

RESCUE 3 (P-300)
Statistical Analysis Plan
Lungpacer Diaphragm Pacing Therapy System

Document No.: CLN-0050
Revision: A

NCT#: NCT03783884

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RESCUE 3 (P-300) Statistical Analysis Plan

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1 STATISTICAL CONSIDERATIONS

1.1 Statistical Design, Method and Analytical Procedures

1.1.1 Overall Design of the RESCUE 3 Study

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 DPTS, 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. 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 >45 days will be excluded.

The RCT will randomize a minimum of 236 subjects or up to 376 subjects at a maximum of 40 investigational sites in the United States, Canada, and Europe. This subject number includes a 15% expected study attrition rate. Randomized subjects will be randomized 1:1 blocked by investigational site to Treatment (Lungpacer DPTS) or Control.

Sites may choose to enroll 1 roll-in subject to obtain additional experience with the investigational device; a second roll-in subject may be enrolled if the first LIVE Catheter placement was unsuccessful. Subjects will be designated as roll-in subjects prospectively and will not be randomized. All roll-in subjects will receive Treatment (Lungpacer DPTS) 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.

Treatment: Treatment (Lungpacer DPTS) group will have LIVE Catheter placement, receive Lungpacer DPT and will be treated with standard of care. Lungpacer DPT is delivered twice daily.

Control: Control group will be treated with Standard of Care only. No placement of the LIVE Catheter.

Standard of care, as cited in clinical practice guidelines, includes daily breathing attempts that are intended to increase respiratory muscle strength and standard methods for management of ICU patients. Standard of Care is defined further in the RESCUE 3 protocol. Inspiratory Muscle Strength Training (IMST) is considered investigational and is prohibited in this study.

The adaptive study design allows for conduct of the study in two phases as shown in **Figure 1** (below).

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Phase 1: At the time the first N=204 enrolled subjects complete the study; the Phase 1 analysis will be conducted. It is expected there will be at least 172 subjects evaluable.

Phase 2: The study will be conducted to a sample size of 236 to 376 subjects as determined from the sample size re-assessment. The sample size re-assessment will occur once 100 subjects have been successfully weaned. 100 subjects successfully weaned is highly likely to occur prior to achieving 236 randomized patients.

1.1.2 Adaptive Study Design Introduction and Rationale

The RESCUE 3 study will be conducted as an adaptive design with sample size re-estimation in accordance with the FDA's guidance "*Adaptive Designs for Medical Device Clinical Studies",* dated 27 July 2016. The Lungpacer DPTS is a first-in-kind technology intended to improve inspiratory muscle strength in patients on mechanical ventilation to promote their successful weaning from mechanical ventilation.

An adaptive study design was chosen for the primary effectiveness outcome of successful weaning for the RESCUE 3 study due to the large variation in required sample size over the range of reasonable assumptions for the Control proportion weaned and the Control proportion expected to die / withdraw life support prior to weaning as observed from IMST studies (Caruso, 2005; Cader, 2010; Martin, 2011; Condessa, 2013; Elbouhy, 2014; Tonella, 2017; Elkins, 2015; Vorona, 2018). A sample size re-estimation will be employed when 100 patients are successfully weaned from mechanical ventilation. The expansion of the sample size will have a pre-determined maximum and will be re-calculated based upon within-trial estimates at the interim analysis. Sample size re-estimation is used to maximize the probability of success for the trial.

The study design for improvement in inspiratory muscle strength as shown by improvement in Maximal Inspiratory Pressure (MIP) is not adaptive, i.e. a fixed sample size design, and requires 204 randomized subjects. Randomization will continue while the analysis is conducted. The sample size re-estimation for superiority in weaning success will be conducted when 100 patients are successfully weaned and may be increased from the initial sample size of 236 subjects randomized up to a maximum of 376 subjects randomized.

A sample size re-estimation was chosen because it has the potential to save time and clinical research resources, and to provide for the optimal treatment of subjects as these designs safeguard subjects from ineffective treatments and / or provide them access to effective treatments in an efficient manner while preserving the scientific integrity of the trial. The sample size calculation for weaning success provided a wide range of potential sample sizes given reasonable assumptions for the Control proportion weaned and the competing risk of death / withdrawal of life support. The sample size re-estimation procedure

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allows the RESCUE 3 trial to either complete as planned given an effect size of 20% or to re-estimate the sample size given an effect size of 15%. Both effect sizes are clinically meaningful.

