Efficacy and Safety of Riluzole in Acute Spinal Cord Injury (SCI).Rationale and Design of AOSpine Phase III Multi-center Double Blinded Randomized Controlled Trial. (RISCIS)

Michael G. Fehlings MD PhD FRCS(C) FACS; Branko Kopjar MD; Robert G. Grossman MD
Univeristy of Toronto, Toronto, Canada; University of Washington, Seattle, WA; The Methodist Hospital, Houston TX

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Introduction

There is convincing evidence from the preclinical realm that the pharmacologic agent riluzole attenuates certain aspects of the secondary injury cascade leading to diminished neurological tissue destruction in animal SCI models. The safety and pharmacokinetic profile of riluzole have been studied
in a multicenter pilot study in 36 patients. Efficacy of riluzole in acute human SCI has not been established.

Phase I/IIa Riluzole Trial

Primary Aim: To develop acute care safety and pharmacokinetic profiles of riluzole in patients who have sustained a traumatic spinal cord injury
Secondary Objectives: To conduct exploratory analyses of neurological outcomes for purposes of
planning a subsequent Phase II b –Phase III randomized study of the efficiency of riluzole for the treatment of acute spinal cord injury

Patient Characteristics

Characteristic	Patient Number N=36
Gender:	
Male	30 (83%)
Female	6 (17%)
Mean Age	39 (Min:18 Max:69)
Neurological Level of Injury:	
Cervical	28 (78%)
Thoracic	8 (22%)
ASIA Impairment Scale (AIS) grade:	
AIS grade A	19 (53%)
AIS grade B	9 (25%)
AIS grade C	8 (22%)
Etiology:	
Motor Vehicle Accident	20(55%)
Fall	9(25%)
Sport related	5(14%)
Assault	2 (6%)

Phase I/IIa Trial Conclusion

Have established feasibility of a multicenter trial evaluating Riluzole in traumatic SCI. Preliminary safety and neurological recovery data appear promising

Phase III RCT

Subjects: A total of 351 patients with acute traumatic SCI will be randomized in a prospective doubleblind placebo-controlled trial involving up to 35 sites internationally.
Randomization will be 1:1 to riluzole 2x100mg daily for 24 hours followed by 2x50mg daily for the following 13 days after injury, or to the same regimen of placebo. Key inclusion criteria include: able to receive study drug within 12 hours of injury; ISNCSCI Impairment Scale Grade A, B or C; level of injury C4-C8 Key exclusion criteria include: injury from penetrating mechanism, significant concomitant head injury

Study Design

Primary outcome measure is change in ISNCSCI Total Motor Score between baseline and 180 days following enrollment.

Secondary outcome measures include ISNCSCI grade, ISNCSCI Sensory Scores, SCIM, SF-36v2, EQ-5D, GRASSP, Pain NRS.

Statistical Design

Sample size of 316 evaluable subjects will have 90% power to detect .37 Cohen's d effect size (i.e. 9 difference in ISNCSCIMS). There is no published minimally significant difference for ISNCSCIMS.
The current effect estimate of 9 is arbitrarily set. Study uses adaptive sequential design that allows sample size change during the interim analysis.

Plan ID	Parameter
Type of the hypothesis	1-Sided
Type I Error (α)	0.025
Power (1 - β)	0.90
Randomization Ratio (Investigational vs. Control)	1:1
Planned Number of Interim Looks	2
Spacing of Looks	60%, 100%
Hypothesis to be Rejected	H0 or H1 (binding)
Boundary Family	Published Function
Boundary to Reject H0	O'Brien-Fleming
Boundary to Reject H1	Gamma (-1)
Difference of Means Assuming H_1	9
Standard Deviation (σ)	24.08
Sample Size	316 (158 per arm)

Current Status

Subject enrollment for this trial began on October 1, 2013. This is a Phase III study of riluzole in
acute SCI. To date, there are 137 subjects enrolled.

Results

Demographics

Demographics		N (%)
Age (N = 119)		48.4±16.1
Gender	Female	19 (16.0%)
	Male	100 (84.0%)
Race	White	85 (71.4%)
	African-American	19 (16.0%)
	Asian	11 (9.2%)
	Pacific Islander	1 (0.8%)
	Native American	1 (0.8%)
	Other	2 (1.7%)

Outcome Measuses

Outcome Measure	N	Mean (SD)
ISNCSCI		
Motor Score Total	126	17.51 (12.99)
Motor Score Upper Total	127	13.27 (10.50)
Motor Score Lower Total	126	4.22 (8.23)
ASIA Impairment Scale		
A	62	48.82%
B	31	24.41%
C	34	26.77%
Neurological Level		
C3	2	1.57%
C4	70	55.12%
C5	30	23.62%
C6	15	11.81%
C7	8	6.30%
Not Done	2	1.57%

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Conclusions

This is a Phase III study of riluzole in acute SCI.