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Clinical Evaluation of a Neuroprotective Drug in Patients With Cervical Spondylotic Myelopathy Undergoing Surgical Treatment

Design and Rationale for the CSM-Protect Trial

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Study Design. Descriptive article and narrative review.

Objective. To explain the rationale and design of the cervical spondylotic myelopathy (CSM)-Protect clinical trial that aims to elucidate the efficacy and safety of riluzole in the context of CSM.

Summary of Background Data. CSM is the most common cause of spinal cord–related dysfunction internationally. Although surgery is effective in preventing the progression of impairment, and in some cases improving functional outcomes, many patients continue to exhibit significant disability in the postoperative setting. Evidence from preclinical studies suggests that glutamate-related excitotoxicity may contribute to the pathology of CSM and that administration of the sodium and glutamate-blocking medication riluzole, when combined with spinal cord decompression, may mitigate this effect and improve neurobehavioral outcomes. Although riluzole is FDA approved and has been shown to be safe and effective in the context of amyotrophic lateral sclerosis, its efficacy and safety in the context of CSM remain unknown.

Methods. Descriptive article with narrative review of the literature.

Results. In addition to providing pertinent preclinical background on the topic, this descriptive article and narrative review discusses the design and current status of an ongoing phase III randomized controlled trial evaluating the efficacy and safety of riluzole, combined with surgical decompression, in the treatment of CSM.

Conclusion. On the basis of current projections, we estimate that the interim analysis for this study will take place in the spring of 2014, at which time an adaptive sample size adjustment may take place.

Key words: cervical spondylotic myelopathy, drug therapy, riluzole, randomized controlled trial.

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Cervical spondylotic myelopathy (CSM) is thought to be the most common cause of spinal cord dysfunction throughout the world.[1,2] In this condition, both static and dynamic pathological factors combine to cause compression of the cervical spinal cord, which can result in progressive neurological dysfunction and disability for the individual affected. There is current evidence to suggest that surgical decompression of the spinal cord can lead to stabilization, and in some cases, improvement in functional, neurological, and quality-of-life status at long-term postoperative follow-up for patients with CSM.[3,4] Despite this, the majority of patients who undergo surgery experience some degree of residual symptomology and disability in the postoperative period. This fact opens the door for the identification of additional therapies that may be combined with surgery to further enhance patients' long-term outcomes. To date, no additional pharmacological or procedural therapy has been definitively shown to impact outcome for patients with CSM positively.

Riluzole is an anticonvulsant medication that is currently FDA-approved for the long-term treatment of patients with amyotrophic lateral sclerosis (ALS).[5] In this context, riluzole has been shown to be safe and to improve survival by several months, when taken at the time of diagnosis and continued indefinitely. In addition to ALS, the efficacy of riluzole is also under investigation in a variety of other neurological conditions, including traumatic spinal cord injury, and psychiatric disorders such as major depressive and bipolar disorder.[6,7]

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In the context of CSM, the results of recent preclinical studies have suggested that the administration of riluzole may augment the effects of surgery to optimize neurobehavioral outcomes.[8] These results, combined with the beneficial effects of riluzole observed in analogous conditions, have led to the identification of this drug as a promising potential therapeutic option for the treatment CSM. However, without evaluation within a multicenter efficacy trial, such effects remain purely speculative.

Empirical evidence of outcome reporting bias (particularly related to treatment harms) during the past decade has led to a call for the registration of clinical trials and publication of protocols prior to trial completion to ensure transparency.[9–11] Criteria for assessing the extent to which randomized controlled trial (RCT) data may be sufficient for addressing the balance of benefits and harms have increasingly incorporated those for evaluating the potential of outcome reporting bias[12] and may involve comparison of published study protocols with trial results reports. In line with the concept of transparency, this article provides details of our RCT protocol.

Given this background, the goal of the current article is to outline the rationale for, and design of, the Efficacy of Riluzole in Patients with CSM undergoing Surgical Treatment Study (CSM-Protect). As discussed in the text hereafter, CSM-Protect is a multicenter North American randomized controlled trial evaluating the efficacy and safety of riluzole in the management of patients with CSM undergoing decompressive surgery. The completion of this study will provide level 1 evidence either confirming or refuting a positive impact of riluzole, as an adjunct to surgical care, in the treatment of CSM.

