A Multi-Center, Randomized, Placebo-Controlled, Double-Blinded, Trial of Efficacy and Safety of Riluzole in Acute Spinal Cord Injury

*Statistical Analysis*

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# Study Overview

This was an international, multi-center, prospective, double-blinded, randomized, placebo- controlled Phase II/III clinical trial to evaluate if riluzole at a dose of 100 mg BID for the first 24 hours followed by 50 mg BID for 13 days was superior to placebo in subjects with acute traumatic spinal cord injury (SCI). The study utilized a randomization ratio of one riluzole subject to one placebo subject (1:1). Additional trial information can be found by visiting ClinicalTrials.gov and searching for NCT01597518.

# Study Objectives

## Primary Objective

The primary objective was to evaluate the superiority of riluzole, at a dose of 100 mg BID the first 24 hours followed by 50 mg BID for the following 13 days after injury, as compared to placebo, in change between 180 days and baseline in motor outcomes as measured by International Standards for Neurological Classification of Spinal Cord Injury Examination (ISNCSCI) Motor Score, in patients with acute traumatic SCI, presenting to the hospital less than 12 hours after injury.

## Secondary Objectives

Secondary objectives were to evaluate the effects of riluzole on overall neurologic recovery, sensory recovery, functional outcomes, quality of life outcomes, health utilities, mortality, and adverse events.

# Efficacy Endpoints

## Primary Efficacy Endpoint

The primary efficacy endpoint was absolute change in International Standards for Neurological Classification of Spinal Cord Injury Examination (ISNCSCI) Total Motor Score (ISNCSCIMS) between 180 days and baseline.

Prior to any unblinding of the data from the study, the literature consensus emerged that the Total Motor Score, which consists of Upper Motor Score and Lower Motor Score, is an unreliable measure. The current consensus is to use Upper Motor Score. With agreement from the DSMB statistician, the study has switched to Upper Motor Score for primary efficacy evaluation.

## Secondary Efficacy Endpoints

The two secondary efficacy endpoints were:

* Change in ISNCSCI grade between baseline and 180 days, and
* Spinal Cord Independence Measure (SCIM) at 180 days

## Other Endpoints

* Change in ISNCSCI Sensory Scores (Light Touch and Pin Prick) between 180 days and baseline
* Change in ISNCSCI Upper Extremity Motor Score between 180 days and baseline (changed to Total Motor Score)
* Change in ISNCSCI Lower Extremity Motor Score between 180 days and baseline
* Change in Short Form 36 Version 2 (SF-36v2™) PCS, MCS and 8 dimensions between 180 days and pre-injury (recall)
* Change in EQ-5D health utility between 180 days and pre-injury (recall)
* Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP) at 14 days or Discharge (whichever occurred first) and 180 days
* Change in Numeric Pain Rating Scale (pain NRS) at 14 days, 84 days and 180 days

# Selection of Study Population

## Inclusion Criteria

* + - * Age between 18 and 75 years inclusive
      * Able to cooperate in the completion of a standardized neurological examination by ISNCSCI standards (includes patients who are on a ventilator)
      * Willing and able to comply with the study Protocol
      * Signed Informed Consent Document (ICD) by patient, legal representative or witness
      * Able to receive the Investigational Drug within 12 hours of injury
      * ISNCSCI Impairment Scale Grade “A,” “B” or “C” based upon first ISNCSCI evaluation after arrival to the hospital
      * Neurological Level of Injury between C4-C8 based upon first ISNCSCI evaluation after arrival to the hospital
      * Women of childbearing potential must have a negative serum β-human chorionic

