NCT03189433

Protocol EGL-4104-C-1702:

Phase 2, Multiple-Site, Open-Label, Randomized, 2-Group, Parallel Study to Assess the Efficacy and Safety of Ryanodex® (EGL-4104) as Adjuvant Treatment in Subjects With Psychostimulant Drug-Induced Toxicity (PDIT)

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8.0 STATISTICAL CONSIDERATIONS

This section presents general information about statistical considerations and concepts such as randomization, covariates, statistical power, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions will be included in a separate document; i.e., the Statistical Analysis Plan (SAP).

8.1 Treatment Groups

The following treatment groups will be assessed:

Group	Description
Group A	Ryanodex®, as adjuvant treatment to SOC
Group B	SOC only

8.2 Description of Study Endpoints

8.2.1 Efficacy Endpoints

8.2.1.1 Primary Efficacy Endpoint

Primary endpoint: Proportion of subjects achieving a total LODS score ≤ 5 at or prior to 60 minutes post-randomization.

8.2.1.2 Secondary Efficacy Endpoints:

- Proportion of subjects who achieved a LODS total score ≤ 5 at planned timepoints.
- [redacted]

- [redacted]

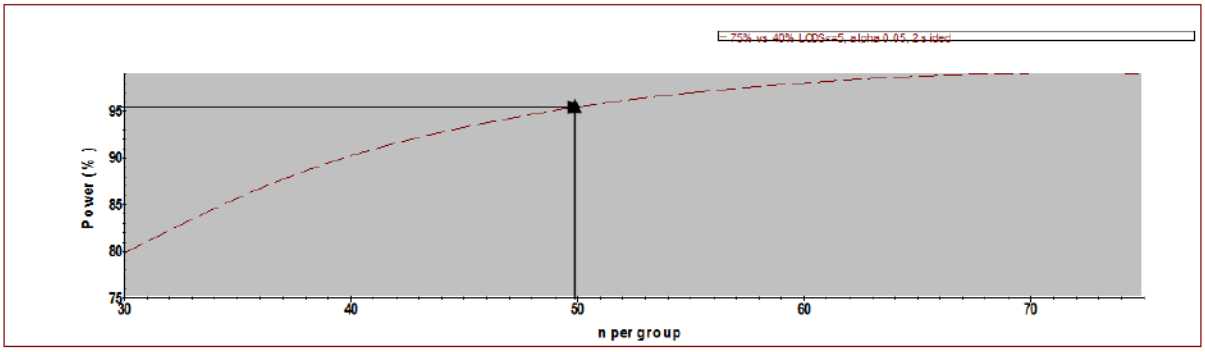
8.2.2 Safety Assessments

- Adverse events (AEs)
- Vital signs (blood pressure, respiratory rate, and pulse)
- Clinical safety laboratory tests (hematology and coagulation parameters, and blood chemistry)
- Electrocardiogram (ECG)
- Physical examination
- Brief neurological examination
- Oxygen saturation (measured with pulse oximeter)
- End-tidal CO_2 ($ETCO_2$)

8.3 Sample Size Determination and Rationale

A total of 100 (50 per treatment group) fully eligible (for efficacy) subjects are planned to be randomized in this study. [redacted] is used for this sample size calculation. The sample size calculation is based on the assumption that [redacted] of subjects who receive SOC therapy and Ryanodex® will achieve a LODS score ≤ 5 at or prior to 60 minutes post-randomization, compared with only [redacted] of subjects who receive SOC therapy alone.
Under the above assumption, [redacted] subjects per treatment group will be required to meet the Type I error rate of 0.05, 2-sided and more than 90% power; for a total of [redacted] subjects for the study. Sample size estimation is depicted in Figure 2.

Figure 2: Sample Size Yielding More than 90% Power for the Study



8.4 Randomization

Subjects who meet all inclusion and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to either Group A (Ryanodex® as adjuvant treatment to SOC) or Group B (SOC only) within each study site. The randomization schedule will be generated using an appropriate block size to help maintain treatment groups of equal size.

