Protocol CLN0016.p. D

LVRC IDE Crossover Study (Crossover from IDE Trial CLN0009, Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study, IDE G110066)

Statistical Analysis Plan (Methodology)

Version 1.0

July 7, 2017

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1. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

The purpose of the statistical analysis plan (SAP) is to provide a detailed and comprehensive description of the planned methodology and analysis for Protocol CLN0016.p. D, the CROSSVER Study. This plan is based on the version CLN0016.p. D, study protocol dated August 24th, 2015.

1.1 Study Objective

The primary objective of this study is to obtain safety and effectiveness data on patients who were enrolled as Control patients in and completed the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) study (CLN0009).

1.2 Study Design

This will be a prospective, multicenter, open label, single-arm study.

1.2.1 Effectiveness Endpoints

- 6MWT: absolute change from baseline at 12 months in the 6 Minute Walk Test
- 6MWT: responder analysis, comparing baseline to 12 months, responders defined as those with an improvement of ≥25 meters[1]
- Forced Expiratory Volume in one second (FEV_1): percent change in FEV_1 results measured using spirometry, comparing baseline to 12 monthsSaint George's Respiratory Questionnaire (SGRQ): absolute difference in SGRQ total score comparing baseline to 12 months.
- SGRQ: responder analysis, comparing baseline to 12 months, responders defined as those with an improvement of ≥4 points[2]
- SGRQ: absolute difference in individual domain scores comparing baseline to 12 months
- FEV1: responder analysis, comparing baseline to 12 months, responders defined as those with an improvement of ≥ 10 %.
- Residual Volume (RV): absolute difference in RV measured using plethysmography, comparing baseline to 12 months[3-5]
- RV: responder analysis, comparing baseline to 12 months, responders defined as those with an improvement (decrease) of .35L
- Vital Capacity (VC): absolute difference in VC measured using plethysmography, comparing baseline to 12 months
- Residual Volume/Total Lung Capacity (RV/TLC): absolute difference in RV/TLC measured using plethysmography, comparing baseline to 12 months [6-8]

1.2.2 Safety Endpoints

The primary safety analysis will tabulate subjects who experience one or more major complication(s) within 12 months post-baseline (and within defined blocks of time post-baseline). Major complications will be determined/adjudicated by the Clinical Events Committee.

Major Complications:

- Death;
- Pneumothorax that requires a chest drainage tube for more than 7 days (from time of chest drainage tube insertion to the time of chest drainage tube removal);
- Hemoptysis requiring blood transfusion(s), arterial embolization, or surgical/endoscopic procedure;
- COPD exacerbation that becomes life-threatening or disabling as a result of an increase in respiratory symptoms requiring in-patient hospitalization of >7 days with or without mechanical ventilation;
- Lower Respiratory Infections (including pneumonia) defined by new or increased clinical symptoms such as fever, chills, productive cough, chest pain, dyspnea and an infiltrate on plain chest x-ray and hospitalization for administration of intravenous antibiotics and/or steroids;
- Respiratory failure defined as a requirement for mechanical ventilatory support (whether via endotracheal tube or mask) for >24 hours; and
- An unanticipated bronchoscopy in order to remove one or more Coils due to a device-related AE. (Note: This definition does not include re-positioning, replacement or removal of the Coil(s) during the initial placement procedure.)

1.3 Analysis Populations

1.3.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include patients who enrolled in the CROSSOVER study, regardless of whether or not treatment was attempted.

1.4 Sample Size and Power Calculation

The CROSSOVER Study was designed to provide an opportunity for qualifying Control subjects from the RENEW study to receive the LVRC treatment once their participation in the randomized phase of the RENEW study was complete; all qualifying subjects who wished to participate and met the enrollment criteria were enrolled. Thus, the study sample size was not based on a primary and null hypothesis, or power calculation and results will only be presented descriptively.

2. ANALYSIS CONSIDERATIONS

2.1 Subject Disposition

The number of subjects screened, enrolled and treated in the study will be presented. Additionally, the number and percentage of subjects who complete the study to 12 months, 24 months, 36 months, 48 months and 60 months, and who terminate the study prematurely (by visit), will be presented including reasons for premature termination.

2.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized. Baseline is defined as the last assessment evaluated prior to treatment. Demographic and baseline characteristics will be presented with summary statistics (sample size (N), mean, standard deviation (SD), median, minimum, and maximum) for continuous variables and frequency distributions for categorical variables.

2.3 Endpoint Analyses

2.3.1 Effectiveness Endpoint Analyses

Summary statistics will be provided for change in 6MWT, percent change in FEV1 (L), absolute change in SGRQ (total and individual domain scores), absolute change in RV (L), absolute change in VC and absolute change in RV/TLC from baseline to the 12 month follow-up visit.