gonadotropin (β-hCG) pregnancy test or a negative urine pregnancy test

## Exclusion Criteria

* Injury arising from penetrating mechanism
* Significant concomitant head injury defined by a Glasgow Coma Scale score < 14 with a clinically significant abnormality on a head CT (head CT required only for patients suspected to have a brain injury at the discretion of the investigator)
* Pre-existent neurologic or mental disorder which would preclude accurate evaluation and follow-up (i.e., Alzheimer’s disease, Parkinson’s disease, unstable psychiatric disorder with hallucinations and/or delusions or schizophrenia)
* Previous history of spinal cord injury
* Recent history (less than 1 year) of chemical substance dependency or significant psychosocial disturbance that may impact the outcome or study participation, in the opinion of the investigator
* Is a prisoner
* Participation in a clinical trial of another Investigational Drug or Investigational Device within the past 30 days
* Hypersensitivity to riluzole or any of its components
* Neutropenia measured as absolute neutrophil count (ANC) measured in cells per microliter of blood of < 1500 at screening visit
* Creatinine level of > 1.2 milligrams (mg) per deciliter (dL) in males or > 1.1 mg per dL in females at screening visit
* Liver enzymes (ALT/SGPT or AST/SGOT) 3 times the upper limit of normal (ULN) at screening visit
* Active liver disease or clinical jaundice
* Subject is currently using, and will continue to use for the next 14 days any of the following medications which are classified as CYP1A2 inhibitors or inducers\*:
  + Inhibitors:
    - Ciprofloxacin
    - Enoxacin
    - Fluvoxamine
    - Methoxsalen
    - Mexiletine
    - Oral contraceptives
    - Phenylpropanolamine
    - Thiabendazole
    - Zileuton
  + Inducers:
    - Montelukast
    - Phenytoin
* \*Note: no washout period required; if these medications are discontinued, subjects are eligible to be enrolled in the trial
* Acquired immune deficiency syndrome (AIDS) or AIDS-related complex
* Active malignancy or history of invasive malignancy within the last five years, with the exception of superficial basal cell carcinoma or squamous cell carcinoma of the skin that has been definitely treated. Patients with carcinoma in situ of the uterine cervix treated definitely more than 1 year prior to enrollment may enter the study

# Screening and enrollment design

Graphical user interface, diagram

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# Safety Evaluation

Safety was monitored through the course of the study by a designated Independent Medical Safety Monitor (IMSM). Trends in serious adverse events (SAEs), laboratory events, and treatment-emergent adverse events (TEAEs) were reviewed by an external Data and Safety Monitoring Board (DSMB). The DSMB evaluated safety information against the pre-specified safety stopping rules.

AEs were classified by body system and preferred term. Relative frequencies of AEs were compared between the riluzole and placebo arms using chi-square test with alpha = 0.05.

# Statistical Testing of Primary Endpoint

The appropriate statistical approach was to test a single one-sided null-hypothesis that the difference between the investigational and the placebo arm was equal to or less than 0. Rejection of the null-hypothesis was consistent with superiority of the investigational treatment to the placebo.

# Determination of Sample Size

The required sample size was 316 evaluable subjects, or 158 subjects per study arm. The rationale for the sample size is as follows.

The statistical analysis tested the null hypothesis of the superiority of riluzole compared to placebo in change of ISNCSCI Motor Score between the baseline and the 180-day follow-up visits (change in ISNCSCIMS). See Table below.

The sample size was calculated to provide 90% power in testing the primary superiority hypothesis. The estimate was calculated by PROC SEQDESIGN for SAS/STAT. Standard deviation for the primary outcome parameter was made using the data from the STASCIS study (data on file with the Sponsor). This estimate was based on subjects with neurological level of injury from C4-C8 at arrival, the ISNCSCI Impairment grade “A,” “B” or “C” and time from injury to arrival of less than 12 hours.

Graphical user interface

Description automatically generated with medium confidence

## Study Success

The study was considered to successfully confirm the working hypothesis if H0 for the primary endpoint was rejected either at interim or the final analysis.

Study success was defined as follows: Investigational treatment (riluzole) was superior to placebo. Study success was achieved if the one-sided null hypothesis of no superiority of riluzole group in change in ISNCSCIMS180-b was rejected.

# Preplanned Subgroup Analysis

A pre-planned sub-group analysis was conducted to evaluate differences in change in ISNCSCIMS180-b among the patients in baseline ISNCSCI Impairment Groups “A,” “B” and “C.” The rationale for this pre-planned analysis was that these groups experience different recovery of ISNCSCIMS which may result in between-group differences in change in ISNCSCIMS180-b.

Motor recovery, as measured by change in ISNCSCIMS between acute admission and 6 months follow-up, is known to vary according to individuals’ baseline level of injury severity, as defined by ISNCSCI grade. The variability in motor recovery depending on the baseline injury severity has been fully incorporated into the sample size estimate calculations. At present, the data from the Phase I study of riluzole in SCI are under analysis. Such data, when available, will be incorporated in the planning of this sub-group analysis. However, this pre-planned sub-group analysis is of interest from an exploratory perspective and will be used for purposes of planning future studies which may serve to further refine riluzole’s role in the treatment of SCI. Statistical details of this analysis was provided in the SAP.

