NCT03600376
Protocol EGL-4104-C-1801:

Phase 3, Multi-Center, Double-Blind, Randomized, 2-Arm, Parallel Study to Assess the Efficacy and Safety of Ryanodex® (EGL-4104) as Adjuvant Treatment in Subjects With Exertional Heat Stroke (EHS)

Document Date: January 3, 2020

[redacted]

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL

9.7.1 Statistical and Analytical Plans

[redacted] lock for the clinical trial protocol EGL-4104-C-1801. Highlights from the statistical analyses proposed for this study are discussed below. [redacted]

9.7.1.1 General Statistical Considerations

All collected study data was to be presented in subject data listings. Statistical analyses were to be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) were to be calculated by treatment group for continuous variables. Frequencies and percentages were to be presented by treatment group for categorical variables.

9.7.1.2 Data Convention and Related Definitions

9.7.1.2.1 Baseline Definition

Baseline body temperature was to be the first rectal temperature ≥ 40.0°C taken during the Screening Phase. Baseline results for other study assessments were to be the value closest in time to the baseline rectal temperature and prior to randomization. The SAP may specify additional data handling rules.

9.7.1.2.2 Duplicate Data

For unplanned duplicate data within a protocol-specified time point, the last measured value was to be used for the analysis. If it is not possible to identify the "last measured value", the average of the duplicate values was to be used.

9.7.1.2.3 Outliers

Data points that appear to be outliers (i.e., clinically identified to be too small or too large) were to be investigated and were not to be excluded from the listings. If the clinician confirms that a data point was truly an outlier and was not clinically possible, two analyses were to be performed, one with the outlier data point and one without it. Any such analysis was to be clearly indicated and footnoted.

9.7.1.2.4 Handling of Missing Data

Every effort was to be made to obtain required data at each scheduled evaluation from all subjects who have been randomized to minimize missing data. The following methods were to be used to handle missing data for efficacy and safety evaluations.

9.7.1.2.4.1 Handling of Missing Data for Efficacy Evaluations

For efficacy data points the following methods were to be used for the post baseline time points with missing assessments:

- If the data point was categorical in nature then the result from the missing data point was to be considered as failure (i.e., non responder) for analysis purposes
- If the missing data point was continuous in nature, then Mixed Model Repeated Measures (MMRM) was to be used to adjust for the missing values
- If the data point was a time-to-event endpoint then the result from the missing data point was to be considered no event and censored based on the last available date/time

9.7.1.2.4.2 Handling of Missing Data for Safety Evaluations

With respect to summaries of AEs, only AEs that were treatment emergent were to be tabulated. Treatment–emergent AEs were defined as AEs with start date and time ≥ date of randomization.

9.7.1.2.5 Sensitivity Analysis

A sensitivity analysis using multiple imputations or tipping point analysis was to be conducted on the ITT population to assess the likelihood that missing data could bias the conclusion of the primary endpoint (i.e., proportion of subjects achieved a GCS score ≥ 13 at or prior to 90 minutes post-randomization) of the study.

9.7.1.2.6 Multicenter Clinical Trials

This study was a multicenter clinical trial. All the data collected from the different study centers was to be presented as a by-subject listing.

9.7.1.2.7 Multiple Comparisons and Type I Error Rate Multiplicity Adjustments

For the primary endpoint only one (1) hypothesis was to be tested, hence there was to be no adjustment for Type I error rate.

For the secondary endpoints, the closed test procedure was to be used to protect the trial-wise error rate. [redacted].

9.7.1.2.8 Covariates and Prognostic Factors

For efficacy analyses, baseline values were to be used as covariates in the analysis models.

9.7.1.2.9 Stratification Factors

The randomization for the study was stratified by study center. This stratification was used to ensure a balanced distribution of subjects among the two treatment groups.

9.7.1.2.10 Subgroup Analysis

Subgroup analyses were to be conducted for the predefined stratification factors presented in Section 9.7.1.2.9 above. Additional subgroup analysis for all the efficacy endpoints was to be conducted using the subgroup of subjects that did not require endotracheal intubation at post-randomization.

9.7.1.2.11 Standard Calculations

Age

Age was to be calculated as the number of completed years between the date of randomization and the subject's birth date as per the formula listed below:

Age (years) = integer of [(date of randomization – date of birth) / 365.25 + 0.5]

Change from Baseline

Change from baseline for a given measurement was to be calculated using below formula.

Change From Baseline = Post baseline result at time t – Baseline result

Percent Change from Baseline

Percent change from baseline for a given measurement was to be calculated using below formula.

Percent Change = [(Post baseline result at time t)/Baseline result– 1]*100

Temperature

For summary purposes, temperature was expressed in Celsius. Entries made in Fahrenheit (° F) was to be converted to Celsius (° C) using below formula.

Temperature (° C) = (Temperature (° F) – 32)*(5/9)

Time to first rectal temperature ≤ 37° C and ≤ 38° C

Time (minutes) to first rectal temperature ≤ 37° C was to be calculated using below formula.

Time to first rectal temperature ≤ 37° C =

Time of first rectal temperature ≤ 37° C– Time of baseline rectal temperature

Time (minutes) to first rectal temperature ≤ 38° C was to be calculated using below formula.

