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

2.0 SYNOPSIS

Name of Sponsor/Company: Eagle Pharmaceuticals, Inc.	**Individual Study Table**	**(For National Authority Use only)**
Name of Finished Product: Ryanodex® (dantrolene sodium) for injectable suspension		
Name of Active Ingredient: Dantrolene sodium		
Title of Study: 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)		
Investigators: [redacted]		
Study Centers: The study was conducted at a single site with 3 additional satellite site locations in the region of Mekkah, Saudi Arabia, during the 2015 Hajj pilgrimage.		
Publication (Reference): None		
Study Period: 22 September 2015 (First Subject Enrolled) - 27 September 2015 (Last Subject Completed Treatment)	**Phase of Development:** 2	
Objectives: <u>Primary</u>: To evaluate the efficacy of Ryanodex for the treatment of EHS, administered as adjunctive treatment to current standard of care (SOC). <u>Secondary</u>: To evaluate the safety and tolerability of Ryanodex for the treatment of EHS by comparing the treatment groups for the incidence of treatment-emergent adverse events (TEAEs), physical and neurological examination findings, clinical laboratory test results, and vital signs.		
Methodology: [redacted]		

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[redacted]

Treatment Groups:

Upon admission to the emergency medical facility and following assessment of study inclusion and exclusion criteria, eligible subjects with probable or definitive EHS were randomized in a 1:1 ratio to one of the following treatment groups:

- Group A: Ryanodex, in addition to immediate implementation of SOC (body cooling and supportive measures)
- Group B: SOC only (body cooling and supportive measures) implemented immediately

Subjects randomized to Group A received an initial dose of Ryanodex (study drug) of 2 mg/kg administered as an IV bolus, in addition to SOC. If the subject did not show adequate clinical response between 30 and 90 minutes after the initial dose, a single repeat dosing of 2 mg/kg of study drug could be administered between 30 and 90 minutes following the initial dose. [redacted]

Subjects who had received up to two 2-mg/kg (up to 4 mg/kg) IV doses of Ryanodex (Group A) during the Treatment Phase of the study could receive additional treatment with Ryanodex at a dose of 1 mg/kg as an IV bolus starting at 90 minutes following the initial dose and continuing every 6 hours for up to 24 hours under the following conditions:

1. If the subject had not achieved an adequate response (defined as rectal temperature ≤ 38.0°C and Glasgow Coma Scale (GCS) score ≥ 13); or,
2. If the subject had achieved an adequate response (defined as rectal temperature ≤ 38.0°C and GCS ≥ 13) but the symptoms began to reappear [redacted]

Clinical assessments and symptoms leading to additional doses of study drug were to be clearly recorded. The total administered dose of Ryanodex in a [redacted] period was not to exceed [redacted]

Stopping the study drug:

If [redacted]

The study protocol included three phases (Screening/Randomization, Treatment Phase, and Follow-up

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Phase), plus a follow-up contact by telephone at approximately [redacted] days after the subject's discharge from the study.

Number of Subjects (Planned and Analyzed):

A total of 100 subjects (50 per arm) were initially planned to be randomized in the study. Due to unforeseen tragic events impacting the location of the study and enrollment plans, 40 subjects were screened to participate, and 34 subjects were randomized (6 subjects were screen failures). A total of 34 subjects were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion:

Male or non-pregnant female subjects were entered into this study if they were diagnosed with probable or definitive EHS as evidenced by all of the following:

- A core body temperature obtained rectally of ≥ 40.0°C (104.0°F)
- In the judgment of the Investigator, the subject was likely 18 years of age or older, and not older than 45 years of age
- 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 beats per minute [bpm]).

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

Ryanodex (dantrolene sodium) for injectable suspension; 250 mg/vial to be reconstituted with 5 mL of sterile water for injection (without a bacteriostatic agent) to yield a 50 mg/mL suspension; administered as a rapid IV push of 2.0 mg/kg or 1.0 mg/kg. Batch numbers of Ryanodex and sterile water for injection were [redacted] and [redacted], respectively.

Duration of Treatment:

Up to 72 hours, from Screening to medical discharge from the study.

Reference Therapy:

Standard of Care (SOC): All subjects in both treatment groups received SOC (efficient cooling and supportive measures).

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was cumulative incidence of subjects who had achieved a GCS score ≥ 13 at or prior to 90 minutes post-randomization.

