[redacted]

| STUDY NUMBER: CR-RR-2020-005 | PLAN VERSION: 2.0 | PLAN VERSION DATE: 28 MAY 2024 |
|---|---|---|

# Statistical Analysis Plan: CR-RR-2020-005

| | |
|---|---|
| **Study Title:** | Evaluation of Oscillation and Lung Expansion (OLE) using The Volara® System for treatment of respiratory complications in patients with neuromuscular disease in the home setting |
| **Study Number:** | CR-RR-2020-005 |
| **Study Phase:** | Post Market |
| **Study Design** | The study is a multi-center, non-randomized, open-label, decentralized pilot study using an observational design comparing a retrospective control period to an active treatment period to evaluate the impact of Oscillation and Lung Expansion (OLE) to treat respiratory complications in 70 patients with neuromuscular disease in the home setting. The study will be conducted at 6 to 10 sites in the United States. |
| **Product Name:** | The Volara® System |
| **Indication:** | The Volara® System is an FDA 510k cleared device (k192143), powered by an internal blower, that delivers oscillation and lung expansion (OLE) therapy using both continuous high-frequency oscillation (CHFO) and continuous positive expiratory pressure (CPEP). The therapy is indicated for mobilization of secretions, lung expansion therapy and the treatment and prevention of pulmonary atelectasis. The device can also provide |

[redacted]

supplemental oxygen when used with an oxygen supply.

**Statistician:** [redacted]

**Sponsor:** Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, Illinois 60015, USA

**Responsible Medical Officer:** [redacted]

**Final Date:** 28 MAY 2024

[redacted]

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## SIGNATURE PAGE

**Study Title:** Evaluation of Oscillation and Lung Expansion (OLE) using The Volara® System for treatment of respiratory complications in patients with neuromuscular disease in the home setting

**Study Number:** CR-RR-2020-005

**Statistician:** [redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the planned analyses of the study.

Prepared by and Date :[redacted]

[redacted]
Worldwide Medical, Baxter Healthcare Corporation

Approved by and Date:[redacted]

[redacted]
Worldwide Medical, Baxter Healthcare Corporation

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | adverse event |
| ATS | American Thoracic Society |
| BMI | body mass index |
| CI | confidence interval |
| eCRF | electronic case report form |
| ED | emergency department |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| ICF | informed consent form |
| ICU | intensive care unit |
| ID | identification |
| IV | intravenous |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIP | maximal inspiratory pressure |
| N | sample size |
| NMD | neuromuscular disease |
| OLE | oscillation and lung expansion |
| PCF | peak cough flow |
| PPS | per protocol set |
| PT | preferred term |
| QOL | quality of life |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | Statistical Analysis Software |
| SD | standard deviation |

| | |
|---|---|
| SOC | system organ class |
| SPO2 | oxygen saturation |
| SRI | severe respiratory insufficiency |
| SS | safety analysis set |
| SVC | slow vital capacity |
| US | United States |
| WHO | World Health Organization |

[redacted]



## 1. STUDY DETAILS

This statistical analysis plan (SAP) is provided to describe the framework for the reporting, summarization, and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on clinical trial protocol CR-RR-2020-005 Revision D, dated 11 MAY 2022.

### 1.1 Study Objectives and Endpoints

The objective of the study is the evaluation of the impact of Oscillation and Lung Expansion (OLE) therapy to treat respiratory complications of neuromuscular disease in patients.

Primary Endpoint:

- Frequency of exacerbations of pulmonary disease requiring medical intervention (e. g. one or more of the following):
    - Hospitalization
    - Emergency Department (ED) Visit
    - Unscheduled Antibiotics for Respiratory Infection
    - Unscheduled outpatient visit

Secondary Endpoints:

- Pulmonary function tests
    - Slow Vital Capacity (SVC)
    - Peak Cough Flow (PCF)
    - Resting Oxygen Saturation (SPO2)
    - Maximal Inspiratory Pressure (MIP)
- Number of hospital admissions
- Total hospital length of stay
- Number of intensive care unit (ICU) admissions