RESULTS

# Termination of Study

Due to the COVID-19 pandemic, screening & enrollment to the RISCIS trial was suspended by the Sponsor (AOSpine North America/AOSNA) on May 1, 2020. At that time, 193 subjects had been enrolled to the study.

# Screening and Enrollment Per Site

Chart, bar chart

Description automatically generated

# Subject Accounting

The follow-up rate at 180-day visit was 82.70% and at 365-day the follow-up rate was 82.40% . The follow-up rate was similar between Riluzole and Placebo groups. At the 180-day follow-up, 69 of 81 (85.19%) of the expected Riluzole subjects and 70 of 87 (80.46%) of the expected placebo subjects attended the visit.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Enrollm**  **ent** | **72 hour** | **7 day** | **14 day** | **84 day** | **180 day** | **365 day** |
| Treated | 193 | 193 | 193 | 193 | 193 | 193 | 193 |
| Enrolled | 193 | 193 | 193 | 193 | 193 | 193 | 193 |
| Ineligible (Excluded for major protocol violation) | 32 | 32 | 32 | 32 | 32 | 32 | 32 |
| Not yet due | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Theoretical | 193 | 193 | 193 | 193 | 193 | 193 | 193 |
| Not yet overdue | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ineligible for F/U (Investigator-withdrawn) | 0 | 0 | 0 | 0 | 0 | 2 | 5 |
| Ineligible for F/U (Patient self-withdrawn) | 0 | 0 | 0 | 1 | 3 | 6 | 10 |
| Ineligible for F/U (Death) | 0 | 0 | 4 | 11 | 15 | 17 | 19 |
| Expected | 193 | 193 | 189 | 181 | 175 | 168 | 159 |
| Actual (Complete in window) | 189 | 139 | 181 | 167 | 124 | 97 | 102 |
| Actual (Any Data) | 193 | 193 | 187 | 177 | 153 | 139 | 131 |
| % Follow-up (Complete in  window) | 97.90% | 72.00% | 95.80% | 92.30% | 70.90% | 57.70% | 64.20% |
| % Follow-up (Any Data) | 100.00% | 100.00% | 98.90% | 97.80% | 87.40% | 82.70% | 82.40% |

Chart

Description automatically generated

# Demographic and Other Baseline Characteristics

In the Treatment group, the mean age was 49.4 years (SD=17.1, range 19-74 years) with a mean Body Mass Index (BMI) of 28.8 (range 17-59). There were 17 females and 79 males.

