Primary Safety Endpoint*

Adverse events for subjects randomized to Treatment (Lungpacer DPTS plus Standard of Care) as compared to subjects randomized to Control (Standard of Care) over the study period and follow-up.

1.7.1.3 *Secondary Effectiveness Endpoints*

- Days on mechanical ventilation from Day 1 to removal from MV associated with successful weaning or Day 30, whichever comes first;
- Change in MIP over time from randomization (baseline);
- Rate of MIP change per day from randomization (baseline) to last available measure;
- Change in Rapid Shallow Breathing Index (RSBI) from randomization (baseline) to last available measure;
- Change in RSBI over time from randomization (baseline);
- Rate of RSBI change per day from randomization (baseline) to last available measure;
- Day 30 mortality.

1.7.1.4 *Observational Data Collection*

- The time to first successful VLT after randomization
- Cessations and re-instatements of mechanical ventilation to study exit;
- Proportion of subjects tracheostomized from randomization (baseline) to study exit;
- Ventilator settings (PS, PEEP, RR, FiO_2, Ventilation Mode, V_T) daily, to last available measure;
- ICU admissions and discharges to day 30;

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- Hospital admission and discharges to day 30.

1.7.2 Primary and Secondary Outcomes for the Clinical Investigation

1.7.2.1 *Primary Effectiveness Outcomes*

- The proportion of subjects who are successfully weaned will be statistically significantly greater for subjects randomized to Treatment compared to subjects randomized to Control.
- The MIP mean change from baseline will be statistically significantly greater for subjects randomized to Treatment compared to subjects randomized to Control.

1.7.2.2 *Primary Safety Outcomes*

A consistent risk profile is observed for subjects randomized to Treatment compared to subjects randomized to Control.

1.7.2.3 *Secondary Effectiveness Outcomes*

- The average days on mechanical ventilation from Day 1 to removal from MV associated with successful weaning or Day 30, whichever comes first, will be statistically significantly smaller for subjects randomized to Treatment as compared to subjects randomized to Control;
- The profile of MIP values over time will have greater average improvement over baseline for subjects randomized to Treatment as compared to subjects randomized to Control;
- The average rate of change of MIP values from randomization to last available measurement will be greater for subjects randomized to Treatment as compared to subjects randomized to Control;
- The RSBI mean change from baseline will be statistically significantly greater for subjects randomized to Treatment compared to subjects randomized to Control;
- The profile of RSBI values over time will have greater average improvement over baseline for subjects randomized to Treatment as compared to subjects randomized to Control;
- The average rate of change of RSBI values from randomization to last available measurement will be greater for subjects randomized to Treatment as compared to subjects randomized to Control;
- The Day 30 mortality will be lower for subjects randomized to Treatment as compared to subjects randomized to Control.

1.7.3 Primary Claims and Intended Performance of the Investigational Device to be Verified

1.7.3.1 *Safety*

- The Lungpacer DPTS is safe for the treatment of the intended study population of patients on mechanical ventilation.
- Treatment with the Lungpacer DPTS results in a risk profile that is consistent with Standard of Care in the intended study population.

1.7.3.2 *Efficacy Claims*

- More subjects treated with the Lungpacer DPTS are successfully weaned from mechanical ventilation by Day 30 as compared to Standard of Care.
- Subjects treated with the Lungpacer DPTS are weaned more quickly from mechanical ventilation by Day 30 as compared to Standard of Care.

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- Subjects treated with the Lungpacer DPTS have greater improvement in inspiratory muscle strength and respiratory function as compared to Standard of Care.

1.8 Design of the Clinical Investigation

1.8.1 General

1.8.1.1 *Description of the Type of Clinical Investigation and Rationale*

1.8.1.1.1 Study Design

This clinical investigation is an open-label, multi-center adaptive RCT to demonstrate the safety and effectiveness of the Lungpacer DPTS (plus Standard of Care) as compared to Control (Standard of Care) in patients aged 18 years or older who are receiving mechanical ventilation. Subjects will have received mechanical ventilation for ≥96 hours (4 days) and failed two weaning attempts.

The adaptive RCT will include 200 to 400 randomized subjects based on a Bayesian group sequential design. Enrollment will be at a maximum of 80 sites at up to 55 investigational sites in the US, and remaining sites in Europe and other Tier 1 countries. All subjects will meet the study inclusion criteria, will not satisfy any exclusion criteria, and will be randomized in a 1:1 block configuration to Treatment or Control.

Prior to randomization, an *anticipated placement date* for the Catheter is identified and recorded in the EDC. This date should fall within 1 day of randomization. The *anticipated placement date* serves as Day 1 for subjects randomized to Treatment or Control.

Once randomized, Treatment subjects should have the Catheter placed on the anticipated placement date. *Missing the anticipated placement date for Treatment subjects can only occur if medically necessary and the reason must be documented in the EDC.*

Randomized Subjects:

- Treatment: Treatment (Lungpacer DPTS) subjects will have Catheter placement, receive Lungpacer DPT and will be treated with Standard of Care. Lungpacer DPT is delivered twice daily according to the device Instructions for Use.
- Control: Control subjects will be treated with Standard of Care only. No placement of the Catheter.

Standard of Care for weaning from MV is consistent with weaning guidelines and further specifies the following conditions to harmonize Standard of Care across study sites and is defined as:

- The protocol-specific VLT replaces the daily physician-directed weaning trial, but no more than one additional weaning trial can be conducted per day for both study groups.

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- Institutions should follow current institutional practices for rehabilitation (e.g., limb movement and mobility exercises) for MV patients.
- Inspiratory Muscle Strength Training (IMST) protocols are **prohibited**.
- Physicians should **minimize sedation** for patients on MV >24 hours if possible.
- Non-Invasive Ventilation (NIV) or high flow oxygen can be used to prevent post-extubation respiratory failure for subjects who pass a VLT or who were removed from MV.

Roll-In Subjects:

One Roll-In subject is allowed for each investigational site and satellite facility (if applicable); a second Roll-In subject is allowed if the first Roll-In subject has an unsuccessful Catheter placement. A second Roll-In subject is allowed if the first Roll-In subject has unsuccessful Catheter placement or at the discretion of the Sponsor for additional training on the investigational device. Investigators must determine prior to screening or obtaining consent, whether the subject will be enrolled as a Roll-In subject or will be randomized. An *anticipated placement date* must be identified and recorded in the EDC for Roll-In subjects; however, Roll-In subjects will not be randomized but will receive all study procedures as for a Treatment subject.

Day 1 for Roll-In subjects is the anticipated placement date. Where the protocol indicates completion of an item by randomization, it must be completed by Day 1 for Roll-In subjects.

All subjects will undergo study procedures according to their study group allocation as given in the **Schedule of Events** (**Table 5**) over the *30-day study* and follow-up period.

1.8.1.1.2 Study Device, Procedures and Evaluations by Treatment or Control Group

The Lungpacer DPTS models will be allocated to sites based on device availability. It is intended that only one model of the Lungpacer DPTS will be available at each site. The Lungpacer DPTS Keystone System/LIVE Catheter has been available since the start of enrollment in the RESCUE 3 study and is expected to be in use through approximately N=100-150 randomized subjects. The AeroPace System/Catheter is intended to be implemented at most sites after regulatory and IRB/EC approval. Subgroup analysis will be conducted for the primary safety and effectiveness endpoints for each device model.

All study processes, measurements and evaluations will be conducted for the Treatment group and Control group with the exception of procedures specific to the investigational device, for example, Catheter utilization and Lungpacer DPT.

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1.8.1.1.3 Study Design Justification

1.8.1.1.3.1 Study Population

The RESCUE 3 patient population is appropriate for Lungpacer DPT because these patients are at high risk of diaphragm dysfunction, co-morbidities and death (Dres, 2017; Jung, 2016; Supinski, 2016) and have no non-invasive alternative treatments. This patient population includes approximately one-third of all patients on mechanical ventilation.

RESCUE 3 excludes those patients whose primary reason for MV is due to causes other than diaphragm weakness (e.g., inability to protect the airway, massive parenchymal lung damage, hypervolemia, end stage heart disease and neuromuscular diseases involving the diaphragm muscle, phrenic nerve and other nerves). An exclusion of absolute value of MIP >50 cm H_2O excludes MV patients with sufficient inspiratory muscle strength that, without other mitigating factors, should allow weaning (Hermans, 2010; Jaber, 2011; Demoule; 2013; Jung, 2016; Supinski, 2016; Dres, 2017). In addition, the study excludes subjects who have received >90 days of mechanical ventilation and, therefore, have less likelihood of treatment benefit within the 30-day study (MacIntrye, 2005; White, 2012).

1.8.1.1.3.2 Use of a Control Group (Standard of Care)

Under Standard of Care, approximately 50% of the RESCUE 3 patient population will recover from mechanical ventilation (Jung, 2016). Therefore, Lungpacer DPT efficacy evaluation must be compared to standard of care as a Control group. According to US and International clinical practice guidelines for weaning critically ill adult patients from mechanical ventilation (Boles, 2007; ATS/CHEST guidelines, 2017), standard of care for patients on MV involves efficient liberation processes that combine sedation optimization, early mobilization and respiratory management. According to ERS/ATS clinical practice guidelines, respiratory management includes use of a Ventilator Liberation Trial (VLT) for the early and systematic detection of patients ready for extubation, and the use of post-extubation NIV for patients at high risk of extubation failure (Boles, 2007; Rochwerg, 2017).

1.8.1.1.3.3 Open-Label Design and Study Outcomes

An open-label RCT design is justified because (1) subjects, surgeons and attending staff will be unblinded during Lungpacer DPT due to the contractions of the diaphragm that are felt and/or observed during treatment, and (2) the primary efficacy outcome of successful weaning is a clinically meaningful and objective outcome that is not subject to bias. Successful weaning is defined as passing the protocol-specific VLT, or removed from MV, and not returned to MV within 48 hours. There are well-defined clinical criteria that determine whether a patient has failed the VLT or cannot tolerate the 48-hour weaning period. For patients removed from mechanical ventilation who achieve 48 hours free from MV, reintubation rates are low and in the range of 10-15% (Silva, 2012).

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Studies using Inspiratory Muscle Strength Training (IMST) to strengthen the diaphragm in patients on MV provide effectiveness data relevant to the expected effectiveness for the Lungpacer DPTS. Recent published meta-analyses of a large number of IMST randomized controlled trials (Elkins, 2015; Vorona, 2018) in patients on MV reported that IMST improved MIP, RSBI and weaning success rate, and reduced the time on mechanical ventilation, and the length of stay in both the ICU and hospital. Similar outcomes will be collected in the RESCUE 3 study.

1.8.1.2 *Measures to Minimize or Avoid Bias*

Study randomization is conducted within an EDC system using an embedded randomization table based on site number and subject number. A subject number is assigned after informed consent is obtained. Once study entry criteria are confirmed to have been met and an anticipated placement date is identified, the subject is randomized after which the Treatment/Control group allocation for that subject number is revealed. Treatment cannot easily be blinded. Potential bias introduced by unblinding is mitigated by the collection of baseline endpoint data prior to randomization and the use of an objective primary endpoint, i.e., successful weaning. All participating physicians and study coordinators are trained in the study protocol, use of the EDC, and the procedure for randomization based on their roles and responsibility. Physicians and coordinators have received GCP or equivalent training according to institutional requirements.

Additional methods to minimize study bias based on randomization are:

- The same inclusion/exclusion criteria are used for all subjects prior to randomization;
- Baseline MIP and RSBI will be measured after consent and prior to randomization;
- Standard of Care, and all study tests and evaluations are conducted for both groups for the study duration;
- Site personnel will be trained and qualified in the use of a standardized protocol to conduct RSBI and MIP measurements according to their role and responsibility;
- A CEC will independently adjudicate adverse events;
- A Data Safety Monitoring Board will assess patient risk and benefit over the course of the study.

1.8.1.3 *Rationale for Primary and Secondary Endpoints Selection and Measurement*

1.8.1.3.1 **Safety Endpoints**

The RESCUE 3 safety endpoints will characterize the risk profile of the Lungpacer DPTS as compared to Standard of Care. The Catheter is similar in design to other central venous catheters (CVCs), therefore, potential adverse effects attributed to CVCs may be expected with the use of the Catheter. In-hospital mortality as high as 30% has been reported for patients on

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mechanical ventilation for ≥ 96 hours, with rates as high as 47% to 70% at 1 year (Cavalcanti, 2017; Kuo, 2016; Demoule, 2016; Zhu, 2015; Lall, 2015; Kirakli, 2015; Jubran, 2013; Damuth, 2015. It is hypothesized that subjects treated with the Lungpacer DPTS will have a comparable risk profile to that of subjects receiving Standard of Care and may improve survival.

1.8.1.3.2 **Effectiveness Endpoints**

Successful weaning is the clinically meaningful endpoint for patients on MV. The protocol for conducting the VLT to determine weaning success is described in *Readiness-to-Wean and VLT Protocol (CLN-0039)***.**

MIP has been shown to be an independent predictor of weaning in patients who are difficult to wean from MV (Bien, 2015; Supinski, 2016), and is correlated with specific indicators of diaphragm strength, weaning success and mortality in these patients (Carlucci, 2009; Supinski, 2016; Ferrari, 2014; Medrinal, 2016). MIP measurements are conducted according to *RSBI/RASS/MIP Protocol (CLN-0037).*

There is an increased risk of co-morbidities and mortality associated with increasing days on mechanical ventilation (Esteban, 2002; Béduneau, 2017; Chastre, 2012; Zhou, 2014; Hui, 2013; Apostolopoulou, 2014). RSBI is an indicator for respiratory function and has predictive value for readiness to wean in patients on mechanical ventilation (Yang, 1991; De Souza, 2015; Nemer, 2009). Details on the technique for measuring RSBI are described in *RSBI/RASS/MIP Protocol (CLN-0037)*. Mortality outcomes to study exit will be collected to assess the impact on survival.

Observational outcomes provide additional information on patient medical status. ICU and hospital admissions and discharges will be utilized for health economic analysis.

1.8.1.4 ***Methods and Timing for Assessing, Recording, and Analyzing Variables***

The following study evaluations, safety evaluations and safety follow-up evaluations are to be performed for Treatment and Control subjects after consent is obtained and within the timeframes defined below and summarized in **Table 5 Schedule of Events**. Study Day 1 is the anticipated placement date as described in **Section 1.8.1.1.1**.

1.8.1.4.1 **Study Evaluations**

- 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

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- Ventilator Settings (PS, PEEP, RR, FiO_2, Ventilation Mode, V_T),
- Protocol-specific Ventilator Liberation Trial
- For Treatment subjects only:
  - Visual Analogue Scale (at the beginning and end of each Lungpacer DPT session)
  - Stimulation Discomfort and Sensation Tool (at the end of each Lungpacer DPT 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 (**not all shown on Table 5)** 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.

1.8.1.4.2 Safety Evaluations and Safety Follow-Up Evaluations

- 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;

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- 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.*

Table 5 indicates the type and timing of evaluations for subjects prior to successful weaning and/or transfer to a facility outside the enrolling institution. Data are collected real-time and reported on eCRFs that are saved to a secure database.