PATHOBIOLOGY OF CSM AND RELEVANCE TO OTHER CONDITIONS

The central events underlying the pathophysiology of CSM are presented in Table 1. In general, with increasing age, a variety of degenerative changes including facet joint capsule and ligamentous hypertrophy, as well as disc degeneration and osteophyte formation, can lead to circumferential spinal canal compromise and compression of the spinal cord, even in the absence of neck movement.[13,14] This static cord compression is often further exacerbated with dynamic motion; whereas neck flexion can result in stretching of the cord over anterior pathology, neck extension results in buckling of the ligamentum flavum and further reduction of spinal canal size.[15,16] The result of both dynamic and static compression is reduced cord perfusion as a result of compressive narrowing and injury to anterior perforating vessels, which primarily supply the medial aspects of the dorsal columns and corticospinal tract.[17,18] Consistent with this idea, correlative postmortem studies have found these regions to be the most susceptible to ischemia, even with mild degrees of compression.[19] In addition to this localized ischemic injury, ongoing cord deformation is thought to compromise its internal angioarchitecture, leading to a regional disruption of the blood spinal cord barrier and resulting in the appearance of vasogenic edema and local infiltration of inflammatory cells.[20] The cumulative chronic effect of these and other changes eventually result in pathological findings of demyelination, necrosis, and gliosis, as well as cystic cavitation within the central gray and medial aspects of the long fiber tracts.[2]

Although there are several clear differences between the pathophysiology of traumatic spinal cord injury and CSM, certain similarities exist that may be exploited for the purposes of therapeutic intervention in both conditions.[19] The ischemic changes that occur during the secondary injury cascade post-traumatic injury lead to further neuronal dysfunction and loss of normal cellular homeostasis.[21,22] One of the specific cellular events that occurs during this process is the abnormal continuous activation of neuronal voltage-gated sodium ion channels, which leads to an increase in intracellular sodium.[23] This increased concentration leads not only to cellular swelling and cytotoxic edema, but also to an influx of calcium through increased sodium-calcium transport exchanger activity.[24,25] The increasing neuronal calcium concentration triggers the release of the excitatory neurotransmitter glutamate into the extracellular space causing increases in local cell death through excitotoxic mechanisms.[26,27] Given that ischemia is thought to be the main precipitant of such neuronal dysfunction and excitotoxicity after SCI, and given that ischemic neural injury is central to the pathophysiology of CSM, it stands to reason that glutamate-related excitotoxicity may also contribute to the final extent of neural injury observed in CSM. Furthermore, findings that slow glutamate-related toxicity may also underlie ALS, Huntington disease, and spinal muscle atrophy type 1, neurodegenerative conditions with a chronic progression akin to CSM, further support a role for this mechanism in this disease process.[28–30] According to this hypothesis, the use of an agent to block such excitotoxicity could theoretically serve to reduce neural injury and improve patient outcomes.

TABLE 1. Main Events Underlying the Pathobiology of CSM

Current Knowledge in the Pathobiology of CSM
Chronic inflammatory response • Recruitment of peripheral macrophages • Activation of resident microglia • FasL/FasR
Apoptosis • Neurons • Oligodendrocytes
Chronic hypoxic ischemic injury • Endothelial cell loss • Disruption of the vessels basement membrane • Chronic compromise of blood spinal cord barrier
Glutamate excitotoxicity

CSM indicates cervical spondylotic myelopathy.

RILUZOLE IN CSM AND OTHER CLINICAL CONDITIONS

Riluzole is a benzothiazole sodium channel-blocking agent that was originally conceived in the 1980s as an antiepileptic drug.[31] Although never having a significant role in the treatment of epilepsy, riluzole was found in several large RCTs to improve tracheostomy free survival by several months in the context of ALS by slowing the degeneration of anterior horn motor neurons.[5] Furthermore, riluzole administration has shown to be safe in the human population with the only significant complication being mild evidence of hepatotoxicity in a small percentage of patients, but only after several months of administration. On the basis of this favorable safety and efficacy profile observed in clinical studies, riluzole is FDA-approved for the chronic treatment of patients with ALS.