Given the follow-up duration of 30 to 32 days, the number of subjects randomized in the trial will be between 236 and 376 subjects. An effect size of 20% would obviously save both time and clinical research resources as the adaptive sample size re-estimation coupled with the short follow-up duration would permit a smaller number of randomized subjects. An added benefit to the sample size re-estimation is that the trial size will *only* increase should it be needed to demonstrate a 15% effect size. An adaptive design is used here to avoid the regret that would be experienced had the trial been designed as a fixed sample size design to detect a 20% effect size, when indeed a 15% effect size was present and thereby avoid having to repeat the trial. Additionally, had the trial been designed conservatively with a 15% effect size in mind, the study would be overpowered should a 20% effect size exist. This adaptive design prevents unnecessary patient exposure to an investigational device while allowing the most efficient use of clinical research resources while maintaining scientific rigor.

The adaptive design parameters are prospectively detailed and are discussed briefly in the study protocol and detailed only in this separate statistical analysis plan in order to preserve the scientific integrity of the RESCUE 3 study and to mitigate the risk of operational bias. The method chosen preserves the Type I error at 5% (Mehta and Pocock, 2011). Please see Section 1.5.2 Sample Size Re-Assessment for more details.

1.1.3 Study Success

The Type I error is controlled at 5% for each phase according to the precedent study design for a breakthrough device as described by Zile (2018). Evaluation of success for Phase 2 does not depend on the success for Phase 1. The study can continue to Phase 2 even if success on Phase 1 is not achieved. Success for each phase is:

Phase 1 Success

- Statistically significant improvement in MIP ($p<0.05$) from baseline to last available measure for subjects randomized to Treatment (Lungpacer DPTS) as compared to Control.
- Demonstration of a positive trend in favor of successful weaning as shown by achieving a conditional power of at least 55% for the final sample size determined using the observed difference between randomized groups and observed nuisance parameters such as attrition, competing risks etc. at the interim analysis. The interim analysis will occur when 100 patients have been successfully weaned.

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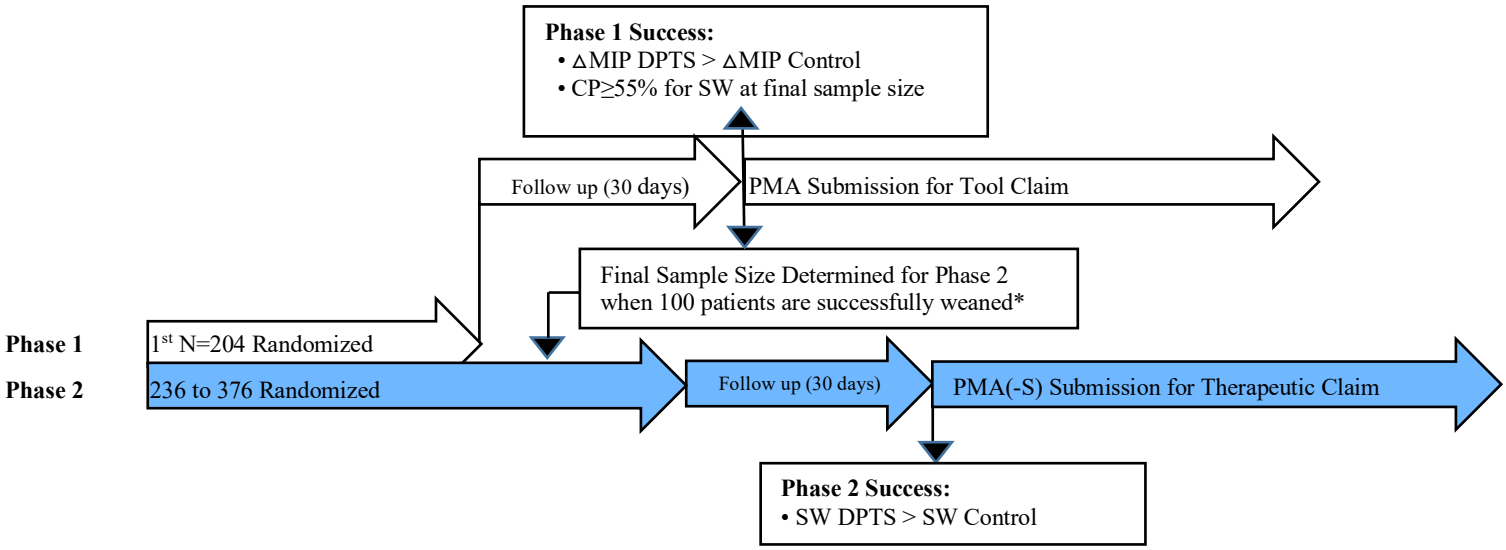
Phase 2 Success

- The proportion of subjects who are successfully weaned will be statistically significantly greater ($p<0.05$) for subjects randomized to Treatment (Lungpacer DPTS) compared to subjects randomized to Control.