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Table 5: Schedule of Events Until Successful Weaning or Outside Transfer

Schedule of Events for Enrolled Subjects																																		
Day	***Consent***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***	***15***	***16***	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***	***25***	***26***	***27***	***28***	***29***	***30***	***31***	***32***
Consent [a]	*x or x*																																
Inclusion/Exclusion [b]	*x or x*																																
Qualifying Protocol-specific VLT (failure) [c,p]	*x or x*																																
RSBI (after brief e.g., 5 min pause) followed by: RASS/MIP [d,e]	*x or x* [d]							*x*							*x*							*x*							*x*		*x*		
SOFA [f]	*x or x*																																
Screening/Lab Tests [f,p]	*x or x*																																
Randomize [g]	*x or x*																																
Catheter Insertion		*t or t*																															
Ventilator Settings [h,p]		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Protocol-Specific VLT		*x* [i]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
AEs and/or SAEs [j]		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
DPT session #1 [k]		*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*		
DPT session #2 [k,l]		*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*	*t*		
Catheter Removal																														*t* [m]			
RESCUE 3 30-Day Follow-up (Study Exit) Worksheet [n]																														*x* [n] *or x* [n] *or x* [n]			
Treatment Subject Questionnaire [o]																														*t*	*t*	*t*	

Legend:

x: All Subjects
t: Treatment Subjects only

Footnotes:

a: Consent can be obtained within 5 days prior to randomization.
b: If the consented subject does not satisfy any exclusion criteria and meets all inclusion criteria, he/she is eligible for the qualifying protocol-specific VLT.
c: A qualifying protocol-specific VLT is performed on or before Day 1; the subject is eligible for enrollment if he/she satisfies the Readiness-to-Wean criteria and fails to pass the qualifying protocol-specific VLT.
d: RSBI/RASS/MIP (baseline assessment) must be performed after consent but prior to randomization. Follow-up tests must be done on Day 7 ± 1, 14 ± 1, 21 ± 1, 28 ± 1 or Day 30 while on MV.
e: For subjects with an oral or nasal endotracheal tube after a VLT is passed, do not remove endotracheal tube before performing RSBI and MIP.
f: SOFA and lab tests must be performed after consent but prior to randomization. These tests do not need to be performed if the subject passes his/her VLT or if MIP > 50 cm H_2O.
g: Prior to randomization, an *anticipated placement date* is identified and should fall within 1 day of randomization. The *anticipated placement date* serves as Day 1 for all subjects.
h: Ventilator settings are to be recorded before the protocol-specific VLT, if possible.
i: If no VLT was performed previously on Day 1, perform the protocol-specific VLT.
j: AEs and/or SAEs are collected daily for all subjects according to the safety evaluations and safety follow-up evaluations schedule provided in Section 1.8.1.4.2.
k: Treatment subject discomfort/pain is assessed using the standard *Visual Analogue Scale* at the *beginning and end* of each Lungpacer DPT session. Discomfort and sensation are evaluated *at the end* of each Lungpacer DPT session using the *Stimulation Discomfort and Sensation Tool.*
l: Start time of DPT session #2 must be ≥3 hours after the end time of DPT session #1, if possible.
m: The Catheter must be removed on Day 30, if it has not already been removed, followed by SAE collection for 48 hours.
n: The RESCUE 3 30-Day Follow-up (Study Exit) Worksheet must be completed on or after Day 30 for any subject not withdrawn or discontinued (Section 1.9.3). If removal from MV has not occurred by Day 30, the worksheet must be completed after the 48-hour safety follow-up evaluation.
o: The Treatment Subject Questionnaire must be completed at study exit or before transfer, whichever comes first.
p: All tests/procedures required for enrollment should be completed within 2 days prior to randomization.

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1.8.1.5 *Equipment for Assessing the Clinical Investigation Variables and Monitoring, Maintenance and Calibration*

Equipment used for clinical evaluations and their maintenance and calibration requirements are given below.

- MIP non-sterile disposables (one-way valve, adaptors, oxygen tubing, disconnect wedge): Non-sterile disposables are provided by Lungpacer in original packaging. They are disposable items that do not require calibration or maintenance.
- MIP pressure manometers: A temperature-compensation digital pressure manometer gauge calibrated to 24-months, is provided by Lungpacer in its original packaging. Each manometer will be calibrated by Lungpacer at the beginning of the study and will be replaced by Lungpacer every two years during the clinical trial.

1.8.1.6 *Procedures for the Replacement of Subjects*

No study subjects will be replaced in the study regardless of reason for study exit (e.g., withdrawal, death, etc.).

1.8.2 Investigational Device and Comparator

1.8.2.1 *Description of the Exposure to the Investigational Device or Comparator*

Subjects randomized to the Treatment group will receive Lungpacer DPT and Standard of Care. Subjects will have the investigational Catheter placed percutaneously into the intended thoracic vein on the left side according to the Catheter IFU. Maximum exposure to the LIVE Catheter will be for 30 days.

Treatment will be delivered by one of the two Lungpacer DPTS models. For any one subject, only one Lungpacer DPTS model may be used to deliver therapy during the subject's participation.

Lungpacer DPT requires mapping to determine which electrodes are adjacent to the phrenic nerves. Lungpacer DPT delivers electrical stimulation via the selected electrodes in six (6) sets of ten (10) stimulations, twice daily for a total of 120 stimulations/day for up to 30 days or until successful weaning from MV. The maximum number of stimulations that the patient could receive is expected to 3600, delivered over the course of 30 days.

Subjects randomized to the Control group will receive Standard of Care only.

1.8.2.2 *Justification of the Choice of Comparator*

The RESCUE 3 patient population includes subjects who are difficult to wean from mechanical ventilation or are on prolonged MV and who will be receiving Standard of Care, which is the comparator in the study. Under Standard of Care, at least 50% of these patients will recover from mechanical ventilation (Jung, 2016). Standard of Care includes daily weaning attempts that are intended to encourage diaphragm use and to strengthen the respiratory muscles over time.

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1.8.2.3 *Other Medical Devices or Medications to be Used During the Clinical Investigation*

The Lungpacer DPT is conducted concurrently with mechanical ventilation. Therefore, mechanical ventilators and other equipment used routinely in the ICU for the care of patients on MV will be used during the clinical investigation. Some examples include intubation and tracheostomy devices, respiratory devices (for suction), bronchoscopy devices and methods for determining Catheter placement (e.g., ultrasound, X-ray). Medication usage will be according to Standard of Care for patients on MV and according to the medical needs of the subject.

1.8.2.4 *Number of Investigational Devices to be Used and Justification*

Appropriate investigational device inventory is provided to conduct RESCUE 3 Diaphragm Pacing Therapy sessions, depending on facility needs.

See Appendices 1 and 2 for the AeroPace System/Catheter and Keystone System/LIVE Catheter configurations and number of investigational devices, respectively.

No other significant changes to the investigational device are expected for the duration of the study.

1.9 Subjects

1.9.1 Inclusion Criteria for Subject Selection

Subjects who meet all of the following inclusion criteria will be eligible for the study:

1) Are 18 years or older, and,
2) Have been mechanically ventilated for ≥96 hours (4 days) and,
3) Have satisfied the Readiness-to-Wean criteria, and,
4) Have failed at least 2 weaning attempts:
   - that were conducted *at least* 48 hours after initiation of MV, and,
   - that were conducted on different calendar days, and,
   - at least one of which was the protocol-specific Ventilator Liberation Trial.

Note: Self-extubation from MV with subsequent reintubation within 48 hours is considered a failed weaning attempt. Institutional weaning attempt is in accordance with the institution's defined standard of practice and weaning attempt must be documented in the subject's medical records.

1.9.2 Exclusion Criteria for Subject Selection

Subjects who satisfy any of the following exclusion criteria will be excluded from the study:

1. MIP (absolute value) >50 cm H_2O.
2. Invasive mechanical ventilation >90 days.
3. Currently on ECMO.
4. Weaning failure due to hypervolemia.

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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/m^2.
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.

1.9.3 Criteria and Procedures for Subject Withdrawal or Discontinuation

Investigators should use their clinical judgement to withdraw a subject from the study if subject health or safety may be compromised from continued enrollment. A subject may be withdrawn or discontinued from study participation at the subject's or investigator's request for the following reasons:

- Adverse event (AE), Serious Adverse Event (SAE), Adverse Device Effect (ADE/SADE), or Unanticipated Adverse Device Effect (UADE/USADE), Death;
- Subject voluntarily withdraws or is withdrawn by his/her legally authorized representative;
- Subject is withdrawn by the investigator; investigators should withdraw subjects for the following reasons:
    - subject requires ECMO;
    - subject requires placement of a neurological pacing/stimulator device or cardiac pacemaker or defibrillator;
    - unsuccessful placement of the Catheter (see Definitions);
    - Other.

The reason for withdrawal or discontinued study participation will be recorded in the eCRF and in the medical record.

1.9.4 Point of Enrollment

The point of enrollment is the time when:

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- the subject is in screening and his/her legally authorized representative or the subject has signed and dated the Informed Consent Form, and,
- the subject has failed at least one weaning attempt, and,
- the subject meets the Readiness-to-Wean criteria, and,
- the subject has failed a qualifying protocol-specific VLT (conducted after informed consent and on a different calendar day than the previous failed weaning attempt(s)), and,
- the subject meets all inclusion criteria, and,
- the subject does not satisfy any exclusion criteria.

After enrollment, an anticipated-placement date can be scheduled.

For Roll-In subjects, the point of enrollment is the same, however, these subjects are not randomized. Roll-In subjects follow the same procedures for Treatment with the exception of randomization. Where the protocol indicates completion of an item by randomization, it must be completed by Day 1 for Roll-In subjects.

1.9.5 Total Expected Duration of the Clinical Investigation

The total expected duration of the study is estimated to be 36 to 48 months. This is based on enrollment of 236 subjects at up to 80 centers activated on a rolling basis.

1.9.6 Number of Subjects Required in the Clinical Investigation

The Lungpacer Diaphragm Pacing Therapy System is a novel, first-of-its-kind FDA-designated breakthrough medical device to treat the population of mechanically ventilated patients who are difficult to wean from MV, an unmet medical need. Through the literature, it is expected that the proportion weaned in the Control group will be about 50% but could range from 40% to 70%. There is similar variation in the proportion of subjects who will die or withdraw life support prior to successful weaning. These estimates along with attrition and the effect size contribute to the final estimated sample size. The range provided in the protocol provides at least 80% power for expected combinations.

The total enrollment for randomized subjects will be 200 to 400 subjects based on a Bayesian group sequential design. One Roll-In subject is allowed per site; a second Roll-In subject is allowed if the first had unsuccessful Catheter placement or at the discretion of the Sponsor for additional training on the investigational device. The data from Roll-In subjects will be analyzed separately. The specifics regarding the sample size calculation for the adaptive design are included in a separate *RESCUE 3 Statistical Analysis Plan (CLN-0050)* to protect the RESCUE 3 study from operational bias. The Type I error is appropriately controlled, and the primary effectiveness endpoints have at least 85% power for anticipated effect sizes.

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1.9.7 Expected Duration of Subject Participation

Treatment Subjects:

- Withdrawal or death
- Unsuccessful placement of the Catheter – 48 hours after placement attempt or Catheter removal to maximum Day 32
- Successful wean/Unsuccessful wean/Transfer – to maximum Day 32

Control Subjects:

- Withdrawal or death
- Successful wean/Unsuccessful wean/Transfer – to maximum Day 32

Maximum study duration for any subject is 32 days.

Successfully weaned is defined as passing the protocol-specific Ventilator Liberation Trial (VLT), or removed from MV, and not returned to MV *within 48 hours.*

1.10 Procedures

Study processes, procedures and evaluations to be conducted are summarized in **Table 6** and described in detail in the sections that follow. All procedures and evaluations will be conducted for both Treatment and Control subjects except as noted in **Table 6** for device-specific procedures for Catheter placement and delivery of Lungpacer DPT. For the timing of evaluations, refer to the **Schedule of Events (Table 5).**

Table 6: Study Processes, Procedures and Evaluations by Study Group

Process	Study Group	Procedures
Informed Consent	Both	• Signature of subject or legally authorized representative (LAR) • Informed Consent can be obtained from a LAR up to 5 days prior to randomization to accommodate LAR availability; however, all tests/procedures required for enrollment must be completed within 2 days prior to randomization. Should the subject's condition change after the consent has been signed but before screening begins, the LAR should be contacted and any change in the subject's condition discussed before proceeding.
Screening	Both	• Informed Consent and at least one failed weaning attempt • Physical exam to include a systems assessment • Medical history up to the day of consent • Medications (that may impact respiratory function) • Vital signs • 12-lead ECG

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Process	Study Group	Procedures
Laboratory Tests	Both	• Blood chemistries: serum creatinine (Cr), sodium (Na), potassium (K), HCO_3, bilirubin, magnesium, phosphorus, calcium (Ca); • Arterial Blood Gas (required for SOFA) • Serum pregnancy test (unless surgically sterile or at least one year post-menopausal) to be performed prior to randomization
Enrollment and Randomization	Both	• Enrollment: o In Screening, and o Meets the Readiness-to-Wean criteria, and o Failed qualifying protocol-specific VLT, and o Meets all inclusion criteria, and o Does not satisfy any exclusion criteria. • Baseline RSBI/RASS/MIP are performed after consent and prior to randomization • Randomization: o Randomized 1:1 in an open-label assignment to Treatment or Control Note: Roll-In Subjects are not randomized; they follow all study processes, procedures and evaluations as for Treatment subjects.
Study Group Treatments	Control	• Standard of Care; no Catheter placement
	Treatment	• Standard of Care • Catheter placement: Refer to the Catheter IFUs. • Lungpacer DPT: Refer to the device IFUs. • Catheter removal: After successful weaning, prior to transfer to a facility outside the enrolling institution, or on Day 30; refer to the Catheter IFUs.
Effectiveness Evaluations	Both	• RSBI • RASS • MIP • Ventilator Liberation Trial (protocol-specific VLT)
Clinical Evaluations	Both	• SOFA is performed after consent but prior to randomization • Medication usage that affects the respiratory system
Additional Data Collection	Both	• The time to first successful VLT after randomization; • Cessations and re-instatements of mechanical ventilation; • Date of tracheotomy, if applicable; • Ventilator settings (PS, PEEP, RR, FiO_2, Ventilation Mode, V_T); • ICU admissions and discharges; • Hospital admission and discharges; • Mortality

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Process	Study Group	Procedures
Safety Evaluations and Safety Follow-Up Evaluations	Both	Safety Evaluations: • AEs and SAEs until withdrawal or death, until after placement attempt or until the Catheter removal, transfer, successful weaning, or unsuccessful weaning by Day 30. Safety Follow-up Evaluations: • Refer to Section 1.8.1.4.2, Safety Evaluations and Follow-up

1.10.1 Screening and Enrollment

A subject is in screening if:

- he/she or his/her legally authorized representative signed the informed consent form, and,
- he/she failed at least one weaning attempt.

A subject is enrolled and can be randomized if:

- he/she is in screening (i.e., informed consent has been signed and subject has failed at least one weaning attempt), and,
- he/she meets the Readiness-to-Wean criteria, and,
- he/she fails a qualifying protocol-specific VLT (conducted after providing informed consent and on a different calendar day than the previous failed weaning attempt[s]), and,
- he/she meets all inclusion criteria, and,
- he/she does not satisfy any exclusion criteria, and,
- he/she is not a Roll-In subject who is enrolled but not randomized.

A subject in screening is a screening failure if he/she:

- fails the initial Readiness-to-Wean criteria, or,
- passes the qualifying protocol-specific VLT, or,
- fails to meet all inclusion criteria, or
- meets one or more exclusion criteria.

Table 7 shows the enrollment requirements for at least one weaning attempt and one additional qualifying protocol-specific VLT.

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Table 7: Ventilator Liberation Trials: Enrollment Eligibility for Consented Subjects

Weaning Attempt	One Calendar Day from Weaning Attempt	Readiness-to-Wean Screen	Protocol-Specific VLT	Eligible
Fail	Elapsed	Pass	Fail	**Yes**
Fail	Elapsed	Fail	n/a	**No**
Fail	Elapsed	Pass	Not Performed	**No**
Fail	Elapsed	Pass	Pass	**No**
Pass	n/a	n/a	n/a	**No**

- Screening procedures should be completed within the 2-day period prior to randomization, excepting the pregnancy test as described in section 1.10.2.
- Should any of the diagnostic tests and procedures be obtained outside the window of acceptability, they should be *repeated before randomization* unless it may affect the safety of the subject.
- The investigator should review all available imaging studies for the subject being evaluated, to identify any anatomical abnormalities that would prevent proper Catheter insertion.
- Medication history should include the medications that affect the respiratory function at time of randomization.
- A de-identified screening log must be completed for all subjects evaluated or screened.

1.10.2 Laboratory Tests

After informed consent, laboratory tests will be performed during screening, but before randomization. They will be analyzed by local/hospital laboratories or hospital medical staff. Laboratory measurements are conducted as given in the **Schedule of Events (Table 5)**. If the subject is female, she must be either surgically sterile, be at least one year post-menopausal, or have a negative result on a serum pregnancy test after consent and prior to randomization.

1.10.3 Clinical Evaluations

Only study staff who have been trained on the conduct of respiratory measurements and clinical evaluations in the study protocol are allowed to administer the clinical evaluations. Only study staff who have been trained and qualified can conduct the RSBI and MIP evaluations.

The following clinical evaluations are conducted according to the **Schedule of Events (Table 5)**:

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- Sequential Organ Failure Assessment (SOFA)
  - The SOFA is a mortality prediction score that is based on the degree of dysfunction of 6 organ systems. The SOFA will be collected after consent but prior to randomization.
- Medication Check
  - Medications affecting respiratory function at randomization will be documented in the eCRF.
  - Whenever medications affecting respiratory function are instituted or stopped after randomization, they will be documented in the eCRF.
- Adverse Events
  - Adverse events and serious adverse events will be collected during the timeframes described in Section 1.8.1.4.2, Safety Evaluations and Follow-up**.**
  - Once a subject is transferred to a facility outside the enrolling institution, the investigator should attempt to obtain information on any SAEs that may have occurred and document these in the eCRF.