In the context of spinal cord-specific conditions, riluzole has been shown to mitigate sodium and glutamate-mediated secondary injury mechanism after traumatic spinal cord injury resulting in improved neurobehavioral and pathological outcomes in several rat studies.[32,33] A phase I/IIa clinical study was recently completed, confirming the safety and feasibility of riluzole administration in human patients with traumatic spinal cord injury.[7,34] As regards CSM, recent work performed by the Fehlings group involving a preclinical chronic cervical compression model in rats compared riluzole administration (for 5 wk from the time of symptom onset) combined with decompression to decompression alone.[8] The results of this investigation demonstrated the group of rats treated with riluzole and decompression to have superior neurobehavioral outcomes as well as greater white matter preservation and reduced astrogliosis on postmortem analysis, than the compression alone group. These experiments are thought to strongly implicate glutamate-related excitotoxicity as an important mechanism underlying the pathophysiology of CSM. Furthermore, they provide biological rationale to support the pursuit of clinical investigation evaluating the addition of riluzole to decompressive surgery in the treatment of human patients with CSM.

TABLE 2. Summary of Centers Participating in CSM-Protect Study as of March 2013

Principal Investigator	Site of Enrollment
Bruce Darden, II, MD	Ortho Carolina Spine Center, Charlotte, NC
Benoit Goulet, MD	Montreal Neurological Institute, Montreal, Quebec, Canada
S. Tim Yoon, MD	Emory University, Atlanta, GA
Christopher I. Shaffrey, MD	University of Virginia, Charlottesville, VA
Michaela G. Fehlings, MD, PhD	University of Toronto Spine Program and Toronto Western Hospital, Toronto, Ontario, Canada
Darrel S. Brodke, MD	University of Utah, Salt Lake City, UT
Praveen Mummaneni, MD	University of California San Francisco (UCSF), San Francisco, CA
Ahmad Nassr, MD	Mayo Clinic, Rochester, MN
Alexander Vaccaro, MD, PhD	Thomas Jefferson University, Philadelphia, PA
W. Bradley Jacobs, MD	University of Calgary, Calgary, Alberta, Canada
K. Daniel Riew, MD	Washington University, St Louis, MO
Jens R. Chapman, MD	University of Washington, Seattle, WA
Paul M. Arnold, MD	University of Kansas, Kansas City, KS
Henry Ahn, MD	St. Michael's Hospital, Toronto, Ontario, Canada
Daniel Sciubba, MD	Johns Hopkins University, Baltimore, MD
Kee Kim, MD	University of California Davis Spine Center, Sacramento, CA

CSM indicates cervical spondylotic myelopathy.

EFFICACY OF RILUZOLE IN PATIENTS WITH CSM UNDERGOING SURGICAL TREATMENT STUDY (CSM-PROTECT)

Study Objectives and Design

The primary objective of the CSM-Protect study is to compare functional recovery at 6-month follow-up between adult patients with CSM undergoing decompressive surgery and receiving either: (1) riluzole of 50 mg BID for the first 14 days before and for the first 28 days after surgery (investigational arm) or (2) a placebo medication (control arm) for the same duration before and after surgery. As secondary objectives, we are evaluating the impact of this riluzole regimen on neurological, disability, pain, and quality-of-life outcomes, as well as on mortality and adverse event rates. We hypothesize that riluzole-treated subjects will experience superior functional recovery as compared with those receiving placebo, while experiencing similar adverse event rates.

To achieve these objectives, we have initiated a randomized, multicenter, placebo-controlled, 2-arm parallel group superiority trial with a sequential adaptive design. One interim data look is planned through the study period after 65% of planned patient enrollment. At this interim analysis, predetermined stopping rules for futility and efficacy will be evaluated, and an adaptive sample size adjustment may be undertaken according to predetermined boundaries, as described in the text hereafter. Stratified block randomization, with balanced group allocation (1:1) will occur, with strata defined by the participating study centers. This trial has been registered with clinicaltrials.gov (no. NCT01257828).