- Total ICU length of stay
- Number of outpatient visits for pulmonary complication (Unscheduled Physician's office, Urgent Care Visits, ED visits)
- Number of antibiotic use days during episodes of pulmonary exacerbation
    - IV (intravenous) antibiotic days
    - Oral antibiotic days
    - Nebulized antibiotic days
- Quality of Life (QOL) Assessment
- Patient/caregiver satisfaction with therapy

## 1.2 Study Design

### 1.2.1 Overall Study Design and Plan

The study will be a multi-center, non-randomized, open-label, pilot study. It is a decentralized study using an observational design comparing a retrospective control period to an active treatment period. Approximately 70 patients will be enrolled from identified clinics that currently treat neuromuscular disease (NMD) patients. All enrolled subjects will receive Oscillation and Lung Expansion (OLE) treatment during the active treatment period. Subjects will be recruited from 6 to 10 sites in the United States (US).

Study subjects will serve as their own control. Medical records will be reviewed for each study subject for the 12-month period prior to initiation of OLE therapy. The study will display the frequency of exacerbations experienced prior to treatment with OLE and the frequency of exacerbations experienced in the active treatment period, during which study subjects receive treatment with The Volara® System. In addition, specific healthcare utilization indicators including hospitalizations, antibiotic use, and ED visits for pulmonary complications will be documented for each study period.

Pulmonary function measures, a quality of life (QOL) assessment and a satisfaction survey will be assessed at baseline and during the active treatment period.

### 1.2.2 Determination of Sample Size

A total of approximately 70 subjects will be enrolled. The sample size for this study is a convenience sample. This is a descriptive study with no formal hypothesis testing.

### 1.2.3 Blinding

The study is open label and will not have blinding of any investigational products.

### 1.2.4 Schedule of Visits and Procedures

All study subjects will complete a virtual home baseline study visit for initiation of the trial and enrollment into the study. Following the baseline visit, each study subject will complete 3 follow-up visits. The first follow-up visit will be approximately 1 month after initiating therapy and will occur virtually or by phone. Follow-up visits 2 and 3 will be done virtually and will occur approximately 3 months and 6 months after initiation of OLE therapy. Pulmonary function measures will be collected at baseline and at the end of each month of therapy during the active treatment period.

## 1.3 Analysis Populations

Three main analysis sets are defined for this study.

### 1.3.1 Definition of Analysis Populations

*Full analysis set* (FAS): all patients who have at least 1 exacerbation event requiring medical intervention in the 12-month pre-treatment historical control period and who received at least one Volara® treatment.

*Per protocol set* (PPS): all patients in the FAS who do not have any protocol deviations that could impact the primary endpoint.

<u>Deviations that could be considered for exclusion in a PPS analysis</u>

- Treatment errors
- Use of prohibited medication known to influence the primary endpoint
- Key exclusion criteria such as:

- Diagnosis with rapidly progressing NMD such as certain types of Motor Neuron Disease (MND)
- Requirement for continuous mechanical ventilation
- Anticipated requirement for respiratory related hospitalization within the next six months
- History of pneumothorax within past 6 months
- History of hemoptysis requiring embolization within past 12 months
- Home use of OLE therapy within the past 12 months
- Inability or unwillingness to perform OLE therapy or study procedures as required

Deviations that should not lead to exclusion of data in a PP analysis

- Patients who violate inclusion/exclusion criteria relating to patient safety
- Issues with documentation of informed consent
- Issues with SAE reporting

Safety analysis set (SS): the set of all patients who have received OLE therapy with The Volara® System.

### 1.3.2 Protocol Deviations

Protocol deviations will be summarized for all patients in the FAS pooled together. Patient counts and number of deviations will be presented for minor protocol deviations, major protocol deviations, and for each category of major protocol deviation.

Protocol deviations will also be listed for the FAS. The listing will include patient ID, age, verbatim description of the protocol deviation, the assigned category of protocol deviation, and major/minor status.

### 1.3.3 Safety Variables

#### 1.3.3.1 Adverse Events

The safety profiles are evaluated by:

- Adverse Events (AEs) / Adverse Device Effects (ADE)

- Serious Adverse Events (SAEs) / Serious Adverse Device Effects (SADE)

### 1.4 Interim Analysis

An interim analysis has not been planned for this study.

## 2. ANALYSIS METHODS

### 2.1 General Principles

Unless otherwise specified, summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum values) will be presented for continuous variables. Counts and, if relevant, percentages will be presented for categorical variables.