Time to first rectal temperature ≤ 38° C =

Time of first rectal temperature ≤ 38° C– Time of baseline rectal temperature

9.7.1.3 Analyses Populations

9.7.1.3.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population was defined as all randomized subjects who received any study treatment. Subjects who achieved a GCS total score of ≥ 13 prior to receiving any study treatment were to be excluded from the ITT population. The ITT population was to be the primary population for the analysis of the primary and secondary efficacy endpoints.

9.7.1.3.2 Per Protocol (PP) Population

The Per Protocol (PP) population was defined as [redacted]

9.7.1.3.3 Safety Population

The Safety population was defined as all randomized subjects who received any study treatment (SOC with Ryanodex or SOC only). This population was to be used for analysis of all safety endpoints using actual treatment received.

9.7.1.4 Analysis of Efficacy Data

All inferential statistical analysis was to be based on a two-sided test with a Type I error rate of 0.05.

The primary analyses of the primary and secondary efficacy endpoints were to be conducted on the ITT population. [redacted]

9.7.1.4.1 Primary Endpoint

The primary efficacy endpoint for this study was cumulative incidence of subjects achieving a GCS score ≥ 13 at or prior to 90 minutes post-randomization.

The number and percentage of subjects who achieved a GCS score ≥ 13 at or prior to 90 minutes post-randomization was to be presented by treatment arm. The [redacted] adjusting for baseline GCS score was to be used to analyze the percentage of subjects achieving GCS score ≥ 13 at or prior to 90 minutes post-randomization and the 95% CI for the treatment difference and p-value for the treatment effect was to be reported.

9.7.1.4.2 Secondary Endpoints

As discussed in Section 9.7.1.2.7, to protect the type I error rate for the secondary endpoints, the closed test procedure was to be used. Discussed below are the approaches that were to be taken for each of the secondary endpoints. These endpoints are presented in the order that were to be tested.

9.7.1.4.2.1 Cumulative incidence of subjects who achieve a GCS score ≥13 at planned time points

The number and percentage of subjects who achieved a GCS score ≥ 13 at each planned time point was to be presented by treatment arm. [redacted].

9.7.1.4.2.2 Actual values, changes from baseline, and percent changes from baseline in GCS scores over time

Actual values, changes from baseline and percent changes from baseline in GCS scores were to be calculated (see Section 9.7.1.2.11 for calculation). Descriptive summary of number of observations, mean, standard deviation, median, and minimum and maximum values was to be presented.

[redacted]

9.7.1.5 Planned Analysis for Safety Data

All safety analyses were to be conducted using the Safety population. All data collected was to be summarized according to the variable type.

For continuous variables, data was to be summarized by treatment using n, mean, standard deviation, minimum, and maximum values. For categorical variables, data was to be summarized by treatment using frequency and percentage. No inferential statistics were planned.

9.7.1.5.1 Adverse Events

Adverse events were to be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (TEAE) were defined as events which started on or after the start date and time of randomization, or which worsened after the start date and time of randomization. TEAEs were to be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries were to be provided:

- Overall (i.e., regardless of severity or relationship to treatment)
- By severity grade (mild, moderate, or severe)
- By investigators causality assessment (related, possibly related, probably related or unrelated)

In addition, separate summaries of serious adverse events, and adverse events resulting in study discontinuation will be presented.

[redacted]

[redacted]

clinically significant) and Abnormal (clinically significant)) with counts and percentages

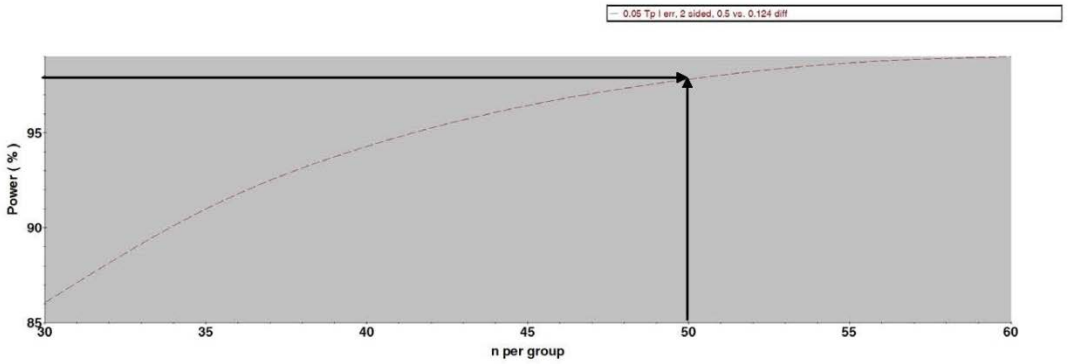
9.7.2 Determination of Sample Size

A total of 100 (50 per treatment group) eligible subjects were planned to be randomized in this study. The nQuery Advisor 6.01 software is used for this sample size calculation. The sample size calculation is based on the assumption that 50% of subjects who receive SOC therapy and Ryanodex will achieve a GCS score ≥ 13 at or prior to 90 minutes post-randomization, compared with only 14.3% of subjects who receive SOC therapy alone.

Under the above assumption, 50 subjects per treatment group were required to meet the Type I error rate of 0.05, 2-sided and over 95% statistical power; for a total of 100 subjects for the study.

Figure 9-3 depicts the statistical power and sample size based on the above specified assumptions with a Type I error rate of 0.05 and 2-sided test.

Figure 9-3: Study Sample Size Estimation



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