Additionally, summary statistics will be provided for the change at each follow-up visit (24 months, 36 months, 48 months and 60 months).

Frequency distributions will be presented for the 6MWT, SGRQ, FEV1 and RV responder rates for each follow-up time period (12 months, 24 months, 36 months, 48 months and 60 months).

2.3.2 Safety Endpoint Analyses

Treatment emergent adverse events (AEs), serious adverse events (SAEs) and major complications will be summarized. AE and major complication summaries will include all events experienced within the first 12 month visit and each follow-up time period. Overall summaries will be presented, but shorter periods of time prior to 12 month visit will be considered as well. In order to assess the safety profile of the LVRC without the interference of the procedure effect, the timing of adverse events and major complications with respect to the treatment visits will be considered.

2.3.2.1 Event Time Periods

In order to assess the safety profile of the LVRC without the interference of the procedure effect, adverse events and major complications will be summarized by time period. Each event will be included in the time period in which the event began, with the periods defined as follows:

- Peri-procedural: 0-30 days post each of the two treatment visits (visit 2 or visit 5)
- Between treatment #1 and visit 5: More than 30 days after visit 2, but prior to visit 5
- Between treatment #2 (or treatment #1 for subjects that miss Visit 5) and 6 months: More than 30 days after visit 5, but prior to 6 months post treatment #1

- Between 6 and 12 months: 6 or more months post treatment #1 through visit 10

Regarding the programming specifications for inclusion of AE records through the 12-month visit and each follow-up time period, please refer to Appendix 4.1 (item F).

2.3.2.3 Adverse Events

MedDRA system organ classes and preferred terms will be summarized for all AEs. Summaries will include event and subject counts. For the events summarized by subject counts, each subject will be counted only once within a system organ class or a preferred term by using the adverse events with the highest severity within each category.

SAE, AEs, and AEs related to device or procedure will be summarized separately. Additionally, summaries for major complications will also be included. A high level summary for SAEs and AEs will also be provided. All summaries will be presented by each follow up time period. Similarly, device or procedure related SAEs and non-SAEs will be presented by severity.

In addition, all information pertaining to AEs noted during the study will also be listed by subject. Details of the line listing by subject will include verbatim term given by the Investigator, preferred term, system organ class, start date, stop date, severity, and device or procedure relatedness. The AE onset will also be shown relative (in number of days) to the day of the procedure.

2.4 Subgroup Analysis

The following subgroup analyses will be presented for effectiveness and safety endpoints.

- US vs. OUS (outside of the US)
- Heterogeneity of emphysema
- Severity of air trapping (RV >225% vs. RV < 225%)

2.5 Interim Analysis

The efficacy and safety analyses as described herein will occur following the completion of the 12-month follow-up visit for all patients per the protocol defined endpoints. Additionally, the analyses will be performed at 24 month follow-up, 36 month follow-up, 48 month follow-up and 60 month follow-up.

There are no formal additional interim analyses planned for this study.

2.6 Protocol Deviations

The frequency of protocol deviations (PD) will be summarized by major and minor as defined in the study protocol deviation plan, by center, by category and by category within major and minor by each time period.

2.7 Additional Descriptive Analysis

Additional descriptive summary statistics will be presented for clinical assessments (such as plethysmography and spirometry measures), procedural and device data, and efficacy results.

For continuous variables, summary statistics (sample size (N), mean, standard deviation (STD), median, minimum, and maximum).

For categorical variables, results will be summarized with frequency distributions by follow-up time period.

2.8 Documentation and Other Considerations

All analyses will be performed using SAS® for Windows, version 9.3 or above.

3. REFERENCE

1. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil 2010; 91: 221-225*.
2. Schünemann HJ, Griffith L, Jaeschke R, Goldstein R, Stubbing D, Guyatt GH.Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. *Journal of Clinical Epidemiology 2003; 56: 1170-1176*
3. O'Donnell, DE et al. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in COPD. *Eur. Respir. J 2004; 23; 832-40.*
4. O'Donnell, DE et al.Effects of Fluticasone Propionate/Salmeterol on Lung Hyperinflation and Exercise Endurance in COPD. *CHEST; 130; 3; Sept. 2006; 647-56* .
5. O'Donnell, DE et al.Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease.*Proc Am Thorac Soc. 2006 Apr; 3(2):180-4. Review.*
6. Tzani, P et al.Effects of beclomethasone/formoterol fixed combination on lung hyperinflation and dyspnea in COPD patients.*CHEST; 130; 3; Sept. 2006; 647-56.*
7. Puhan MA, Chandra D, Mosenifar Z, Ries A, Make B, Hansel NN, Wise R, Sciurba B for the National Emphysema Treatment Trial (NETT) Research Group. The minimal important difference of exercise tests in severe COPD. *Eur Respir J. 2011: 27: 784-90*.
8. Celli, B. et al.Improvements in Resting Inspiratory Capacity and Hyperinflation with Tiotropium in COPD Patients with Increased Static Lung Volumes.*CHEST; 124; 5; Nov. 2003; 1743-48.*

