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TITLE: Potential North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury: A Consortium of Military, Veterans Administration, and Civilian Hospitals

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14. ABSTRACT The first military (WRAMC) and four new civilian hospitals have joined NACTN. 198 patients were enrolled in national data registry; NACTN PIs are analyzing the data and preparing a manuscript on the occurrence of acute injury complications. NACTN has received ORP approval for the data registry protocol and the NACTN Data Management Center has expanded to accommodate increasing patient numbers. Modifications submitted to TATRC include: Stemnion (approved and project underway); FY 2007 and riluzole mods (the latter to replace the originally proposed anti-Nogo study) are in the review/contracting continuum. In anticipation of approval, all NACTN personnel met in February 2008 to discuss the riluzole protocol/safety study, and the centers are working with local IRBs and ORP to fulfill all regulatory requirements for the data registry. The final riluzole protocol will be submitted to the ORP HRPO for HSRRB review after securing IRB approval from one NACTN site. National ASIA training for all clinical NACTN personnel will be held in Louisville June 2-3, 2008. NACTN is collaborating with three other clinical networks: the European Union Clinical Trial Network, the Canadian SCI Translational Research Network and NIH-funded NETT. GRASSP validation is nearing successful completion and preliminary STASCIS data suggest that early decompression of the spinal cord (< 24h) is associated with improved neurological recovery.					
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INTRODUCTION: In order to conduct clinical trials that are capable of indicating the effectiveness of promising therapies for spinal cord injury and insuring patient safety, the Christopher Reeve Foundation (CRF) created the North American Clinical Trials Network (NACTN) in 2004. NACTN is a network of hospitals that is enrolling newly injured patients into a data registry, defining and adhering to standard protocols and providing the infrastructure and expertise necessary to conduct trials of therapy for spinal cord injury. The expansion of NACTN into military and new civilian hospitals insures the infrastructure needed to conduct high-quality collaborative phase I and phase II-III randomized clinical trials with the statistical power to determine the effectiveness of potential therapies. Additionally, the development of more reliable and sensitive outcome measures for use in trials of therapy will mean that even small levels of recovered function are identified, enabling further refinement of the interventions to elicit more robust recovered function.

BODY: To that end, the following tasks have been addressed during the contract period May 14, 2007 – May 13, 2008:

1. Expansion of Phase I baseline assessment research protocols for hospitals joining NACTN, working with the United States Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO) and local IRBs. Status:

- Data Registry Protocol/Informed Consent Forms: The Methodist Hospital, the Universities of Texas Health Science Center, Toronto, Virginia, Louisville and Maryland and the Rehabilitation Institute of Chicago/Northwestern University, had their amended consent forms and supportive documents approved by ORP HRPO and have submitted the approved protocol documents to their local IRBs. The Universities of Texas and Virginia have received local IRB approval and that documentation has been submitted to USAMRMC ORP/HRPO for final review and approval.

WRAMC has received secondary level local IRB approval and has now submitted the research protocol, consent form and supportive documents to USAMRMC ORP/HRPO; approval is pending and we have been assured that the approval letter will be forthcoming shortly from ORP. Upon receipt, WRAMC can begin consenting patients to the NACTN data registry.

The University of Miami and Thomas Jefferson University are in the process of submitting the master BAA Proposal #06059005, consent forms and supportive documents to their local IRBs in preparation for submission to USAMRMC ORP/HRPO.

- Riluzole Protocol: final revisions have been made to the riluzole protocol, per the review and recommendations of Dr. Jeffrey Stephenson, Regulatory Compliance Specialist, IBA and TATRC. Submission to USAMRMC/HRPO will be made upon receipt of local IRB approval for The Methodist Hospital.
- The Methodist Hospital (TMH) is preparing its local IRB application for submission, review and approval. This will then be reviewed by the full Human Subject Research Review Board (HSRRB). TMH will distribute the final version of the master protocol to all NACTN sites to facilitate their submission to their local IRBs.

2. Enroll patients with SCI to expand NACTN's statistical model of the functional outcomes of SCI that are stratified and characterized by neurological, physiological and radiological parameters. Goal: 200 patients throughout the network. Status:

Effective May 13, 2008, a total 198 patients have been enrolled into the NACTN Data Registry. 168 acute care forms and partial three-, six- and 12-month follow-up forms have been completed on 130 patients. (Appendix A, data tables)

The Data Registry is a core function of the North American Clinical Trials Network for the Treatment of Spinal Cord Injury. Two vital purposes are served by the Registry. The first is to provide a statistical and scientific platform to develop the data, logistics and collaborations necessary to conduct Phase I and Phase II clinical trials of emerging neuroprotective and neuroregenerative therapies, particularly those that can be administered in the very early stages of injury. A second and equally important purpose is to develop high quality, standardized, and validated acute care and follow-up data on a representative national sample of male and female adult patients who have suffered a spinal cord injury with neurological deficits. This acute care and follow-up data will prove to be invaluable to characterize the trajectory (natural history) of individuals who have suffered a spinal cord injury.

The registry was initially designed and patient enrollment was accomplished through the collaboration of five premier regional clinical centers: the Methodist Hospital (Houston) the University of Texas Health Sciences Center at Houston, Memorial Hermann Hospital, the University of Toronto, Toronto Western Hospital, the University of Virginia Hospital, and the Rehabilitation Institute of Chicago. In 2007 three new clinical centers joined the registry including the University of Louisville, the University of Maryland Medical Center, and the Walter Reed Army Medical Center. In 2008 two additional clinical centers, the University of Miami and Thomas Jefferson Hospital joined the registry. The rapid expansion of the registry is testimony to the national and international recognition of the significant information the registry can acquire to advance treatment and care of spinal cord injured patients.

The attached tables provide a profile of SCI cases currently in the registry database. To date 384 SCI patients have been contacted for permission to acquire prospective, standardized acute care treatment data and quarterly follow-up data for up to one-year after acute care discharge. Slightly more than one-half (198) of all patients eligible for the registry have consented to participate (Table 1). The following text summarizes registry database information on 168 of 195 registry-enrolled patients with the remaining records of 27 patients under quality control review for subsequent inclusion in the database.

Among the 168 acute care cases, about a third were classified as severe complete (ASIA grade A) SCI injuries at admission with the remaining two-thirds distributed across ASIA grades B through E (Table 2)

About 80% of the SCI cases were white males and the median age at injury for all patients was 42 years-of-age (Table 3) The leading circumstances of injury were falls (38%), motor vehicle accidents (35%), and recreation accidents (17%) with 7% due to assault (penetrating) SCI injuries. Alcohol played a probable role in 27% of all SCI injuries (Table 4).

The vast majority of SCI injuries are closed injuries (95%) with 72% reported as cervical (Table 5). About 60% of the injuries arrived by EMS directly from the scene of injury to a NACTN registry hospital with 50% arriving within 1 hour of injury and two-thirds were stabilized by EMS during transit. (Table 6) Approximately 50% of the patients arrived at a registry hospital with severe or critical associated injuries to the head & neck, chest, or abdomen (Table 7).

Surgical stabilization and decompression was the primary treatment mode (anterior and/or posterior surgery) for 75% of the patients and decompression was achieved in 68% of all patients (Table 8).

More than half of all SCI patients experienced at least one complication during acute care stay with 39% having three or more acute care complications (Table 9). The leading types of complications were pulmonary (23%), infection (21%), and hematologic complications (16%), whereas neuropsychiatric, cardiac, skin, and GI/GU complications each accounted for about 10% of the total number of acute care complications for 167 SCI patients (Table 10). The acute care case fatality rate was 3%.

The median length of hospital stay for 166 patients discharged from acute care was about 2 weeks with a third exceeding a 3 week length of stay. About two-thirds of the patients were discharged to a rehabilitation hospital, and 23% were discharged to home care (Table 11).

Table 12 contrasts the ASIA grades at discharge to the ASIA grades at admission for 144 SCI patients. The greatest levels of improvement in ASIA grade were seen among ASIA grade B and C patients, and only 3 of the 144 patients deteriorated in ASIA grade during the course of acute care.

In summary, the NACTN registry protocol has achieved its stated milestones. The registry protocol has demonstrated that it is feasible in a cost-efficient manner to acquire standardized and validated research information that can support multicenter clinical trials in a network of clinical centers (Safety and Pharmacokinetics of Riluzole in Patients with Acute Traumatic Spinal Cord Injury) and that the registry can simultaneously provide a research database to support observational studies on critical dimensions of current care for SCI patients.

3. Expansion of NACTN to include military, Veterans Administration and additional civilian hospitals. Status:

Walter Reed Army Medical Center (WRAMC) and the University of Louisville and the University of Maryland joined the network in June 2007. Research Agreements were negotiated with their respective Grants and Contracts Offices (for WRAMC, with the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. [HJF]); their year-end narrative and financial reports are due to CRF in July 2008.