Unless otherwise specified, data listings will include patient ID, sex, and age at baseline (rounded down to the nearest whole number).

Unless otherwise noted, all analyses will be performed using SAS/Graph® 9.4 software, SAS/STAT® 15.1 software, and BaseSAS® 9.4. Copyright © 2016, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. All Rights Reserved

Unless otherwise specified, the estimated mean and median for a set of values will be displayed to 1 more significant digit than the original values, standard deviations will be displayed to 2 more significant digits, and minimum and maximum values will be displayed with the same number of significant digits as the original values. If an original value has more than 2 decimal places, the significant digits will be counted as if there are 2 decimal places. All percentages will be displayed with 1 decimal place unless more decimal places are needed to show 1 significant digit (i.e., a percentage of 0.01 will be shown as 0.01 as opposed to 0.0).

#### 2.1.1 Definition of baseline

Unless otherwise specified, baseline is defined as the values collected at the baseline visit. The value closest to the start of treatment will be used for baseline if multiple values are available.

Change from baseline variables will be calculated as the post-treatment value minus the value at baseline.

### 2.1.2 Study Periods

The study periods include the 12-month pre-treatment historical control period, 6-month pre-treatment historical control period, and the active treatment period. The active treatment period begins once a subject has started therapy with The Volara® System.

### 2.1.3 Visit Windows

The study visits for the active treatment period can be obtained from the eCRF and need not be derived programmatically. The visits will be displayed as: Baseline, 1-month, 2-month, 3-month, 4-month, 5-month, 6-month.

Results from unscheduled study visits will not be included in table summaries. These values will only be presented in the listings.

### 2.1.4 Completion and Discontinuation

A patient is considered to have completed the study when he/she ceases active participation in the study because the patient has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations). Any other cases are classified as discontinuation.

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation electronic case report form (eCRF), including:

- Protocol Violation
- Withdrew Consent
- Lost to Follow-Up
- Adverse Device Effect
- Other

Regardless of the reason, all data available for the patient up to the time of completion/discontinuation should be recorded on the appropriate eCRF.

### 2.2 Patient Disposition

Patient disposition will be summarized and will include:

- Number of patients screened
- Number of patients who screen fail. These patients will also be summarized by primary reason for screen failure from the study. The percentage associated with each reason will have the total number of patients who screen fail as the denominator.
- Number of patients enrolled
- Number of patients included in chart review for 12-month pre-treatment period
- Number of patients eligible for treatment
- Number of patients treated with study device
- Number of patients in the FAS
- Number of patients in the PPS
- Number of patients in the SS
- Number of patients who completed the study
- Number of patients who discontinued (withdrew early) from the study. These patients will also be summarized by primary reason for withdrawal from the study. The percentages associated with each reason for early withdrawal will have the total number of patients who withdrew early as the denominator.

A listing of all patients enrolled in the study will be created including patient ID, age, sex, completion status, reason for discontinuation (if applicable), and the number of days that the patient remained in the study. The number of days the patient was in the study will be calculated using the following:

$$(Date\ of\ Study\ Completion/Discontinuation - Date\ of\ Enrollment) + 1$$

### 2.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized descriptively for the FAS population. A listing will also be provided for this population.

#### 2.3.1 Demographics

Demographics (age, race, ethnicity, sex) will be summarized descriptively.

#### 2.3.2 Other Baseline Characteristics

Baseline characteristics including height, weight, and BMI will be summarized descriptively.

#### 2.3.3 Medical History

All neuromuscular disease and pulmonary disease medical history will be listed.

#### 2.3.4 Concomitant Medications

All pulmonary and respiratory related concomitant medications will be listed.

### 2.4 Endpoint Analyses

#### 2.4.1 Primary Endpoint

The primary endpoint analysis will be carried out on the FAS with a supportive analysis performed on the PPS.