4. APPENDIX

4.1 Programming Specifications

A. Required margins: at least 1.25 inches on the binding margin and at least 1 inch on all other sides. All output should have the following header at the upper left margin:

PneumRx - BTG International
Protocol: CLN0016.p. D

and the following header (right-justified) at the upper right margin:

Page n of N
DDMMMYYYY

Tables/appendices/listings should be internally paginated (i.e., page numbers should appear sequentially within each table).

All output should have SAS program name in the lower right and the data source(s) used to generate the output in the lower left:

Data
Source: xxx PROGRAM: XYZ.sas

B. In general, data listings should be sorted by subject number and visit/start dates, unless specific instructions to do otherwise.

C. The following algorithm should be used to impute adverse event start dates for which only partial information is known:

- Missing day and month
  - If the year is same as the year of treatment (LVRC), then the day and month of treatment (LVRC) is assigned to the missing fields.
  - If the year is prior to or after the year of treatment, then January 1 is assigned to the missing fields.
- Missing month only
  - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only
  - Then the first day of the month is assigned to the missing day.

If the AE date of resolution is complete and the imputed start date as above is after the resolution date, the start date is imputed using the resolution date.

Adverse events with partially missing stop dates are imputed a resolution date as follows:

- *year is missing* – the date is left missing.
- *month is missing* – impute "December."

- *day is missing* – impute last date of that month.

D. Complete dates for concomitant medications (CM) with missing or partially missing start dates are imputed using the same algorithm described for adverse event onset dates. If the end date is missing or partially missing, the imputation rule is applied in the following order:

1) *year is missing* – the medication is considered to have been received at all periods after the period determined by the start date. The date is left missing.
2) *month is missing* – impute "December."
3) *day is missing* – impute last date of that month.

E. Date imputations are applied to the process of assigning treatment period and study day and should be retained in the derived database, but the data listings should display the original, partially missing dates.

F. Specifications regarding the inclusion of AE/CM/PD records

1) up to 12-month visit are defined as follows:
- Completed 12 month visit – then include all records with AE/CM/PD onset dates ≤ the actual 12 month visit date.
- Missing 12 month visit – then include all records with AE/CM/PD onset dates ≤ 13 months post treatment #1 date.

2) 12 – 24 month are defined as follows:
- Completed 24 month visit – then include all records with AE/CM/PD onset dates ≤ the actual 24 month visit date and ≥ actual 12 month visit date.
- Missing 24 month visit – then include all records with AE/CM/PD onset dates ≤ 25 months post treatment #1 date and ≥ actual 12 month visit date.

3) 24 – 36 month are defined as follows:
- Completed 36 month visit – then include all records with AE/CM/PD onset dates ≤ the actual 36 month visit date and ≥ actual 24 month visit date.
- Missing 36 month visit – then include all records with AE/CM/PD onset dates ≤ 37 months post treatment #1 date and ≥ actual 24 month visit date.

4) 36 – 48 month are defined as follows:
- Completed 48 month visit – then include all records with AE/CM/PD onset dates ≤ the actual 48 month visit date and ≥ actual 36 month visit date.
- Missing 48 month visit – then include all records with AE/CM/PD onset dates ≤ 49 months post treatment #1 date and ≥ actual 36 month visit date.

5) 48 – 60 month are defined as follows:
- Completed 60 month visit – then include all records with AE/CM/PD onset dates ≤ the actual 60 month visit date and ≥ actual 48 month visit date.
- Missing 60 month visit – then include all records with AE/CM/PD onset dates ≤ 61 months post treatment #1 date and ≥ actual 48 month visit date.

G. Unless otherwise noted, the mean (standard deviation) of a set of values should be printed out to one (two) more decimal(s) than the raw value.

e.g., raw: xx
mean and standard deviation: xx.x and xx.xx
range (minimum and maximum): xx, xx

H. All table percentages should be reported with one decimal point unless otherwise noted.

I. Missing data should be represented on patient listings as 1) dashes "–," and properly footnoted: "– = data not available" or 2) "n/a," with footnote "n/a = not applicable," whichever is appropriate.

J. Times should be printed in the format "HH:MM." "HH" represents the 2-digit hour portion of the time. "MM" represents the 2-digit minute portion of the time. Both hour and minute portions of time are zero-filled on the left if they have only one digit. Missing time portions should be represented on patient listings as dashes ("10:--" and "--:--"). Times that are missing because they are not applicable for the patient should be printed as "n/a," unless otherwise specified.