Rationale, Design and Early Trial Performance of AOSpine North America Multi-center Double Blind Randomized Controlled Trial of Safety and Efficacy of Riluzole in CSM (CSM – Protect Trial)

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Background

Cervical spondylotic myelopathy (CSM) is the most common cause of spinal cord impairment.

While there is emerging evidence from the recently completed AOSpine North America prospective study that surgical decompression is an effective treatment for CSM, many patients have substantial residual neurological and functional impairment.

Further improvement in treatment of CSM is warranted.

Compelling evidence from preclinical models of nontraumatic and traumatic spinal cord injury (SCI) suggest a benefit of adding a neuroprotective drug which targets sodium/glutamate excitotoxicity to the treatment of patients with CSM undergoing surgical decompression.

Subjects

A total of 270 (300 to adjust for loss-to-follow up) patients undergoing surgical decompression for CSM will be randomized in this ongoing prospective double-blinded controlled trial involving 15 sites in North America.

Randomization will be 1:1 to riluzole 2x50mg daily for 14 days before the surgery and 28 days after the surgery or to the same regimen of placebo.

Primary outcome measure is change in mJOA between baseline and 6 months following the surgery.

Secondary outcomes include ASIA, SF36v2, NDI, EQ5D, Pain VAS and complications.

Outcomes evaluations will occur at 6 and 12 months.

Statistical Design

Sample size of 270 subjects total will have 80% power to detect .35 Cohen's d effect size (i.e. 0.9 difference in mJOA). 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)	0.80
Randomization Ratio (Investigational vs. Control)	1:1
Planned Number of Interim Looks	2
Spacing of Looks	65%, 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 (-2)
Difference of Means Assuming H_1	0.9
Standard Deviation (σ)	2.57
Sample Size	270 (135 per arm)

Results

Demographics

Demographics		N (%)
Age (N = 195)		58.4 (9.9)
Gender	Female	87 (44.6%)
	Male	108 (55.4%)
Race	White	163 (83.7%)
	African-American	16 (8.2%)
	Asian	9 (4.6%)
	Alaska Native	1 (0.5%)
	Unknown	3 (1.5%)
	Other	3 (1.5%)
Surgery	Anterior	83 (46.1%)
	Posterior	94 (52.2%)
	Ant + Pos	3 (1.7%)

203 subjects currently enrolledAnalysis reflects current data available for each demographic and outcome. N values are outlined for each.

Results Continued

Primary and Secondary Outcomes

Outcome Measure		Mean (Standard Deviation)
mJOA (N = 195)		11.8 (1.5)
ASIA	Motor Total (N = 190)	95.5 (6.0)
	Sensory Light Touch (N = 190)	105.6 (10.9)
	Sensory Pin Prick (N = 189)	106.0 (9.9)
SF36v2 PCS (N = 192)		33.0 (9.8)
Pain VAS	Pain in Arm and Shoulder (N = 194)	4.8 (2.9)
	Pain in Neck (N = 194)	4.7 (2.9)
NDI (N = 193)		42.6 (20.5)
EQ-5D (N = 194)		0.6 (0.2)

Conclusions

In spite of the benefits of the surgical intervention, patients with CSM experience significant residual impairment and neurological compromise. Adding neuroprotective treatment with riluzole may improve outcomes of surgery.

This study will bring Level I evidence about efficacy of riluzole as adjuvant to surgical decompression in patients with moderate to severe CSM.

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