##### 2.4.1.1 Derivation of Primary Endpoint

Exacerbations of pulmonary disease are defined as changes in respiratory status requiring intervention. Documentation of pneumonia or respiratory infection, change in chest x-ray, changes in requirement for respiratory support necessitating any of the interventions below will be considered an exacerbation of pulmonary disease:

- Hospitalization
- ED Visit
- Unscheduled Antibiotics for Respiratory Infection
- Unscheduled outpatient visit

Pulmonary exacerbation events that occurred during the 12-month pre-treatment period and the active treatment period will be recorded in the data. Pulmonary exacerbation events that occurred prior to the Volara® start date occurred in the pre-treatment period. Pulmonary exacerbation events that occurred on or after the Volara® start date occurred in the active treatment period. The paired difference in pulmonary exacerbation events for each subject will be calculated as follows:

$$Number\ of\ pulmonary\ exacerbations\ in\ active\ treatment\ period - Number\ of\ pulmonary\ exacerbations\ in\ 6\ months\ prior\ to\ treatment\ start$$

#### 2.4.1.2 Analysis of Primary Endpoint

The primary endpoint of the study, frequency of exacerbations of pulmonary disease requiring medical intervention, will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum. The paired difference in the frequency of exacerbations of pulmonary disease requiring medical intervention between study periods (active treatment period - 6-month pre-treatment historical control period) will also be analyzed descriptively with n, mean, standard deviation, minimum, median, maximum and 95% two-sided confidence interval (CIs) for the mean paired difference. All pulmonary exacerbation events that occurred in the 12-month pre-treatment period and the active treatment period will be listed.

### 2.4.2 Secondary Endpoints

All secondary endpoint analyses will be performed on the FAS.

#### 2.4.2.1 Pulmonary Function Tests

##### 2.4.2.1.1 Derivation of Pulmonary Function Tests

Pulmonary function test results will be recorded in the data at baseline and at the end of each month of therapy during the active treatment period. During these visits, the following procedures and assessments will be conducted:

- Slow Vital Capacity (SVC)
- Peak Cough Flow (PCF)

- Resting Oxygen Saturation (SPO2)
- Maximal Inspiratory Pressure (MIP)

#### 2.4.2.1.2 Analysis of Pulmonary Function Tests

Pulmonary function tests (SVC, PCF, SPO2, MIP) that were acceptable by ATS Standards, deemed the 'Best Measurements' for the series based on ATS acceptability, and completed in accordance with the study protocol will be analyzed descriptively at each time-point (Baseline, 1-month, 2-month, 3-month, 4-month, 5-month, 6-month), using n, mean, standard deviation, minimum, median, and maximum. Change from baseline values will also be presented in a similar manner. Subjects with SPO2 measures collected in the same setting across all study visits will be tabulated. SPO2 measures across all settings will be listed.

### 2.4.2.2 Number of Hospital Admissions

#### 2.4.2.2.1 Derivation of Number of Hospital Admissions

The number of hospital admissions that occurred during the pre-treatment period and active treatment period will be recorded in the data.

#### 2.4.2.2.2 Analysis of Number of Hospital Admissions

The number of hospital admissions will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum. All hospital admissions that occurred in the 12-month pre-treatment period and the active treatment period will be listed.

### 2.4.2.3 Hospital Length of Stay

#### 2.4.2.3.1 Derivation of Hospital Length of Stay

Total hospital length of stay will be determined for each study subject by calculating the number of days spent in the hospital for each admission, from time of admission to time of discharge. Date of admission and date of discharge will be recorded in the data for each study period. The sum of all hospital days for each subject will be calculated for the 6-month pre-treatment and active treatment periods. The number of days spent in the hospital for each admission will be calculated as follows (standardized to the number of days):

$$Date\ of\ Discharge - Date\ of\ Admission + 1$$

#### 2.4.2.3.2 Analysis of Hospital Length of Stay

The number of inpatient hospital days will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum.

### 2.4.2.4 Number of ICU Admissions

#### 2.4.2.4.1 Derivation of Number of ICU Admissions

The number of ICU admissions that occurred during the pre-treatment period and active treatment period will be recorded in the data.

#### 2.4.2.4.2 Analysis of Number of ICU Admissions

The number of ICU admissions will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum. All ICU admissions that occurred in the 12-month pre-treatment period and the active treatment period will be listed.

