SIMULSTAT

Statistical Analysis Plan

Version 1.0
17JUN2019

Prepared by Simulstat, Inc

FRESCA Medical

Protocol 18-01

Non-Inferiority Study of the FRESCA Airbox Positive Airway Pressure System versus the (predicate) FRESCA Positive Airway Pressure System for the treatment of Obstructive Sleep Apnea

NCT 03999944

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FRESCA Medical
Protocol: 18-01
Statistical Analysis Plan v1.0 (17JUN2019)

Approval Page

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AHI	Apnea-Hypopnea Index
BMI	Body Mass Index
CI	Confidence Interval
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ITT	Intent-to-Treat
mITT	Modified Intent-to-Treat
NI	Non-Inferiority
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Event Device Effect

2. INTRODUCTION

Protocol 18-01 describes the collection and analysis of clinical study data on the safety and effectiveness of the FRESCA Airbox Positive Airway Pressure System which is intended to treat Obstructive Sleep Apnea by delivering a therapeutic breathing pressure to the patient.

The first-generation (predicate) FRESCA Positive Airway Pressure System received FDA market clearance in June 2018 via a de novo request. The investigational device that is the subject of this clinical study is a modified Positive Airway Pressure System that incorporates additional features such as auto-adjusting pressure and expiratory pressure relief. The results of this clinical study will be used to support a 510(k) submission to obtain FDA market clearance for the investigational device.

This statistical analysis plan (SAP) document provides details of the statistical analyses to be finalized prior to database lock and performed to assess the safety and effectiveness.

3. STUDY OBJECTIVE

The objective of this study is to demonstrate that the FRESCA Airbox Positive Airway Pressure System is non-inferior to the (predicate) FRESCA Positive Airway Pressure System.

4. STUDY DESIGN

4.1 General Study Design and Plan

This is a prospective, open-label, randomized, crossover assignment non-inferiority study conducted at up to 6 sites. Site participation is expected to be approximately 10 weeks from first subject enrollment until completion of the last study visit. After obtaining informed consent, subjects will attend a screening visit for inclusion/exclusion criteria evaluation.

Screening phase

- Collect informed consent
- Medical history/sleep history
- Weight, BMI, vitals
- Document medications
- Assess inclusion/exclusion criteria

- Schedule titration night and two additional sleep nights

Successfully screened subjects will undergo a PSG titration study using a standard CPAP device.

PSG Titration Night

- Perform PSG and adjust pressure to identify effective therapeutic pressure (i.e., AHI < 10).
- The PSG titration night will be scored by the study site's authorized personnel.

At the conclusion of a valid PSG titration night (i.e., ≥ 4 hours of sleep with no equipment recording failures and results in analyzable data for AHI and ODI), the subject will be assessed for proper fit to the FRESCA mask. The subject will breathe on the investigational flow generator and mask set to the titrated pressure for at least a 30-second interval to confirm proper mask fit.

Subjects who complete a valid PSG titration night and demonstrate proper FRESCA mask fit will be randomized to one of two sequences of in-lab PSG sleep nights, preferably on consecutive nights. The number of allowable calendar days between the two randomized sleep nights is 0 – 10 days.

Sequence 1 Subjects:

Night 1: Use of the predicate FRESCA device set to PAP at the PSG-titrated pressure.

Night 2: Use of the investigational FRESCA device set to Auto-Adjusting Pressure with EPR.

a. The auto-adjusting pressure range will be set with the lower bound at 2 cmH_2O below the PSG-titrated pressure and the upper bound at 5 cmH_2O above the PSG-titrated pressure (not to exceed 20 cmH_2O).
b. The EPR setting will be set to 3.

Sequence 2 Subjects:

Night 1: Use of the investigational FRESCA device set to Auto-Adjusting Pressure with EPR.

a. The auto-adjusting pressure range will be set with the lower bound at 2 cmH_2O below the PSG-titrated pressure and the upper bound at 5 cmH_2O above the PSG-titrated pressure (not to exceed 20 cmH_2O).
b. The EPR setting will be set to 3.

Night 2: Use of the predicate FRESCA device set to PAP at the PSG-titrated pressure.

The study will employ a central scorer to score these two randomized PSG sleep nights. The central scorer will be blinded to the randomization sequence.

4.2 Randomization

Each subject will be assigned a sequential subject ID as they enter the screening visit. A subject is considered enrolled and eligible for randomization if they sign the informed consent document, meet all inclusion and exclusion criteria, complete a valid PSG titration study that identifies a therapeutic pressure setting (i.e., AHI < 10/hr.) and have a successful FRESCA mask fit. Treatment sequence assignments will be generated in a 1:1 ratio, using a block size of 4, for a subject to be randomized to either Sequence 1 (predicate FRESCA device on night 1 and investigational FRESCA device on night 2) or Sequence 2 (investigational FRESCA device on night 1 and predicate FRESCA device on night 2).

