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

2. SYNOPSIS

Name of Sponsor/Company:

Eagle Pharmaceuticals, Inc.

Name of Finished Product:

Ryanodex® (EGL-4104) (dantrolene sodium) for injectable suspension)

Name of Active Ingredient:

Dantrolene sodium

Protocol: EGL-4104-C-1801

Title of the Study: 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)

Investigator: Nawfal Aljerian, MD, MHPE

Study Center: Four (4) Emergency Departments in the Makkah region of Kingdom of Saudi Arabia

Publications (reference): None

Studied Period:	**Phase of Development:**
(first subject enrolled): 21 August 2018 **(last subject completed):** 13 August 2019	Phase 3

Objectives:

Primary Objective:

To evaluate the efficacy of Ryanodex® for the treatment of exertional heat stroke (EHS), administered as adjunctive treatment to current standard of care (SOC), compared to administration of SOC only.

Secondary Objective:

To evaluate the safety and tolerability of Ryanodex for the treatment of EHS, administered as adjunctive treatment to current SOC.

Methodology:

Study EGL-4104-C-1801 was a Phase 3, multi-center, double-blind, randomized, 2-arm parallel study of Ryanodex for the adjuvant treatment of EHS administered intravenously (IV), to current

SOC.

Standard of care (SOC) for the treatment of EHS is defined as effective body cooling and supportive measures, which is to be implemented as quickly as available after diagnosis of heat stroke.

Due to the life-threatening nature of EHS, rapid assessment for inclusion into the study and subsequent immediate treatment was to occur [redacted]

Number of Subjects (Planned and Analyzed):

Planned: 100 **Analyzed:** 17

Diagnosis and Main Criteria for Inclusion:

Male or non-pregnant female subjects were to be entered into this study if they were diagnosed with known or suspected EHS as evidenced by meeting all of the following criteria at Screening:

- Subjects had a core body temperature obtained rectally of ≥ 40.0°C (104.0°F);
- In the judgment of the Investigator, the subject was likely to be at least 18 years of age
- Subject had recent history or suspected recent history (prior 24 hours) of performing intense physical activity (exertional activity)
- The subject had impaired consciousness level as evidenced by a GCS score < 13
- The subject had tachycardia (heart rate ≥ 100 bpm).

Diagnosis and Main Criteria for Exclusion:

Male or non-pregnant female subjects were to be excluded from entering this study if they were diagnosed with known or suspected EHS and met any of the following criteria at Screening:

- The subject was diagnosed with or was suspected to have an acute clinically severe infection, which in the opinion of the Investigator may have increased the subject's risk for participating in the study and/or may have impaired the ability of performing and/or interpreting study assessments.
- The subject had severe hyperthermia secondary to a condition other than heat stroke (e.g., serotonin syndrome, thyrotoxicosis, pheochromocytoma, or brain hemorrhage).
- The subject required endotracheal intubation as a supportive measure prior to, or at the

time of entering the study.

- The subject required administration of sedative drugs (e.g. midazolam, ketamine) for the treatment of psychiatric symptoms (e.g. aggressiveness, agitation) prior to, or at the time, of entering the study. NOTE: The use of sedative drugs, such as benzodiazepines, for the treatment of psychiatric symptoms or seizures appearing after the subject had entered the study, was allowed.
- There was likelihood of head trauma in the past six (6) months, or other significant cardiovascular, pulmonary, hepatic, endocrine, or renal illness that in the opinion of the Investigator may have increased the subject's risk for participating in the study and/or may have impaired the ability of performing and/or interpreting study assessments.
- A female subject had a positive pregnancy test (urine) or evidence of active lactation. NOTE: Pregnancy test may have been waived if female subject was an unmarried Muslim and performing such a test would be in conflict with her religious faith and cultural background, according to the Investigator.
- Recent history, suspected recent history (prior 30 days), or current myocardial infarction.
- A known history of allergy or hypersensitivity to dantrolene.
- A known history of seizure disorders or epilepsy.
- Known concomitant or prior use (within the past 2 weeks) of calcium channel blockers.

Test Product, Dose and Mode of Administration, Batch Number:

Ryanodex (dantrolene sodium) for injectable suspension; 250 mg/vial to be reconstituted in 5 mL of sterile water for injection (without a bacteriostatic agent) to yield a 50 mg/mL suspension; was to be administered as a rapid IV push of 2.5 mg/kg or 1 mg/kg, as described in the protocol.