### 2.4.2.5 ICU Length of Stay

#### 2.4.2.5.1 Derivation of ICU Length of Stay

Total ICU length of stay will be determined for each study subject by summing the calculated number of days spent in the ICU for each admission, from time of admission to time of discharge. Date of admission and date of discharge will be recorded in the data for each study period. The sum of all ICU days for each subject will be calculated for the pre-treatment period and for the active treatment period. The number of ICU days for each admission will be calculated as follows (standardized to the number of days):

$$Date\ of\ Discharge - Date\ of\ Admission + 1$$

#### 2.4.2.5.2 Analysis of ICU Length of Stay

Total ICU length of stay will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum.

#### 2.4.2.6 Number of Outpatient Visits for Pulmonary Complication

##### 2.4.2.6.1 Derivation of Number of Outpatient Visits for Pulmonary Complication

The number of outpatient visits for pulmonary complication that occurred during the pre-treatment period and active treatment period will be recorded in the data.

##### 2.4.2.6.2 Analysis of Number of Outpatient Visits for Pulmonary Complication

The number of outpatient visits for pulmonary complication will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum. All outpatient visits for pulmonary complication that occurred in the 12-month pre-treatment period and the active treatment period will be listed.

#### 2.4.2.7 Number of Antibiotic Use Days for Pulmonary Exacerbation

##### 2.4.2.7.1 Derivation of Number of Antibiotic Use Days for Pulmonary Exacerbation

Total number of antibiotic use days for pulmonary exacerbation will be determined by summing the calculated number of days of antibiotic use for each episode, from time of initiation to time of discontinuation. Date of initiation and date of discontinuation of antibiotic use for each pulmonary exacerbation will be recorded in the data for each study period. Antibiotic use will be further categorized and individual totals will be provided for 1) oral, 2) intravenous, and 3) nebulized antibiotic use for pulmonary complications that occur during the pre-treatment period and during the active treatment period. The number of antibiotic use days for each pulmonary exacerbation will be calculated as follows (standardized to the number of days):

$$Date\ of\ Discontinuation - Date\ of\ Initiation + 1$$

##### 2.4.2.7.2 Analysis of Number of Antibiotic Use Days for Pulmonary Exacerbation

The number of antibiotic use days for pulmonary exacerbation will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum.

#### 2.4.2.8 Quality of Life (QOL) Assessment

##### 2.4.2.8.1 Derivation of Quality of Life (QOL) Assessment

Severe Respiratory Insufficiency (SRI) questionnaire results for the Respiratory Complaints scale at baseline, 1-month, 3-month and 6-month study visits will be recorded in the data.

##### 2.4.2.8.2 Analysis of Quality of Life (QOL) Assessment

QOL assessments for the overall Respiratory Complaints scale score will be analyzed descriptively at each time-point (Baseline, 1-month, 3-month, 6-month) using n, mean, standard deviation, minimum, median, and maximum. Change from baseline values will also be presented in a similar manner. Individual responses to each Respiratory Complaints survey question will be summarized descriptively using frequencies and percentages. The Severe Respiratory Insufficiency Questionnaire guidance for scoring the Respiratory Complaints scale will be implemented.[1]

## Guidance for scoring

Please provide the following values for each item:

| | | |
|---|---|---|
| completely untrue | => | 1 |
| mostly untrue | => | 2 |
| sometimes true | => | 3 |
| mostly true | => | 4 |
| always true | => | 5 |

The majority of items need to be recoded following the instructions given below:

| value | | recoded value |
|---|---|---|
| 1 | → | 5 |
| 2 | → | 4 |
| 3 | → | 3 |
| 4 | → | 2 |
| 5 | → | 1 |

Items which need to be recoded:

1, 2, 4, 5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 19, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 34, 35, 38, 39, 40, 42, 43, 45, 46, 47, 48.

Next, the scales need to be calculated as indicated below. For this purpose at least 50% of the items per scale must be correctly addressed. Please find the item number indicated in brackets [a, b, c.....]. This process of transformation produces a score between 0 and 100 with higher values indicating a better health-related quality of life according to content of the scale.

## Respiratory Complaints

$$SRI - RC = \frac{Mean\ [2,5,12,19,22,24,25,29] - 1}{4} \bullet 100$$

#### 2.4.2.9 Patient/caregiver Satisfaction with Therapy

##### 2.4.2.9.1 Derivation of Patient/caregiver Satisfaction with Therapy

Satisfaction questionnaire results for prior therapy at baseline and for The Volara® System at 1-month, 3-month and 6-month study visits will be recorded in the data.