Effective April 2008, the University of Miami (Jackson Memorial Hospital) and Thomas Jefferson University agreed to join NACTN and the NACTN teams are working with their local IRBs for data registry approvals. CRF will negotiate Research Agreements with both institutions immediately upon notification by DOD that FY'07 funds have been released.

4. Characterize the biomechanical, anatomical and neurological differences between military and civilian injuries and differences in their outcomes. Status: This task has yet to be initiated due to the length of time it has taken to (1) negotiate the award contract with HJF and (2) hire the WRAMC study coordinator. WRAMC has been unable to enroll any patients into the data registry, pending regulatory approval of protocol, consent forms and supporting documents (see Task #1, above)

5. Expand the Data Management Center at the University of Texas School of Public Health to incorporate the increased numbers of patients in the study. Status:

- All computer systems have been revised and updated to accommodate the NACTN version 3.1 data protocols
- Coding forms have been revised to include the itemization of approximately 2,700 variable fields
- The MS Access interface and export procedures have been revised to accommodate all of the new variables in the NACTN version 3.1 data protocol
- The database capacity has been expanded to include reporting of patient reasons for not agreeing to participate in the Data Registry
- A code book for NACTN version 3.1 has been created for use in developing new computer programs for statistical analysis
- All computer systems have been revised and updated to accommodate the NACTN version 3.1 data protocols
- The documentation of coding forms has been revised to include the itemization of approximately 2,700 variable fields
- The MS Access interface and export procedures have been revised to accommodate all of the new variables in the NACTN version 3.1 data protocol.

- The database capacity has been expanded to include reporting of patient reasons for not agreeing to participate in the Data Registry
- An expanded data quality control program was developed to catch logical inconsistencies across fields of NACTN version 3.1 data protocol and has now been completed
- A code book for NACTN version 3.1 for use in developing new computer programs for statistical analysis has been created.

6. Further validate quantitative measurements to assess neurological recovery, including the Graded Refined Assessment of Strength, Sensibility and Prehension (GRASSP) test and computerized measurement of the force generated by the isometric contraction of muscles. Status:

- GRASSP is presently being validated across seven North American and European sites (including NACTN's Toronto and RIC centers). (Two important points to be made with respect to GRASSP. (1) as of this writing, no DOD funds were used to underwrite this activity and (2) it is a tangible outcome of the partnership between NACTN and the European Union Clinical Trials Network (EUCTN); the two Canadian sites are members of the new Canadian SCI Translational Research Network [SCI TRN].). (Appendix B, the task force's interim progress report) Since it was issued, the following has transpired: (a) a manuscript is in preparation and the findings to-date will be presented at the June 2008 American Spinal Injury Association (ASIA) annual meeting; (b) an international responsiveness study will be launched to apply the test in acute tetraplegic patients (50 subjects) with six-month and one-year follow-up; NACTN has agreed that two of its sites will participate in this phase of the GRASSP study; (c) two issues will be addressed by the task force: (i) determination of what extent of change [improvement] in function is needed to warrant a clinically meaningful effect and (ii) patient reported outcomes [required by the FDA]; and (d) the test will be modified as needed to eliminate redundant and less sensitive elements, thereby shortening the time required to do the test.
- The project to develop the technology for computerized measurement of the force generated by the isometric contraction of muscles is well underway; presently, Dr. Grossman and colleagues are testing reliability and validity of the instrument. (Appendix C, photographs)
- Upon release of the FY'07 DOD funds, NACTN plans to initiate NOA, its Neurological Outcomes Assessment initiative. At a January 2008 meeting, Drs. Robert Grossman, Martin Schwab (University of Zurich and EUCTN) and Naomi Kleitman (NINDS SCI Repair and Plasticity program officer) and Susan Howley discussed NACTN strategy behind NOA and agreed that NACTN will keep its colleagues at ASIA fully informed of its efforts so as to be complementary to that group's efforts. At a June 5-6 international spinal cord meeting in Barcelona, Drs. Grossman and Fehlings will meet with several of their EUCTN colleagues. They will discuss next steps for NOA, including formation of a steering committee to organize an initial workshop and working groups to move forward on specific outcome instrument development. It is intended that this initiative will be an international collaboration between NACTN, EUCTN and the Canadian SCI TRN. (Appendix D, written by Drs. Grossman and Schwab, provides more details on this effort)

7. Expanded NACTN contributes to ongoing Surgical Treatment of Acute Spinal Cord Injury Study (STASCIS). Status:

Michael Fehlings, MD, PhD, STASCIS Co-Principal Investigator (and NACTN Principal Investigator) presented one-year results from the STASCIS trial at the April 2008 meeting of the American Association of Neurological Surgeons (AANS). He reported that a significant number of patients (24%) who received decompressive surgery <24h post injury showed a two-grade or better improvement on the ASIA scale, versus only 4% in the delayed treatment group. Additionally, the early treatment patients experience fewer complications. Several NACTN sites have been participating in the STASCIS study, including the universities of Toronto, Maryland and Virginia. (Appendix E, a summary of Dr. Fehling's presentation to the AANS meeting)

8. Develop protocols for Phase II of anti-Nogo antibody treatment for SCI. Status:

Novartis/anti-Nogo clinical trial: as discussed in earlier quarterly reports, the Phase I trial is still ongoing, due to the amendment of the study protocol to change the mode of administration from infusion to repeated intrathecal bolus injections. An additional cohort of 12 patients will be treated (the first has been enrolled in Germany and treatment is underway). As required by the FDA in preparation for the Phase II expansion to U.S. sites, Novartis is conducting a pilot toxicity study of the anti-Nogo antibody in rats; results will be incorporated into the IND submission. In parallel, the company is organizing its U.S. team and in that context, Manoj Malhotra, MD, Medical Director, Neuroscience, US Clinical Development and Medical Affairs, Novartis Pharmaceuticals Corporation visited with Dr. Grossman at The Methodist Hospital to discuss the planned Phase II trial and NACTN's role therein.

9. Riluzole safety study. Status:

Pending FDA approval of expansion of the Novartis anti-Nogo clinical trial into the U.S., NACTN investigators plan a safety and pharmacokinetics trial of riluzole in acute spinal cord injury patients. Riluzole, a benzothiazole anticonvulsant Na⁺ channel blocker is neuroprotective and promotes functional neurological recovery following SCI in rodents (Schwartz and Fehlings, 2001) and was shown to promote increased survival and attenuate neurological dysfunction in patients with amyotrophic lateral sclerosis (Lacomblez et al, 1996; Hugon, 1996; Bensimon et al, 1994). NACTN submitted a riluzole modification to W81XWH-07-1-0361 to Dr. Kenneth C. Curley on December 15, 2007. Regulatory approval activities in connection with this modification are detailed above at (Task #1). (Appendix F, the riluzole protocol that will be submitted to USAMRMC/HRPO upon receipt of local IRB approval for The Methodist Hospital)

The AO Foundation (based in Switzerland) is providing its Op Verdi electronic data capture system pro bono for the riluzole trial.

In preparation for the trial, an initial NACTN-wide training in neurological exams was organized during March-April of the contract year. It will be held at the University of Louisville/Frazier Rehab (a NACTN site) on June 2-3, 2008. Activities include ASIA training by nationally recognized experts in neurological exams, SCIM/FIM/WISCI reviews, in-depth reviews of the NACTN Manual of Operations, the data forms and registry, the DOD regulatory process and an Op Verdi presentation. (Appendix G, meeting agenda and participant roster)

A final training meeting for all NACTN assessors is planned for end-of-summer to insure absolute standardization across all clinical sites prior to the start of the riluzole safety trial.

10. "Stemnion" study. Status:

NACTN submitted a December 15, 2007 modification ("Stemnion") to W81XWH-07-1-0361 to test the potential of amnion-derived multipotent progenitor cells (AMPCs) in promoting recovery after spinal cord injury. Period of performance for this project is 1/1/2008 – 12/31/2010. USAMRMC Animal Care and Use Review Office approved the Stemnion protocol effective February 26, 2008. CRF entered into a one-year Research Agreement with the Regents of the University of California on behalf of its Irvine Campus on April 7, 2008 for Aileen Anderson, PhD, whose laboratory will perform the research. (Appendix H, first quarterly report) The first payment was disbursed on April 22, 2008 following final execution of the above-referenced Research Agreement.