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FIGURE 1: RESCUE 3 ADAPTIVE STUDY DESIGN



	Randomized Sample Size and Analysis Timing	Clinical Evidence	Assumptions	Submission
Phase 1	First N=204 randomized complete study participation	• The MIP mean change from baseline (ΔMIP) will be statistically significantly greater for subjects randomized to Lungpacer DPTS (DPTS) compared to subjects randomized to Control. • The conditional power (CP) for Phase 2 must be greater than or equal to 55% at final sample size*	15% attrition, α=0.05 power = 90% ΔMIP DPTS = 12 ± 20 ΔMIP Control = 2 ± 20	PMA submission to support tool claim.
Phase 2	N=236 – 376 randomized patients complete study participation	• The proportion of subjects who are successfully weaned will be statistically significantly greater for subjects randomized to Lungpacer DPTS (SW DPTS) compared to subjects randomized to Control (SW Control).	• SW Control = 40% - 60% • N=200 (15% attrition), p=0.05, power > 85% SW DPTS = SW Control + 20% • N=318 (15% attrition), p=0.05, power > 80% SW DPTS = SW Control + 15%	PMA or PMA-S submission to support therapeutic claim.

*The interim assessment for sample size re-estimation requires 100 patients weaned. Simulations revealed that it is highly likely this will occur prior to 236 randomized patients completing the study. Simulations revealed that for an assumed ≥ 50% SW Control and effect sizes of 10% - 20% that there is ≥ 95% probability that the randomized sample size will be ≤ 236. For an assumed SW Control = 40% and effect sizes of 15 – 20% simulation revealed that there is ≥ 50% probability that the randomized sample size will be ≤ 248 when 100 patients have been successfully weaned.

1.1.4 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 patients randomized to DPTS and requires successful placement of the LIVE Catheter according to the LIVE

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Catheter Instructions for Use. Subjects with unsuccessful placement are included in the ITT but not the mITT group. The mITT and ITT groups are the same for subjects randomized to Control.

- **Successful Placement:** LIVE Catheter was successfully inserted into the left subclavian vein, positioned according to the LIVE Catheter IFU and the diaphragm was stimulated.
- **Unsuccessful Placement:** Unsuccessful placement is defined as (i) the LIVE Catheter never entered the left subclavian vein, or, (ii) the LIVE Catheter entered the left subclavian vein, but the diaphragm could not be stimulated, or, (iii) the LIVE Catheter positioning is not in accordance with the LIVE Catheter IFU.

The **per protocol population (PP)** is a subset of the mITT population for patients randomized to DPTS and is defined by completion of at least 50% of the protocol-required number of stimulations (Stims) in at least one phrenic nerve (the sidedness of the phrenic nerve can change from left to right or in both phrenic nerves), who have not had any major protocol deviations and who have observed data for evaluation of the primary endpoint. Major protocol deviations include major inclusion/exclusion criterion violation or a major protocol deviation. The criterion for a deviation meeting the classification of "major" will be reviewed and determined by an independent designee.

Roll-In Subjects: A study subject is identified as a potential roll-in subject while in screening and after identification of an "anticipated placement date" as described in the RESCUE 3 protocol. A subject may then be designated as a roll-in subject once the subject meets the enrolled definition but he or she is **never** randomized. Roll-in subjects receive Treatment (Lungpacer DPTS plus Standard of Care), and their data will not be included in the endpoint evaluation. Sites may choose to enroll up to two Roll-In subjects to obtain additional experience with the investigational device.

1.1.5 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. P-values 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.