Study Setting

This trial takes place within the setting of AOSpine North America Research Network, a clinical research consortium, funded by AOSpine North America, which is dedicated to

the study of spinal cord-related conditions. The central trial management center is at the AOSpine Methods Core where the central electronic online data capture system is held. Dr. Michaela G. Fehlings heads the trial steering committee that also consists of several content experts, a pharmacologist, a trial methodologist, and a statistician. At present, a total of 16 centers from the consortium are involved in this trial (Table 2). At each of these sites, there is a designated primary site investigator supported by at least one professional study coordinator, who is responsible for day-to-day operations. Prior to commencing enrollment, all sites received research ethics board approval.

Screening and Eligibility

Since January 2012, patients with CSM at participating sites who are being scheduled for elective decompressive surgery are screened according to a predefined set of enrollment criteria. A summary of the study flow is depicted in Figure 1.

Main Inclusion Criteria

1. Male or female patients with at least one symptom and sign of myelopathy accompanied with magnetic resonance imaging evidence of degenerative-related spinal cord compression. Evidence of compression is determined on the basis of midsagittal T2-weighted magnetic resonance imaging according to the method described previously by Fehlings *et al*.[35]
2. Between the age of 18 and 75 years.
3. Modified Japanese Orthopedic Association (mJOA) scale score of less than or equal to 14 at screening (Table 3).
4. Scheduled for elective surgical decompression of the cervical spinal cord.

Our decision to not include patients with less severe functional deficit (*i.e.*, mJOA > 14) was based on 2 main considerations. The first was related to our desire to minimize the impact of ceiling effects with respect to the primary outcome of change in mJOA at 6 months of follow-up. The second point relates to the fact that surgery for patients with mild CSM remains controversial, with some authors continuing to advocate for initial nonsurgical management in this context. Given that this trial was intended to evaluate the impact of riluzole as an adjunct to surgical decompression for patients with CSM, we thought it unreasonable to include patients where the role of surgery remains contested.