Key Research Accomplishments:

- Expansion of NACTN into military and new civilian hospitals [details provided above at (3)] and concomitant expansion of baseline protocols for these sites, via USAMRMC Office of Research Protections and local IRBs
- Selection of riluzole for the first NACTN clinical trial, a safety and pharmacokinetics study in acute spinal cord injury; IND application to the FDA that resulted in FDA exemption from the IND regulations; development of riluzole protocol; submission to USAMRMC/HRPO will be made upon receipt of local IRB approval for The Methodist Hospital
- Progress in the development and validation of GRASSP; an international responsiveness study now planned; findings to be disseminated to the field via a manuscript in preparation (two NACTN sites will participate) and a presentation at the June 2008 ASIA meeting

- One-year STASCIS results indicating that patients who receive decompression surgery <24h post-injury show improved neurological recovery and fewer complications than those in the delayed treatment group
- NACTN manuscript in preparation about complications in acute-injury spinal cord injury in development
- The enrollment of 198 patients into the NACTN data registry effective May 13, 2008

Reportable Outcomes:

- Product Line Review (Neuroscience/Therapeutics) presentation by Robert G. Grossman, MD, September 11, 2007, Fort Detrick, MD (Appendix I)
- NACTN poster presentation by Robert G. Grossman, MD at the September 2007 international meeting, State of the Art in Spinal Cord Injury Research and Clinical Application, Kartause Ittingen, Switzerland (Appendix J)
- NACTN presentation by Robert G. Grossman, MD at the January 2008 NY Academy of Sciences/NY State Spinal Cord Injury Research Program Symposium, New York, NY (Appendix K)
- Pharmacokinetics (PK) and Pharmacodynamics (PD) of Riluzole in Patients with Traumatic Acute SCI presentation by Diana Chow, PhD, February 18, 2008, Houston, TX (Appendix L)
- NACTN patient brochure (Appendix M)

Conclusion:

There have been two real challenges inherent in our efforts to meet NACTN's stated tasks as envisioned in proposal W81XWJ-07-1-0361. The greatest and most consistent obstacle to timely progress has been the need to work through the regulatory processes: administrative, local and ORP/HRPO. By way of example, it took 12 months to receive approval for the data registry protocol. With respect to the riluzole protocol, while it is anticipated that NACTN will be poised to begin the riluzole trial by the end of the summer, the regulatory process will extend considerably beyond that date. This confounding hurdle has also meant that NACTN has been unable to even begin Task #4 above, characterizing the biomechanical, anatomical and neurological differences between military and civilian injuries and differences in their outcomes.

The addition of unanticipated cohorts in the Phase I anti-Nogo antibody safety study and the concomitant change of drug delivery method, plus the obstacles encountered by Novartis at the US FDA, all thwarted NACTN's ability to develop the protocols for the Phase II anti-Nogo antibody study, as stated in the original research proposal (Task #8). Instead, the network was compelled to identify another promising therapeutic and begin the lengthy process of protocol development. We believe we have made excellent progress toward the start of the riluzole study; as noted in the paragraph above, the actual start of the trial will depend upon the timeliness of the regulatory process, both local and ORP/HRPO.

All that notwithstanding, at the conclusion of the first of the two-year period of performance, NACTN has successfully achieved most of its stated goals, as delineated above. NACTN is considerably strengthened by the addition of new sites and the expertise brought by the new Principal Investigators. This is leveraged by the strengthened ties with other existing international clinical networks (EUCTN and NETT) and ties forged with emerging networks (the Canadian SCI TRN). NACTN plans to continue adding new military and civilian centers during the second year of the contract and thus we anticipate being in a unique position to meet our goal of translating the most promising potential therapies to the clinic.

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Appendices

Appendix A	NACTN Data Tables
Appendix B	Interim Report, GRASSP
Appendix C	Photographs, Computerized Muscle Technology
Appendix D	Neurological Outcomes Assessment Initiative
Appendix E	STASCIS Summary, One-Year Results
Appendix F	Riluzole Protocol Source Worksheet Riluzole Label Riluzole Hypersensitivity Riluzole IND Exempt Letter
Appendix G	NACTN Training Meeting
Appendix H	Stemnion, First Quarterly Report
Appendix I	PLR, Grossman Presentation
Appendix J	State of the Art in SCI Meeting, Grossman Presentation
Appendix K	NY Academy of Sciences Meeting, Grossman Presentation
Appendix L	PK and PD of Riluzole in Patients, Chow Presentation
Appendix M	NACTN Brochure

North American Clinical Trials Network (NACTN)

Table 1. Registry Screening and Enrollment

<u>Status</u>	<u>Number</u>
Screened	384
Enrolled	195
Withdrawn	7
In Database	168

North American Clinical Trials Network

Table 2. ASIA Grade at Admission

<u>Grade</u>	<u>Number</u>	<u>Percent</u>
A	57	33.9
B	18	10.7
C	16	9.5
D	33	19.6
E	26	15.5
NR	18	10.7
Total	168	100

North American Clinical Trials Network

Table 3. Patient Demographics

<u>Characteristic</u>	<u>Number (N=168)</u>	<u>Percent</u>
Gender		
Male	132	78.6
Female	36	21.4
Age¹ (yrs)		
< 20	14	8.3
20-65	130	77.4
>65	24	14.3
Race		
White	124	73.8
Other	44	26.2

¹Median age at injury = 42.0 yrs of age

North American Clinical Trials Network

Table 4. Circumstances of Injury

<u>Characteristic</u>	<u>Number (N=168)</u>	<u>Percent</u>
Cause of Injury		
Fall	64	38.1
MVA	58	34.5
Recreation	29	17.3
Assault	12	7.1
Other	4	2.4
Unknown	1	0.6
Alcohol Involved		
Probable	46	27.4
Unlikely	107	63.7
Unknown	15	8.9

North American Clinical Trials Network

Table 5. Injury Type and SCI Region

<u>Characteristic</u>	<u>Number (N=168)</u>	<u>Percent</u>
Injury Type		
Closed	160	95.2
Open	8	4.8
Injury Region¹		
Cervical	121	72.0
Thoracic	33	19.6
Lumbar/Sacral	11	6.6
SCIWORA	3	1.8

¹Highest level reported when injury involved multiple levels

North American Clinical Trials Network

Table 6. Patient Transfer and EMS Stabilization

<u>Characteristic</u>	<u>Number (N=168)</u>	<u>Percent</u>
Transfer		
From Scene¹	100	59.5
Hospital Transfer²	68	40.5
EMS Stabilization		
Collar and Board	112	66.6
Collar Only	18	10.7
Board Only	6	3.6
Sandbags and Board	5	3.0
None Reported	27	16.1

¹Median time: Scene to Registry Hospital, 1.1 hrs

²Median time: Intermediate Hospital to Registry Hospital, 9.7 hrs

North American Clinical Trials Network

Table 7. Abbreviated Injury Scale for 168 SCI Admissions

Body Region	Severe AIS 4	Critical AIS 5	Total	Percent of 168
Head & Neck	35	23	58	34.5
Chest	9	17	26	15.5
Abdomen	2	2	4	2.4
Total	46	42	88	
Percent of 168	27.4	25.0	52.4	

North American Clinical Trials Network

Table 8. Surgery and SCI Decompression

Surgery	<u>Number (N=168)</u>	<u>Percent</u>
Posterior	73	43.4
Anterior	29	17.3
Both	24	14.3
None	42	25.0
Decompression Achieved	115	68.5
Confirmed by MRI	65	38.7

North American Clinical Trials Network

Table 9. Incidence of Complications

Complications	<u>Number (N=167¹)</u>	<u>Percent</u>
None	75	44.9
1	25	15.0
2	18	10.8
3+	49	29.3

¹One subject had no complication form.

North American Clinical Trials Network

Table 10. Complications by Type

<u>Complication Type</u>	<u>Total (N = 339)</u>	<u>Percent of Total</u>
Pulmonary	78	23.0
Infection	70	20.6
Hematology	55	16.2
Neuropsychiatric	37	10.9
Cardiac	33	9.7
Skin	32	9.4
GI/GU	32	9.4
Stabilization	2	0.6

87 patients with complications
339 complications experienced by these 87 patients

North American Clinical Trials Network

Table 11. Hospital Stay and Discharge Status

<u>Hospital Stay</u>	<u>Number (N=168)</u>	<u>Percent</u>
< 8 days	44	26.2
8-14	42	25.0
15-21	22	13.1
> 21	58	34.5
Still in hospital	2	1.2
Discharge Status		
Rehab Hospital	110	65.5
Home Care	39	23.2
Long-Term Acute Care	2	1.2
Nursing Home	10	5.9
Dead	5	3.0
NA	2	1.2

North American Clinical Trials Network

Table 12. Percent ASIA Change at Discharge

Admission Asia Grade	Better	Same	Worse	Number
A	14%	86%	-----	56
B	22%	72%	6%	18
C	44%	56%	-----	16
D	9%	85%	6%	33
E	-----	100%	-----	26

15 January 2008

To: Nancy Adams, CGA
Manager, Finance
Rick Hansen Foundation

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Executive Vice President
Christopher and Dana Reeve
Foundation

Benjamin J. Eckers
Global Health Economics and
Outcomes Research
Novartis Pharmaceuticals

From: Cheryl Niamath
Administrative Manager
ICORD

RE: Development of the Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP): Reliability and Validity. *Interim Report, November 2007.*

On behalf of Dr. Armin Curt, I am pleased to provide you with the interim report for the above-named project. The overall objective for the assembly of the GRASSP was to develop a clinical research measure that would be specifically designed to capture information of hand function from the whole cervical SCI population, to reveal integrated sensory and motor impairment data, and to discriminate the population according to level of lesion. As you will read in the attached report, thanks to support from your combined agencies the project is progressing well, with North American data collection completed, European data collection partially completed, and data analysis underway.

