NCT02513095
Protocol EGL-4104-C-1502:

Phase 2, Single-Site, Open-Label, 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: November 2, 2016

[redacted]

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

This section presents statistical methods used in the analyses as described in the final statistical analysis plan (SAP) dated 30 November 2015 and an SAP addendum dated 06 April 2016. Both documents were prepared by [redacted] and approved by the Sponsor before final database lock. Changes from analyses planned in the protocol are listed separately in Section 9.8.2. [redacted]

Subsequent to the approval of the SAP Addendum, a few items received further clarification or adjustment:

- Subjects who were intubated and/or heavily sedated at Baseline were eligible for the study, but were not considered fully evaluable on the GCS.
- It was stated that the modified Intent-to-Treat (mITT) Analysis Set should contain all Intent-to-Treat (ITT) subjects who were fully evaluable on the GCS at Baseline and who had at least 1 post-Baseline GCS assessment in the interval from 0 through 90 minutes post-randomization. Although the description of this analysis set changed after database lock, none of the subjects included/excluded in this set changed as a result.

- The final analyses did not treat GCS scores of 2 as 'missing' (as specified in the SAP Addendum), but reverted to the original planned handling to ensure that any potential post-Baseline deterioration of subjects would be captured.

9.7.1.1 General Considerations

Baseline core body temperature was the first rectal temperature ≥ 40.0°C taken during the Screening period. [redacted]

The main focus of all efficacy analyses was to describe the course of subject recovery during the study and to obtain estimates of the treatment effect. In general, all efficacy and safety variables were summarized using descriptive statistics. Continuous variables were summarized by descriptive statistics (sample size [n], mean, standard deviation [SD], 2-sided 95% confidence interval [CI] around the mean; median, minimum, and maximum). Categorical variables and binomials (such as occurrence of events) were summarized in frequency tables which display the number and percentage of subjects reporting a particular response or outcome. All observed significance levels ("p-values") that were reported were from 2-sided statistical tests unless otherwise specified, and were regarded as exploratory. Individual subject data were presented in listings.

All analyses, summaries, and listings were generated using SAS® version 9.4 or later.

9.7.1.2 Data to be Analyzed

Data to be analyzed were collected using Inform version 5.5. Data handling was the responsibility of [redacted] The data were inspected for inconsistencies by performing validation checks. All data collected during the study were reported.

9.7.1.3 Analysis Sets

The Enrolled Analysis Set included:

- Subjects who gave informed consent prior to participation.
- Subjects whose family member or authorized representative gave informed consent for the subject prior to participation.
- Subjects who entered the study under a waiver of informed consent.

Waiver of a subject's informed consent occurred in the event the subject was unable to consent due to his/her medical status and a family member or authorized representative was not available at the time of hospital admission.

Once the study subject was capable of providing his/her own informed consent, then the subject was re-consented. If the subject was unwilling to provide consent at that time, the

subject was withdrawn from the study; and no further study procedures or testing were performed.

The Randomized Analysis Set contained all enrolled subjects who were randomized. For analyses and displays based on the Randomized Analysis Set, subjects were classified according to randomized treatment.

- The ITT Analysis Set included all randomized subjects for whom SOC was initiated. Generally, the ITT population mimics 'real-world' clinical practice more closely than other analysis populations because no one is excluded. In this study, the ITT population was used as the primary efficacy population. All ITT analyses used the randomized treatment assignment.
- [redacted]
- The Safety Analysis Set included all randomized subjects who received any study treatment (SOC and Ryanodex or SOC only). The Safety Analysis Set was used for analysis of all safety endpoints using actual treatment received.

All efficacy was analyzed by planned treatment arm. Classification of subjects with respect to the ITT, [redacted] and Safety Analysis Sets was conducted prior to the final database lock.

9.7.1.4 Missing Data

Imputation of data in the mixed-model repeat measure (MMRM) analyses was not required, as the MMRM method provided appropriate weighting of the sample means based on the amount of data that each subject contributes.

Imputation of data was not required for any time-to-event analysis. Subjects were censored at the earlier of the 72 hours or discontinuation from the study.

Imputation of missing data was done on cooling rate (based on rectal temperature), using straight-line interpolation for non-monotonically missing data points only.

All other efficacy analyses methods consisted of descriptive statistics for observed cases.

[redacted]

9.7.1.5 Adjustments for Covariates and Factors to be Included in Analyses

Analysis of covariance (ANCOVA) models, including repeated-measure ANCOVA models, included the subject's respective Baseline value as a covariate.

Study site (location) was originally planned as a stratification factor in various analyses. Study sites were [redacted] The specific analysis sections of the original SAP described how study site was to be used in the models (where applicable). Due to the actual study size, study site was deleted from all models and no tables or figures by study site were produced.