[redacted]

Duration of Treatment: Up to six (6) hours from Screening to End of Study/Early Termination visit

Reference Therapy, Dose and Mode of Administration, Batch Number:

Standard of Care (SOC): All subjects in both treatment groups were to receive SOC. Standard of care for the treatment of EHS was defined as effective body cooling and supportive measures.

Supportive Measures: All subjects were to receive adequate supportive measures depending on their clinical status

Batch Number: Not applicable

CRITERIA FOR EVALUATION

<u>Efficacy</u>

Primary Endpoint: Cumulative incidence of subjects achieving a GCS score ≥ 13 at or prior to 90 minutes post-randomization.

Secondary Endpoints:

- Cumulative incidence of subjects who achieve a GCS score ≥ 13 at planned time points;
- Actual values, changes from baseline, and percent changes from baseline in GCS scores over time;
- [redacted]

Dantrolene Plasma Concentration Data

Blood sample was to be collected for the purpose of determining the plasma concentration of dantrolene sodium and was only to be used to demonstrate that treatment was administrated as assigned. This assessment was considered as not needed (Protocol Amendment 1; 11 July 2019) for subjects randomized in 2019 because well-established roles and processes exist to accurately document administration of study drug (Ryanodex).

Safety

Safety was assessed using the following parameters:

- Adverse Events;
- Vital Signs (heart rate, blood pressure, respiratory rate, core body temperature);
- Clinical safety laboratory tests (hematology, coagulation parameters, and blood chemistry);
- ECG monitoring;
- Oxygen saturation (measured with pulse oximeter);
- End-tidal CO_2 ($ETCO_2$)
- Physical exam
- Brief neurological exam
- Use of concomitant medications

Statistical Methods:

A Statistical Analysis Plan (SAP) was finalized prior to database lock. Statistical methods in the SAP were to take precedence over those described in this protocol. All collected study data was to be presented in subject data listings. Statistical analyses was to be performed using SAS® for Windows, version 9.4 or later.

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 was to be used for this sample size calculation. The sample size calculation was based on the assumption that 50% of subjects who receive SOC therapy and Ryanodex was to 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

assumptions, 50 subjects per treatment group were to be required to meet the Type I error rate of 0.05, 2-sided and over 95% statistical power to detect the difference between treatments; for a total of 100 subjects for the study.

Baseline:

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.

Analysis Populations:

The safety population was to include all randomized subjects who received any study treatment (SOC only or SOC plus Ryanodex). The safety population was to be used to analyze all safety endpoints using actual treatment received.

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

The Per Protocol population (PP) was to include all ITT subjects who met all inclusion/exclusion criteria, had a baseline and at least 1 post-baseline GCS total score, and had no major protocol deviations that could affect the efficacy assessments.

The ITT and Per Protocol populations were to be analyzed using planned treatment assignments. Classification of subjects with respect to the ITT, PP, and Safety populations was to be conducted prior to the database lock.

Efficacy Analysis:

The primary analyses of the primary and secondary efficacy endpoints were to be conducted on the ITT population. The PP population analyses of primary and secondary endpoints were to be considered supportive. For the primary endpoint, Logit model was to be used to compare proportion of subjects achieving a GCS score ≥ 13 at or prior to 90 minutes post-randomization between treatment groups.

For the secondary endpoints, the data was to be summarized and compared according to the variable type:

- Continuous data summaries was to include:
- Descriptive summary of number of observations, mean, standard deviation, median, and minimum and maximum values.
- Mixed Model Repeated Measures (MMRM) for inferential statistics was to be used if the Normality assumption is met.
- Non-parametric methods were to be used for inferential statistics if the Normality assumption was not met.
- Categorical data summaries was to include:
- Frequency counts and percentages.

- Logit model for inferential statistics
- Time-to-event data summaries was to use:
- Kaplan-Meier (K-M) methods to depict the data and Cox proportional hazards model for inferential statistics.

Safety Analysis:

The Safety Population was to be used for the safety analysis. No modeling or inferential statistics was to be conducted on the safety assessments.

Other:

Demographics, subject disposition, dosing parameters, and prior/ concomitant medications were to be summarized. Other concomitant therapies and medical history were to be listed.