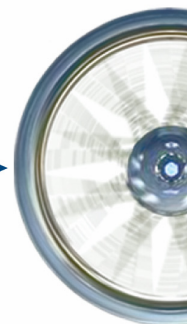
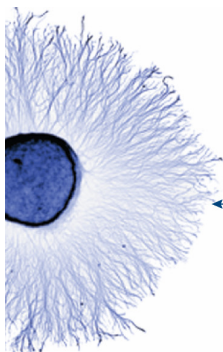
If you have any questions about this interim report, please contact Dr. Armin Curt (curt@icord.org or 1-604-822-2673).

A final report on this project will be prepared in November, 2008.

CNiamath

from cells to community: solutions for spinal cord injury

Founding partners:



Development of the Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP): Reliability and Validity.

Interim Report, November 30, 2007

GRASSP Design Team: Susan Duff, Claudia Rudhe, Molly Verrier, Armin Curt, Michael Fehlings and Sukhvinder Kalsi-Ryan

Introduction:

Funding for the development of the GRASSP was approved in August of 2006 at which time the study protocol was refined and plans for a multi-centre reliability and validity trial were finalized. Seven centers were recruited to participate in the trial, three from Europe and four from North America. The centers involved are listed in Table 1. Once centers were invited to participate, two clinicians were recruited at each site. Workshops were organized to train the assessors (one in Europe and one in North America).

A manual was prepared with all of the necessary information required for site involvement. The manual was sent to all of the North American centers 6 weeks prior to the workshop.

In Europe the assessors were brought together in Zurich on November 27, 2006 and were provided training in the use of the GRASSP and the protocol by Claudia Rudhe. European data collection commenced in early December 2006. The assessors from the North American centers were brought together in Toronto for a workshop. The workshop consisted of an overview of the study protocol, how the study is to be organized at each centre, the funding allocated to each site and all of the necessary forms and paperwork were provided. The workshop was held on January 13, 2007 at the Toronto Rehabilitation Institute in Toronto. The workshop was organized and conducted by Sukhvinder Kalsi-Ryan with the assistance of Professor Molly Verrier and Dr. Armin Curt. North American data collection commenced in February of 2007. Each centre was required to submit an ethics protocol for data collection at their respective site. A draft IRB was provided 6 weeks prior to the workshop electronically.

Table 1: Sites/Centers Involved

North America
1. Rehabilitation Institute of Chicago, Chicago USA
2. Toronto Rehabilitation Institute, Toronto Canada
3. Vancouver General Hospital and G.F. Strong, Vancouver Canada
4. Thomas Jefferson University, Philadelphia USA
Europe
5. Balgrist University Hospital, Zurich Switzerland
6. Krakenhaus Hohe Worte , Bayreuth Germany
7. Traumacenter Murnau, Murnau Germany

Protocol:**Reliability and Validity Protocol for the Standardization of the GRASSP**

Objectives: To test the GRASSP for test retest and inter-rater (between two assessors) reliability and construct and concurrent validity.

Sample Size: The proposed sample size was 40+. The sample size was based on an interclass correlation coefficient (ICC) set *a priori* for the summative score of the GRASSP (an estimated ICC of 0.8 or greater with an alpha of 0.05 and a beta of 0.80). The number of measurements per subject would be 3. To accommodate for the variation in the population 8 was added for an approximate sample size of 40. Each North American centre was expected to enroll 10 subjects each (more if feasible).

Inclusion criteria: 1) Traumatic Tetraplegia, 2) level of lesion C4 to T1 as classified by the ASIA score, 3) ASIA classification A, B, C, or D (stable neurologically, defined by an unchanged ASIA score in the last 6 months), 4) age: 16 - 65, 5) medically & neurologically stable and 6) able to give informed consent.

Data Collection: All subjects were assessed three times in one week, twice by assessor 1 and once by assessor 2. The GRASSP protocol was administered during each test session. The ASIA, Capabilities of the Upper Extremity Questionnaire (CUE), and the Spinal Cord Independence Measure (SCIM) were also administered once over the one week period by either assessor or research coordinator if involved. Please note assessor 1 performed two assessments and assessor 2 only one assessment; this was required for all ten subjects enrolled in the study. The North American centers conducted the full protocol while the centers in Europe conducted the inter rater reliability and validity. (Two assessments by two assessors were done).

Analysis: Data once collected was entered into excel tables at the site of collection and then sent to Toronto for analysis. De-identified hard copies of the score sheets were also sent to Toronto. Data was and will be analyzed to determine the reliability coefficient, percent agreement, and kappa statistic to determine test-retest and inter-rater reliability. Testing for construct validity will be conducted on the above sample. The first test score from each individual will be used in the analysis of construct validity. Construct validity will be established with the known group method. For hypotheses testing the groups will be defined by level of lesion according to ASIA and corresponded to scores on the GRASSP. Analysis will determine whether these groupings are appropriate. The CUE and SCIM were administered to establish concurrent validity with the GRASSP.

Data Collection

Data was collected between Dec 2006 and September 2007. All data collected in North America was entered electronically at the respective sites and sent to Toronto electronically. Hard copies were couriered after invoicing. All hard copy data has been stored in a locked locking facility at the University of Toronto. Hard copies of all European data were sent to Toronto where it was entered electronically. Table 2 describes the sample and where portions of the total n=72 came from.

Table 2: Data Collected

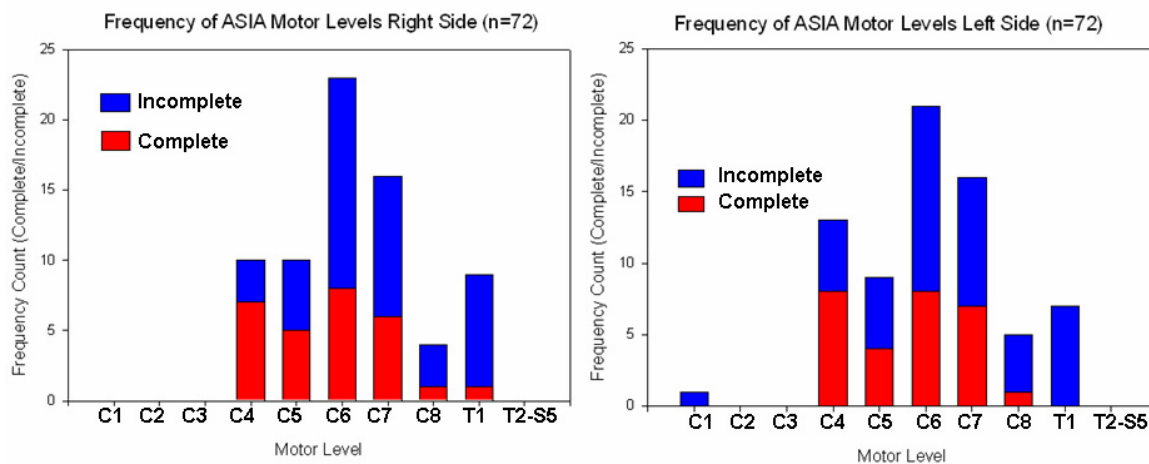
Site	Inter-rater Reliability	Test Retest Reliability	Validity
Chicago	10	10	10
Toronto	15	15	15
Vancouver	10	10	10
Philadelphia	10	10	10
Balgrist	9		9
Bayreuth	8		8
Murnau	10		10
Totals	72	45	72