8.5 Blinding

This is an open-label study; no blinding of study drug will be performed.

8.6 [redacted]

[redacted]

8.7 General Statistical Considerations

Baseline body temperature will be the first rectal temperature >39.5° C taken during the Screening Phase. Baseline results for other study assessments will be the value closest in time to the baseline rectal temperature and prior to randomization. The SAP may specify additional data handling rules.

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

8.7.1 Data to Be Analyzed

[redacted] will analyze the study data. Data handling will be the responsibility of [redacted]. The data will be inspected for inconsistencies by performing validation checks.

All data collected during the study will be reported. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the SAP prepared by [redacted]nd approved by the Sponsor before database lock. The statistical analysis will be performed by [redacted]

8.8 Analysis Populations

8.8.1 Intent-to-Treat (ITT) population

The Intent-to-Treat (ITT) population is defined as [redacted]. The ITT population will be the primary population for the analysis of primary and secondary endpoints.

8.8.2 Modified Intent-to-Treat (MITT) population

The Modified Intent-to-Treat (MITT) population is [redacted]

The MITT analysis of primary and secondary endpoints will be considered supportive.

8.8.3 Per Protocol (PP) Population

The Per Protocol (PP) population is defined [redacted].

8.8.4 Safety Population

The Safety population is defined as any subject who received any study treatment (SOC only or SOC with Ryanodex®). This population will be used for the analysis of safety parameters.

8.9 Covariates

For efficacy analyses, the baseline values will be used as covariates in the analysis models. [redacted].

8.10 Missing Data

For efficacy evaluation appropriate methods will be used to handle any missing data. The details of techniques for handling of missing data will be included in the SAP for the study which will be finalized prior to database lock.

8.11 Analysis Methods

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial. All inferential statistical analysis will be based on a two-sided test with a Type I error rate of 0.05.

All the efficacy analyses presented here will be conducted using the ITT, [redacted] populations. All safety analyses will be conducted using the Safety population. Study data summaries will include the following:

8.11.1 Subject Disposition

The disposition of all subjects screened will be provided. [redacted].

8.11.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group using appropriate descriptive statistics.

8.11.3 Concomitant Medications/Therapies

[redacted]

8.11.4 Efficacy Analyses

8.11.4.1 Primary Analysis

The primary analysis will be conducted on the Intent-to-treat (ITT) population.

Primary Endpoint:

[redacted] will be used to compare the proportion of subjects achieved a total LODS score ≤ 5 at or prior to 60 minutes post-randomization.

Secondary Endpoints:

- Proportion of subjects who achieved a LODS total score ≤ 5 at planned timepoints.
- [redacted]

All secondary endpoints data will be presented and summarized according to the variable type:

- Continuous data summaries will include:
  - Number of observations, mean, standard deviation, median, and minimum and maximum values.
  - [redacted]
- Categorical data summaries will include:
  - Frequency counts and percentages.
  - [redacted]
- Time-to-event data summaries will be using
  - Kaplan-Meier (K-M) methods to depict the data and Cox proportional hazards model for inferential statistics.

8.11.5 Supportive Analysis

[redacted]

[redacted]

8.12 Safety Analyses

The Safety population will be used for the analysis of safety endpoints.

For continuous variables data will be summarized by treatment using n, mean, SD, minimum and maximum values. For categorical variables data will be summarized by treatment using frequency and percentage. [redacted]

8.12.1 Adverse Events

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Overall (i.e., regardless of severity or relationship to treatment)
- By severity grade (mild, moderate, severe, or life threatening for SAEs)
- By relationship to clinical trial treatment according to the mapping scheme below:
  - Potentially related: will include all adverse events with a relationship rating of "definitely", "probably" or "possibly".
  - Unlikely/not related: will include all adverse events with a relationship rating of "unlikely" or "unrelated".

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

8.12.2 Clinical Laboratory Evaluations

[redacted]

8.12.3 Other Safety Data

[redacted]

8.13 [redacted]

[redacted]