1.10.4 Randomization

All screening procedures must be completed, and the subject must be enrolled, before randomization can be triggered within in the EDC.

An *anticipated placement date* for Catheter insertion must be identified *prior to* subject randomization. The anticipated placement date for the Catheter should fall within 1 day of randomization. This date serves as Day 1 for subjects randomized to Control or Treatment.

Proper planning of the randomization is critical. The Catheter placement should be conducted within one day of randomization to allow for optimal therapy within the 30-day study period. Missing this date can occur only if *medically necessary,* the reason must be documented in the EDC, and it must be recorded as a protocol deviation.

For all subjects, to trigger randomization in the EDC, EDC entries must be made for: (1) the date of informed consent, (2) the anticipated placement date, and (3) confirmation of study eligibility criteria.

Randomization is 1:1 in an open-label assignment to Treatment or Control.

Roll-In Subjects:

An *anticipated placement date* must be identified for Roll-In subjects. However, Roll-In subjects will not be randomized but will receive all study procedures as for a Treatment subject. Day 1 for Roll-In subjects is the anticipated placement date. Where the protocol indicates completion of an item by randomization, it must be completed by Day 1 for Roll-In subjects.

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1.10.5 Catheter Placement and Removal

The subject is prepared for Catheter insertion in the same way as for insertion of a central venous catheter. The intended Catheter insertion route is percutaneously into the intended thoracic vein on the left side via standard Seldinger technique using ultrasound guidance as needed. The target placement of the Catheter tip is in the right side of the mediastinum in the superior vena cava (SVC) above its junction with the right atrium and parallel to the vessel wall, and its distal tip positioned at a level above either the azygous vein or the carina of the trachea, whichever is better visualized.

The AeroPace System/Catheter includes the ability to view an intravascular electrogram which can be used to monitor for appropriate placement of the Catheter distal tip at the level of the cavoatrial junction. Refer to the AeroPace Catheter Instructions for Use (650-0227, 650-0228) regarding use of the intravascular electrogram during catheter placement.

Refer to the Catheter Instructions for Use, which provide detailed step-by-step instructions for the intended use. In brief, in addition to device description, intended use and warnings and precautions, it provides the following procedural instructions:

- Pre- Catheter Insertion and Subject Assessment Activities
- Preparation for Catheter Insertion (e.g., sterile technique)
- Catheter Insertion Instructions
- Removal of the Catheter

See also **Section 1.6.3** for additional risk mitigation considerations for catheter placement.

1.10.5.1 *Catheter Insertion and Removal During the Treatment Period*

Treatment subjects will have the Catheter placed in accordance with the Catheter Instructions for Use on the anticipated placement date (Day 1). The Catheter must be removed by Day 30 of the study.

Unsuccessful placement is defined as (i) the Catheter never entered the intended thoracic vein on the left side, or, (ii) the Catheter **entered** the intended thoracic vein, but the diaphragm could not be stimulated, or, (iii) the Catheter positioning is not in accordance with the Catheter IFU.

- If the Catheter cannot be inserted into the subject and never entered the subject's blood vessel (e.g., anatomical issues) the subject should remain in the study for safety follow-up evaluation for 48 hours after the insertion attempt and then the subject should be withdrawn from the study.
- If the Catheter entered the subject's blood vessel but could not be properly placed (e.g., obstruction, improper positioning per IFU), and the Catheter was removed, if the investigator

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determines another Catheter could be placed, the subsequent placement must be performed within the 48 hours following the previous Catheter removal.

- If the Catheter entered the subject's blood vessel but could not be properly placed (e.g., obstruction, improper positioning per the IFU) and the Catheter was removed, and the investigator determined that another Catheter insertion is not merited, the subject should remain in the study for safety follow-up evaluation for the 48 hours following the Catheter removal, after which the subject should be withdrawn from the study.
- If the Catheter entered the subject's blood vessel and was properly placed but diaphragm recruitment was unsuccessful (e.g., diaphragm cannot be stimulated), the Catheter should be removed and the subject should remain in the study for safety follow-up evaluation for the 48 hours following the Catheter removal, after which the subject should be withdrawn from the study.
- If the Catheter is removed for any reason during the study and the investigator determines that another Catheter placement is safe and merited, the placement should be performed as soon as clinically possible following the removal of the prior Catheter.
- If a subject has successfully weaned from MV, the Catheter should be removed.

1.10.6 Lungpacer Diaphragm Pacing Therapy (DPT)

Lungpacer Diaphragm Pacing Therapy is delivered only while subjects are on mechanical ventilation.

Refer to the device *Instructions for Use,* which provide detailed step-by-step instructions for the intended use. In addition to device description, intended use, and warnings and precautions, it provides the following procedural instructions:

- Workflow/Buttons and Screens
- Device Set Up
- Mapping and Therapy

1.10.6.1 *Mapping*

To initiate Lungpacer DPT, ventilation settings should be adjusted, if possible, to allow the patient to take *spontaneous breaths*. Lungpacer DPT consists of Mapping and determination of Threshold Stimulation (Stim) Intensity, and delivery of Therapy Stimulation Sets at every session.

Mapping of left and right electrodes must be conducted prior to delivery of Lungpacer DPT at every session. This process identifies suitable electrode combinations that capture the left and right phrenic nerves and their corresponding threshold Stim Intensities (i.e., Stim Threshold), which are the minimum intensities that cause diaphragm contraction on the left and right sides. Electrode recruitment for phrenic nerve capture is manually determined by palpation of the diaphragm (i.e., contraction) and/or by observing deflection of the ventilator pressure waveform. The AeroPace

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System has the option to use breath detection to automatically identify the electrodes that capture the phrenic nerves during mapping. The Stim Threshold for the Therapy session is identified by manually delivering a series of single Stims starting at low Stim Intensity and increasing in increments until diaphragm contraction is observed. Stims should be delivered during the end-expiratory period, if clinically possible, to facilitate detection of diaphragm contractions by palpation. Using this process, the Stim Thresholds for the left and right electrodes are determined, which are shown on the Therapy Screen as Stim Intensities of 100%. The AeroPace System has the option to automatically determine the Stim Threshold for both left and right sides during Mapping.

Mapping must be conducted prior to each Therapy session. Although secured externally, the Catheter may change position within the vein thereby altering the position of the electrodes on the catheter relative to the phrenic nerves. Such movement may be due to changes in the subject's position or fluid status from one Therapy session to the next.

See the Instructions for Use for each system for details of the Mapping process.

1.10.6.2 *Therapy Delivery / Lungpacer DPT Sessions*

Upon successful completion of Mapping, the user will initiate delivery of Lungpacer DPT. Lungpacer DPT is modelled on classic muscle rehabilitation therapy, which initially consists of exercise at low weights and progresses to heavier weights as the muscle develops or recovers over time. In the same way, each Lungpacer DPT subject is advanced through the progressive diaphragm muscle training regime at his or her own rate, based on the subject's comfort and the investigator's clinical judgement. For every Lungpacer DPT session, the objective is to deliver stimulation at the highest Stim Intensity that is possible (as shown on the Therapy screen) for a given subject and to provide the longest Stim Duration (up to 1.2 seconds) that is safe and comfortable for the subject, and that is suitable for the ventilator settings. Step-by-step instructions for this process are provided in **Table 8**.

Vital signs and oxygen saturation will be monitored by the clinician during Lungpacer DPT. If the clinician administering the Therapy observes the oxygen saturation falling below an acceptable percentage and this is sustained, Lungpacer DPT should be stopped so the subject can be re-evaluated. Lungpacer DPT should be stopped and re-evaluated for cardiac rhythm change or any other undesired effects of stimulation such as superficial muscle twitch or brachial plexus recruitment. In such cases, see the system IFUs for how to reduce undesired effects of stimulation (650-0141, 650-0146, 650-0227, and 650-0228).

The complete process for a Lungpacer DPT session takes approximately 15-30 minutes to conduct. Additional time may be required for Mapping in patients for whom the Catheter or patient re-positioning is required. Lungpacer DPT is delivered in 6 sets with 10 stimulations/set, in 2 sessions during the day for a total of 120 stimulations per day as described in **Table 9**.

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Table 8: Lungpacer DPT Procedure Steps

Procedure Step	Notes and Instructions	
Ventilator Settings and Inspiration Duration	• Lungpacer DPT can be delivered using any mode of Continuous or Spontaneous Ventilation, meaning any ventilation mode that allows for the patient to take spontaneous breaths, for example Pressure Support or Volume Control. These modes allow the patient to have a longer inspiration duration. • If clinically possible, adjust the ventilation settings such that the subject has an inspiration duration of approximately 1.2 seconds. This allows the Stim Duration, the length of time over which a stimulation is delivered, to be set at the maximum of 1.2 seconds. This results in a stimulated diaphragm contraction of approximately 1.2 seconds. • If the subject is on Continuous *Mandatory* Ventilation, the stimulations should be delivered in synchrony with mechanical ventilation. NOTE: Ventilator modes where pressure is maintained constant by allowing flow to be constantly changing can lead to higher volumes due to negative pressure induced by the Lungpacer DPT.	
Mapping (Electrode Selection and Stimulation Thresholds)	During Mapping, the control unit is used to select suitable electrode combinations on the Catheter to be used during Therapy. These electrodes are in close proximity to the left and right phrenic nerves. Stimulation Thresholds, which are the minimum, "baseline" amounts of energy needed to stimulate the nerves, are also determined in Mapping. Mapping will be conducted automatically when using the Auto Mode of the AeroPace System. • The Catheter position within the vein may change between DPT sessions which may alter electrode positioning relative to the phrenic nerves; therefore, Mapping must be conducted at the start of *every DPT session*. Mapping is not necessary for a Make-up DPT session (see section 1.10.6.4), that is conducted only after a brief pause from the day's first DPT session. • Mapping should be conducted according to the device Instructions for Use. • DPT may be delivered when only one hemidiaphragm is successfully mapped, if clinically necessary. Otherwise, both hemidiaphragms should be mapped so that DPT can be delivered to both hemidiaphragms.	
Deliver DPT	• The goal of DPT is to deliver stimulation at the highest Stim Intensity and for the longest Stim Duration that is comfortable for the subject, and that is suitable for the ventilator settings. The right and left Stim Intensities are increased incrementally by the operator during the initial DPT stimulations to reach the maximum possible Stim Intensity, or Therapy Level, based on patient comfort. • Deliver the first few stimulations at the baseline Stim Threshold established in Mapping. Assess for patient comfort and increase the intensities for each side as needed. Repeat until the maximum intensities for each side are reached which are the Therapy Levels	

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Procedure Step	Notes and Instructions	
	to be used for that session. Deliver the remainder of the session's 60 stimulations at this level of intensity, if patient comfort permits. • If the ventilator is set to Continuous Spontaneous Ventilation, a breath can be initiated by delivering a stimulation . The ventilator will trigger a breath when the stimulation causes the diaphragm to contract. If the ventilator is set to Continuous Mandatory Ventilation, allow the ventilator to initiate a breath. Once the breath has been initiated by the ventilator, manually deliver the stimulation as quickly as possible during the inspiration period. This will be conducted automatically when using the Auto Mode of the AeroPace System. • If not already adjusted, increase the Stim Duration to as close to 1.2 seconds as clinically possible. This allows the Stim Duration, the length of time over which a stimulation is delivered and the diaphragm contraction, to be maximized. • A single Therapy Session is complete when 6 sets of 10 Stims are successfully delivered. The patient may rest between sets as needed.	

Table 9: Lungpacer Diaphragm Pacing Therapy: Treatment Parameters

LUNGPACER DPT	SESSIONS	SETS	STIMULATIONS
• Daily • 2 sessions/day • 6 sets/session • 10 stimulations/set • Total = 120 stimulations per day	**2** • At least 3 hours apart from end of first session to start of second session, if possible • 6 sets/session	**6** • Rest period between sets as needed • 10 stimulations/set	**10** • Observed by diaphragm contraction and/or by the ventilator pressure waveform

1.10.6.3 *Other Equipment in Use During Mapping and Therapy*

- Ventilator

  The therapy sessions can be conducted in conjunction with all ventilators.

  - Therapy sessions can be conducted with multiple ventilator modes, which will be documented in the eCRF.

- Heart Rate Monitor

  The subject's heart rate should be monitored during Lungpacer DPT as part of ICU Standard of Care. Lungpacer DPT is not expected to affect the subject's heart rate or rhythm. If heart rhythm changes occur, consider adjusting the position of the subject or the position of the Catheter to alleviate the change in rhythm.

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If changes in heart rate or rhythm occur or persist, the therapy may be halted at the investigator's discretion.

1.10.6.4 *Lungpacer DPT Sessions Through Day 30*

Lungpacer DPT should be conducted twice daily for a maximum of 30 days until the subject passes the VLT, is removed from MV, the Catheter is removed, or the subject is withdrawn, is deceased or is transferred to an outside facility. Maximum exposure to Lungpacer DPT stimulation is expected to be an average of 120 stimulations x 30 days = 3600 stimulations.

Lungpacer Diaphragm Pacing Therapy (DPT) should be conducted:

- twice daily while the subject is on MV from Day 1 until Day 30;
- prior to the daily VLT for at least one of the two daily sessions;
- at least 3 hours apart from the end of the first DPT session to the beginning of the second DPT session, if possible;
- following a failed VLT;
- following a successful VLT without a successful wean (resumes MV in <48 hours).

Lungpacer DPT should <u>not</u> be conducted:

- during a VLT;
- during the 48-hour window after a successful VLT;
- after successful weaning.

There may be study days when it is not clinically feasible to conduct two therapy sessions separated by 3 hours, e.g., when the subject is undergoing a scheduled procedure, or is undergoing a long VLT. In such cases, consider:

- Conducting the first therapy session of 60 stimulations in the morning, assessing the subject's tolerance to the therapy. If the session was well tolerated, after a brief pause (e.g., 5-10 minutes) proceed with providing an additional 60 stimulations. This will 'make up' for a session missed on a previous day. Mapping is not necessary for a "make-up" DPT session, since the sessions occur in close proximity. Conduct the scheduled afternoon session of 60 stimulations as planned. NOTE: 'Make up' DPT sessions should be completed at the beginning of the next calendar day, and if this is not achieved, the session will simply be 'missed' and documented as a protocol deviation.
- If there are circumstances when the clinician knows in advance that only one DPT session can be conducted on a given day (e.g., due to lack of research resources), conduct the first DPT session of 60 stimulations, assess the subject's tolerance to the therapy and after a brief

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pause (e.g., 5-10 minutes) proceed with providing an additional 60 stimulations to assure an average of 120 stimulations are provided daily. However, every attempt should be made to separate the treatment sessions by 3 hours, if at all possible.

1.10.7 Weaning from Mechanical Ventilation

Weaning from mechanical ventilation is a two-step process:

Step 1: Successful VLT

A Ventilator Liberation Trial (VLT) determines whether a subject, after removal from MV, can breathe on his/her own for a specific period of time that predicts a high likelihood for successful weaning. When the protocol-specific VLT is successful, the subject can begin a 48-hour weaning period as defined in Step 2.

Removal from MV due to physician-directed extubation, self-extubation, or a successful physician-directed VLT, can also be used to initiate the 48-hour weaning period in Step 2.

Step 2: Successfully Weaned

Successfully weaned is defined as passing the protocol-specific Ventilator Liberation Trial (VLT), or removed from MV, and not returned to mechanical ventilation *within 48 hours*.

These steps are described in more detail in below.

1.10.7.1 *Successful VLT*

The protocol-specific VLT should be conducted according to *Readiness-to-Wean and VLT Protocol (CLN-0039)*. This protocol-specific VLT replaces the daily physician-directed weaning trial. **No more than one additional weaning trial can be implemented per day for both study groups**.

- Subjects must satisfy the Readiness-to-Wean criteria prior to conducting the VLT.
- Subjects must pass both the Readiness-to-Wean and the VLT to qualify as having had a successful VLT (**Table 10**).
- The *required time period* during the VLT to PASS the VLT is:
    - For subjects with nasotracheal or endotracheal tube: **30 to 120 minutes**
    - For subjects with tracheostomy: **12 to 18 hours**
- Do not conduct Lungpacer DPT during the VLT.