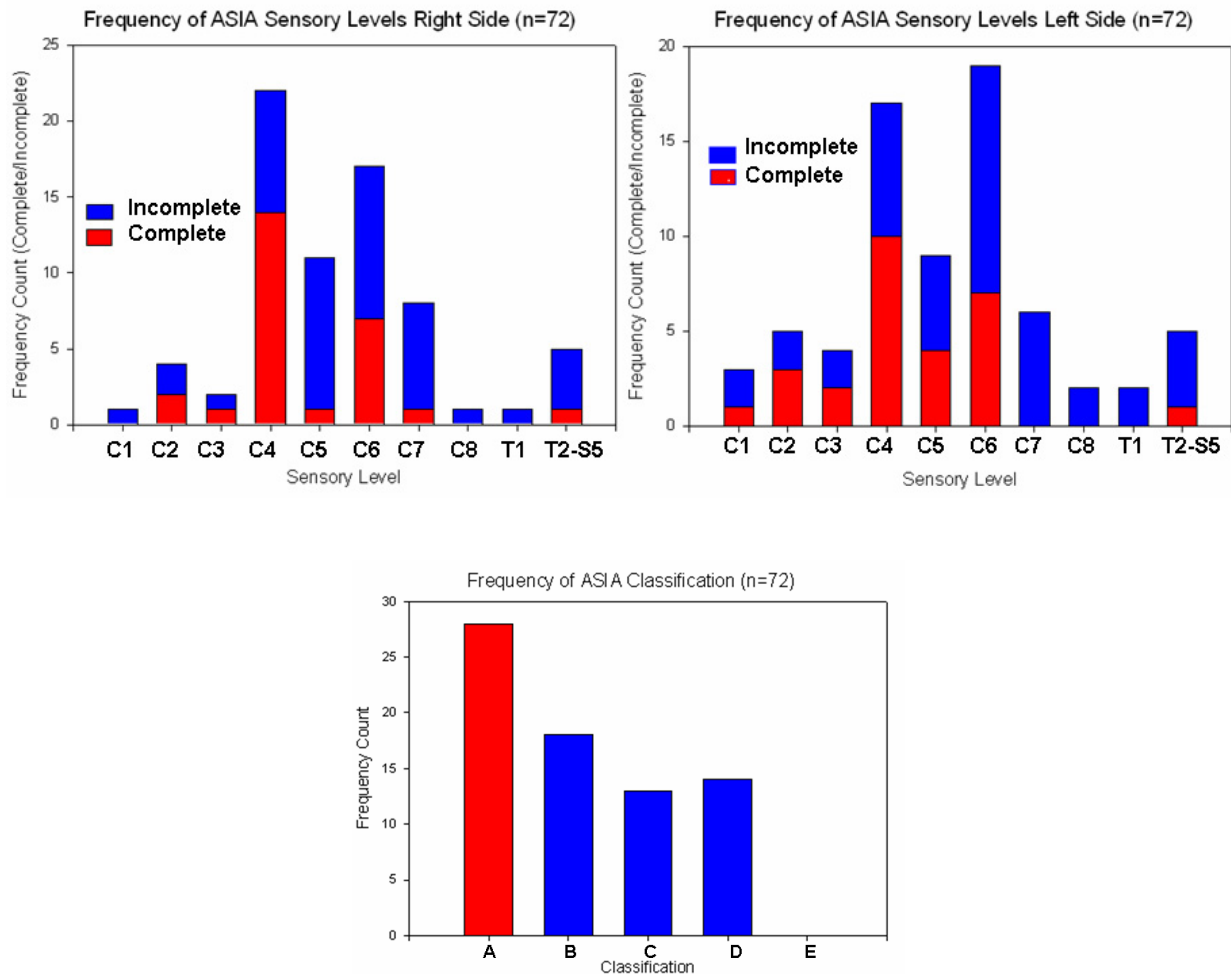
In summary 72 data sets were collected in total. Forty five sets provide data for test retest reliability and 72 sets provide data for inter rater reliability and validity analysis. All data has been pooled in excel tables and is imported into SAS for analysis.

Analysis

1. Descriptive histograms illustrate the subgroups of the sample according to ASIA motor and sensory levels and classification. These figures simply summarize the sample for descriptive purposes. For the sample collected 61.1% have incomplete injuries, 52.5% have C6 or C7 ASIA motor levels, and 66% have C4 to C6 ASIA sensory levels.

Figure 1: Description of Sample





2. Reliability analysis has been commenced with the item score for each sensory test location, each muscle tested and each functional task tested. Lists of weighted kappa statistics with p values are available in Table 3. Reliability of sensory tests is not as high as hypothesized; however, this may be a characteristic of the population. As previously documented inter rater and test retest reliability values are developed on normals. Sub-analyses are required to determine the nuances of sensory differences between completeness and level of injury. Reliability of the strength module is high of note for the small muscles of the hand which has not previously been documented in the literature. Reliability of prehension is high. Reliability of the tone scale is moderate and consistent (Modified Ashworth Scale) consistent with previous studies. Reliability of domains within the GRASSP is promising as shown by initial analysis on a complete dataset. Inter-rater and test retest reliability is within hypothesized ranges except for sensory tests, test retest reliability is generally higher. Reliability data is now available for tests specific to the hand for the tetraplegic population.

Table 3: Reliability Values of Sensory Test Locations within the GRASSP

	Inter	Wt Kappa with P<0.0001	Test Retest	Wt Kappa With P<0.0001
R	SWM1	0.688	SWM1	0.793
	SWM2	0.648	SWM2	0.660
	SWM3	0.613	SWM3	0.695
	SWM4	0.562	SWM4	0.680
	SWM5	0.641	SWM5	0.736
	SWM6	0.616	SWM6	0.787
L	SWM1	0.574	SWM1	0.571
	SWM2	0.626	SWM2	0.669
	SWM3	0.663	SWM3	0.765
	SWM4	0.707	SWM4	0.782
	SWM5	0.621	SWM5	0.782
	SWM6	0.757	SWM6	0.757
R	S2PD1	0.710	S2PD1	0.543
	S2PD2	0.761	S2PD2	0.600
	S2PD3	0.649	S2PD3	0.671
L	S2PD1	0.736	S2PD1	0.736
	S2PD2	0.609	S2PD2	0.690
	S2PD3	0.730	S2PD3	0.876

Table 4: Reliability Values of Strength and Tone Tests within the GRASSP

STRENGTH					TONE				
	Inter	Wt Kappa with P<0.0001	Test Retest	Wt Kappa With P<0.0001		Inter	Wt Kappa with P<0.0001	Test Retest	Wt Kappa With P<0.0001
R	ST1	0.831	ST1	0.752	R	T1	0.675	T1	0.875
	ST2	0.761	ST2	0.759		T2	0.620	T2	0.771
	ST3	0.854	ST3	0.858	L	T1	0.659	T1	0.859
	ST4	0.698	ST4	0.839		T2	0.689	T2	0.813
	ST5	0.773	ST5	0.858					
	ST6	0.832	ST6	0.931					
	ST7	0.854	ST7	0.883					
	ST8	0.782	ST8	0.876					
	ST9	0.757	ST9	0.830					
	ST10	0.831	ST10	0.790					
	ST11	0.780	ST11	0.904					
L	ST1	0.758	ST1	0.749					
	ST2	0.837	ST2	0.783					
	ST3	0.647	ST3	0.735					
	ST4	0.827	ST4	0.849					
	ST5	0.859	ST5	0.863					
	ST6	0.915	ST6	0.937					
	ST7	0.853	ST7	0.863					
	ST8	0.827	ST8	0.859					
	ST9	0.859	ST9	0.837					
	ST10	0.874	ST10	0.759					
	ST11	0.890	ST11	0.913					

Table 5: Reliability Values of Qualitative and Quantitative Prehension

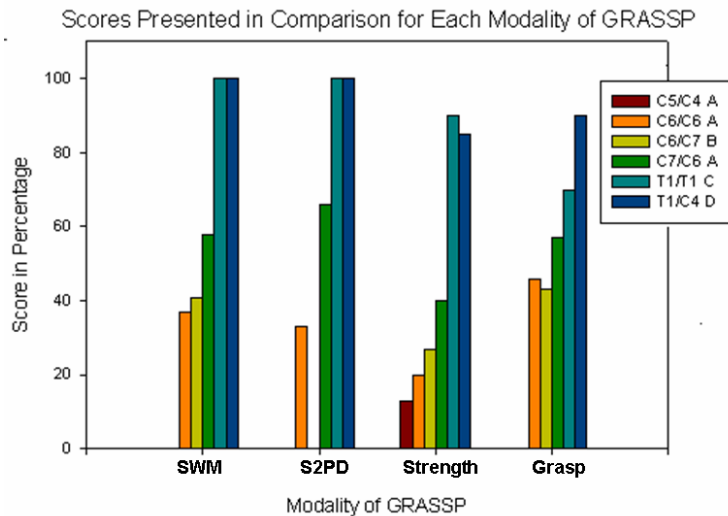
QUANTITATIVE GRASP					QUALITATIVE GRASP				
	Inter	Wt Kappa with P<0.0001	Test Retest	Wt Kappa With P<0.0001		Inter	Wt Kappa with P<0.0001	Test Retest	Wt Kappa With P<0.0001
R	QN1	0.765	QN1	0.748	R	QL1	0.830	QL1	0.846
	QN2	0.859	QN2	0.855		QL2	0.829	QL2	0.909
	QN3	0.783	QN3	0.872		QL3	0.759	QL3	0.852
	QN4	0.744	QN4	0.736	L	QL1	0.765	QL1	0.906
	QN5	0.776	QN5	0.685		QL2	0.801	QL2	0.909
	QN6	0.667	QN6	0.521		QL3	0.792	QL3	0.916
L	QN1	0.851	QN1	0.855					
	QN2	0.826	QN2	0.859					
	QN3	0.760	QN3	0.739					
	QN4	0.803	QN4	0.834					
	QN5	0.851	QN5	0.792					
	QN6	0.605	QN6	0.583					

The raw reliability values do render a varying degree of inter and test retest reliability ranging from substantial to almost perfect repeatability based on Landis and Koch. In summary these values do not hold as much value as a summary score which is still under development and once completed will be evaluated with reliability analyses. The statistical analysis for the summary scores will be tailored for continuous variables rather than analyses for categorical variables which have been done for the items in each module. The values tabled above suggest that all tests within the GRASSP have good to excellent reliability and reliability is enhanced when the same assessor repeats the evaluations.