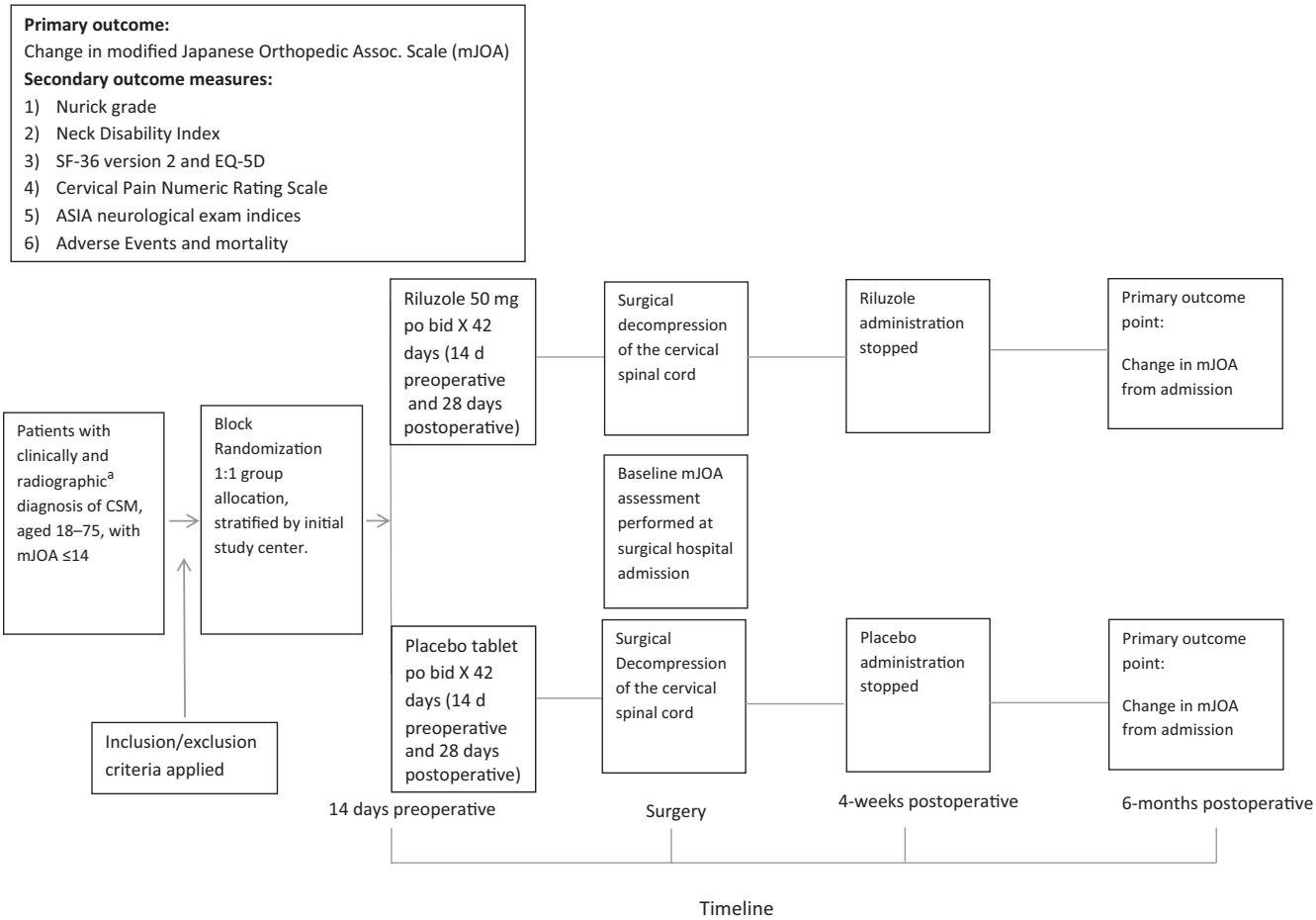

Figure 1. Study flow diagram. mJOA indicates modified Japanese Orthopedic Association Scale Score; ASIA, American Spinal Injury Association; CSM, cervical spondylotic myelopathy.

TABLE 3. Modified Japanese Orthopedic Association Scoring System

Definition	Score Allotted
Upper extremity motor dysfunction	
Unable to move hands	0
Unable to eat with a spoon but able to move hands	1
Unable to button shirt but able to eat with a spoon	2
Able to button shirt with great difficulty	3
Able to button shirt with slight difficulty	4
No dysfunction	5
Lower extremity motor dysfunction	
Complete loss of motor and sensory function	0
Sensory preservation without ability to move legs	1
Able to move legs but unable to walk	2
Able to walk on flat floor with a walking aid	3
Able to walk up- and/or downstairs with aid of handrail	4
Moderate to significant lack of stability but able to walk up-&/or downstairs without handrail	5
Mild lack of stability but able to walk unaided with smooth reciprocation	6
No dysfunction	7
Sensory dysfunction upper extremities	
Complete loss of hand sensation	0
Severe sensory loss or pain	1
Mild sensory loss	2
No sensory loss	3
Sphincter dysfunction	
Unable to micturate voluntarily	0
Marked difficulty in micturition	1
Mild-to-moderate difficulty in micturition	2
Normal micturition	3
Total score	18

Modified from: Benzel et al.[39]

Key Exclusion Criteria

1. Previous surgery for CSM
2. Concomitant symptomatic lumbar stenosis
3. Presentation with symptoms due to cervical spine trauma (*i.e.*, central cord syndrome)
4. Myelopathy secondary to oncological or infection-related spinal cord compression
5. Pregnant or nursing females
6. Evidence of hepatic or renal impairment
7. History of recent substance abuse
8. Systemic Infection or active malignancy
9. Unlikely or unable to comply with follow-up

Enrollment and Randomization

Those patients who satisfy the screening criteria and agree to study participation are enrolled and randomized at 1:1 to 1 of the 2 treatment arms at 15 to 21 days prior to surgery. The process of random treatment allocation is controlled by a permuted stratified block randomization generated by the biostatistician at the central trial management center who is in no way associated with determining study eligibility. For each subject, randomization occurs by opening the lowest sequential number of the site-specific sealed randomization envelops. The envelope contains a unique randomization number that corresponds to the number on a prestocked medication container containing either riluzole or placebo. Throughout randomization and follow-up, the subjects, physicians, and data collectors remain blinded to group allocation.