##### 2.4.2.9.2 Analysis of Patient/caregiver Satisfaction with Therapy

Patient/caregiver satisfaction with prior therapy at baseline and with The Volara® System at 1-month, 3-month, and 6-month timepoints will be analyzed descriptively using frequencies and percentages. Patient/caregiver satisfaction scores will be summarized for each question.

### 2.5 Safety Analyses

All safety analyses will be performed on the SS.

#### 2.5.1 Adverse Events

##### 2.5.1.1 Derivation of Adverse Events

*Pre-treatment adverse event* – An adverse event that starts between the date of signing the informed consent form (ICF) and the start of study therapy

*Treatment-emergent adverse event (TEAE)* – An adverse event that starts on or after the start of study therapy

In case of incomplete information on study treatment or AE onset, events will be classified as treatment-emergent unless there is sufficient data to rule out the possibility that the event started after the start of study treatment.

The number of events per patient will be calculated as follows:

$$\frac{Number\ of\ Total\ Events}{Number\ of\ Patients\ in\ Safety\ Set}$$

##### 2.5.1.2 Analysis of Adverse Events

An AE overview summary table will be prepared to include the number of patients, the percentage of patients (%), the number of events, and the number of events per patient, for the following categories:

1. Any adverse event
2. Any treatment-emergent adverse event (TEAEs)
3. Treatment emergent non-serious AEs
4. Treatment-emergent serious AEs (SAEs)
5. Treatment-emergent study device-related AEs
6. Treatment-emergent study device-related SAEs
7. Treatment-emergent AEs leading to discontinuation
8. Treatment-emergent AEs leading to death

Additional listings and tables on the above categories (with the exception of #1 and #3) will be given by SOC and PT. Pre-treatment AEs (those occurring between informed consent and device use) will also be listed. For SAE listings, the seriousness criteria will be included in the listing.

The tables below will display the total number of patients, the percentage of patients (%), the number of events, the number of events per patient, system organ class (SOC), and preferred term. Table summaries will be produced for:

- Treatment-emergent AEs by severity
- Treatment-emergent SAEs by severity
- Treatment-emergent AEs by relationship to study device
- Treatment-emergent SAEs by relationship to study device
- Treatment-emergent adverse events in ≥5% of patients

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order by the percentage of patients.

Adverse event listings will be sorted by patient ID, and adverse event start date. They will include SOC, PT, verbatim term, adverse event start and end date and its duration, relationship to study device, severity, action taken, and seriousness.

### 2.6 Other general principles

#### 2.6.1 Handling of Dropouts or Missing data

All data collected up to the point where the patient drops out will be used for analyses. Missing data will not be imputed.

#### 2.6.2 Multicenter Studies

This study was conducted as a decentralized, home-based study recruiting patients from 6 to 10 sites in the US. Data from all sites will be pooled together for analyses.

#### 2.6.3 Multiple Comparison/Multiplicity

No formal statistical tests are calculated for this study, so no multiplicity adjustments are needed.

#### 2.6.4 Rounding and Decimal Places

The estimated mean and median for a set of values will be displayed to 1 more significant digit than the original values, standard deviations will be displayed to 2 more significant digits, and minimum and maximum values will be displayed with the same number of significant digits as the original values. All percentages will be displayed out to 1 decimal place.

## 3. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

Mean adherence to prescribed treatment regimen will not be analyzed.

## 4. REFERENCES

1. Windisch W. Severe Respiratory Insufficiency Questionnaire English Scoring. https://www.atemwegsliga.de/files/eigene-dateien/pdf/Scoring_English1a60.pdf