3. Based on the protocol validity analyses will be conducted on the total scores for each module in the GRASSP with the ASIA. The sample will be sub-grouped according to ASIA motor and sensory levels and the GRASSP scores will be compared to the current classification to determine the construct validity. A second validity analysis will be conducted with the summary score as well. Concurrent validity will be evaluated with the SCIM and CUE results.

4. A Summary score for the GRASSP is required for presentation of the data collected on an individual. This score is required to represent one's impairment and should be weighted based on the potential gain (in function or independence) one has according to motor or sensory level. Therefore, the summary score is being designed not only to represent hand and upper limb impairment but the potential capability of the intact elements. Also with all of the modules and actual items collected a succinct method to present an individual according to the GRASSP is required for an integrated summary. Figure2 is an example of the GRASSP representation of 6 individuals and how one can potentially be described with the data collected. This visual method could be done serially to see differences over time as well.

Figure 2: Histogram illustration of GRASSP results.



Dissemination of the GRASSP has begun as the work progresses. The project and collaboration have been highlighted to date and as of last month plans to present reliability and validity data have been initiated.

The following presentations have been made:

1. The GRASSP Protocol – The Value of Spinal Cord Injury (SCI) Research Networks to the Development of Outcome Measures.
 - a. Poster Presentation ASIA Annual Meeting June 2007, Tampa Bay FL
2. The Graded and Redefined Assessment of Sensibility Strength and Prehension (GRASSP Protocol) – Development and Validation of a Hand Function Measure for the Tetraplegic Population.
 - a. Podium Presentation - International Conference for the Management of the Upper Limb in Tetraplegia September 2007, Philadelphia PA
3. Quantification, Sensitivity and Reliability for the Sensory Module of the Graded and Redefined Assessment of Sensibility Strength and Prehension (GRASSP) Hand Measure
 - a. Poster Presentation – Sixth Annual Tator-Turnbull Lectureship November 2007, Toronto CAN

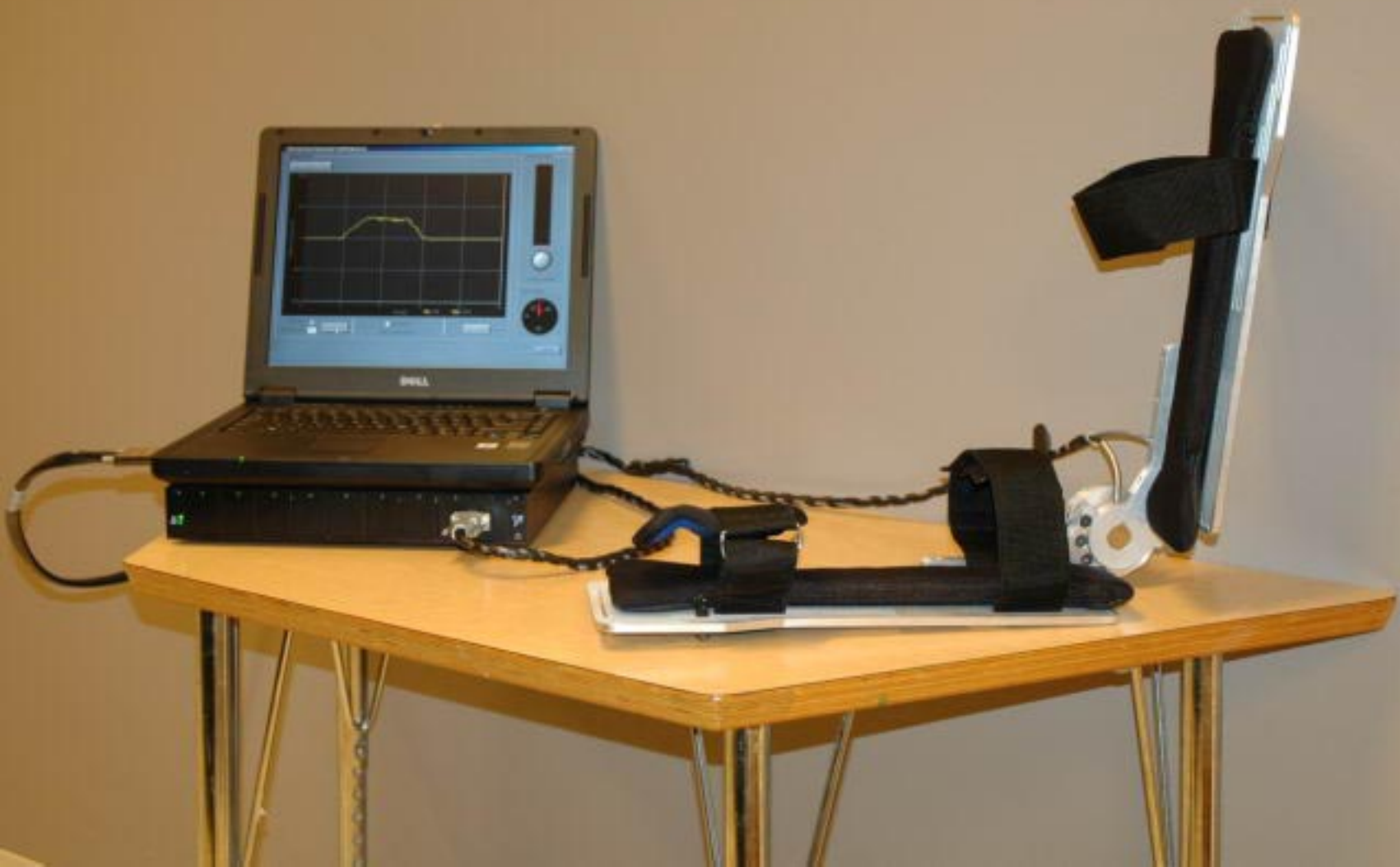
The following presentations have been submitted for meetings in 2008, with acceptance pending:

1. Reliability and Validity of the Graded and Redefined Assessment of Sensibility Strength and Prehension (GRASSP).
 - a. ASIA Annual Meeting 2008, San Diego CA

Report prepared by Sukhvinder Kalsi-Ryan and edited/approved by Molly Verrier, Michael Fehlings, Armin Curt

GRASSP Project Finances, 1 December 2006 to 30 November 2007

		Actual	
	Funding Allocation	Expenditures	Commitments
Description			
RHF contribution (\$16,500US)	18,480.00		
CRF contribution (\$16,500US)	19,143.30		
Novartis contribution (\$16,500US)	18,675.34		
Salaries + Benefits		7,701.78	
Travel expenses		7,875.06	
Technical supplies		256.09	
Meeting expenses		3012.77	
Participant honoraria		4,100.00	
European centre costs (27 patients)			14,300.00
Upcoming Travel (Zurich)			3,000.00
Committed salaries + benefits			6,550.00
Additional data analysis (Toronto)			4,000.00
Additional admin expenses (Toronto, Vancouver)			3,000.00
Additional meeting expenses			2,500.00
Totals	56,298.64	22,945.70	33,350.00
Projected Balance at end of project			2.94





Neurological Outcomes Assessment Task Force

Purpose and Goal

At the meeting in Ittingen, Switzerland, 6–8 September 2007 “State of the Art in Spinal Cord Injury Research and Clinical Application”, supported by the Christopher Reeve Foundation, a consensus was developed that there is a pressing need for more accurate methods of quantitatively measuring the course of recovery and the functional outcomes of individuals who have sustained spinal cord injury. There is consensus that the currently available measurement instruments do not detect improvements in motor, sensory and autonomic functions that are apparent to examiners and to patients. The lack of sensitivity and reproducibility of clinical measurements has probably contributed to the inability to detect improvement in function in human clinical trials of therapies that were effective in animal experiments.