Randomization will be managed within the electronic data management system that will contain the assigned randomization number and treatment sequence assignment.

4.3 Study Assessments

Table 1 displays the Time and Events Schedule.

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Table 1: Schedule of Visits and Procedures

Visit	Screening Visit ≤45 days prior to PSG Titration Night	PSG Titration Night	Night 1	Night 2	Study Exit Visit[1]
Informed Consent	X				
Medical History	X				
OSA History	X				
Weight measure	X				
Height measure	X				
BMI	X				
Vital Signs	X				
Inclusion/Exclusion Review	X				
Confirm eligibility	X	X			
Schedule study nights	X				
Medication Review	X	X	X	X	
Randomization[2]			X		
PSG Procedure		X	X	X	
Sleep Scoring		X	X	X	
Adverse Events		X	X	X	X

[1] Study exit visit can be performed at the conclusion of the final sleep night.
[2] Randomization can be performed upon completion of a successful Titration Night and subject enrollment.

5. PLANNED SAMPLE SIZE DETERMINATION

A sample size calculation was performed for the primary analysis of demonstrating non-inferiority of FRESCA Airbox treatment against the predicate (control) FRESCA treatment. It is planned to enroll up to 50 subjects across up to 6 study sites to yield at least 38 evaluable (mITT) subjects. Using 38 evaluable subjects for the primary analysis will provide 85% power to demonstrate non-inferiority assuming the mean difference between treatments is 0. These calculations also assume a 1-sided alpha level of 0.025%, standard deviation of 5 units, and a NI margin of 5 units. Sample size calculations were performed using the POWER procedure in SASv9.4, assuming a 2-group t-test between treatments, assuming a period effect in the ANOVA model as described in Section 10.1.

6. STUDY ENDPOINTS

The primary efficacy measure in this study is AHI with mean AHI being the primary effectiveness endpoint. The difference in mean AHI between the new and predicate devices will be tested after treatment intervention in this cross-over study design. The secondary efficacy measure in this study is ODI with mean ODI being the secondary effectiveness endpoint.

Safety endpoints include procedure-related adverse events, device-related adverse events, serious adverse events (SAE), and unanticipated adverse device event (UADE).

7. ANALYSIS POPULATIONS

The intent-to-treat (ITT) population will include all subjects who are considered enrolled.

The modified intent-to-treat (mITT) population will include ITT subjects with a Valid PSG Study during study nights 1 and 2.

8. GENERAL STATISTICAL CONSIDERATIONS

All analyses will be pooled across the enrolling sites, except otherwise stated, and conducted using SASv9.4 or higher. All baseline summary tables will include each sequence group and all subjects combined, while all effectiveness and safety table will include each treatment group. All listings will include all subjects in the ITT population.

Descriptive statistics will be used to summarize all endpoints. For continuous variables the descriptive statistics will include the number of subjects, mean, standard deviation, median, and range. The descriptive statistics for categorical variables will include the number of subjects and percent (%).

Formatting of numerical results will include the following:

- Mean values will be reported to 1 additional decimal place than collected.
- Standard deviation values will be reported to 2 additional decimal places than collected.
- Median and range values will be reported as the data are collected.
- Percentages will be reported to 1 decimal place.
- Confidence intervals will be reported to the same number of decimal places as the mean values.
- P-values being reported to 3 decimal places.

In-text tables will be brought in from post-text tables for the clinical study report.

9. SUMMARY OF STUDY POPULATION DATA

9.1 Subject Disposition

Subject disposition will be summarized for all enrolled (ITT) and mITT populations. Numbers and percentages of subjects within each sequence group who completed each night and analysis populations will be displayed. In addition, reasons for withdrawal from the study will be included in this same summary.

A listing of subject disposition and analysis set inclusion will be provided and will include subject number, sequence group, inclusion in ITT population, inclusion in mITT population, outcome of study completion, and reason for withdrawal. An additional listing of protocol deviations will be provided, sorted by subject, and will include subject number, sequence group, deviation event, study night, deviation date, action taken, and if IRB reporting was required.

9.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by sequence group for the mITT and PP populations. Two additional summaries will be provided, one each for demographics and baseline characteristics, providing descriptive statistics for subjects in the mITT population and subjects excluded from the mITT population. These two additional summaries will provide baseline demographic and baseline characteristics information for subjects completing Valid PSG nights (PSG Success) and subjects that did not complete a Valid PSG night.

Demographics to be summarized include:

- Age
- Gender
- Race
- Ethnicity

A listing of demographics will be provided and will include subject number, sequence group, age, gender, race, and ethnicity. The demographics of height, weight, and BMI will be included in the vital signs listing.