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Table 10: Ventilator Liberation Trials to Qualify for a "Successful VLT"

Type of VLT	Readiness-to-Wean Result	VLT Result	Off MV
Protocol-Specific VLT	Fail	n/a	No
	Pass	Fail	No
	Pass	Pass	Yes

- If the subject passed both the Readiness-to-Wean screen and the protocol-specific VLT for the required time period, he/she has had a successful VLT and **should remain OFF MV** to evaluate his/her potential of being successfully weaned.
    - In the event of removal from MV due to physician-directed extubation, self-extubation or a successful physician-directed VLT, the 48-hour weaning period can be initiated for the subject to determine successful weaning. For a physician-directed extubation for which a VLT was not conducted, the ventilator mode settings prior to removal from MV should be recorded.
    - After enrollment into the study, in the event that the subject has passed the Readiness-to-Wean and the VLT criteria but the physician deems their medical condition is such that they cannot be removed from MV, the physician should document this as a protocol deviation and document the reasoning in the medical record. In these instances, the MIP assessment should not be conducted.

1.10.7.2 *Procedures after a Successful VLT*

If a subject has a successful VLT, the following efficacy evaluations must be conducted.

- RSBI/RASS/MIP
    - MIP should not be done if the subject has a successful VLT, but the physician deems that the subject cannot be removed from MV (see section 1.10.7.1)
    - For subjects with oral or nasal endotracheal tube, do not remove the endotracheal tube before performing the RSBI and MIP

1.10.7.3 *Successful Weaning*

"Successfully weaned" is defined as passing the protocol-specific Ventilator Liberation Trial (VLT), or removed from MV, and not returned to MV within 48 hours.

- Time 0 to start the 48-hour weaning period begins immediately after passing the protocol-specific VLT or removal from MV.

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- To be considered "successfully weaned", subjects must be breathing spontaneously for 48 hours consecutively, after having a successful VLT or removal from MV.

Note: "Removed from MV" includes removal from mechanical ventilation support without being physically removed from the mechanical ventilator. E.g., if a subject passes their VLT with ventilator settings of 5/0 (Pressure Support of 5 cmH_2O; PEEP 0 cmH_2O) and are then kept at this setting or are moved to a tracheostomy collar for the 48-hour weaning period, this constitutes removal from ventilation support and meets the definition of "removed from MV".

1.10.7.4 *Weaning Failure*

If the subject is **NOT** able to spontaneously breathe without mechanical ventilation for the entire consecutive 48-hour period, a **weaning failure** has occurred.

Subjects with a weaning failure should be treated with Standard of Care. For Treatment subjects, Lungpacer DPT should be re-initiated until successful weaning or study exit.

1.10.7.5 *Use of Non-Invasive Ventilation (NIV) or High Flow Oxygen*

Non-Invasive Ventilation (NIV) or high flow oxygen can be used to prevent post-extubation respiratory failure for subjects who pass a VLT or who were removed from MV. A decision to utilize NIV or high flow oxygen must be documented in the medical chart.

1.10.7.6 *Night-time or "Rest" Invasive Mechanical Ventilation*

Subjects who have passed a VLT, or have been removed from MV, and are in the 48-hour weaning period *should not* be placed back on invasive MV at night or to briefly rest. If this occurs, they will be considered to have re-initiated MV and this will be recorded as a **weaning failure**.

1.10.7.7 *Procedures After Successful Weaning*

If a subject has successfully weaned, the following activities and evaluations must be conducted.

- Catheter removal for Treatment subjects (see Section 1.10.8, Discontinuation of Therapy and Catheter Removal);
- Safety Follow-up Evaluations (see Section 1.8.1.4.2, Safety Evaluations and Safety Follow-up Evaluations).

1.10.8 Discontinuation of Therapy and Catheter Removal

For subject discontinuation from Lungpacer DPT, the following requirements for the Catheter removal apply:

- The Catheter must remain in place until the subject has successfully weaned to reduce the need/risk of re-insertion if the subject fails to wean, unless removal is medically necessary, but must be removed by Day 30.

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- The Catheter must be removed as soon as practically possible but within 24 hours of a subject being successfully weaned.
- After the Catheter is removed, safety follow-up evaluations should be conducted as described in Section 1.8.1.4.2.

When the Catheter removal is to take place, the following activities are conducted in accordance with the Catheter Instructions for Use

- The Catheter is removed from the subject using the same procedure as removal of a central venous catheter,
- Closure of the access site is achieved by the institution's Standard of Care, as for closure of a central venous catheter access site.

1.10.9 Type and Duration of Follow-Up

1.10.9.1 *Safety and Observational Data Follow-up*

- Safety Follow-up Evaluations are conducted as follows:
  - Treatment Subjects:
    - Withdrawal or death – no follow-up
    - Unsuccessful placement of the Catheter – SAEs for 48-hours after placement attempt or the Catheter removal
    - Successful wean/Unsuccessful wean/Transfer – SAEs to Day 30, or 48 hours after the 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*
- Other data collection is continued through Day 30 and the completion of safety follow-up evaluations for the following outcomes, as applicable:
  - The time to first successful VLT after randomization;
  - Cessation and re-instatement of mechanical ventilation;
  - Date of tracheotomy, if applicable;
  - Ventilator settings daily (last available measure);
  - ICU discharges and re-admissions;

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- Hospital discharges and re-admissions; and
- Mortality.

1.10.9.2 ***Follow-Up for Subjects Transferred to Facility Outside the Enrolling Institution***

If at all possible, study subjects should remain at the investigational site for the duration of the study or, at a minimum, until successful weaning. Treatment with the Lungpacer DPTS should be conducted for the longest possible duration or until successful weaning, which can only be accomplished at the investigational site.

If it is necessary to transfer a subject, he/she should not be transferred until successfully weaned or until completing the entire duration of the study, if not successfully weaned. However, if it becomes necessary to transfer a study subject to an outside facility, such as an ICU outside the enrolling institution, an outside rehabilitation unit, or a long-term acute care facility within the 30-day study period, **follow-up information should be obtained for all transferred subjects**.

A member of the research team should contact the outside facility and request follow-up information for the subject as specified below in Section 1.10.9.2.2, Post Transfer Follow-up Data Collection.

1.10.9.2.1 **Transfer Procedures and Catheter Removal**

- Control subjects can be transferred after the following study procedures are completed:
  - RSBI/RASS/MIP; and
  - a protocol-specific VLT.
- Treatment (Lungpacer DPT) subjects can be transferred after the following study procedures are completed:
  - RSBI/RASS/MIP;
  - a protocol-specific VLT;
  - Catheter removal and documentation on the CRF;
  - 48-hour safety follow-up evaluation (see Section 1.10.9.1) after Catheter removal; and
  - Treatment Subject Questionnaire.

1.10.9.2.2 **Post-Transfer Follow-Up Data Collection**

Every attempt should be made to obtain the following information from the outside facility to which the patient is transferred.

- Date and time of removal from MV or confirmation that subject was NOT removed from MV

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- Return to MV date and time, if applicable
- Serious Adverse Events
- ICU discharges and re-admissions
- Hospital discharges and re-admissions
- Mortality
- Date of study exit (e.g., Day 30)
- Exit or 30-Day Case Report Form must be completed by the enrolling center using *RESCUE 3 30-Day (Study Exit) Follow-up Worksheet (CLN-0040).*

If the subject is transferred to a facility outside the enrolling institution but returns to the enrolling site within 30 days of randomization, all study procedures and assessments should be completed as for an enrolled subject.

1.10.10 Study Evaluations

1.10.10.1 *Readiness to Wean*

The protocol-specific Readiness-to-Wean screen determines the readiness of a subject to participate in a VLT. The subject must pass this test prior to conducting a VLT.

The protocol-specific Readiness-to-Wean screen requires a clinical assessment using objective measurements as follows:

- Clinical Assessment
  - Adequate cough/reflex when suctioning,
  - Absence of severe tracheobronchial secretions after suctioning, if needed,
  - Subject is over the hyper-acute phase of the critical illness (screening only).

- Objective Measurements
  - Able to follow one-step commands. If on sedation, assess during the daily sedation interruption (i.e., sedation vacation/holiday),
  - Hemodynamic stability,
  - Pressors: no more than one (e.g., norepinephrine ≤10 μg /min; phenylephrine ≤100 μg /min),
  - Stable respiratory status:
    - FiO_2 ≤0.50
    - SpO_2 >90%
    - PEEP ≤8 cm H_2O

- If the patient fails the Readiness-to-Wean screen during **screening** (i.e., prior to enrollment), the patient does not satisfy one of the study inclusion criteria and cannot be enrolled into the study.

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- If the subject fails the Readiness-to-Wean screen after he/she has been enrolled in the study, a protocol-specific VLT cannot be conducted. The clinician should continue to follow study procedures and repeat the Readiness-to Wean screen the following day.

1.10.10.2 *Ventilator Liberation Trial (VLT)*

The protocol-specific VLT provides a standardized method to ensure common criteria for weaning are used across all study sites. Refer to *Readiness-to-Wean and VLT Protocol (CLN-0039)*.

Consent must be obtained before performing the qualifying protocol-specific VLT. The qualifying protocol-specific VLT must be used to determine whether a patient can be included in the study, i.e., the patient must fail the protocol-specific VLT to be enrolled.

After enrollment in the study, the protocol-specific VLT should replace the institution's daily VLT. The protocol-specific VLT is conducted daily and the site can conduct no more than one additional VLT on the same calendar day.

After the subject has been randomized, the protocol-specific VLT requires the following:

- RSBI, RASS and MIP measurements should be completed prior to conducting the VLT, if possible.
- Lungpacer DPT sessions for Treatment subjects must be completed prior to initiating the VLT.
- Subjects must pass the Readiness-to-Wean screen before initiating the VLT.
- VLTs must be conducted daily from Day 1 to study exit as tolerated, while on MV and while in the enrolling institution.
- VLTs should be conducted on a Pressure Support of 0 cm H_2O (up to 5 cm H_2O at physician's discretion); PEEP 0 cm H_2O.
- Subjects with a nasotracheal or endotracheal tube must breathe without mechanical ventilation for 30 to 120 minutes to pass the VLT; subjects with a tracheostomy must breathe without mechanical ventilation for 12 to 18 hours to pass the VLT (Jubran, 2013).
- Specific VLT failure criteria are specified in the VLT protocol.

1.10.10.3 *Rapid Shallow Breathing Index*

The Rapid Shallow Breathing Index (RSBI) is an effective method for evaluation of respiratory function as measured by the ratio of the Respiratory Rate to Tidal Volume in Liters (Example: 24/0.500 = 48). The RSBI measurement is conducted according to *RSBI/RASS/MIP Protocol (CLN-0037)*.

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RSBI measurements will be conducted according to the **Schedule of Events (Table 5)** as follows:

- At least 5 minutes prior to the RASS/MIP measurement.
- With a respiratory rate obtained when the subject is on PS 0 cm H_2O/PEEP 0 cm H_2O for 60 seconds.
- With the Tidal Volume measured at the 60-second time point.
- If the subject cannot tolerate the PS 0 cm H_2O/PEEP 0 cm H_2O setting during the RSBI measurement for 60 seconds, this must be documented in the medical record (no protocol deviation).
- First RSBI measurement must be performed after the subject is consented, but prior to randomization.
- Every 7 days ± 1 day during mechanical ventilation.
- Prior to transfer to an outside facility, if before Day 30.
- Prior to DPT, for Treatment subjects.
- Prior to the daily VLT on days when required.
- At study exit, if on mechanical ventilation.

1.10.10.4 *RASS*

The Richmond Agitation and Sedation Scale (RASS) is a validated and reliable method to assess a patient's level of sedation in the intensive care unit. The RASS can be used in all hospitalized patients to describe their level of alertness or agitation.

1.10.10.5 *Maximal Inspiratory Pressure*

Maximal Inspiratory Pressure (MIP) is an effective method for evaluation of respiratory strength (Caruso P, 1999). Although volitional, with proper training and adherence to procedures, MIP data can be collected reproducibly (Martin, 2014; Supinski, 2016). MIP improvement over time has been shown to be indicative of future weaning success (Martin, 2014; Vorona 2018). The MIP measurement must be conducted according to *RSBI/RASS/MIP Protocol (CLN-0037),* to standardize this method across all study sites.

RASS and MIP measurements will be conducted according to the **Schedule of Events Table 5** and conducted as follows:

- ≥5 minutes after the RSBI measurement.

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- RASS is to be completed and passed just prior to conducting the MIP.
- First RASS/MIP measurement must be performed after the subject is consented, but prior to randomization.
- Every 7 days ± 1 day during mechanical ventilation.
- Prior to transfer to an outside facility, if before Day 30.
- Prior to DPT, for Treatment subjects.
- Prior to the daily VLT on days when required.
- At study exit, if on mechanical ventilation.

A small number of designated study personnel will be responsible for conducting the Maximal Inspiratory Pressure measurements and will undergo training and qualification for conducting the RSBI/RASS/MIP protocol.

1.10.10.6 *Discomfort Scale (Pain), Lungpacer DPT Sensation and DPT Experience Questionnaire for Treatment Subjects*

Timing of the Treatment subject discomfort/pain evaluation, Lungpacer DPT discomfort/sensation evaluation and the Treatment Subject Questionnaire evaluating the Lungpacer DPT experience are conducted as follows (refer to the **Schedule of Events** in **Table 5**):

- Discomfort/pain will be assessed using the standard *Visual Analogue Scale (CLN-0030)* at the beginning and end of each Lungpacer DPT session.
- Subject discomfort and sensation are evaluated at the end of each Lungpacer DPT session using the *Stimulation Discomfort and Sensation Tool (CLN-0030).*
- *Treatment Subject Questionnaire (CLN-0041)* is conducted after Catheter removal at study exit or prior to transfer, whichever comes first.

1.11 Monitoring Plan

The study will be monitored in compliance with EN ISO 14155, 21 CFR Part 812, ICH GCP Guidelines (E6 (R2) Section 5) and any other applicable local or national regulations.

The Sponsor's clinical representatives or contracted clinical monitors will be responsible for the monitoring of the study which is detailed in a separate monitoring plan.

1.11.1 Monitoring Visits and Audits

The Sponsor or a representative of the Sponsor (including clinical representatives and contracted clinical monitors with designated monitoring and/or auditing roles and experience) may visit the

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institution prior to initiating the study and will visit periodically thereafter to monitor acceptability of facilities, the agreement between eCRF entries and original source documentation, adherence to the protocol, Good Clinical Practice (GCP), and to applicable local regulations, and the maintenance of adequate clinical records. The Sponsor or representatives of the Sponsor with monitoring roles will have access to subject study records which include demographic and medical admissions data, medication sheets, laboratory data including imaging, study worksheets and other source documentation. Sponsor clinical representatives may have access to these study records to assist the site clinical staff in conducting study procedures.

The first monitoring visit will occur within one month of subject enrollment. The frequency of other monitoring visits will depend on subject enrollment. Once the study has been completed or terminated, a close-out or termination visit will be made. At the Sponsor's discretion, sites may be closed prior to study completion, if necessary, e.g., due to lack of enrollment. The investigator will cooperate with the Sponsor's representative(s) for the review and verification of all eCRFs, study supplies and inventory records, and any additional records requested for review.

The Sponsor or Sponsor's contracted clinical monitors may conduct audits at the investigational site(s). Audits may include, but are not limited to, device supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

1.11.2 Source Data Monitoring

All information contained in a subject's eCRF must have corresponding source documentation. This source documentation includes, but is not limited to, notes taken at subject visits recording the date of the visit, vital signs, physical findings, adverse events, concomitant medications, laboratory reports, hospital records, worksheets, ventilator data, imaging data, electronic data collection devices and clinic records.

The eCRF will not be considered a source document. Source document worksheets will be developed for data that does not exist anywhere in the EMR or medical chart such as DPT sessions or protocol-specific VLT procedures. Source data verification will be performed by means of intermittent on-site and/or remote monitoring. Details will be provided in a separate monitoring plan.

The records of the study may be subject to audit by Sponsor representatives (Clinical, Quality Assurance or designee) or by government regulatory authorities (e.g., US Food and Drug Administration). The investigator agrees to allow access to the required subject records in the event of such an audit.

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2 STATISTICAL CONSIDERATIONS

2.1 Statistical Design, Method and Analytical Procedures

2.1.1 General Statistical Design

The RESCUE 3 clinical investigation is an open-label, multi-center, adaptive, randomized controlled trial (RCT) to demonstrate the safety and effectiveness of the Lungpacer DPTS (and standard of care) as compared to Control (standard of care only) in patients aged 18 years or older who are receiving mechanical ventilation. Subjects will have received mechanical ventilation for ≥96 hours (4 days) and failed at least two weaning attempts.