[redacted]

9.7.1.6 Multicenter Studies

This study was conducted at a single main site [redacted]) and [redacted] satellite site locations [redacted]). [redacted]. Randomization to treatment arms was stratified by study site. All data were pooled for analyses. A term for treatment-by-center (study site) interaction was not included in the primary analysis model, but the presence of such an interaction was explored via graphical methods (e.g., Forest plots) to assess whether the interaction was quantitative (i.e., the treatment effect was consistent in direction but not size of effect) or qualitative (i.e., the treatment was beneficial at some but not other treatment locations).

9.7.1.7 Subject Disposition

The disposition summary included all subjects. The summary included the number and percentage of subjects who were screened, enrolled, screen-failed (with reasons for failure), were randomized, were treated, completed the study, or discontinued prematurely, along with

the primary reason for discontinuation. The informed consent status and (where applicable) the reasons why informed consent was not obtained were also presented. The summary was presented by treatment arm.

9.7.1.8 Subject Characteristics

Subject characteristics included, but were not limited to: age, sex, race, country of origin, height, approximate and actual body weight, [redacted] GCS score at Baseline, [redacted].

Subject characteristics were obtained at screening or prior to discharge from the study and were summarized for all randomized subjects. If it was not possible to obtain all of the planned information at screening due to a subject's poor medical condition at enrollment, an attempt was made to obtain it prior to subject discharge. All recorded data were included in subject data listings.

Summaries included descriptive statistics for continuous variables (sample size, mean, and SD, median, minimum, and maximum) and for categorical variables (sample size, frequency, and percent).

Subject characteristics were summarized using the Randomized Analysis Set. No inferential statistics were planned.

9.7.1.9 Efficacy Analyses

9.7.1.9.1 Primary Analyses

The primary null hypothesis was that restoration of level of consciousness (defined as a return to GCS scores ≥ 13) of subjects with probable or definitive EHS was not different for subjects treated with SOC plus adjuvant Ryanodex therapy compared to subjects treated with SOC only. [redacted], the primary endpoint was the cumulative incidence of subjects achieving a GCS score ≥ 13 at or prior to 90 minutes post-randomization in the ITT Analysis Set.

The number and percentage of subjects who achieved a GCS score ≥ 13 at or prior to 90 minutes post-randomization were presented by treatment arm. A 2-sided 95% Wilson CI for each treatment group proportion and a 2-sided 95% Newcombe CI for the treatment difference were calculated. [redacted]

9.7.1.9.2 Sensitivity Analyses of the Primary Efficacy Variable

[redacted]

9.7.1.9.3 Secondary Analyses

The secondary endpoints were the following:

- Cumulative percentage of subjects who achieved a GCS score ≥ 13 at planned time points in the ITT and [redacted] Analysis Sets
- Actual values, changes from Baseline, and percent changes from Baseline GCS scores over time (at planned time points) in the ITT and [redacted] Analysis Sets
- [redacted]

The cumulative incidence of subjects who achieved a GCS score ≥ 13 at each planned time point was presented as supportive data to the primary analysis. The analysis included the number and percentage of subjects achieving the endpoint at or prior to each time point.

GCS actual values, changes from Baseline, and percent changes from Baseline were described by treatment group and planned time point using basic descriptive statistics (N, mean, median, SD, 2-sided 95% CI around the mean, minimum, maximum).

[redacted]

[redacted]

9.7.1.9.4 Exploratory Analyses

[redacted]

9.7.1.9.5 Subgroup Analyses

[redacted]

9.7.1.10 Safety

All safety variables were summarized using the Safety Analysis Set. All post-Baseline data were included.

9.7.1.10.1 Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. For each study treatment, numbers of events and incidence rates were tabulated by preferred term and system organ class. For each subject, an event that occurred one or more times after randomization contributed one observation to the numerator of the incidence rate. The denominator of the rate comprised all randomized subjects who received any treatment (i.e., the Safety Analysis Set). If the severity or seriousness of the AE changed, the overall severity or seriousness were the maximum severity or seriousness of the multiple occurrences.

Adverse events were listed for each subject and summarized by MedDRA system organ class and preferred term.

For this study, "treatment-emergent" AEs (TEAEs) were defined as AEs that started or worsened in severity on or after the initiation of first administered study treatment (SOC and Ryanodex, or SOC only). The incidence of all TEAEs, SAEs, related AEs, and related SAEs, was tabulated by treatment arm, overall and by maximum intensity. AEs leading to death, and AEs leading to withdrawal of subjects also were tabulated for each treatment group. Deaths due to any cause during the study were tabulated by treatment arm. Cases of rhabdomyolysis and ARF were identified at Baseline; any new cases that were identified post-Baseline or which worsened after the Baseline were reported as AEs. Post-Baseline severe respiratory distress or other medically important emergent events were reported as AEs. However, only AEs which occurred or worsened on or after the initiation of first administered study treatment were tabulated as TEAEs.

[redacted].

9.7.1.10.2 Clinical Laboratory Evaluations

[redacted].

9.7.1.10.3 Exploratory Safety Endpoints

[redacted]

- [redacted]
- [redacted]

[redacted].

9.7.1.10.4 Vital Signs Measurements, Physical Findings and Other Safety Evaluations

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[redacted]

[redacted] [redacted]

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