Treatment Description

Subjects assigned to the active treatment arm receive riluzole at a dose of 50 mg orally every 12 hours for the first 14 days before injury and continue receiving it for the first 28 days, postoperatively. Subjects randomly assigned to the control arm receive a placebo capsule that is identical in shape, size, and color to the riluzole capsule for the same duration and at the same interval. At the time of randomization and after the surgery, enrolled subjects receive the medication containers containing the allotted quantity of riluzole or placebo tablets, accompanied with detailed instructions for use. Drug-related compliance will be assessed and recorded throughout the study period. Regarding surgical treatment, all details, including the approach (anterior *vs.* posterior), the type of operation (laminectomy *vs.* laminoplasty *vs.* discectomy *vs.* corpectomy), the number of decompressed levels, and use of graft material and/or instrumented fusion techniques are left to the discretion of the site-specific surgeon. Postsurgical treatment, including the institution of rehabilitation measures, is left to the standard of care at the participating study site.

Outcome Measures and Follow-up

Primary Outcome

The primary outcome of interest is improvement in functional status as measured by the change in mJOA scale score between the preoperative hospital admission and at 6 months postoperatively. From the standpoint of clinical meaningfulness, mJOA, more than any other outcome measure, is thought to define the capabilities and limitations in day-to-day life for patients with CSM. Furthermore, mJOA has become the central tool for functional outcome assessment in CSM and has been incorporated as the main outcome of interest in many previous and current clinical studies in the field. The time point of 6 months was chosen on the basis of empirical

TABLE 4. Schedule of Events Throughout Study Period

	Screening	Enrollment (15–21 d Before the Surgery)	Admission	Procedure (Day 0)	Predischarge	35 ± 5 d	180 ± 30 d	365 ±30 d	Unscheduled Visit
Informed consent	X								
Inclusion/exclusion	X								
Pregnancy test (if applicable)	X								
Demographics	X								
Medical history		X							
Clinical laboratory	X		X			X			
Operative data				X					
mJOA	X	X	X			X	X	X	
Nurick Score		X	X			X	X	X	
NDI		X	X			X	X	X	
Pain NRS		X	X			X	X	X	
SF-36v2.0		X	X			X	X	X	
EQ-5D		X	X			X	X	X	
ASIA indices (complete)		X	X			X	X	X	
Grip strength		X	X			X	X	X	
Bazaz Dysphagia Scale		X	X			X	X	X	
Adverse events			X	X	X	X	X	X	X
Concomitant therapy		X	X		X	X	X	X	X
Randomization		X							
Study medication dispensing		X	X						
Medication compliance diary			X			X			

mJOA indicates modified Japanese Orthopedic Association Scale Score; NDI, Neck Disability Index; ASIA, American Spinal Injury Association; NRS, numeric rating scale.

evidence from an earlier study showing that the majority of functional change and recovery after surgical decompression occurs by this time point.

Secondary Outcomes

In addition to mJOA, a variety of validated secondary measures will be used to assess functional (Nurick Score), disability (Neck Disability Index), quality of life (SF-36 version 2, EQ-5D), pain (Cervical Pain Numeric Rating Scale), and neurological (American Spinal Injury Association indices) outcomes at several different follow-up points. In addition, major and minor adverse events have been predefined and are recorded on an ongoing basis throughout the study period. All major adverse events will be reported to the data safety monitoring board at the time of occurrence. Lastly, the mortality rate will also be assessed and compared between the 2 treatment groups. The schedule for these assessments at each follow-up point is outlined in Table 4.