Patients who may not benefit from Lungpacer DPT, including patients with weaning failure due to hypervolemia, neuromuscular paralysis, current sepsis, hemodynamic instability and certain respiratory or cardiac disorders will be excluded from RESCUE 3. Similarly, patients with inspiratory muscle strength greater than (absolute) 50 cm H_2O, as measured by Maximal Inspiratory Pressure (MIP), will be excluded; patients who have received invasive mechanical ventilation for >90 days will be excluded.

The RCT will randomize a minimum of 200 subjects or up to 400 subjects at a maximum of 80 investigational sites in the United States, Europe and other Tier 1 countries. This subject number includes a 15% expected study attrition rate. Randomized subjects will be randomized 1:1 blocked by investigational site to Treatment or Control. No more than 25% of the randomized subjects can be enrolled at any given site and at least 20% of the randomized subjects will be enrolled in the United States by the end of Phase 2 of the study.

Sites may choose to enroll 1 Roll-In subject to obtain experience with the investigational device; a second Roll-In subject may be enrolled if the first Catheter placement was unsuccessful or at the discretion of the Sponsor for additional training on the investigational device. Subjects will be designated as Roll-In subjects prospectively and will not be randomized. All Roll-In subjects will receive Treatment and standard of care. Data will be collected for Roll-In subjects as collected for randomized Treatment subjects and analyzed separately from the randomized study population.

The adaptive study design allows for conduct of the study in two phases:

Phase 1: Interim analyses will occur at N=150 and N=200 subjects with the opportunity to complete. Success in Phase 1 will be measured by a statistically significant p-value on MIP (adjusted for the two-look design) and, simultaneously, a sufficiently high conditional power for success on the weaning endpoint.

Phase 2: Interim analyses will occur at N=200, 250, 300, 350, 400 (the maximal sample size). Success in Phase 2 will be measured by a sufficiently high posterior probability of superiority of Lungpacer DPTS compared to Control.

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The primary objective of this randomized, controlled, open-label, adaptive multi-center clinical trial is to determine the safety and effectiveness of the Lungpacer DPTS plus Standard of Care to successfully wean subjects from mechanical ventilation, by study Day 30, as compared to subjects randomized to Standard of Care alone.

The primary effectiveness objectives will include:

1) To prove that the cumulative incidence for successful weaning by Day 30 for subjects randomized to Treatment is superior to that in subjects randomized to Control, and,

2) To prove that mean improvement in inspiratory muscle strength, as shown by the change in Maximal Inspiratory Pressure (MIP) from randomization to last available measure, in subjects randomized to Treatment is superior to that in subjects randomized to Control.

The primary safety objective is to characterize the adverse event profile (i.e., assessment of adverse events) in subjects randomized to Treatment as compared to subjects randomized to Control to support an observed consistent risk profile between groups Adverse events and incidence rates will be summarized by system organ class and lower level term.

Secondary endpoints are listed in Section 1.7.1.3.

2.1.2 Analysis Groups

The Intent-to-Treat (ITT) population is defined as all subjects who were randomized, with study group defined by the randomization.

The modified Intent-to-Treat (mITT) population is a subset of the ITT population for the Treatment group and requires successful placement of the Catheter. Successful placement is defined as insertion of the Catheter into the intended thoracic vein (left subclavian or left jugular), positioned according to the Catheter Instructions for Use, and the diaphragm was stimulated. Subjects with unsuccessful placement are included in the ITT group but not the mITT group. The mITT and ITT groups are the same for Control subjects.

The per-protocol population (PP) is a subset of the mITT population and is defined by completion of at least 50% of the protocol-required number of stimulations (Stims) in at least one phrenic nerve for those subjects randomized to Treatment without a major protocol deviation that precludes efficacy evaluation, and who have observed data for evaluation of the primary effectiveness endpoint. The sidedness of the phrenic nerve stimulation can change from left to right or occur in both phrenic nerves. Major protocol deviations include major inclusion/exclusion criteria deviations or major protocol deviations that would render the data collected for the subject difficult to interpret. The criterion for a deviation meeting the classification of “major” will be reviewed and determined by an independent designee.

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Roll-In Subjects: See **Definitions** section. Data for these subjects will be collected as required for subjects randomized to the Treatment group but the results will be reported separately.

2.1.3 Analytic Procedures

Descriptive statistics for continuous variables will include the number of observations, mean, standard deviation, minimum, median and maximum. Descriptive statistics for categorical variables will include the number and percent in each category out of the total number of observed responses. Results will be considered statistically significant if the two-sided p-value is <0.05, unless otherwise specified below.

When the arithmetic mean is found not to be an appropriate measure of central tendency, alternative statistics will be considered (e.g., median, interquartile range). When the distribution of a variable does not support the use of parametric statistics, nonparametric approaches or data transformations may be implemented. If data transformations are used, they will be specified in the final clinical report.

2.2 Sample Size, Level of Significance and Power of the Clinical Investigation

The Lungpacer Diaphragm Pacing Therapy System is a novel, first-of-its-kind breakthrough device intended to improve inspiratory muscle strength and weaning success in difficult to wean patients on mechanical ventilation. Through the literature, it is expected that the proportion weaned in the Control group will be about 50% but could range from 40% to 70%. There is similar variation in the proportion of subjects who will die or withdraw life support prior to successful weaning. These estimates along with attrition and the effect size contribute to the final estimated sample size. The range provided in the protocol provides approximately 85% power for expected combinations. Each phase uses a group sequential design (frequentist for the MIP endpoint and Bayesian for weaning success).

Specifics regarding the adaptive design are summarized below and described in detail in a the *RESCUE 3 Statistical Analysis Plan (SAP, CLN-0050).* The design includes borrowing an effective sample size of 64 patients from the previously completed RESCUE 2 study, described in detail in the RESCUE 3 SAP.

2.3 Attrition Rates

Up to fifteen percent (15%) of randomized subjects will not have observed data for primary effectiveness endpoints.

2.4 Pass/Fail Criteria to be Applied to the Results of the Clinical Investigation

The pass/fail criteria are described in detail in *RESCUE 3 Statistical Analysis Plan (CLN-0050)*.

2.5 Assessment of Comparability of Randomized Groups and Evaluation for Pooling of Data

2.5.1 Demographic/Baseline Characteristics and Protocol Administration

Demographic and baseline characteristics will be summarized by randomized group. Categorical variables will be summarized by counts and percentages. Continuous variables will be summarized by n, mean, standard deviation (SD), median, minimum, and maximum. Subject follow-up and early

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discontinuation will be summarized along with the reason for early discontinuation by randomized group. Protocol deviations will be collected and summarized by randomized group.

Summary tables describing the study population will be produced using subjects in the ITT and mITT populations by randomized group. The randomized groups will be compared at time of randomization with respect to the following parameters to assess their comparability: age, gender, race/ethnicity, BMI, Maximal Inspiratory Pressure (MIP), hours on mechanical ventilation before randomization, primary reason for mechanical ventilation, SOFA score at randomization, presence of tracheostomy tube at randomization, and history of COPD. Should additional important parameters be identified prior to the analysis, they will be evaluated in the same manner. Any of the variables that are significant at a two-sided α=0.05 will be evaluated as covariates or strata variables in the model for the primary effectiveness analysis as an additional or supporting analysis to the primary effectiveness endpoint. Continuous variables will be evaluated both as stratification variables by dichotomizing the subjects into two groups based on the median or other appropriate value and as continuous variables in the statistical models.

2.5.2 Pooling of Data for Primary Effectiveness Endpoints

For each of the primary effectiveness endpoints, pooling will be evaluated. Pooling will be evaluated for investigational centers, Lungpacer DPTS device model (Keystone System/LIVE Catheter and AeroPace System/Catheter), and geography (US, OUS). Investigational centers with less than 10 randomized subjects will be combined for this purpose.

The statistical model for the improvement in inspiratory muscle strength (as shown by improvement in MIP) comparison will be an analysis of variance model. Two models will be fit to the data, one for each pooling factor. Each model will include the dependent variable change in MIP and independent variables to include a variable for the fixed effect of pooling factor and the interaction between the pooling factor and randomized group in the observed mITT population. If the interaction term for investigational center and randomized group is statistically significant at α=0.15, a random investigational center variable will be included in the model to incorporate the additional variability in the effect size for investigational centers as an additional analysis to the primary effectiveness analysis. If the interaction term between geography and randomized group is statistically significant at α=0.15, the treatment effect will be summarized for each subgroup determined by geography. Device model will be evaluated in the same manner as geography. It is important to note that the study is not powered to demonstrate superiority in MIP improvement within subgroups defined by geography or device model and, therefore, it is not an expectation that superiority in improvement in MIP will be statistically significant within the subgroups. If none of the interaction terms are statistically significant, the data will be pooled for analysis.

For the Phase 2 primary effectiveness endpoint of successful weaning, additional sensitivity analysis will be performed in addition to the Bayesian borrowing analysis. In these analyses, a random effect

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for study center will be included in the specification of the log hazard. The treatment effect will be summarized for each subgroup determined by geography (US vs. OUS) and by device model. It is important to note that the study is not powered to demonstrate superiority in proportion weaned within subgroups defined by geography or device model and therefore it is not an expectation that superiority in proportion weaned will be statistically significant within the subgroups.

2.6 Endpoints, Outcomes and Statisticial Analyses

2.6.1 Primary Effectiveness - Change in Maximal Inspiratory Pressure (MIP)

Objective: To prove that mean improvement in inspiratory muscle strength as shown by the change in Maximal Inspiratory Pressure (MIP) from randomization to last available measure in subjects randomized to Treatment is superior to that in subjects randomized to Control.

Subjects Included in Analysis: All mITT subjects will be included in the analysis.

Endpoint: Change in MIP as measured at randomization and last available measure.

Hypothesis:

H_0: The mean change in MIP from randomization to last available measure in subjects randomized to Treatment is the same as that in subjects randomized to Control, $\mu_T = \mu_C$

H_1: The mean change in MIP from randomization to last available measure in subjects randomized to Treatment is superior to that in subjects randomized to Control, $\mu_T > \mu_C$

Sample Size Rationale: Change in MIP observed in RESCUE 1 was 13.9 cm H_2O ± 20.6 cm H_2O in N=9 subjects. Martin et al. (2011) showed that the SHAM group's pre- to post-training MIP change was not significant (-43.5 ± 17.5 cm H_2O vs. -45.1 ± 19.5 cm H_2O, p=0.39) while the IMST group's MIP increased (-44.4 ± 18.4 cm H_2O vs. -54.1 ± 17.8 cm H_2O, p<0.0001). Those results correspond to an average increase in absolute value for MIP of 1.6 cm H_2O for the SHAM group and 9.7 cm H_2O for the IMST group, for a mean difference between IMST and SHAM of 8.1 cm H_2O. A recent meta-analysis (Vorona, 2018) of inspiratory muscle rehabilitation in critically ill adults found a mean difference in improvement from baseline to end of treatment between IMST and Control of 6.22 cm H_2O (95% CI: 4.71, 7.72) in N=15 randomized controlled trials. The same meta-analysis found in N=3 trials *without* high of risk of bias and that employed rigorous techniques for the measurement of MIP, a mean difference of 9.49 cm H_2O (95% CI: 7.04, 11.95) was reported.

Based on the results of IMST studies, a mean difference of approximately 10 cm H_2O in change from baseline MIP for Treatment subjects as compared to Control subjects represents a clinically meaningful outcome because improvement in MIP is associated with improved weaning outcomes (Elkins, 2015; Vorona, 2018). Based on RESCUE 2 data, the sample size calculation for the MIP endpoint in the RESCUE 3 trial assumes an increase in mean MIP of 6.9 ± 17 cm H_2O over the mean baseline value in

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the Control group compared to a mean increase of 15.6 ± 17 cm H_2O in the Treatment group, which is a mean difference of about 10 cm H_2O, consistent with the IMST studies. The assumption for the mean MIP change from baseline for the Treatment group is supported by the results obtained in the RESCUE 1 study, in which subjects treated with Lungpacer DPT showed a mean MIP change from baseline of 13.9 ± 20.6 cm H_2O in N=9 subjects.

Given two-sided Type I error controlled at 5%, power=90%, and accounting for an expected 15% attrition rate, approximately 200 patients are required for the MIP endpoint. The Phase 1 analyses occurring at N=150 and N=200 require $p<0.0167$ on a t-test to declare success. The 0.0167 threshold accounts for the two analyses for MIP.

Primary Statistical Analysis: The change in MIP from randomization to last available measure will be calculated for each subject. The randomized groups will be compared using the two-sample t-test in the observed mITT sample.

Additional Analysis: Additional analyses include those summarized in *Section 2.5.2 Pooling of Data for Primary Effectiveness Endpoints and Section 2.9 Handling of Missing Data for Primary Effectiveness Endpoints*.

Further, an analysis of variance model will also be fit with dependent variable change in MIP and independent variables to include study group and randomization MIP. Other covariates may be evaluated depending on the statistical significance of the comparison of baseline factors between randomized groups. The randomization MIP and change in MIP will be summarized for subject groups defined by randomization assignment and whether or not the final MIP measurement was associated with successful weaning. These analyses will be completed in both the mITT and PP study groups.

2.6.2 Primary Effectiveness Outcome – Successful Weaning

To prove that the proportion (cumulative incidence) successfully weaned by Day 30 for subjects randomized to Treatment is superior to that in subjects randomized to Control.

Subjects Included in Analysis: All mITT subjects randomized in RESCUE 3 will be included in the analysis. Note that borrowed subjects from RESCUE 2 are used to construct an informative prior for borrowing historical information on weaning.

Endpoint(s): Successfully weaned is defined as passing a Ventilator Liberation Trial (VLT), or removed from MV, and not returned to MV within 48 hours. The date and time of being successfully weaned will be the date and time of first cessation of mechanical ventilation in which the 48-hour follow-up criteria have been met.

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Hypothesis Test:

H_0: The hazard ratio for successful weaning is the same in subjects randomized to Treatment (Lungpacer DPTS) as compared to those randomized to Control, HR=1.

H_1: The hazard ratio for successful weaning is greater than 1, indicating subjects wean faster with Treatment (Lungpacer DPTS) as compared to Control, HR>1.

Sample Size Rationale: The sample size depends on three criteria: cumulative incidence for successful weaning in the Control (standard of care) group, hazard for mortality / withdrawal of life support in the Treatment (Lungpacer DPTS) and Control groups, and the expected effect size of the Treatment (Lungpacer DPTS) as compared to the Control group. Assumptions for successful weaning and mortality can be ascertained from the medical literature for patients on mechanical ventilation. However, these rates range widely and will depend on the proportion of subjects who are difficult to wean or have had prolonged MV randomized in the study.

Mortality rates range from 10-50% (Martin, 2011; Fialkow, 2016; Béduneau, 2017) and rates of successful weaning in ICU patients on mechanical ventilation are reported to range from 40% to 70% after the initial weaning attempt failure (Boles, 2007, Funk, 2010; Peñuelas, 2011). Therefore, sample size estimates utilize a range based on these lower and upper bounds for mortality and Control weaning success. This range extends from the lower 200s to the upper 300s after accounting for 15% attrition.

Thus, Phase 2 includes interim analyses at every 50 subjects with opportunity to complete from a minimum of N=200 to a maximum of N=400 subjects. Success in Phase 2 will be declared based on the posterior probability of superiority of Lungpacer DPTS to Control exceeding a predefined threshold (99.25% at N=200, 99.00% at N=250, continuing to 98.25% at N=400).

Primary Statistical Analysis: The Phase 2 posterior probability of superiority will be computed assuming a piecewise linear model for the time to successful weaning, thus providing flexibility in the estimation of the baseline (control) hazard. The design will also employ borrowing an effective sample size of 64 subjects from the completed RESCUE 2 study. The borrowing will be based on propensity score matching of the RESCUE 2 subject covariate data to the accumulating covariate data in RESCUE 3, thus borrowing as much as possible from RESCUE 2 subjects which most resemble RESCUE 3 subjects. Complete details of the propensity score calculations and the calculation of the posterior probability of superiority are contained in the RESCUE 3 SAP.

Additional Statistical Analysis: Additional analyses include those summarized in *Section 2.5.2, Pooling of Data for Primary Effectiveness Endpoints*.

2.6.3 Primary Safety Outcome

To characterize the adverse event profile (i.e., assessment of adverse events) in subjects randomized to Treatment as compared to subjects randomized to Control to support an observed consistent risk profile for subjects randomized to Treatment compared to subjects randomized to Control.