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

The Lungpacer Diaphragm Pacing Therapy is a novel, first-of-its-kind therapy for this patient population. As indicated in the literature, the proportion weaned in the control group is expected to be about 50% but could range from 40% to 70%. There is similar variation in the proportion 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. It is important to have accurate estimates for these items to appropriately calculate the sample size. The RESCUE 3 adaptive design involves a sample size re-estimation using within-study estimates for the final sample size calculation for the trial. The sample size for Phase 1 is 204 randomized study subjects which provides 90% power using a two-sided Type I error of 5% (see Section 1.5.1 for more details). The sample size for Phase 2 is 236 to 376 randomized study subjects. Sample size re-estimation will be employed at the end of Phase 1 to determine the final sample size for Phase 2. The maximum sample size provides at least 80% power using a two-sided Type I error of 5% per reasonable assumptions detailed in Appendix A (see Section 1.5.2 and Appendix A for more details).

1.3 Attrition Rate

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

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

1.4.1 Demographics / 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 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 population 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, BMI, hours on mechanical ventilation before randomization, MIP, primary reason for mechanical ventilation, SOFA score at randomization, presence of tracheostomy tube at randomization, and history of COPD. 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.

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1.4.2 Pooling of Data for Primary Effectiveness Endpoints

For each of the primary efficacy endpoints, pooling will be evaluated. Pooling will be evaluated for investigational centers 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. It is important to note that the study is not powered to demonstrate superiority in MIP improvement within subgroups defined by geography 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.

The statistical model for proportion weaned will be a regression model for the sub-distribution of a competing risk by Fine and Gray (1999). Two models will be fit to the data, one for each pooling factor. Each model will 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 between randomized group and study center is statistically significant at α=0.15, a stratified analysis will be performed for investigational center and compared to the primary effectiveness analysis for proportion weaned as an additional analysis to the primary analysis. The stratified analysis permits the comparison between randomized groups without utilizing a degree(s) of freedom for the stratification variable. 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 (US vs. OUS). It is important to note that the study is not powered to demonstrate superiority in proportion weaned within subgroups defined by geography and therefore it is not an expectation that superiority in proportion weaned will be statistically significant within the subgroups. If none of the interaction terms are statistically significant, the data will be pooled for analysis.

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1.5 Endpoints, Outcomes and Statisticial Analyses

1.5.1 Phase 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 (Lungpacer DPTS) 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_o: The mean change in MIP from randomization to last available measure in subjects randomized to Treatment (Lungpacer DPTS) 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 (Lungpacer DPTS) 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). In RESCUE 3, the sample size calculation for the MIP endpoint in the RESCUE 3 trial assumes an increase in mean MIP of 2 ± 20 cm H_2O over the mean baseline value in the Control group compared to a mean increase of 12 ± 20 cm H_2O in the Treatment (Lungpacer DPTS) 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 (Lungpacer DPTS) group is supported by the results obtained in the RESCUE 1 study in which subjects treated with Lungpacer DPTS showed a mean MIP change from baseline of 13.9 ± 20.6 cm H_2O in N=9 subjects.

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Given two-sided Type I error controlled at 5%, Power=90%, and the two-sample T-test, the required number of subjects with baseline and follow-up MIP is 172 (86 per randomized group). It is expected that up to 15% of patients randomized to the Treatment (Lungpacer DPTS) group will not qualify for the mITT analysis group, and therefore the sample size of 172 was increased by 15% to result in a randomized sample size of 204 (102 per group). The first N=204 randomized subjects will be required to complete their study participation such that it is expected that at least 86 per randomized group will have a baseline and follow-up 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 1.4.2 Pooling of Data for Primary Effectiveness Endpoints and Section 1.7 Handling of Missing Data.

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.

1.5.2 Phase 1 and 2 Primary Outcome – Successful Weaning

Phase 1: To demonstrate a "positive trend" in the proportion successfully weaned by Day 30 for subjects randomized to Treatment (Lungpacer DPTS) as compared to subjects randomized to Control.

Phase 2: To prove that the proportion successfully weaned by Day 30 for subjects randomized to Treatment (Lungpacer DPTS) is superior to that in subjects randomized to Control.

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

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

Hypothesis Test:

H_0: The cumulative incidence (proportion) for successful weaning (CI) is the same in subjects randomized to Treatment (Lungpacer DPTS) as compared to those randomized to Control, $CI_{LungpacerDPT} = CI_{Control}$

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H_1: The cumulative incidence (proportion) for successful weaning (CI) is not the same in subjects randomized to Treatment (Lungpacer DPTS) as compared to those randomized to Control, $CI_{LungpacerDPT} \neq CI_{Control}$

Sample Size Rationale: The sample size depends on three criteria: proportion of successful weaning in the Control (standard of care) group, hazard for mortality / withdrawal of life support in Treatment (Lungpacer DPTS) and Control groups, and the expected effect size of the Treatment (Lungpacer DPTS) and 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.