## 5. APPENDIX

### 5.1 Appendix 1: List of Tables, Listings, and Figures

| Table Number | Analysis Population | Table Name |
|---|---|---|
| 14.1.1 | N/A | Patient Overview |
| 14.1.2 | FAS | Patient Disposition |

| | | |
|---|---|---|
| 14.1.3 | FAS | Protocol Deviations |
| 14.1.4 | FAS | Categorical Demographic and Baseline Characteristics |
| 14.1.5 | FAS | Continuous Demographic and Baseline Characteristics |
| 14.2.1.1 | FAS | Primary Endpoint: Exacerbations of Pulmonary Disease Requiring Medical Intervention |
| 14.2.1.2 | PPS | Primary Endpoint: Exacerbations of Pulmonary Disease Requiring Medical Intervention |
| 14.2.2 | FAS | Pulmonary Function Tests |
| 14.2.3 | FAS | Medical Interventions for Exacerbations of Pulmonary Disease |
| 14.2.4.1 | FAS | Quality of Life Assessment - Respiratory Complaints Overall Score |
| 14.2.4.2 | FAS | Quality of Life Assessment - Respiratory Complaints |
| 14.2.5.1 | FAS | Patient/caregiver Satisfaction with Prior Therapy at Baseline |
| 14.2.5.2 | FAS | Patient/caregiver Satisfaction with The Volara® System |
| 14.3.1.1.1 | SS | Summary of Adverse Events |
| 14.3.1.1.2 | SS | Treatment Emergent Adverse Events by SOC and Preferred Term |
| 14.3.1.1.3 | SS | Serious Treatment Emergent Adverse Events by SOC and Preferred Term |
| 14.3.1.1.4 | SS | Treatment Emergent Adverse Events Related to Study Device by SOC and Preferred Term |
| 14.3.1.1.5 | SS | Serious Treatment Emergent Adverse Events related to Study Device by SOC and Preferred Term |
| 14.3.1.1.6 | SS | Treatment Emergent Adverse Events Leading to Discontinuation by SOC and Preferred Term |
| 14.3.1.1.7 | SS | Treatment Emergent Adverse Events Leading to Death by SOC and Preferred Term |

| | | |
|---|---|---|
| 14.3.1.1.8 | SS | Treatment Emergent Adverse Events in ≥5% of Patients by SOC and Preferred Term |
| 14.3.1.2.1 | SS | Treatment Emergent Adverse Events by SOC, Preferred Term, and Severity |
| 14.3.1.2.2 | SS | Serious Treatment Emergent Adverse Events by SOC, Preferred Term, and Severity |
| 14.3.1.3.1 | SS | Treatment Emergent Adverse Events by SOC, Preferred Term, and Relationship with Study Device |
| 14.3.1.3.2 | SS | Serious Treatment Emergent Adverse Events by SOC, Preferred Term, and Relationship with Study Device |

| **Listing Number** | **Analysis Population** | **Listing Name** |
|---|---|---|
| 16.2.1 | N/A | Patient Disposition |
| 16.2.2 | FAS | Protocol Deviations |
| 16.2.3.1 | N/A | Patient Overview |
| 16.2.4.1 | FAS | Demographic and Baseline Characteristics |
| 16.2.4.2 | FAS | Medical History |
| 16.2.4.3 | FAS | Pulmonary Concomitant Medications |
| 16.2.4.4 | FAS | Respiratory Support and Respiratory Concomitant Medications |
| 16.2.6.1 | FAS | Exacerbations of Pulmonary Disease Requiring Medical Intervention |
| 16.2.6.2 | FAS | Pulmonary Function Tests |
| 16.2.6.3 | FAS | Medical Interventions for Exacerbations of Pulmonary Disease |
| 16.2.6.4.1 | FAS | Quality of Life Assessment - Respiratory Complaints Overall Score |
| 16.2.6.4.2 | FAS | Quality of Life Assessment - Respiratory Complaints |
| 16.2.6.5 | FAS | Patient/caregiver Satisfaction with Prior Therapy and The Volara® System |
| 16.2.7.1.1 | SS | Pre-Treatment Adverse Events |
| 16.2.7.1.2 | SS | Treatment Emergent Adverse Events |
| 16.2.7.1.3 | SS | Serious Pre-Treatment Adverse Events |

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| 16.2.7.1.4 | SS | Serious Treatment Emergent Adverse Events |
| 16.2.7.1.5 | SS | Treatment Emergent Adverse Events Related to Study Device |
| 16.2.7.1.6 | SS | Serious Treatment Emergent Adverse Events Related to Study Device |
| 16.2.7.1.7 | SS | Treatment Emergent Adverse Events Leading to Discontinuation |
| 16.2.7.1.8 | SS | Treatment Emergent Adverse Events Leading to Death |