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Patients Included in Analysis: All ITT subjects randomized in RESCUE 3 will be included in the analysis.

Endpoint: Adverse events.

Hypothesis Test: A single hypothesis test associated with a specific safety endpoint is not being proposed for the primary safety outcome. Fisher's exact test may be used to compare the number of subjects with an event or in a category of events out of the total number of subjects randomized between groups as a tool to understand the adverse event profile associated with the Lungpacer DPTS as compared to Control.

Primary Statistical Analysis: Adverse events will be classified based on MedDRA terminology and summarized for each randomized group. Number of adverse events and incidence rates will be summarized by system organ class and lower level term. Each subject will be counted only once within a system organ class or lower level term by using the adverse event with the highest severity. Subgroups of events will also be summarized to include serious events; those related to the procedure or device; and serious device or procedure related events. Lastly, adverse events may be summarized by the time course of their occurrence relative to randomization (i.e., within 0 - 7 days, and beyond 7 days after the day of randomization to the end of the adverse event monitoring period) as well as by geography (US vs OUS), device model (Keystone System and AeroPace System), and catheter insertion site (left subclavian vein and left jugular vein).

2.7 Secondary Outcomes

Secondary outcomes may be used to support additional claims. Details regarding those secondary endpoints that will be evaluated for additional claims as well as description of any borrowing employed on those endpoints, are provided in the RESCUE 3 SAP. Data for secondary outcomes that are not used to support additional claims may be included in labelling per agreement with FDA, and will be limited to summary statistics (e.g., mean, standard deviation, number and percent) and will not include 95% confidence intervals or p-values.

2.8 Interim Analysis and Criteria for Termination of the Study on Statistical Grounds

The details regarding the adaptive design are provided in the RESCUE 3 SAP.

2.9 Handling of Missing Data for the Primary Endpoints

The primary safety endpoint will have no missing data as all ITT subjects will be monitored for adverse events during the study period.

The change in MIP endpoint is not expected to have a lot of missing data in the mITT population. Subjects will be included in the analysis even when MIP is observed only at baseline. However, if a subject is missing his/her baseline MIP value, multiple imputation will be used to impute the change in MIP for the subject based on the observed values for his/her randomized group as a supportive or

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sensitivity analysis for the missing data. Ten (10) imputations will be performed and the multiply-imputed datasets will be combined to produce an analysis of the change in MIP comparison between randomized groups that accounts for the missing data and includes additional variation due to the imputation.

The successful weaning endpoint will have no missing data in the mITT sample.

2.10 Procedures for Reporting Any Deviations from the Original Statistical Plan

The RESCUE 3 Statistical Analysis Plan (CLN-0050) will supersede the clinical investigational plan. The SAP will be finalized prior to the first interim analysis. Any changes made to the SAP after finalization will be reported in the study report.

2.11 Minimum and Maximum Number of Subjects to be Included for Each Investigational Site

No more than 25% of the randomized subjects will be randomized at any of the investigational sites and at least 20% of the randomized subjects will be enrolled in the United States at end of Phase 2 of the study.

2.12 Specification of Subgroups for Analysis

The primary effectiveness endpoints will be summarized within subgroups as defined below. The study is not powered to demonstrate superiority in primary effectiveness endpoints within subgroups and therefore it is not an expectation of this analysis that superiority will be statistically significant within the subgroups.

1) Underlying disease state that is recorded in the EDC as the "*reason for mechanical ventilation*" and includes the subgroups of COPD, ARDS/ARF, Surgical, Pneumonia independent of COPD, ARDS, Surgical, and Other;
2) Tracheostomy versus endotracheal tube at study entry;
3) Age, gender, and race/ethnicity;
4) Geography (US vs OUS);
5) Device model (Keystone System and AeroPace System).
6) Catheter insertion site (left subclavian vein and left jugular vein).

3 DATA MANAGEMENT

3.1 Procedures for Data Management

Lungpacer has contracted with a Clinical Research Organization (CRO), which will be responsible for study data management according to a plan developed for this study in collaboration with the Sponsor and according to the CRO's Standard Operating Procedures (SOPs).

The details of data review, database cleaning and data querying are described in a Data Management Plan (DMP) that is maintained by the CRO and Sponsor. This plan may be updated throughout the

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investigation as amended data management requirements and investigation-specific data conventions are determined.

3.1.1 Case Report Forms

A web-based electronic data capture (EDC) database will be used to record and manage study data. An eCRF, comprised of individual case report forms, will be completed for every subject who has a completed Informed Consent form and is screened for the study. An eCRF completion guideline for participating investigational sites describes general instructions on eCRF completion within the EDC system. Site personnel are provided training on how to enter data in the EDC according to their designated responsibility.

Data, as it becomes available, will be entered in the eCRF. The CRFs will be completed electronically, with reasons documented for missing data. All eCRFs must be kept in good order and updated so they always reflect the latest observations on the subjects participating in the study. Sites are expected to enter data in a timely manner.

The Principal Investigator must certify for each subject that all data entered into the EDC is correct. This verification is conducted after all data has been entered, there are no outstanding queries, and the eCRF has been fully monitored. The Principal Investigator's signature will indicate that he/she has made a thorough inspection of the data and certifies the contents of the case report forms as accurate and complete.

3.1.2 Source Documentation

All original source documentation (e.g., laboratory results, treatment records, audit queries, worksheets, etc.) will be retained by the investigator or institution unless specified otherwise by the protocol. Legible reproductions of the original laboratory reports for selected tests or variables may be included with completed eCRFs. The study manager will indicate which reports, if any, need to be reproduced.

3.1.3 Data Queries

Queries may be generated by the data management department of the CRO and Sponsor or by the monitor during a remote or on-site monitoring visit. All corrections made to the eCRF will be captured in the database audit trail.

3.1.4 Confidentiality

This clinical investigation will comply with Regulation EU 2016/679 (General Data Protection Regulation), HIPAA, and any additional requirements imposed by national law concerning data protection.

A study code identification number will be used to protect the subject's identity. Only pseudonymized subject data will be entered by the study personnel into a secure database, transferred in an electronic

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form and processed by the Sponsor and/or the Sponsor's contract research organization (CRO). Subject personal data will be processed at all times in accordance with applicable legal requirements and will be used solely for the purposes of conducting this clinical study and to aid future scientific research in the treatment of patients on mechanical ventilation. In general, only specific site personnel will have direct access to subject personal data. Sponsor clinical representatives may have limited access to subject personal data such as imaging, as needed to assist the clinical site with study procedures. A study monitor will also have access to personal data but only to verify the quality of the data collected for the study. It may also happen that representatives of national or international public health authorities (for example, the US Food and Drug Administration or Competent Authorities) are granted direct access to subject personal data, if required by applicable law. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give subject names or include any identifiable references to subjects. The Sponsor will not store any pseudonymized personal subject data longer than the mandatory retention periods defined by the applicable laws. Sponsor will delete or anonymize any personal subject data after the applicable retention period has expired.

The study informed consent document informs all subjects about data protection provided for this study and that they are entitled to access their personal data processed for the study and to request rectification, restriction, deletion or exportation of this data.

3.2 Procedures for Verification and Validation of EDC System

The EDC system used for **RESCUE 3** is verified and validated by the study CRO in accordance with their SOPs for EDC verification and validation.

The required clinical study data will be recorded on electronic Case Report Forms (eCRFs). eCRF completion guidelines and instructions for electronic data-entry are developed in conjunction with the Sponsor and the CRO.

3.3 Procedures for Data Retention

The CRO's procedures for study data retention will be followed. All information collected in the eCRFs will be stored in a secure validated database.

3.4 Specified Retention Period

Sponsor record retention period is up to fifteen years (or per specific country regulations) from the end of the clinical study. Investigators must retain study-related documentation for 2 years for the latter of the following dates: The date on which the investigation is terminated or completed, or the date that the records were no longer required for purposes of supporting a premarket approval application, or per their institutional requirements or specific country regulations, whichever is the greater. Site Data will be provided to sites by the study CRO on digital media at the end of the study.

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3.5 Clinical Quality Assurance

The study will be conducted and monitored by the Sponsor's clinical representatives or contracted clinical monitors. The Sponsor may also choose to monitor or co-monitor with the contracted clinical monitors at any given time.

Monitoring will be conducted as described in Section 1.11, *Monitoring Plan*. The Sponsor, or the Sponsor's representative, may conduct audits at the investigational site(s). Audits may include, but are not limited to, device supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

4 AMENDMENTS TO THE CIP

This protocol may be amended as necessary by the Sponsor. Any protocol amendments will be documented via an incremented version of this protocol with the relevant revision history. Changes to the protocol will be reviewed and approved through the controlled document process in accordance with Lungpacer's SOPs. Substantial amendments to the protocol must undergo the same approval process by the Sponsor, investigators, IRBs/ECs, and regulatory authorities as for the original protocol.

5 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

5.1 Investigator Deviations from the CIP

The investigator must not deviate from the **RESCUE 3** CIP except as specified below:

- With the written permission of Lungpacer, requests for deviations, and reports of deviations, may be accepted if the deviation does not affect subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.
- Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of Lungpacer and IRBs/ECs.
    - Emergency deviations shall be documented including the emergency action and subject outcome and must be provided to Lungpacer and the IRB/EC within 5 working days.
- A deviation is acceptable if conducting the study or a protocol-defined test would be considered a safety risk for the subject. If this is the case, the reason for not performing the study test or procedure must be documented in the medical record.

Protocol deviations will be reviewed during monitoring visits. As appropriate, investigators will be required to identify corrective and preventive actions to prevent further deviations. An investigator may be disqualified from the study for repeated and/or egregious protocol deviations.

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6 DEVICE ACCOUNTABILITY

6.1 Investigational Device Disposition

Access to investigational devices shall be controlled in accordance with Lungpacer's SOPs. The investigational devices shall be used only in this clinical investigation and according to the clinical trial protocol. Lungpacer shall keep records of the type and number of all investigational devices from shipment of the devices to the investigational sites until return or disposal. Principal Investigators agree to keep records documenting the receipt, use, return and disposal of the investigational devices.

6.2 Clinical Supplies Accountability

Ultimate accountability for the receipt, dispensation and record-keeping of all investigational devices lies with the investigator. Federal regulations require that storage of the investigational devices be in a secure enclosure, access to which is limited, to prevent theft or diversion. The investigator(s) may not supply the investigational device to any person outside of this protocol.

The investigational devices provided for use in this study are intended for use only in the clinical trial outlined in this protocol and will be used only in subjects appropriately consented and randomized in this trial. The use of the supplies for other clinical or preclinical situations is strictly prohibited. The use of the investigational supplies by the investigator, sub-investigators or any third party, outside of the provisions stated in this protocol, without the express written permission of Sponsor, is strictly prohibited. The possession and use of the supplies by investigators must be closely controlled and monitored. All investigational supplies that are not used on a subject will be returned per the Sponsor's instructions provided at the study site close out visit.

The PI or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

- the date of receipt,
- identification of each investigational device (lot number/serial number or unique code),
- the expiry date, if applicable,
- the date or dates of use,
- subject identification,
- date on which the investigational device was returned/removed from subject, if applicable, and,
- the date of return to Lungpacer of unused, expired or malfunctioning investigational devices, if applicable.

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6.3 Investigational Device Accountability Record

In accordance with federal regulations (21 CFR 812.140(a)(2)), all investigators are required to keep accurate records showing final disposition of all investigational materials. The Study Coordinator in charge of the investigational supplies may keep the records and sign a device accountability log. These records must be available to the Sponsor/CRO on request, showing accurate reconciliation of each and every shipment of investigational devices.

The device accountability log is updated through the course of the trial, verified at the end of the study and is to be signed by the Principal Investigator. The original will be stored in the investigator's file. A Sponsor/CRO monitor will make a photocopy of the original, which will be filed in the eTMF.

7 REGULATORY COMPLIANCE

7.1 Statements of Compliance

- This clinical investigation will be conducted in compliance with the principles that have their origin in the latest version of the Declaration of Helsinki, October 2013.
- This clinical investigation will comply with Medical Device Regulation (EU) 2017/745 of 5 April 2017, 21 CFR Parts 11, 50, 54, 56, and 812 requirements of FDA, the requirements of the IRBs/ECs, EN ISO 14155, and other applicable regional or national regulations, whichever provides the greater protection of the individual.
- The clinical investigation sites in the US comply with the Health Insurance Portability and Accountability Act (HIPAA) (42 U.S.C. § 300gg; 29 U.S.C. 1811 et seq.; 42 U.S.C. § 1320d et seq.) and the associated HIPAA Privacy Rule (45 CFR Part 160 and Subparts A and E of Part 164).
- This clinical investigation will comply with Regulation (EU) 2016/679 of 27 April 2016 (General Data Protection Regulation) for general data protections requirements.
- This clinical investigation will not begin until required approval(s)/favorable opinion(s) have been obtained from the applicable IRBs/ECs or regulatory authorities.
    - Any additional requirements imposed by an IRB/EC or regulatory authority will be followed in the conduct of this clinical trial.
- The Sponsor has obtained clinical trial insurance that will cover expenses in the event of any physical injury resulting from research procedures.

7.2 Investigational Review Board or Ethics Committee

Regulations require that a registered IRB/EC oversee all investigational studies. The study may also utilize a central IRB or regional EC, as appropriate. This board or committee, the makeup of which must conform to national regulations and any local guidelines regarding such, will approve all aspects of the study, including said protocol and written Informed Consent to be used, prior to initiation of the study. The investigator will provide Sponsor/CRO with a copy of the communication from the committee to the

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investigator indicating approval of the protocol and consent form(s). Substantial amendments to the protocol must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects.

7.3 Provision of Investigational Device

Investigational devices that are functional will not be shipped to the institution and the study will not commence at a participating institution until the following are completed:

- Clinical trial agreement (signed);
- IRB/EC approval letter (and national regulatory approval if required);
- Lungpacer and IRB/EC approved informed consent form (and national regulatory approval if required).

A subject cannot be enrolled until the site initiation visit has occurred, activation requirements are met, and the primary investigator and other required study personnel have completed training.

Activation requirements include (among others):

- Completed Delegation of Authority Form;
- Training completed for the Principal Investigator and other study site personnel for whom training is required at the time of activation;
- Primary investigator CV and any sub-investigators' CVs participating at the time of activation;
- Clinical Investigational Plan signed by the primary investigator;
- IRB/EC membership list or Assurance Document as applicable;
- Financial disclosure from the primary investigator and any co- or sub-investigator;
- Appropriate trial personnel to conduct research study; and,
- Appropriate research certifications (e.g., GCP/MPG) as required by institution or competent authority in each country.

7.4 Principal Investigator's Study Reporting Responsibilities

Investigators participating in this study agree to the following reporting responsibilities:

- The investigator will be responsible for providing the required annual report to the IRB/EC for the duration of the study, if applicable. Copies of the investigator's report and/or copies of the IRB/EC extension approval must be sent to Sponsor/CRO.
- Investigator's Final Report: A summary report must be submitted to the IRB/EC and Sponsor/CRO per the site's IRB/EC requirements after the study's completion or termination.

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- Other reports as required by 21 CFR Part 812.150(a).

8 INFORMED CONSENT PROCESS

8.1 General Informed Consent Process

The informed consent document must be approved by the IRB/EC prior to study initiation and must conform to all applicable regulations. The informed consent document will allow, in addition to data collected at the enrolling institution, for data on mortality, ICU and hospital admissions or discharges to be collected up to Day 30 even if the subject has been successfully weaned, discharged home or transferred to a facility outside the investigational institution.

The Principal Investigator is responsible for assuring that informed consent is obtained from every subject, or his or her legally authorized representative (LAR), prior to the subject's participation in the study, written informed consent signed and dated in accordance with EN ISO 14155 and US federal regulations 21 CFR 50 and 21 CFR 812.

Informed consent will be obtained after the investigator or their designee has provided a full explanation, both verbally and in writing, of the purpose, risks and discomforts involved and potential benefits of the study and allowed adequate time for consideration to participate. The consent can be obtained up to 5 days prior to randomization. The subject or LAR will not be unduly coerced, influenced, or induced for subject participation in the study in any way.

The signed and dated copy (signed by the PI, study sub-investigator, or PI designee, and by the subject or the subject's LAR) of the informed consent must be maintained in the institution's records and is subject to inspection by a representative of the Sponsor/CRO. The subject, or LAR, will be provided with a copy of the signed and dated informed consent form and the information presented to them.

The names of the subjects enrolled during the study will be kept confidential.