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.

The trial is initially designed with a 20% effect size in mind with an option to re-estimate the sample size given a smaller effect size observed, i.e. ~15%, at the Phase 1 analysis. As can be seen in **Appendix A, Table A.1**, a sample size of 236 subjects randomized to achieve at least 100 evaluable subjects per randomized group provides at least 85% power for a 20% increase in the proportion successfully weaned for Treatment (Lungpacer DPTS) as compared to the Control group. **Appendix A, Table A.2** provides the same set of sample size calculations for a 15% effect size. A sample size of 376 randomized to achieve at least 318 evaluable was chosen from these calculations to provide 80% power for a 15% effect size, assuming a Control proportion weaned of 40% and a 14% proportion who die/withdraw life support prior to weaning in the Control group. Fifteen percent (15%) attrition was used. The maximum sample size provides *at least 85%* power for many of the scenarios in **Table A.2**.

The final sample size for this objective will be determined at the interim analysis for sample size re-assessment. Sample size calculations were performed using PASS 14. The Type I error is controlled at 5% for the sample size re-estimation given the requirement that the conditional power be at least 44% per Mehta and Pocock (2011).

The minimally clinically significant effect size is 10% for subjects successfully weaned with Lungpacer DPTS as compared to Control. A 10% difference from Control was considered a minimally clinically meaningful improvement in a large RCT evaluation of three weaning strategies (VENISE Trial, Girault, 2011) using rate of extubation, a surrogate of successful weaning, as the primary outcome. Application of a similar clinically meaningful effect size of 10% to Lungpacer DPTS (and standard of care) as compared to Control (standard of care) was accepted by Lungpacer's consulting

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clinical experts. The RESCUE 3 trial is not powered for a 10% effect size because the corresponding sample size calculations start at 412 randomized / 350 evaluable subjects and increased upwards.

Sample Size Re-Assessment: A sample size re-assessment will occur at an interim analysis that will take place when 100 subjects have been successfully weaned. Simulations have determined that in most scenarios there is a 95% probability that this will occur prior to the initial trial size of 160 subjects weaned. The sample size re-assessment will be conducted per the methods of Mehta & Pocock (2011). The initial trial sample size is 160 patients weaned and the maximum is 200 patients weaned or 376 patients randomized whichever is met with the lower number of randomized patients. Per the calculations provided in Mehta and Pocock (2011), the *promising zone* is defined by greater than or equal to 44% conditional power and less than 90% conditional power for the initial trial size of 160 patients weaned. The *unfavorable* zone is defined by less than 44% conditional power. Greater than 90% conditional power for 160 patients weaned is defined as the *favorable* zone.

When 100 patients have been weaned, the conditional power for the initial sample size of 160 patients weaned will be calculated. The sample size will be increased beyond 160 patients weaned (the initial sample size) when the conditional power is in the promising zone to a maximum of 376 patients randomized, otherwise, the study will be completed to the randomized sample size that will provide the initial sample size of 160 patients weaned.

Phase 1 Effectiveness Endpoint: Positive Trend for Successful Weaning

An interim analysis will take place when 100 subjects have been successfully weaned. Simulations have determined that, with the exception of simulations using a 40% Control weaning rate, there is a 95% probability that this will occur prior to 236 subjects randomized. When 100 patients have been weaned, the conditional power for the initial sample size of 160 patients weaned will be calculated. If the conditional power is in the promising zone, the sample size will be re-calculated up to a maximum of 376 patients randomized with the goal of achieving 90% conditional power.

Demonstration of a **positive trend in favor of successful weaning,** which is the success criteria for Phase 1 of the study for successful weaning and for pre-market approval with a successful outcome for MIP, will be shown by achieving a conditional power of at least 55% for the **final sample size** determined using the observed difference between randomized groups and observed nuisance parameters such as attrition, competing risks etc. at the sample size re-assessment.

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Phase 2 Effectiveness Endpoint Successful Weaning

The Phase 2 effectiveness endpoint will prove that the proportion successfully weaned by Day 30 for subjects randomized to Treatment (Lungpacer DPTS) is statistically significantly superior to that in subjects randomized to Control.