SUMMARY OF RESULTS

Efficacy:

The primary objective of this Phase 3 study was to evaluate the efficacy of Ryanodex for the treatment of EHS when administered as an adjunctive treatment to the current standard of care (SOC), compared to the administration of SOC only. Standard of care, comprised by body cooling and supportive measures, should be considered as an active control. Evaluations of efficacy were made using the Glasgow Coma Scale (GCS) [redacted]

The primary endpoint for the study was the cumulative proportion of subjects achieving a GCS ≥ 13 at or prior to 90 minutes post randomization. At baseline, subjects in the SOC + Ryanodex group were reported with a median GCS score of 5.0. Subjects in the SOC only group were reported with a median score of 4.5.

At or prior to 90 minutes post randomization, a greater proportion of subjects in the SOC + Ryanodex group were reported with GCS scores ≥ 13 than in the SOC only group.

[redacted]

Safety:

This study was designed to assess the safety of Ryanodex in the adjuvant setting with standard of care (SOC) therapy on subjects diagnosed with Exertional Heat Stroke (EHS). Subjects were

randomized to receive Ryanodex plus SOC or SOC treatment alone. Safety evaluations were based on the assessment of treatment emergent adverse events (TEAEs), [redacted]

A total of 17 subjects were enrolled, nine of which were randomized to the SOC + Ryanodex treatment group. Subjects were to receive an initial dose of Ryanodex of 2.5 mg/kg administered as an IV bolus within [redacted] after randomization, in addition to SOC which was initiated [redacted] after diagnosis of hyperthermia.. [redacted]

A total of four subjects (44.4%, 4/9) received [redacted] Ryanodex doses. [redacted]

A total of 14 AEs were reported for 12 subjects (70.6%, 12/17) in groups SOC + Ryanodex or SOC only groups. By treatment group, nine AEs were reported for seven subjects (77.8%, 7/9) in the SOC + Ryanodex group and five AEs for five subjects (62.5%, 5/8) in the SOC only group. Based on severity, two severe AEs were reported, one in each treatment group. No AEs were reported that led to death or study treatment interruption or discontinuation.

[redacted]

Based on the MedDRA version 21.0 classification, the most commonly reported system organ classes were metabolism and nutrition disorders (17.6%, 3/17) and nervous system disorders (17.6%, 3/17), followed by gastrointestinal disorders, investigations, and vascular disorders, each reported at an incidence of 11.8% (2/17). The remaining categories were reported in < 10% of subjects. Of the three subjects with AEs in the system organ class of metabolism and nutrition disorders, two subjects (22.2%, 2/9) were in the SOC + Ryanodex treatment group with the remaining subject (12.5%, 1/8) in the SOC only group. All subjects with AEs reported in the category of nervous system disorders were randomized to the SOC only treatment group with three events of seizure (by PT) reported for three subjects (37.5%, 3/8).

Of the two severe AEs, one subject in the SOC + Ryanodex treatment group was reported with the AE of coma scale abnormal (by PT) in the system organ class of investigations. In the SOC only group, one subject was reported with dyspnoea (by PT) in the system organ class of respiratory, thoracic, and mediastinal disorders.

There were three SAEs reported for three subjects (17.6%, 3/17). One subject (11.1%, 1/9) was randomized to the SOC + Ryanodex and two subjects (25.0%, 2/8) to the SOC only group.

In the SOC + Ryanodex, the SAE reported was presented by PT as coma scale abnormal. In the SOC group, the SAEs were reported in each subject by PT as seizure and dyspnoea, respectively.

[redacted]

CONCLUSIONS

Study EGL-4104-1801 was a Phase 3, multicenter, double blind, randomized, 2-arm, parallel, active controlled trial to evaluate the safety and efficacy of Ryanodex as adjuvant treatment to standard of care (SOC), compared to SOC only, in subjects with Exertional Heat Stroke (EHS). [redacted]

Ryanodex (dantrolene sodium) for injectable suspension was administered as a rapid IV push. Glasgow Coma Scale (GCS) was used to assess subjects' neurologic condition in the study. The primary efficacy endpoint was the cumulative incidence of subjects achieving a GCS score ≥ 13 at or prior to 90 minutes post-randomization. [redacted]. A greater proportion of subjects in the SOC + Ryanodex treatment group achieved a GCS score ≥ 13 at or prior to 90 minutes post randomization, compared to the SOC only group. In addition, the cumulative incidence of GCS score ≥ 13 over time was higher in the SOC + Ryanodex group at all planned time points throughout the study.

[redacted]

Date of Report: 6 January 2020