A. Motor Function

1. Statistical analysis of recovery of function requires quantitative measurement of the strength of individual muscles representative of the functional status of spinal segments. A practical method of quantitation of muscle strength is measurement of the torque generated by isometric contraction of selected muscles. The data can be correlated with ASIA scale testing of the muscles.
2. Hand Function. Further validation of the Zurich/Toronto hand-function test
3. Trunk balance, standing balance
4. Weight-bearing
5. Gait analysis – WISCI, timed walking, stride length, foot falls
6. Development of tests of corticospinal/descending tract function – quantification of rapid succession (alternating) movements, use of transcranial magnetic stimulation
7. Measurement of spasticity
8. Development of the use of EMG in measurement of motoneuron and root damage.

B. Sensory Function

1. Light touch. Quantitative measurement of spinal segments with Von Frey hairs. Comparison with ASIA sensory scale. Photographic documentation of segments tested.
2. Deep pressure sense
3. Vibratory sense
4. Pain/temperature perception
5. Presence of pain; dysesthesia.
6. Measurement by means of cutaneous electrical stimulation
7. Measurement by means of somatosensory evoked potentials of long ascending tracts.

C. Autonomic Function

1. Bladder function – cystometry
2. Sympathetic function – sweating, segmental testing.

D. SCIM/FIM scores for assessment of quality of activities of daily living

E. Construction of Outcome Scores: Determination of the degree of change in functions that can be reliably measured. Selection of outcome measures to be used as primary and secondary outcomes.

F. Data collection forms/transmission to Data Management Center

1. Paper forms
2. Electronic forms
3. Data transmission via internet.

Organization of Working Groups

Organization – at the direction of an Executive Committee, five working groups will be formed, each consisting of individuals with particular interest and expertise in motor, sensory, autonomic function, development of scales/scoring and data management, respectively. It will be important that qualified WRAMC and other relevant military experts are members of these committees.

The kickoff meeting will be of the entire working group, which would initially divide into three working groups – motor, sensory and autonomic functions. Once the new instruments have been developed, the scales/scoring and data management groups would meet to conduct their work. It is suggested that, minimally, the chairmen of the three function groups be included on these committees. Follow-up meetings will be held to review validation and train examiners.

Next Steps

1. Form an Executive Committee that will have overall responsibility for and decision-making authority over the progression of the outcomes project.
2. Consult with EUCTN and SCI TRN colleagues and identify appropriate individuals for the five working groups; chairs must be identified for each committee
3. Organize kickoff meeting, out of which will fall detailed action plans timelines for each working group.
4. As appropriate, the Executive Committee will update ASIA/SCOPE representatives on their goals and progress.

To Print: Click your browser's **PRINT** button.

NOTE: To view the article with Web enhancements, go to:
<http://www.medscape.com/viewarticle/573672>



STASCIS: Early Surgery in Spinal Cord Injury Improves Outcomes, Lowers Complications

Caroline Cassels

Medscape Medical News 2008. © 2008 Medscape

April 29, 2008 (Chicago, Illinois) — Early decompressive surgery significantly improves outcomes and reduces complication rates in patients with spinal cord injury (SCI), a large multicenter study suggests.

Presented here at the American Association of Neurological Surgeons (AANS) 76th Annual Meeting, preliminary, 1-year results from the Surgical Treatment of Acute Spinal Cord Injury Study (STASCIS) showed 24% of patients who received decompressive surgery within 24 hours of their injury experienced a 2-grade or greater improvement on the American Spinal Injury Association (ASIA) scale, compared with 4% of those in the delayed-treatment group.

"A 2-grade improvement is a large change that is, without question, of clinical importance. It is still not a home run and far from a cure, but what it means is that 1 in 5 individuals is walking away from an injury they wouldn't normally walk away from," principal investigator Michael Fehlings, MD, PhD, head of the Krembil Neuroscience Centre at the University Health Network, in Toronto, Ontario, told *Medscape Neurology & Neurosurgery*.

Furthermore, he said, complication rates among individuals who received early intervention were about 20% lower than in those whose treatment was delayed.

According to Dr. Fehlings, the role and timing of decompression in SCI is controversial. In large part, he said, the debate centers on whether timing of surgery makes any difference to outcomes.

"Many people believe that it is better to stabilize patients first and that the timing of the intervention doesn't really matter. This prevailing attitude is based on the idea that all of the damage occurs during the initial trauma," he said.

However, he added, there is now strong evidence to suggest there is a biologic rationale for using decompressive surgery early on to mitigate progressive secondary injury.

"During the primary injury, the blood vessels in the spinal cord are mechanically disrupted, but then there are chemical reactions that occur that cause further damage. This secondary injury initiates a cascade of events that includes the release of calcium and sodium, which causes further damage and leads to cell death," said Dr. Fehlings.

Lower Complication Rate

To determine whether early surgical intervention would limit spinal cord damage and improve outcomes, the investigators recruited 170 consecutive patients from 10 centers in Canada and the United States who had subaxial cervical SCI and imaging evidence of spinal cord compression.

The investigators chose 24 hours as the cutoff point for early decompression based on pilot data indicating that it may be an optimal time point for the prevention of secondary injury.

According to Dr. Fehlings, whether patients were in the "early" or "delayed" group was determined by natural variations in the length of time it took them to reach the study center.

Patients were eligible for the study only if they were enrolled within 24 hours of injury and had to undergo surgery within 7 days of SCI. Outcomes were assessed at 6 months and 1 year postinjury.

In addition to an average 2-grade or greater improvement in ASIA scores, Dr. Fehlings said, the investigators found that complications, particularly those involving the cardiopulmonary system and urinary tract, were lower in the early surgery group — 37.1% vs 48.6%.

"Going into this study, I was prepared that we might not see a difference in outcomes. But I think that the fact that we are seeing reductions in complications and improved neurological outcomes is amazing," said Dr. Fehlings.

"Our initial estimates of a sample size required to show a difference was on the order of around 400 patients, and the fact that we saw any difference at all, particularly with 170 patients, was a bit of a surprise," he added.

A Medical Emergency

While further study is required to validate these findings, Dr. Fehlings said the results suggest that, like stroke, where timing of treatment is critical to outcome, SCI should be considered a medical emergency.

In fact, he said, based on the current literature and emerging data from STASCIS, the Spine Study Trauma Group, a consensus-based group of the world's 40 top spine surgeons, has recommended that patients with an acute SCI, without other life-threatening conditions, should have early decompression surgery within 24 hours of injury.

Furthermore, he noted, early intervention offers clinicians the opportunity to apply other, so-called regenerative treatments that may augment the effect of surgery and further improve recovery in SCI patients.

One such treatment may be Cethrin (Alseres Pharmaceuticals), a recombinant protein antagonist of a molecule known as Rho, which inhibits nerve cell regeneration and repair, which is showing "very promising results" in SCI patients.

A second study presented at the AANS meeting by Dr. Fehlings and colleagues shows that this so-called regenerative treatment is safe and well-tolerated and has potential neurological benefit.

"With the emergence of the era of regenerative medicine and the resulting treatments that are now finding their way into the clinic, we have an opportunity to optimize the milieu for recovery in spinal cord injury patients," he said.

The study was supported by the Spine Trauma Study Group, the North American Clinical Trials Network, the Cervical Spine Research Society, the American Association of Neurological Surgeons and Congress of Neurological Surgeons, the Krembil Foundation, and the Canadian Spinal Cord Injury Translational Research Network. The authors have no relevant conflicts to report.

American Association of Neurological Surgeons 76th Annual Meeting: [Abstract 600](#). Presented April 28, 2008.

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Confidentiality Statement

This document is the intellectual property of the Investigators. The information provided in this document is strictly confidential and is available for review to potential Sponsors, investigators, potential investigators, appropriate Ethics Committees, Investigational Review Boards, Food and Drug Administration and government regulatory bodies in other countries. No disclosure should take place without written authorization from the protocol developing investigators, except to the extent necessary needed to obtain informed consent from potential patients.

Title Page

Protocol title:	Safety and Pharmacokinetics of Riluzole in Patients with Acute Traumatic Spinal Cord Injury	
Protocol number:	1016	
Version:	1.0	6 June 2008
Sponsors	Department of Defense and Christopher Reeve Foundation	
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Local Medical Monitors	In addition to Dr. Williams, who will function as the overall Medical Monitor, there will be a Medical Monitor in place at each clinical site	TBD by Principal Investigator at each site.