Primary Statistical Analysis: The primary statistical analysis will model the time to the event of interest (i.e., successful weaning) in the presence of competing events, which include death and withdrawal of life support. Day 1 is the start date. Subjects who do not meet one of the endpoints by study exit will be censored at the time of study exit. Subjects who transfer out of the facility will be followed for the primary efficacy endpoint after transfer to the outside facility, to study Day 30. The primary statistical model will utilize the cumulative incidence function. The event of interest, successful weaning, will be compared between randomized groups using Gray's test (Gray, 1998). The probabilities will be summarized for successful weaning and each competing event for the duration of the study. The 95% confidence intervals will be provided for the probabilities on study Day 30 (29 elapsed days after randomization). Lastly, descriptive statistics will be prepared by randomized group for the time to successful weaning or day 30 in days. Various imputations for patients who die/withdraw life support and/or censor prior to successful weaning may be used.

Additional Statistical Analysis: Additional analyses include those summarized in Section 1.4.2 Pooling of Data for Primary Effectiveness Endpoints and Section 1.7 Handling of Missing Data, will be conducted in the mITT sample. The primary statistical analysis will also be conducted in the per protocol sample.

1.5.3 Phase 1 and Phase 2 Primary Safety Outcome

To characterize the adverse event profile (i.e., assessment of adverse events) in subjects randomized to Treatment (Lungpacer DPTS) 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.

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

Endpoint: Adverse events collected during the adverse event monitoring period.

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.

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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, therapy or device; and serious device, therapy 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).

1.6 Secondary Outcomes

Secondary outcomes are supportive in nature and not intended to support additional claims. Data may be included in labelling per agreement with the 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).

1.6.1 Change in Rapid Shallow Breathing Index (RSBI)

Outcome: To determine change in Rapid Shallow Breathing Index (RSBI) from randomization to last available measure in subjects randomized to Treatment (Lungpacer DPTS plus Standard of Care) as compared to Control (Standard of Care).

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

Endpoint: RSBI as measured at randomization and last available measure.

Statistical Analysis: The change in RSBI from randomization to last available measure will be calculated for each subject. The randomized groups will be compared using the two-sample t-test. Additionally, an analysis of variance model will be used with dependent variable change in RSBI and independent variables to include study group and randomization RSBI. The analyses will be completed in the mITT and PP groups.

1.6.2 Survival after Randomization

Outcome: Survival after randomization in subjects randomized to Treatment (Lungpacer DPTS plus Standard of Care) as compared to Control (Standard of Care).

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

Endpoint: Time to death.

Statistical Analysis: Kaplan-Meier analysis will be used to compare survival in the study groups. Subjects who discontinue the study early will be censored at time of early discontinuation. Survival and its 95% CI will be summarized from randomization to study Day 30 (29 days from randomization).

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This analysis will be completed in both the ITT and PP groups. The study is not expected to find a difference in mortality.

1.7 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 their baseline MIP value, multiple imputation will be used to impute the change in MIP for the subject based on the observed values for their randomized group as a supportive or 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 may have a small amount of missing data in the mITT sample. Subjects are evaluable in the analysis upon death / withdrawal of life support, successful weaning or completion of the study to Day 30. Only those subjects censored from the analysis prior to study Day 30 are considered missing data. Subjects transferred to an outside facility are followed for successful weaning at the outside facility within the 30-day study period. As a supportive or sensitivity analysis to the primary effectiveness analysis, imputation will be performed. The imputations will include a “worst case,” “tipping point,” and “best case” imputation. The “worst case” imputation imputes failures for subjects randomized to Treatment (Lungpacer DPTS) and successes for subjects randomized to Control at the time of censoring. The “best case” analysis would do the opposite, and the “tipping point” analysis completes the imputations between the “best case” and “worst case” imputations. These analyses taken together constitute a sensitivity analysis for the study conclusions that account for the missing data.

1.8 Procedures for Reporting Any Deviations from the Original Statistical Plan

This SAP will supersede the clinical investigational plan. The SAP will be finalized prior to the analysis of the final study data. Any changes made to the SAP after finalization will be reported in the study report.

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

No more than 20% of the randomized subjects will be randomized at any of the investigation sites.