Secondary efficacy endpoints consisted of the following:

- Cumulative incidence of subjects who had achieved a GCS score ≥ 13 at planned time points
- Changes from Baseline, and percent changes from Baseline in GCS scores over time
- [redacted]

[redacted]

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- [redacted]
  - [redacted]
  - [redacted]

Safety:

Safety was evaluated by the following parameters:

- Adverse events
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]

Dantrolene Plasma Concentration Data:

A single blood sample was collected at 2 hours (± 15 minutes) post-Baseline for the purpose of establishing the plasma concentration of dantrolene. The plasma concentration results were used to demonstrate that treatment was administered as assigned.

[redacted]

- [redacted]
- [redacted]

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Statistical Methods:

Sample Size: The planned sample size of 100 subjects (50 per group) was based on the predicted number of subjects who may be diagnosed with probable EHS during the 2015 Hajj. This sample size was planned to provide about [redacted] power to detect a difference between treatment means that was equivalent to 50% of the standard deviation (SD) (i.e., a moderate or medium-sized treatment effect) for any measure that had an approximately normal distribution, using a two-tailed Student t-test or F-test conducted at a significance level of 5%. Also, assuming that [redacted] of subjects who received SOC therapy with adjuvant Ryanodex treatment achieved a GCS ≥ 13 at 90 minutes post-randomization, compared to only [redacted] of subjects who received SOC only, the planned sample size would provide about [redacted] power for a 2-sided chi-square test to detect the difference between treatments at a significance level of [redacted].

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

Analysis sets: The Safety analysis set included all randomized subjects who received any study treatment (SOC only or SOC and Ryanodex). The Safety analysis set was used to analyze all safety endpoints using actual treatment received. The Intent-to-Treat (ITT) analysis set included all randomized subjects for whom SOC was initiated, and was used as the primary efficacy analysis set. [redacted] The ITT, [redacted] analysis sets were analyzed using planned treatment assignments. Classification of subjects with respect to the ITT, [redacted], and Safety analysis sets was conducted prior to the final database lock.

Efficacy Parameters:

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. Any observed significance levels ("p-values") that were reported were to be regarded as exploratory, descriptive statistics.

The primary null hypothesis was that restoration of level of consciousness (defined as a return to GCS scores ≥ 13) in subjects with probable or definitive EHS was not different for subjects treated with Ryanodex in addition to immediate implementation of SOC (body cooling and supportive measures), compared to subjects treated with SOC only (body cooling and supportive measures) implemented immediately. [redacted] the primary endpoint was the cumulative incidence of subjects who had achieved a GCS score ≥ 13 prior to or at 90 minutes post-randomization in the ITT analysis set. The number and percentage of subjects who achieved a GCS score ≥ 13 are presented by treatment arm. A two-sided 95% Wilson confidence interval (CI) for each treatment group proportion and a two-sided 95% Newcombe CI for the treatment difference were calculated. The odds ratio and its two-sided 95% CI were also calculated and reported. The cumulative incidence of subjects who achieved a GCS score

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≥ 13 at or prior to each planned assessment time point is presented as supportive data. S[redacted]

Secondary endpoints were analyzed for the ITT analysis set. Endpoints that consisted of actual values, changes from Baseline, or percent changes from Baseline were described by treatment group and planned time point, using basic descriptive statistics (N, mean, median, SD, two-sided 95% CI around the mean, minimum, maximum). Changes from Baseline in GCS and [redacted] were submitted to a repeated measures analysis employing a restricted maximum likelihood-based (REML), repeated-measure mixed model to obtain more precise estimates of treatment effect. SAS® Proc Mixed was used to perform the analysis. Each model included fixed terms for treatment group, time point, and treatment-by-time point interaction, with the Baseline value as covariate (as applicable), and subject as a random factor. An unstructured covariance matrix failed to converge when applied to pre-lock data, so a first-order autoregressive [AR (1)] covariance structure was used. An empirical ("sandwich") estimator for the variance-covariance matrix and the denominator degrees of freedon (DDFM) = BETWITHIN option for calculation of DDFM were used to take account of possible misspecification of the true covariance matrix. Predicted least square means, treatment differences between least square means, and two-sided 95% CI for the treatment differences are reported, overall and by planned time point, for all subjects in the analysis set.