SAMPLE SIZE, INTERIM ANALYSIS, AND ADAPTIVE TECHNIQUES

The primary outcome of interest, change in mJOA, has been used to provide an estimate of the sample size required to perform an adequately powered study. On the basis of a previously completed multicenter surgical CSM series containing approximately 145 patients, the mean change in mJOA at 6 months postoperatively was 2.81 with a standard deviation of 2.57. These data are representative of what we can expect at 6 months for patients within the placebo arm of this trial. At present, the largest uncertainty in determining a reasonable sample size pertains to the estimation of the riluzole-related treatment effect size. We used the Cohen *d* effect size approach with a value of 0.35, which reflects a small to moderate effect. This translates to a 0.9 difference in mean mJOA change between the treatment and placebo groups. Therefore, to obtain 80% power with a 1-sided $\alpha = 0.025$, the estimated total sample size requirement is 270 patients. To account for loss of power due to losses to follow-up and possible adjustments for baseline factors, we plan to enroll 300 patients.

After 65% of study subjects have been enrolled, a planned interim analysis will take place. At this point, a blinded statistician will evaluate the data with respect to predefined statistical stopping rules for efficacy and futility. The efficacy evaluation will follow the O'Brien-Fleming distribution and the futility will follow the γ (-2) distribution. Because the main assumption underlying the determination of the sample size estimate is the effect size associated with riluzole administration, we also plan an adaptive sample size adjustment at this interim analysis, if indicated. Such an adaptive trial design is increasingly recommended and recognized as an effective method to increase trial efficiency as well as the possibility of detecting a drug effect, if one truly exists.[36]

Trial Monitoring

Throughout the course of the trial, all subject-related source data will be transcribed into the online electronic data capture system OpenClinica (OpenClinica, LLC, Waltham, Massachusetts) that will be maintained at the central trial management center. Professional clinical research monitors will perform quality assurance on the data entered into the electronic system and perform individual site visits to ensure that the data on record are true, accurate, reliable, and complete.

Statistical Methods

In the final trial analysis, those subjects who break protocol will be dealt with on an intention-to-treat basis and therefore analyzed in the group to which they were originally randomized. For the primary efficacy analysis, the mean change in mJOA scale score between admission and 6 months of follow-up will be compared between the active and control groups using an unpaired 1-tailed Student *t* test, with an overall *P* value of 0.025 used to define significance. The actual *P* value will follow the O'Brien-Fleming distribution as explained earlier and will assure conditional 80% power through the study, should sample size adjustment occur. Unpaired univariate statistics will also be used to evaluate differences between the treatment groups with respect to the secondary outcomes described earlier. After these primary analyses have been completed, secondary adjusted analyses will be performed using regression techniques to control for variables of clinical prognostic significance. Finally, any missing follow-up data will be imputed through a multiple imputation procedure that is thought to be less susceptible to bias than the complete case analysis technique. Moreover, multiple imputation is the preferred method for handling missing outcome data in therapeutic trials, as recommended by the Food and Drug Administration.[37,38]

CONCLUSION AND CURRENT TRIAL STATUS

Preclinical studies suggest that glutamate-related excitotoxicity contributes to the pathology of CSM. Riluzole, a sodium and glutamate-blocking medication that is FDA-approved for the treatment of ALS, has been shown to mitigate such excitotoxicity in both CSM and traumatic spinal cord injury animal models, leading to improved neurobehavioral outcomes. To investigate the efficacy and safety of riluzole formally, combined with surgical decompression, in the treatment of CSM, a multicenter, double blinded, RCT has been undertaken, and patients are being enrolled currently. At the timing of writing, a total of 52 patients have been enrolled in CSM-Protect. On the basis of current projections, we estimate that the interim analysis will take place in the spring of 2014, at which time an adaptive sample size adjustment may take place.

➢ Key Points

- ❑ Preclinical studies suggest that glutamate-related excitotoxicity contributes to the pathology of CSM.
- ❑ Riluzole is a sodium and glutamate-blocking medication, FDA approved for the treatment of ALS that has shown to mitigate such

excitotoxicity in both traumatic spinal cord injury and CSM animal models, leading to improved neurobehavioral outcomes.

- A randomized, multicenter, placebo-controlled phase III trial with a sequential adaptive design is currently underway to evaluate the efficacy and safety of riluzole, combined with surgical decompression, in the treatment of CSM.

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