In the Control group the mean age was 47.6 years (SD=16.0, range 20-74 years) with a mean Body Mass Index (BMI) of 28.4 (range 19-51). There were 18 females and 79 males.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Riluzole**  **(N=96)** | | **Control**  **(N=97)** | | **Riluzole -**  **Control** | | **P-value** | | |
| Age at consent (years) 1 | | | | | | | | | |
| n | 96 | | 97 | |  | | 0.453 | | |
| Mean | 49.4 | | 47.6 | | 1.8 | |  | | |
| SD | 17.1 | | 16.0 | |  | |  | | |
| 95% CI |  | |  | | -2.9 - 6.5 | |  | | |
| Median | 51 | | 50 | |  | |  | | |
| Range | 19 - 74 | | 20 - 74 | |  | |  | | |
|  | | | | | | | | | |
| Gender, n (%) 2 | | | | | | | | | |
| Male | 79  (82.3) | | 79  (81.4) | |  | | 1.000 | | |
| Female | 17  (17.7) | | 18  (18.6) | |  | |  | | |
|  | | | | | | | | | |
| Height (cm) 1 | | | | | | | | | |
| n | 92 | | 90 | |  | | | | 0.733 |
| Mean | 175.5 | | 175.0 | | 0.5 | | | |  |
| SD | 8.6 | | 10.1 | |  | | | |  |
| 95% CI |  | |  | | -2.3 - 3.2 | | | |  |
| Median | 177 | | 177 | |  | | | |  |
| Range | 150 - 193 | | 151 -  205 | |  | | | |  |
|  | | | | | | | | | |
| Weight (kg) 1 | | | | | | | | | |
| n | 90 | | 89 | |  | | | | 0.682 |
| Mean | 88.4 | | 87.2 | | 1.3 | | | |  |
| SD | 20.8 | | 20.6 | |  | | | |  |
| 95% CI |  | |  | | -4.8 - 7.4 | | | |  |
| Median | 86 | | 83 | |  | | | |  |
| Range | 45 - 191 | | 50 - 166 | |  | | | |  |
|  | | | | | | | | | |
| Body mass index 1 | | | | | | | | | |
| n | 86 | | 84 | |  | | | | 0.675 |
| Mean | 28.8 | | 28.4 | | 0.4 | | | |  |
| SD | 6.0 | | 5.8 | |  | | | |  |
| 95% CI |  | |  | | -1.4 - 2.2 | | | |  |
| Median | 28 | | 27 | |  | | | |  |
| Range | 17 - 59 | | 19 - 51 | |  | | | |  |
|  | | | | | | | | | |
| Race, n(%) 2 | | | | | | | | | |
| White | 69  (71.9) | | 71  (73.2) | |  | | | | 0.496 |
| Black or African American | | 13  (13.5) | | 15  (15.5) | |  | |  | |
| Asian | | 10  (10.4) | | 7 (7.2) | |  | |  | |
| Native Hawaiian or other Pacific Islander | | 1 (1.0) | | 0 | |  | |  | |
| American Indian or Native American | | 1 (1.0) | | 0 | |  | |  | |
| Other | | 1 (1.0) | | 4 (4.1) | |  | |  | |
| Subject did not answer | | 1 (1.0) | | 0 | |  | |  | |
|  | | | | | | | | | |
| Ethnicity, n(%) 2 | | | | | | | | | |
| Hispanic or Latino | | 2 (2.1) | | 3 (3.1) | |  | | 1.000 | |
| Not Hispanic or Latino | | 92  (95.8) | | 92  (94.8) | |  | |  | |
| Unknown | | 2 (2.1) | | 1 (1.0) | |  | |  | |
| Subject did not answer | | 0 | | 1 (1.0) | |  | |  | |

# Summary of Injury Characteristics

|  |  |  |
| --- | --- | --- |
|  | **N** | **Mean (Std. Dev)** |
| **Age (years)** | 193 | 48.47 (16.49) |
| **ISNCSCI** |  |  |
| Motor Score Total | 189 | 17.44 (13.01) |
| Motor Score Upper Total | 190 | 13.33 (10.66) |
| Motor Score Lower Total | 191 | 4.07 (7.96) |
|  | **N** | **%** |
| **Gender** |  |  |
| Female | 35 | 18.13% |
| Male | 158 | 81.87% |
| **ASIA Impairment Scale** |  |  |
| A | 101 | 52.33% |
| B | 38 | 19.69% |
| C | 52 | 26.94% |
| D | 1 | 0.52% |
| Not Done | 1 | 0.52% |
| **Neurologic Level** |  |  |
| C3 | 2 | 1.04% |
| C4 | 104 | 53.89% |
| C5 | 49 | 25.39% |
| C6 | 22 | 11.40% |
| C7 | 10 | 5.18% |
| C8 | 1 | 0.52% |
| T2 | 1 | 0.52% |
| Not Done | 4 | 2.07% |

# Primary Outcomes

## Summary Plot of Outcomes

*Please refer to R Code BLOCK 1 for the codes to generate the following graphs*

Chart, box and whisker chart

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Graphical user interface

Description automatically generated with medium confidence

## Primary Statistical Testing of Motor Outcomes

*Please refer to R Code BLOCK 2 for the codes to generate the following table*

Two sample, one-tailed T-test with null hypothesis that the difference in outcomes at 6 months is the same between placebo and Riluzole group. Alternative hypothesis is that the difference in the Riluzole group is greater.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Placebo (mean) | Riluzole (mean) | P-Value |
| Change in Upper Extremity Motor Scores at 6 Months | 14.65 | 16.42 | 0.7907 |
| Change in Lower Extremity Motor Scores at 6 Months | 16.10 | 17.55 | 0.6767 |
| Change in Total Motor Scores at 6 Months | 31.11 | 34.00 | 0.7209 |