1.10 Specification of Subgroups for Analysis

The primary efficacy endpoints will be summarized within subgroups defined by the underlying disease state which is recorded in the EDC as the “*reason for mechanical ventilation*” (i.e., COPD, ARDS/ARF, surgical, pneumonia independent of COPD, ARDS/ARF, surgical, and Other). Additionally, primary

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efficacy endpoints will be summarized by age, gender, and race/ethnicity. It is important to note that the study is not powered to demonstrate superiority in primary efficacy endpoints within subgroups and therefore it is not an expectation of this analysis that superiority will be statistically significant within the subgroups.

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RESCUE 3 (P-300) Statistical Analysis Plan

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APPENDIX A: SAMPLE SIZE CALCULATIONS FOR PHASE 2

TABLE A.1 Sample Size Calculation for RESCUE 3 Assuming 20% Difference Between Randomized Group using PASS 14 Logrank Tests Accounting for Competing Risks

Cumulative Incidence at Day 30*					Total Sample Size (Per Group) Assumes No Attrition [Number of Patients Weaned Required]		
Successful Wean		Difference (Lungpacer – Control)	Death/Withdrawal of Life Support (Hazard per Day)		Two-Sided Type I error is controlled at 5%		
					Power		
Control	Lungpacer		Control	Lungpacer	80%	85%	90%
0.40	0.60	0.20 HR=1.83	0.14 (0.0069)	0.11 (0.0069)	172 (86) [88]	198 (99) [101]	232 (116) [118]
		0.20 HR=1.87	0.24 (0.0132)	0.19 (0.0132)	162 (81)	184 (92)	216 (108)
		0.20 HR=1.91	0.34 (0.0213)	0.27 (0.0213)	152 (76)	172 (86)	202 (101)
0.50	0.70	0.20 HR=1.79	0.14 (0.0077)	0.11 (0.0077)	156 (78) [95]	178 (89) [108]	208 (104) [127]
		0.20 HR=1.86	0.24 (0.0151)	0.18 (0.0151)	136 (68)	156 (78)	182 (91)
		0.20 HR=1.95	0.34 (0.0256)	0.24 (0.0256)	118 (59)	136 (68)	158 (79)
0.60	0.80	0.20 HR=1.87	0.14 (0.0088)	0.10 (0.0088)	116 (58) [87]	132 (66) [99]	154 (77) [116]
		0.20 HR=2.02	0.24 (0.0181)	0.16 (0.0181)	92 (46)	104 (52)	122 (61)
		0.20 HR=2.33	0.34 (0.0351)	0.19 (0.0351)	64 (32)	72 (36)	84 (42)

*Elapsed day 29.

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Table A.2 Sample Size Calculation for RESCUE 3 Assuming 15% Difference Between Randomized Group using PASS 14 Logrank Tests Accounting for Competing Risks

Cumulative Incidence at Day 30*					Evaluable Sample Size (Per group) Assumes No Attrition [Number of Patients Weaned Required]		
Successful Wean		Difference (Lungpacer – Control)	Death/Withdrawal of Life Support (Hazard per Day)		Two-Sided Type I error is controlled at 5%		
					Power		
Control	Lungpacer		Control	Lungpacer	80%	85%	90%
0.40	0.55	0.15 HR=1.58	0.14 (0.0069)	0.12 (0.0069)	318 (159) [151]	362 (181) [172]	424 (212) [201]
		0.15 HR=1.61	0.24 (0.0132)	0.21 (0.0132)	292 (146)	334 (167)	390 (195)
		0.15 HR=1.63	0.34 (0.0213)	0.29 (0.0213)	278 (139)	318 (158)	372 (186)
0.50	0.65	0.15 HR=1.54	0.14 (0.0077)	0.12 (0.0077)	294 (147) [169]	336 (168) [193]	394 (197) [226]
		0.15 HR=1.58	0.24 (0.0151)	0.20 (0.0151)	262 (131)	300 (150)	350 (175)
		0.15 HR=1.64	0.34 (0.0256)	0.27 (0.0256)	224 (112)	256 (128)	300 (150)
0.60	0.75	0.15 HR=1.57	0.14 (0.0088)	0.11 (0.0088)	230 (115) [164]	262 (131) [188]	308 (154) [220]
		0.15 HR=1.65	0.24 (0.0181)	0.18 (0.0181)	186 (93)	214 (107)	250 (125)
		0.15 HR=1.80	0.34 (0.0351)	0.24 (0.0351)	136 (68)	156 (178)	182 (91)

*Elapsed day 29.