If new information about the safety of the procedure or product becomes available during the conduct of the study this will be provided in both verbal and written form to the subject, or LAR, by the PI or designee as soon as possible.

8.2 Informed Consent Process by Subject's LAR

Informed consent may be given by a subject's Legally Authorized Representative (LAR) only if the subject is unable to make the decision to participate in a clinical investigation per (21 CFR part 50, subpart B sec. 50.20) (e.g., seriously ill or unconscious subject, under the effects of narcotics or sedatives). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand. If the subject regains the physical/mental ability to sign the Informed Consent on his/her own, he/she must be reconsented. Where applicable, local regulations for LAR consent must be followed.

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9 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

In this trial, all adverse events (AEs) that occur will be documented in a timely manner in the EDC. All SAEs or UADEs will be documented in a timely manner and reported to the Sponsor within the time frames listed below under "Reporting." The investigator at the site should follow subjects with AEs until the event has resolved, the condition has stabilized, or the subject exits the trial, whichever comes last, and to report such follow-up information to the Sponsor. AEs will be recorded in detail on the AE eCRF. An unblinded CEC will adjudicate all SAEs and UADEs according to the definition of an SAE and UADE. All CEC adjudications are considered final.

9.1 Definitions

Adverse event (AE): any untoward medical occurrence, observations, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

1) This definition includes events related to the investigational medical device or the comparator.
2) This definition includes events related to the procedures involved.
3) For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE): adverse event related to the use of an investigational medical device.

1) This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
2) This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Device Deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, including malfunctions, use errors, and inadequate labelling.

Serious Adverse Device Effect (SADE): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE): adverse event that led to any of the following:

(a) death;

(b) serious deterioration in the health of the subject, that resulted in any of the following:

i. a life-threatening illness or injury,
ii. permanent impairment of a body structure or a body function,
iii. hospitalization or prolongation of patient hospitalization,

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iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

v. chronic disease,

(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Event (SAE, Germany): a serious adverse event is any undesired event occurring in a clinical investigation or a performance evaluation study requiring an authorization, which has led, or could have led, or could lead directly or indirectly to the death or severe health impairment of volunteers, users or other persons regardless of whether the event was caused by the medical device (Section 2 number 5 MPSV).

Unanticipated Adverse Device Effect (UADE/USADE): any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.2 Reporting

9.2.1 Investigator Responsibilities

9.2.1.1 *Adverse Events and Device Deficiencies*

After obtaining informed consent, certain study related procedures, e.g., MIP and the VLT, are conducted prior to enrollment. Any SAE that a subject experiences that is associated with the study procedures or assessments, from the point of consent to the point of enrollment should be recorded in the subject record.

AEs and SAEs on all subjects that occur from the point of enrollment onwards, irrespective of potential causal relationship to the device, procedure or study, will be reported to Lungpacer and its CRO within 24 hours of the investigator's first knowledge of the event. Suspected SAEs or device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken, or, b) intervention had not been made, or, c) if circumstances had been less fortunate should also be reported within this timeframe.

9.2.1.2 *Process for Reporting Adverse Events and Device Malfunctions*

Each reported AE will be assessed by the investigator for its primary suspected relationship to the device or procedure and its severity:

- Not Related: An AE which cannot be attributed to the study device or initial study procedure.

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- Unknown Relationship: The relationship of the AE to the device or procedure cannot be determined.
- Possible: The clinical event occurs within a reasonable time sequence to study procedure/study device and there is some evidence to "possibly" suggest a causal relationship. However, the influence of other factors such as underlying disease, concomitant medications, or concurrent treatment may have contributed to the event.
- Probable: The temporal sequence between the device use or procedures and the event is such that the relationship is likely or subject's condition or concomitant therapy could have caused the AE.
- Definite: The clinical event occurs in a plausible time relationship to study procedure/study device and cannot be explained by any concurrent disease or other devices, drugs or chemicals.

The investigator will forward information to the Sponsor and the CRO, via the eCRF, about an SAE promptly and complete the AE and SAE eCRF, even if the information is incomplete or it is obvious that more data will be needed to form any conclusions. Additional information regarding the SAE will be recorded on the follow-up SAE eCRF. The investigator will be responsible for forwarding initial and follow-up information as per relevant local regulatory requirements to the applicable IRB/EC. The investigator must report a UADE/USADE to the Sponsor and reviewing IRB/EC within 24 hours after learning of the effect.

All AEs should be reported on the eCRF as soon as practicably possible. AEs will be recorded by their final medical diagnosis and not by each separate symptom. For all AEs, the causal relationship with the device and with the study procedure will be established by the investigator. The information for the event will include the date of onset and resolution, the action taken, the corrective treatment and how the subject recovered with or without sequelae. In case of death, information obtained from detailed death records, including the relationship of death to the investigational device and/or the study procedure, will be well documented. The date on which subject expired, what attempts were made to treat the event that led to death, the performance and functioning of the device during the event will be noted.

Device deficiencies which could have led to a SAE must be reported to the Sponsor within three business days. All devices alleged to be deficient must be returned to the Sponsor within five business days.

9.2.2 Sponsor Responsibilities

9.2.2.1 *Adverse Events and Device Deficiencies*

National reporting procedures for adverse events are described in the RESCUE 3 Safety Plan.

- The Sponsor will report to the FDA (United States):

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- Any Unanticipated Adverse Device Effect (UADE or USADE) within 10 working days after the Sponsor first receives notice of the adverse effect.

- The Sponsor will report to Health Canada (Canada):
  - Serious adverse events:
    - within 10 days after the Sponsor becomes aware of an incident, if the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person, or
    - within 30 days after the Sponsor becomes aware of an incident, if the incident has not led to the death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur.
  - Incidents that occur outside Canada are reported only for events for which the Sponsor intends to conduct corrective actions or as required by a regulatory body.
- The Sponsor or the sponsor's representative will report to the national Competent Authority of each European country where the investigational study has commenced:
  - An SAE that indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by Sponsor of a new reportable event or of new information in relation with an already reported event.
  - Any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken, or, b) intervention had not been made, or, c) if circumstances had been less fortunate: immediately, but not later than 7 calendar days following the date of awareness by the Sponsor of the new reportable event or of new information in relation with an already reported event.
  - All other SAE and device deficiencies with an SAE potential: Report at least 7 calendar days following the date of awareness by the Sponsor.
  - Non device- or procedure-related SAE are exempted for reporting.

9.3 Anticipated Potential Adverse Events

Anticipated potential adverse events (AEs) consist of those related to the investigational medical device or the procedures involved in using the device, as well as AEs that occur because the patient population for this study is critically ill and receiving treatment for multiple comorbidities. Anticipated potential AEs that may be encountered in the conduct of this study including potential AEs related to the use of the Lungpacer DPTS are listed in Section 1.6, *Risks and Benefits of the Investigational Device and Clinical Investigation*. It is possible that there are additional risks that have not been foreseen.

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Adverse events associated with the management and care of patients on mechanical ventilation being treated in the ICU setting may also occur in this patient population.

9.4 Emergency Contact Details

In case of an immediately reportable adverse event, the investigators should contact their local Lungpacer Clinical Study representative or the study CRO. Contact details for Lungpacer Study Management, EU Authorized Representative, Data Protection Representative, and Data Protection Officer and for the study CRO are provided in the **RESCUE 3** Investigator Site File, as applicable.

9.5 Data Safety Monitoring Board/Clinical Events Committee

A Clinical Events Committee (CEC) will operate according to the study CEC Charter which specifies the conduct of the CEC, including but not limited to goals, processes, roles, and responsibilities.

The CEC will be unblinded and will adjudicate all Serious Adverse Events and those events warranting adjudication during the clinical investigation. The CEC will not adjudicate observations. The CRO Safety Project Manager will assemble event dossiers, which will contain the event narrative, redacted source documentation, redacted CRFs from the study database, and any other information pertinent to the adjudication.

The CEC (which is unblinded to the study allocation arm) reviews the pertinent de-identified subject data as it pertains to the adjudication of the event, including the subject's medical chart, laboratory or pathology findings, imaging data, postmortem reports, and other relevant data. An independent 2+1 adjudication model will be used. Once a serious event is ready for adjudication, two CEC members will be notified, and separate online adjudication sessions will be held where they will be presented with the dossier to review. In the case of discordance between assessments from the first two adjudicators, the CEC Chair will be provided with the same event dossier reviewed by the other CEC members. The CEC Chair's adjudication will be performed on-line in a manner identical to that utilized for the adjudication sessions with the two initial members, but only to review the discordant entries. The CEC Chair's adjudication will serve as the final vote.

Results from event adjudications will be captured in the Part 11-compliant adverse event tracking database. Details regarding adjudications will also be captured directly in the web-based Adjudication Module upon completion of event adjudications.

A Data Safety Monitoring Board will also conduct certain safety assessments throughout the trial and will conduct any planned interim analyses according to a DSMB Charter for the study. The DSMB may recommend a stop in trial enrollment for safety reasons. Study stopping rules are described in Section 9.6.

9.6 Study Stopping Criteria

The DSMB is to be notified immediately and an Ad Hoc DSMB Meeting scheduled to discuss and review the corresponding medical records if:

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- If there is an SAE reported with the outcome of death and assessed by the site to have a Probable, Definite, or an Unknown relationship to the study device and/or procedure.
    - For deaths deemed Not Related or Possibly Related to study device and/or procedure, the event is to be adjudicated by the CEC prior to the DSMB being notified of the event. If the death is then adjudicated by the CEC to have a Possible, Probable, or Definite relationship to study device and/or procedure, the DSMB will be notified immediately, and an Ad Hoc meeting scheduled.
- If there is a massive hemothorax/massive pneumohemothorax, defined as rapid blood loss of more than 30% of blood volume (1500-2000 mL), and adjudicated by the CEC to be possibly, probably, or definitely related to the device and/or the procedure and that occur for given subject until study exit.

For those events that may meet the stopping rule criteria and require DSMB review **prior** to CEC adjudication, the DSMB review will be completed within 4 to 6 weeks. CEC adjudication will occur concurrently with DSMB review and be completed within 4 weeks. For those events that may meet the stopping rule criteria and are first adjudicated by the CEC, the CEC adjudication will be completed within 4 weeks and the DSMB will meet within 2 weeks of the CEC decision.

Enrollment of new subjects will not be suspended until after the DSMB meets and determines whether the events reviewed require stopping of study enrollment.

The study will be paused at the occurrence of pre-defined incidence of death or massive hemothorax / pneumohemothorax, defined as rapid blood loss of more than 30% of blood volume (1500-2000 mL), that are probably or definitely device-related or procedure-related. The pre-defined incidence (i.e., number of subjects required to trigger the stopping rule) will vary according to the number of subjects randomized to the Treatment group, as described in the RESCUE 3 DSMB charter. Lungpacer Medical Inc. shall notify FDA and other regulatory bodies within 24 hours of stopping study enrollment based on the stopping rules.

10 VULNERABLE POPULATION

EN ISO 14155 defines a vulnerable subject as an individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

This protocol may include subjects who are incapable of giving informed consent due to their physical or mental state. Individuals incapable of giving informed consent due to their status at the time of screening are being asked to participate through the subject's representative (e.g., legally authorized representative (LAR), person of trust) as defined by national law. These vulnerable subjects according to the ISO 14155 definition will then be asked to provide their informed consent if and when they become capable of providing it

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themselves and the consent process will be performed without undue delay. Informed consent processes shall be conducted according to national law, IRB/EC procedures and institutional requirements.

The protection of the rights and welfare of study participants will be overseen by the responsible IRB/EC (§14.1) and the Principal Investigator.

When the subject's participation in the trial ends, he/she will continue to be followed by a physician according to routine Standard of Care.

11 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

11.1 Criteria for Suspension or Premature Termination

The Sponsor reserves the right to terminate an investigator/investigational site or the study itself for any of the following reasons:

- Failure to secure subject informed consent including protection of personal data prior to enrollment
- Failure to report serious adverse device effects within 24 hours of discovery
- Repeated investigational plan deviations
- Repeated failure to appropriately complete case report forms
- Failure to enroll an adequate number of subjects
- Loss of or unaccounted for investigational product inventory
- Failure to follow GCP
- Business reasons

11.2 Subject Follow-Up in the Case of Study Termination

RESCUE 3 investigators and their research institutions are required by contract with Lungpacer to conduct certain follow-up procedures in the case of study or site termination.

Upon receipt of a notice of termination, the site must immediately stop enrolling subjects in the study. Investigators must continue to perform the follow-up testing in accordance with the study protocol and to provide the study data (including CRFs) for subjects who were enrolled in the study prior to the notice of termination, unless instructed otherwise by Lungpacer in writing. Lungpacer, the investigators, and research institutions agree that any termination requested shall not commence until such date as subjects in the study can be transitioned out of the study without adverse medical effect to such subjects.

Investigators shall promptly respond to requests from regulatory authorities and Lungpacer for information relating to the conduct of the study. Investigators and their research institutions shall comply with Lungpacer's instructions regarding the return of confidential information and Sponsor property.

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12 LISTING ON CLINICALTRIALS.GOV

The RESCUE 3 study is an applicable clinical trial for listing on ClinicalTrials.gov under FDAAA 42 U.S.C. 282(j) and is listed on ClinicalTrials.gov under NCT03783884.

13 PUBLICATION POLICY

The Sponsor is interested in seeing the results of this investigational study published within a suitable period following study completion. To this end the Sponsor will appoint a suitable writing committee to direct the writing of scientific reports, journal papers and congress presentations with input and coordination by the Sponsor. Journal articles produced by the committee will comply with the current version of the recommendations for scientific writing and publication of the International Committee of Medical Journal Editors. All reports generated by this study will be in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Declaration of Helsinki. The first publication of study results shall be made as a multi-center publication with all sites contributing data having the opportunity to provide comments to the writing committee. Authorship will be defined by the writing committee for each publication, at the start of the corresponding working process.

The National Principal Investigators for each participating country will systematically be among authors; other investigators may also appear among authors depending on contributions to the manuscripts (cf. ICMJE criteria); all investigators contributing data to the study report will systematically appear in a specific list that will be registered as such and therefore accessible in PubMed searches (“collaborators” in PubMed).

The investigators agree to cooperate with the writing committee in preparing such a manuscript. If such a multi-center publication is not submitted for publication within twelve (12) months after study conclusion, the individual investigators may publish the results from their individual sites but must submit a copy of all manuscripts and/or abstracts to the Sponsor for review and comment thirty (30) days prior to its submission for publication. Similarly, any subsequent publications from the sites, including data collected during the trial from the enrolled subjects and pertaining to the Sponsor’s technology must be submitted to the Sponsor for review and comment (30 days) prior to submission. As the Sponsor may wish to develop follow-on manuscripts, sites are strongly encouraged to coordinate any publication interests with the Sponsor early in the publication development process. Notwithstanding the foregoing, the Sponsor maintains the right at all times to delay publication of the study data depending on regulatory considerations.

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APPENDIX 1

AeroPace System Information

Lungpacer Diaphragm Pacing Therapy (DPT) is delivered in concert with the patient's MV support, using the investigational Lungpacer Diaphragm Pacing Therapy System (DPTS) under the supervision of a medical operator. Lungpacer DPT consists of 6 sets of 10 transvenous stimulations to the left and right phrenic nerves to stimulate the diaphragm, delivered twice daily for a total of 120 stimulations per day. A typical therapy session lasts about 15 to 30 minutes. Therapy is delivered for 30 days for a maximum of 3600 stimulations.

The AeroPace System is a model of the Lungpacer DPTS. The AeroPace System consists of a sterile, single-use, disposable catheter (the AeroPace Catheter), a Catheter Cable, a bedside Neurostimulation Console (control unit), which includes a touchscreen and Handheld Controller, an Airway Sensor, and an Airway Sensor Cable. The AeroPace System can be operated manually (Manual Mode) or using automated features (Auto Mode) for Placement, Mapping and Therapy. The Airway Sensor and Airway Sensor Cable are required to operate the system in Automatic Mode.