# SECONDARY OUTCOMES

## ASIA Difference at 6 months

*CODE BLOCK 3*

Chart, treemap chart

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A screenshot of a computer

Description automatically generated with low confidence

## Neurological Level Change at 6 Months

*Code Block 4*

Text, letter

Description automatically generated

Chart, treemap chart

Description automatically generated

A screenshot of a computer

Description automatically generated with low confidence

## SF36 Change at 6 months

*Code Block 5*

Chart, box and whisker chart

Description automatically generated

## SCIM Score Change at 6 Months

*Code Block 6*

Chart, box and whisker chart

Description automatically generated

P:0.071

## VAS Score Change 6 Months

*Code Block 7*

Chart, box and whisker chart

Description automatically generated

P:0.067

# Multivariate Models

## Variable Selection

All the available variables in the data base were examined a-priori for selection based on clinical relevance. Below is a table of the variables available for selection

|  |  |  |
| --- | --- | --- |
| Variable | Selected (Y/N) | Explanation |
| Age | Y | Age has been shown to be a significant predictor of outcomes in other studies |
| Weight/Height/BMI | N | No studies have been isolated body habitus as a predictor of outcomes in SCI |
| Comorbidities | Y | Numerous co-morbidities were recorded. It established that comorbidity conditions, particularly in the frail elderly are associated with changes in outcomes in SCI.  We decided to use the Charlson Comorbidity Index which was primary recorded in the trial. The CCI is a numeric grade that takes into account 16 different comorbidities. |
| Gender | Y |  |
| Race | Y |  |
| Ethnicity | N | Given that Race was already included we decided not to include ethnicity |
| Neurological Level | Y |  |
| ASIA Grade | Y |  |

Note after graphing the variable Age with the outcome variables no obvious division was found for splines

## Conceptual Model

**Cofounders:**

* Age
* Co-morbidities
  + CCI
* Race
* Gender

**Outcomes:**

Upper Extremity Motor/Lower Motor/ Total Motor Difference at 6 Months

**Exposure:**

Riluzole vs. Placebo

**Modifier:**

ASIA Grade

Neurological Level

## Types of Models

Two types of models were selected.

1. A mixed effect model with the random effects being the ASIA grade and Neurological level was fitted on all date.
2. A separate Multivariate Linear Regression model was then fitted for each ASIA Grade.

## Linear Mixed Effect Model

*Graphical user interface, application

Description automatically generatedCode Block 8*

*Chart

Description automatically generated*

Table

Description automatically generated

## Linear Models

*Code Block 9*

### All Patients

Table

Description automatically generated

### ASIA A

Table

Description automatically generated

### ASIA B

Table

Description automatically generated

### ASIA C

Table

Description automatically generated

## Graphs of All Linear Models

Chart

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# Binary/MCID Results

While a MCID is not fully established in the literature, it is generally accepted that 5 points in the Total Motor and 2 points in the Upper/Lower motor aggregates can be viewed to represent MCID. In this section we dichotomize outcomes based on the MCID Cutoff

*Code Block 10*

### UEM

Chart

Description automatically generated

Non reach significance (alpha: 0.05)

### LEM

Chart, bar chart

Description automatically generated

Non reach significance (alpha: 0.05)

### Total Motor

Chart, bar chart

Description automatically generated

Non reach significance (alpha: 0.05)

# Summary of all Results

Legend

Effect Towards Riluzole

\*

Statistical Significance

## Univariate

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All** | **ASIA A** | **ASIA B** | **ASIA C** |
| Upper Extremity Motor Change (6months) |  |  |  |  |
| Lower Extremity Motor Change (6months) |  |  |  |  |
| Total Motor Change (6months) |  |  |  |  |

## Multi Variate

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Mixed Effect** | **ALL** | **ASIA A** | **ASIA B** | **ASIA C** |
| **Upper Extremity Motor Change (6months)** |  |  |  |  |  |
| **Lower Extremity Motor Change (6months)** |  |  |  |  |  |
| **Total Motor Change (6months)** |  |  |  |  |  |

## Binary

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All** | **ASIA A** | **ASIA B** | **ASIA C** |
| **Upper Extremity Motor Change (6months)** |  |  |  |  |
| **Lower Extremity Motor Change (6months)** |  |  |  |  |
| **Total Motor Change (6months)** |  |  |  |  |

## Secondary Outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **6 Month Improvement** | **ALL** | **ASIA A** | **ASIA B** | **ASIA C** |
| **SF36 Physical Score** |  |  |  |  |
| **SF36 Mental Score** |  |  |  |  |
| **SCIM** |  |  |  |  |
| **EQ5D VAS Score** |  |  |  |  |