[redacted]

Safety Parameters:

Incidence of TEAEs, serious adverse events (SAEs), related AEs, and related SAEs reported during the study was tabulated by treatment arm, overall and by maximum intensity. Deaths due to any cause during the study were tabulated by treatment arm. AEs were recorded from start of screening/randomization. [redacted]

[redacted]

[redacted]

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[redacted] **Other:** Demographics, subject disposition, dosing parameters, and [redacted] are summarized. [redacted]		

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Summary – Conclusions:

<u>Efficacy Results</u>:

- A greater proportion of subjects treated with SOC and Ryanodex exhibited a clinically meaningful improvement in their neurological functioning (GCS ≥ 13) within 90 minutes (29.4%) and within 24 hours post-randomization (47.1%), compared to SOC only-treated subjects (11.8% and 23.5%, respectively) (ITT Analysis Set).
- A greater proportion of subjects treated with SOC and Ryanodex achieved a clinically meaningful improvement (GCS score ≥ 13) in their neurological functioning as early as 45 minutes post-randomization compared to subjects treated with SOC only, and that difference in favor of the SOC and Ryanodex group remained unchanged at the end of the Treatment Phase (2 hours post-randomization) (ITT and mITT Analysis Sets).
- The odds of achieving a GCS score ≥ 13 within 90 minutes post-randomization was about 3 times greater for subjects in the SOC and Ryanodex group than for subjects who received SOC only, and remained almost unchanged at or prior to 24 hours post-randomization (ITT Analysis Set).
- Among fully evaluable subjects at Baseline, the odds of achieving a GCS score ≥ 13 within 90 minutes post-randomization was about 6 times greater in the SOC and Ryanodex group than for subjects who received SOC only (mITT Analysis Set).
- Among fully evaluable subjects at Baseline, the mean change from Baseline in GCS score was higher in the SOC and Ryanodex group (3.1; p=0.017) compared with the SOC only group (1.1; p=0.179); the mean percent change from Baseline in GCS score was also higher in the SOC and Ryanodex group (55.6%; p=0.073) compared with the SOC only group (20.2%; p=0.212). In both cases, the within-group p-value clearly favors the SOC and Ryanodex group, compared with the SOC only group (mITT Analysis Set).
- The proportion of subjects who achieved complete normalization in their level of consciousness (GCS score = 15) was greatest at 24 hours post-randomization and was greatest in the SOC and Ryanodex group (41.2%) than in the SOC only group (23.5%) (ITT Analysis Set).
- Duration of SOC was substantially shorter in the SOC and Ryanodex group compared to the SOC only group (ITT Analysis Set).
- The time to reach first rectal temperature ≤ 38°C was similar in both treatment groups (ITT Analysis Set).
- The median time to reach first rectal temperature ≤ 38°C was shorter in the SOC and Ryanodex group (90.0 minutes) than in the SOC only group (103.0 minutes). In addition, the time at which at least 75% of the subjects had first rectal temperature ≤ 38°C was also shorter in the SOC and Ryanodex group (125.0 minutes) than in the SOC only group (195.0 minutes) (mITT Analysis Set).
- Overall mean cooling rates were similar in both treatment groups (ITT and mITT Analysis Sets).

Subjects treated with Ryanodex in addition to SOC, exhibited greater clinically meaningful improvement in their neurological functioning compared to SOC only-treated subjects. The observed incremental improvement in neurologic functioning constitutes a clinically relevant benefit, known to be associated

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with lower risk of EHS-related complications, and decreased long-term morbidity and mortality.

Safety Results:

- Ryanodex was safe and well-tolerated by subjects in the SOC and Ryanodex group.
- No new and/or unexpected safety signals were detected.
- The overall incidence of TEAEs was similar in both groups.
- No treatment-related TEAEs were reported.
- No subjects withdrew due to TEAEs.
- There were no clinically meaningful differences in laboratory abnormalities between the two treatment groups.
- There were no clinically meaningful differences in vital signs, ECGs, $ETCO_2$, or oxygen saturation between the two treatment groups.
- The safety profile of Ryanodex in this study population was consistent with the known and well-characterized safety profile in the currently approved indications.

Conclusion:

Overall, Ryanodex administered to EHS subjects was safe and well tolerated. The safety profile of Ryanodex in this severely ill population was consistent with its known and well-characterized safety profile in the currently approved indications.

Subjects treated with Ryanodex, in addition to SOC, exhibited greater clinically meaningful improvement in their neurological functioning compared to SOC only-treated subjects. The observed incremental improvement in neurologic functioning constitutes a clinically relevant benefit, known to be associated with lower risk of EHS-related complications, and decreased long-term morbidity and mortality.

The results of the study provide clinical evidence of the therapeutic benefit that Ryanodex may deliver to patients with EHS.