The AeroPace Catheter is an 8.5 Fr, 23 cm, triple-lumen central venous catheter that is similar in appearance, composition, and functionality to commonly used catheters for central venous access. It contains 30 electrodes, arranged in two arrays. The distal array of 9 (nine) electrodes is intended to capture the right phrenic nerve and the proximal array of 21 (twenty-one) electrodes is intended to capture the left phrenic nerve. The Catheter's distal lumen is used for guidewire insertion and is rated for high-pressure injection. Its medial and proximal lumens are for standard fluid or medication delivery with a flow rate of 17 mL/min. The AeroPace Catheter can be placed into the left subclavian vein or left jugular vein using aseptic technique and the standard Seldinger technique. The AeroPace Catheter is packaged in the AeroPace Catheter Kit with single-use accessories required to complete the catheter insertion procedure. The target position of the Catheter tip is in the right side of the mediastinum in the superior vena cava (SVC) above its junction with the right atrium and parallel to the lateral vessel wall of the SVC. Its distal tip is positioned at a level above either the azygous vein or the carina of the trachea, whichever is better visualized. An intravascular electrogram (ECG) signal can be used during the positioning of the Catheter to determine the location of the distal electrode (near the tip) relative to the atrium.

The AeroPace Catheter has been evaluated for safety and compatibility in the Magnetic Resonance (MR) environment. There are certain conditions in which the AeroPace Catheter may remain indwelling, should the subject require an MRI. Refer to the AeroPace Catheter Instructions for Use for these conditions.

The AeroPace Neurostimulation Console (Console) is a control unit with a user interface to control stimulation settings, providing a workflow for electrode mapping and delivery of Lungpacer DPT. The AeroPace System can be used in Manual Mode when an Airway Sensor is not connected to the Console. In Manual Mode, during Catheter Placement, the user provides confirmation to the Console that the Catheter is positioned so that transvenous stimulation of the left phrenic nerve and diaphragm stimulation are achieved. This is determined by user palpation of the abdomen or observation of deflection of the ventilator waveform. Once the AeroPace Catheter is placed, in Manual Mode, the operator conducts a mapping process, delivering a series of low-level stimulations and providing inputs to identify the left- and right-side electrode combinations that contract each respective hemidiaphragm. Using the Manual Mode for delivering Therapy, the operator initiates each stimulation, or up to 10 sequential stimulations, to deliver a total of 60 stimulations per session.

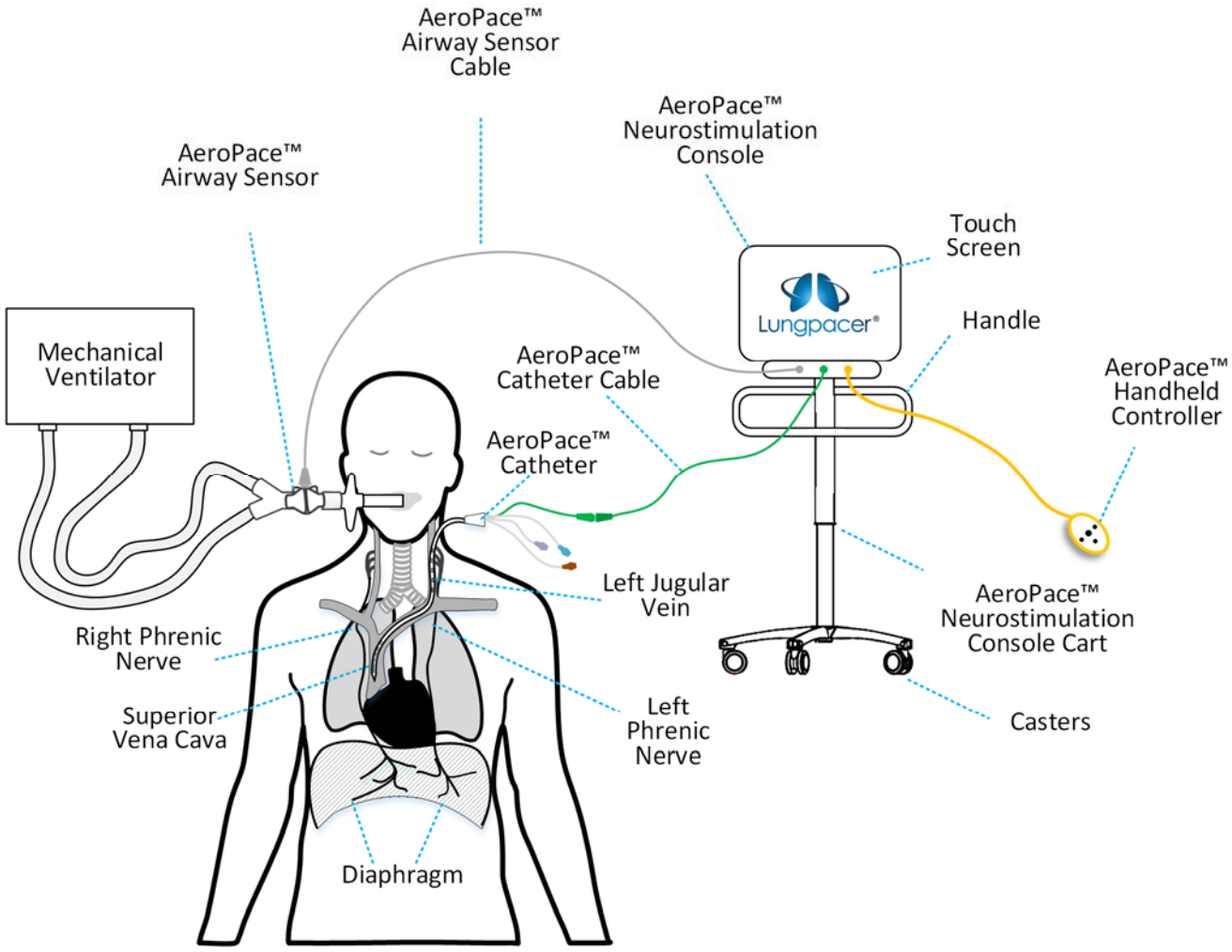
The AeroPace System can be used in Auto Mode for Placement, Mapping and Therapy. Auto Mode uses the AeroPace Airway Sensor, connected to the Console and to the ventilator circuit, to detect airway pressure changes that indicate diaphragm stimulation has occurred in Placement and Mapping Mode, and to identify the beginning of ventilator breaths in Therapy Mode. In Auto Mode, Placement to confirm a suitable position of the left-side

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electrodes, and Mapping of the left-side and right-side electrodes are conducted based on diaphragm activation detected by airway pressure changes without the need for operator input. During Therapy in Auto Mode, the operator sets the Console to deliver up to 10 stimulations which occur successively at the onset of inspiration as determined by the AeroPace Airway Sensor. In both the Auto Mode and the Manual mode, the Stimulation Intensity (up to 27.0 mA) and Stimulation Duration (up to 1.2 seconds) of the Lungpacer DPT delivered is determined by the user based on patient comfort.

The AeroPace Catheter is single-use for a maximum of 30 days. The Airway Sensor is single-patient use for a maximum of 30 days. For complete instructions on use of the AeroPace System refer to the AeroPace System and AeroPace Catheter Instructions for Use.

The AeroPace System is illustrated below. The AeroPace Neurostimulation Console on the Console Cart is shown with the touchscreen, handle for convenient cable storage, and Handheld Controller. The AeroPace Catheter, shown inserted in the left jugular vein, is electrically connected via the Catheter Cable to the Console. The AeroPace Airway Sensor is connected pneumatically in line with the patient's ventilator circuit between the Y-piece and the patient's endotracheal tube or tracheostomy tube and electrically to the Console by way of the Airway Sensor Cable.



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AeroPace System Component Names, Model Numbers, and Versions

Component	US (RESCUE 3) Part/Model Number	EU (RESCUE 3) Part/Model Number
AeroPace Catheter Kit	000-0036	000-0038
AeroPace Catheter	100-0025	100-0025
AeroPace Catheter Cable	000-0043	000-0044
AeroPace Neurostimulation Console	000-0055	000-0056
Neurostimulation Software		
Application Controller Software	750-0074	750-0074
System Health Monitor Software	750-0075	750-0075
User Interface Software	750-0076	750-0076
AeroPace Neurostimulation Console Cart	000-0057	000-0058
AeroPace Handheld Controller	000-0039	000-0040
AeroPace Airway Sensor Cable	000-0045	000-0046
AeroPace Airway Sensor	000-0041	000-0042

Number of AeroPace System Components at Investigational Sites

Per study site or satellite site, the following investigational device inventory is provided to conduct Lungpacer DPT, depending on facility needs.

- One to two Neurostimulation Consoles
- One to two Catheter Cables
- One to two Airway Sensor Cables
- One to two Handheld Controllers

The following investigational devices are provided per Treatment subject:

- One AeroPace Catheter Kit. Additional sterile Catheter Kits will be provided per Treatment subject based on institutional policy on CVC management. Additional sterile guidewires are provided for the catheter insertion procedure.
- One AeroPace Airway Sensor. Additional Airway Sensors will be provided per Treatment subject based on institutional policy on ventilator circuit management.

All investigational devices are tracked, and use, disposal, or return will be confirmed during Sponsor visits, after completion of the clinical trial, and for reconciliation against clinical study shipping logs.

The AeroPace Catheter materials that will be in direct contact with tissues or body fluids are listed below.

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AeroPace Catheter Materials Contacting Tissues or Body Fluids

Item	Material
Electrodes	Gold
Catheter Shaft and Catheter Tip Extrusion	Pebax loaded with 20% barium sulfate

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APPENDIX 2

Lungpacer DPTS (Keystone/LIVE Catheter) Information

Lungpacer Diaphragm Pacing Therapy (DPT) is delivered in concert with the patient's MV support, using the investigational Lungpacer Diaphragm Pacing Therapy System (DPTS) under the supervision of a medical operator. Lungpacer DPT consists of 6 sets of 10 transvenous stimulations to the left and right phrenic nerves to stimulate the diaphragm, delivered twice daily for a total of 120 stimulations per day. A typical therapy session lasts about 15 to 30 minutes. Therapy is delivered for 30 days for a maximum of 3600 stimulations.

The Keystone System/LIVE Catheter is a model of the Lungpacer DPTS. The Lungpacer DPTS consist of a sterile, single-use, disposable catheter (the LIVE Catheter), an Intermediate Cable, and a bedside Lungpacer Control Unit (Keystone LCU), which includes a touchscreen and Handheld Controller.

The LIVE Catheter is a 9.5 French, single-lumen central venous catheter that is similar in appearance, composition, and functionality to commonly used catheters for central venous access. The LIVE Catheter is available in 19 cm, 21 cm, and 23 cm lengths. It contains 18 electrodes, arranged in two arrays. The distal array of 6 (six) electrodes is intended to capture the right phrenic nerve and the proximal array of 12 (twelve) electrodes is intended to capture the left phrenic nerve. The LIVE Catheter's single lumen is to be used for guidewire insertion and subsequent fluid delivery or blood sampling. The flowrate for the lumen is 30 mL/min, and it is not rated for high pressure/Power Injection. The LIVE Catheter can be placed into the left subclavian vein using aseptic technique and the standard Seldinger technique. The LIVE Catheter is packaged in the LIVE Catheter Kit with single-use accessories required to complete the catheter insertion procedure. The target position of the Catheter tip is in the right side of the mediastinum in the superior vena cava (SVC) above its junction with the right atrium and parallel to the lateral vessel wall of the SVC. Its distal tip positioned at a level above either the azygous vein or the carina of the trachea, whichever is better visualized.

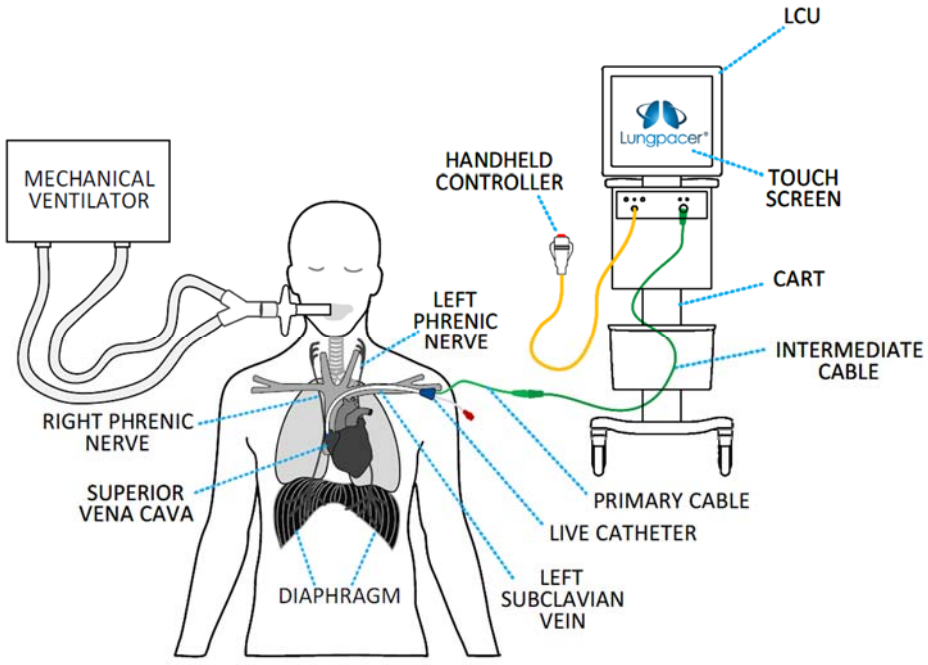
The LIVE Catheter has not been evaluated for safety and compatibility in the Magnetic Resonance (MR) environment. Scanning a patient who has this device may result in MR image artifact or patient injury due to heating or migration of the device. This information is provided in the LIVE Catheter Instructions for Use. Removal of the LIVE Catheter prior to MRI is recommended but should be determined by the physician.

The Keystone LCU is a control unit with a user interface to control stimulation settings, providing a workflow for electrode mapping and delivery of Lungpacer DPT. During Catheter Placement, the user provides confirmation to the LCU that the catheter is positioned so that transvenous stimulation of the left phrenic nerve and diaphragm stimulation are achieved. This is determined by user palpation of the abdomen or observation of deflection of the ventilator waveform. Once the LIVE Catheter is placed, the operator conducts a mapping process, delivering a series of low-level stimulations and providing inputs to identify the left- and right-side electrode combinations that contract each respective hemidiaphragm. When delivering Therapy, the operator initiates each stimulation, or up to 10 sequential stimulations, to deliver a total of 60 stimulations per session. The Stimulation Intensity (up to 13.5 mA) and Stimulation Duration (up to 1.2 seconds) of the Lungpacer DPT delivered is determined by the user based on patient comfort.

The LIVE Catheter is single-use for a maximum of 30 days. For complete instructions on use of the Keystone System and LIVE Catheter refer to the Lungpacer DPTS (Keystone) System and LIVE Catheter Instructions for Use.

The Lungpacer DPTS is illustrated below. The Keystone LCU on the cart is shown with touchscreen and Handheld Controller. The LIVE Catheter, shown inserted in the left subclavian vein, is electrically connected via the Intermediate Cable to the LCU.

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Lungpacer DPTS Component Names and Part Numbers

Component	US (RESCUE 3) Part Number	EU (RESCUE 3) Part Number
LIVE Catheter Kit		
19 cm length	000-0007[1]	000-0032-01[1]
21 cm length	000-0008[2]	000-0033-01[2]
23 cm length	000-0009[3]	000-0034-01[3]
LIVE Catheter		
19 cm length	100-0001	100-0001
21 cm length	100-0002	100-0002
23 cm length	100-0003	100-0003
Intermediate Cable	000-0015	000-0030-01
Lungpacer Control Unit (LCU) Keystone System	000-0026	000-0027
LCU Software		
Application Controller Software	750-0062	750-0062
System Health Monitor Software	750-0063	750-0063
User Interface Software	750-0064	750-0064
Handheld Controller	000-0013	000-0029-01

[1] Contains LIVE Catheter part number 100-0001
[2] Contains LIVE Catheter part number 100-0002
[3] Contains LIVE Catheter part number 100-0003

Number of DPTS Components at Investigational Sites

Per study site or satellite site, the following investigational device inventory is provided to conduct Lungpacer DPT, depending on facility needs.

- One to two LCUs
- Two to four Intermediate Cables

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- Two to four Handheld Controllers

The following investigational devices are provided per Treatment subject:

- One LIVE Catheter Kit

Additional sterile LIVE Catheter Kits of each length and sterile guidewires are provided to each site to allow for differences in patient anatomy. All investigational devices are tracked, and use, disposal, or return of investigational product will be confirmed during Sponsor visits, after completion of the RESCUE 3 trial, and for reconciliation against clinical study shipping logs.

The LIVE Catheter materials that will be in direct contact with tissues or body fluids are listed below.

LIVE Catheter Materials Contacting Tissues or Body Fluids

Item	Material
Electrodes	Platinum, Iridium
Catheter Shaft & Catheter Tip Extrusion	Polyurethane loaded with 20% barium sulfate

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