Baseline characteristics include:

- AHI
- ODI
- AI
- SE (%)
- Minimum Sleep SpO_2 (%)
- Mean Sleep SpO_2 (%)
- Wakefulness (min)
- Stage N1 (min)
- Stage N2 (min)
- Stage N3 (min)
- REM (min)

A listing of the baseline characteristics will be provided in the PSG Data as described in Section 9.5.

9.3 Vital Signs

Vital signs collected at the baseline visit will be summarized descriptively by sequence group and include heart rate, diastolic blood pressure, systolic blood pressure, and oral temperature. A listing will be provided of vital signs collected at baseline and will include subject number, sequence group, oral temperature, heart rate, systolic/diastolic blood pressure, height, weight, and BMI.

9.4 Medical History

Medical history will be collected at baseline and a listing will be provided, sorted by subject, and will include subject number, sequence group, condition, start date, stop date, and if the condition is ongoing.

10. EFFICACY ANALYSES

The population for analysis for the primary outcomes is the mITT population. This population consists of the enrolled, intent-to-treat population who has evaluable data for both nights of PSG evaluation. Evaluable data includes nights that are considered valid PSG nights, defined as having at least 4 hours of recorded sleep time with no equipment (recording or therapeutic) failures and results in analyzable data for AHI and ODI values.

Mask settings, product information and malfunction measures will be summarized by sequence group and study night, with corresponding listings provided for each.

A listing of PSG night parameters will be provided and will include subject number, sequence group, study night, AHI value, ODI value, arousal index (AI), sleep efficiency (SE %), Minimum Sleep SpO_2 (%), Mean Sleep SpO_2 (%), Wakefulness (min), Stage N1 (min), Stage N2 (min), Stage N3 (min), and REM (min).

10.1 Primary Efficacy Analysis

The primary endpoint in this study is mean AHI values. It is hypothesized that the new device treatment will be non-inferior to the predicate device treatment in mean AHI. The following 1-sided hypothesis will be tested for AHI:

$H0: \mu NEW - \mu PREDICATE \geq 0 + \Delta$
versus
$HA: \mu NEW - \mu PREDICATE < 0 + \Delta$

Where μNEW represents the mean AHI for the new device treatment, μPREDICATE represents the mean AHI for the predicate device treatment, and Δ represents the non-inferiority margin. This analysis will assume a non-inferiority (NI) margin of 5 units and a 1-sided alpha level of 2.5%. A 2-sided 95% confidence interval (CI) will also be provided around the difference between treatments, where non-inferiority will also be demonstrated if the upper bound of the 95% CI is less than or equal to the NI margin of 5 units. In this scenario the 2-sided 95% CI equates to testing the 1-sided non-inferiority hypothesis.

The hypothesis will be tested using a t-test between treatments from an analysis of variance (ANOVA) model with treatment, sequence, and period as fixed effects and subject as a random effect. This model assumes no carry over effect.

The population for this primary endpoint analysis is the mITT population. The mITT population, by definition, will not have any missing data and hence, there will not be any imputation methods applied.

10.2 Sensitivity Analyses for Primary Endpoint

A sensitivity analysis will be conducted on the primary endpoint to assess a site effect. This sensitivity analysis will be conducted in a similar manner as for the primary endpoint. The model described for the primary endpoint will also include a term for site

in the ANOVA model. If the term for site is significant at the 2-sided alpha of 5% then it will be concluded that a site effect exists. Sites having less than 2 subjects in either treatment group will be pooled together into one site.

The primary analysis will also be conducted for the ITT population. There will be two sensitivity analyses using the ITT population, the first will use all ITT subjects and apply a multiple imputation method for missing AHI values. Missing values will be imputed based on baseline characteristics of sex, age, and baseline AHI value. The second sensitivity analysis will include all ITT subjects with observed data collected.

10.3 Secondary Analysis

Mean ODI will be summarized descriptively by treatment group. The population for this secondary analysis is the mITT population.

10.4 Efficacy Subgroup Analyses

Descriptive statistics of the primary endpoint will be provided for the following subgroups using the mITT population:

- Gender (Female, Male)
- BMI (<30, 30-40) kg/m^2
- Investigational Study Site

10.5 Other PSG Measurements

All other PSG measurements will be summarized descriptively by sequence and night.

11. SAFETY ANALYSES

11.1 Adverse Events

Adverse events will be summarized descriptively by treatment group, system organ class, and preferred term. An additional summary will be provided for device and procedure related adverse events by treatment group, system organ class, preferred term and severity. Any SAEs or UADEs will be individually reported. A listing of all adverse events will be generated.

12. CHANGES FROM PROTOCOL

12.1 Changes from Protocol Revision B to SAP Version 1

The following changes from the protocol are:

1. A central randomization list was generated and used for subject treatment assignment rather than using a site stratified randomization list as described in Section 10.4 of the protocol.

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