Investigational Plan Amendments and Changes Signature Page

Version	Name	Signature
1.0 May 07, 2008	Robert G. Grossman, MD Chairman of Neurosurgery Director, The Neurological Institute	<i>Robert G. Grossman M.D.</i>

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1 Purpose and Hypotheses

1.1 Purpose

The primary aim of this study is to develop acute care safety and pharmacokinetic profiles of riluzole in patients who have sustained a traumatic spinal cord injury. Secondary objectives are to conduct exploratory analyses of functional 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.

1.2 Spinal Cord Injury

Acute traumatic spinal cord injury (SCI) results in a devastating loss of neurological function below the level of injury and adversely affects multiple systems within the body. The pathobiology of SCI involves a primary mechanical insult to the spinal cord and activation of a delayed secondary cascade of events, which ultimately causes progressive degeneration of the spinal cord.

Whereas cell death from the mechanical injury is predominated by necrosis, secondary injury events trigger a continuum of necrotic and apoptotic cell death mechanisms. These secondary events include vascular abnormalities, ischemia-reperfusion injury, glutamate excitotoxicity and disturbances in ionic homeostasis, oxidative cell injury, and an extensive inflammatory response.

Clinical guidelines for the management of SCI have been established and are widely accepted by physicians who treat patients with SCI (Hadley et al., 2002). These guidelines include stabilization of the vertebrae and cardiopulmonary and metabolic support of the patient. However, beyond supportive care there are no medical or surgical treatments that have been clearly demonstrated to improve functional outcome in human SCI. Clinical trials with methylprednisolone (NASCIS II and III) (Bracken et al., 1997, Bracken et al., 1990) and GM-1 ganglioside (Geisler et al., 2001) have provided suggestive but equivocal evidence of benefit.

In light of the overwhelming impact of SCI on the individual, new therapeutic interventions are urgently needed. As discussed below, there is compelling evidence that riluzole, a sodium channel blocking agent with anti-glutamatergic activity, shows considerable promise for improving the outcome of SCI.

1.3 Sodium Channel Blockers

SCI results in a deleterious accumulation of intracellular sodium $[Na^+]_i$ within neurons (Stys, 2004), the resulting membrane depolarization associated with cellular inability to remove $[Na^+]_i$ favors further Na^+ influx via non-inactivating Na^+ channels. This in turn results in a reversal of function by Na^+/Ca^{2+} exchangers allowing Ca^{2+} to be pumped into cells while Na^+ is pumped out into the extracellular environment. Thus, an approach to prevent Ca^{2+}/Na^+ toxicity is to make use of Na^+ channel blockers.

Pharmacological antagonism of voltage-gated Na^+ channels has been demonstrated to prevent axonal degeneration and preserve the function of traumatized spinal cord white matter tracts and to reduce damage to myelin (Rosenberg et al., 1999). Focal

administration of tetrodotoxin (TTX) directly into the contused rodent spinal cord resulted in a significant attenuation of axonal loss and less axoplasmic pathology in comparison to vehicle-treated animals (Rosenberg et al., 1999). Furthermore, despite the fact that glial cells are rich in Na⁺ channels, TTX treatment did not enhance glial cell survival following SCI (Rosenberg et al., 1999). Thus, the neuroprotective effects of Na⁺ channel blockade were likely exerted on neurons and spinal cord axons to reduce intra-cellular increases in [Na⁺]_i and to reverse operation of axonal Na⁺/Ca²⁺ exchangers. Additionally, Na⁺ channel blockade may preserve spinal cord white matter by preventing the disruption of the axonal Na⁺/H⁺ antiporter system as TTX and procaine were shown to maintain compound action potentials following acute compression in an *ex vivo* model of SCI (Agrawal and Fehlings, 1996).

1.4 Riluzole

1.4.1 Efficacy

Riluzole, a benzothiazole anticonvulsant Na⁺ channel blocker, has been shown in two randomized controlled trials to promote increased survival and attenuate neurological dysfunction in patients with amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disorder characterized by motoneuron and corticospinal tract degeneration (Lacomblez et al., 1996, Hugon, 1996, Bensimon et al., 1994b). A recent Cochrane review has confirmed that the evidence for safety and efficacy in this clinical scenario is persuasive (Miller et al., 2007).

Given the data in the setting of ALS, it is not surprising that riluzole has been examined in other disease models characterized by sodium and glutamate toxicity. Several studies from a number of independent laboratories, in various species of animals, have shown that riluzole is neuroprotective and promotes functional neurological recovery in models of brain and spinal cord ischemic and traumatic injury (Heurteaux et al., 2006, Ates et al., 2007, Lang-Lazdunski et al., 1999, Schwartz and Fehlings, 2001). Other authors have found that the effects of riluzole are synergistic with the effects of methylprednisolone, which is the only drug used in routine clinical practices to attenuate secondary injury effects after SCI (Mu et al., 2000). In a recent study of prolonged administration of riluzole in Huntington's disease, no benefit was found in slowing disease progression but riluzole was well tolerated. Adverse effects were virtually similar in 357 patients treated with riluzole, compared to 180 placebo patients. Thirteen patients had elevation of liver enzymes and five patients discontinued treatment due to elevation of enzymes (Landwehrmeyer et al., 2007).

Riluzole exerts neuroprotective properties in the injured cord following systemic administration by sparing gray and white matter in rostro-caudal regions surrounding the injury epicenter (Schwartz and Fehlings, 2001). In addition to its ability to antagonize Na⁺ channels, riluzole is also known to inhibit presynaptic Ca²⁺-dependent glutamate release (Wang et al., 2004). However, given the lack of synaptic connections within white matter, the axon sparing property attributed to riluzole can likely be assigned to its ability to decrease the levels of [Na⁺]_i and intracellular calcium [Ca²⁺]_i.

The use of riluzole as a therapy for SCI is potentially feasible, as it has already received approval from the Food and Drug Administration for treatment of amyotrophic lateral

sclerosis (ALS)(Miller et al., 2007) at a dose of 100 mg/day. Notably, riluzole is without potent neurotoxic and cardiotoxic adverse effects (Bensimon et al., 1994a), although potential hepatotoxicity has been noted (Bensimon and Doble, 2004). While riluzole is administered for the lifetime of the patient with ALS, it would appear that the duration of therapy in the setting of spinal cord injury would not need to exceed 14 days, based on preclinical animal models and given the anticipated duration of sodium and glutamate mediated secondary injury (Schwartz and Fehlings, 2001, Park et al., 2004).

1.4.2 Pharmacology of Riluzole

In human studies, riluzole has been administered orally in a dose of 50 mg BID. The half-life of riluzole is 12 hours. Most drugs reach steady state plasma concentrations in 4-5 half lives and the same is assumed for riluzole. Riluzole is highly bound to plasma proteins – 97.5%, like phenytoin. In patients taking other drugs that bind to plasma proteins, there would be competition for the binding sites and presumably more free Riluzole in the plasma with greater drug activity. Riluzole is metabolized in the liver by an enzyme of the cytochrome P (CYP) 450 family. There are multiple CYP genes. Most of the drugs metabolizing enzymes are in the CYP 1, 2 & 3 families. Riluzole is specifically metabolized by a member of the CYP 1A2 subfamily whose substrates include acetaminophen, caffeine and warfarin. Other drugs that are metabolized by CYP 1A2 are Tacrine (Cognex), Omeprazole (prilosec) and quinilone antibiotics and theophylline. Co-administration of Riluzole and these drugs can increase Riluzole blood concentration.. The activity of the CYP 1A2 enzyme is lower in women and in the Japanese population, and possibly in other Asian populations (no data available). Presumably in these populations the activity of the drug would be greater, although no sex differences were noted in the ALS studies with Riluzole.

1.5 Aims

This study is designed to evaluate the safety and preliminary efficacy of riluzole in patients with acute spinal cord injury. The ultimate goal of this study is to set the stage for a Phase III randomized controlled trial.

1.5.1 Primary Aim

This study will evaluate safety of riluzole in subjects with acute traumatic spinal cord injury.

1.5.2 Secondary Aims

1. To collect information about efficacy outcomes in SCI subjects treated with riluzole.
 - Neurological motor outcomes as measured by ASIA Motor Score
 - Neurological sensory outcomes as measured by ASIA Sensory Score
 - ASIA Impairment grade
 - Brief Pain Inventory (Short Form)
 - Spinal Cord Independence Measure (SCIM)

2. To obtain information about pharmacokinetics and pharmacodynamics of riluzole and relate that information to toxicity and efficacy outcomes.

2 Study Design

2.1 Design

The study is designed as a multi-site, single arm active treatment pilot study involving 36 subjects. The primary safety endpoint follow-up period for the pilot study is 3 months. Neurological outcome will be assessed after 6 months. Patients will be followed as long as it is clinically indicated, since they are under the care of the physicians participating in this study.

A non-treated control arm drawn from the North American Clinical Trials Network (NACTN) database will be used to compare rates of complication and neurological recovery. Cases will be matched for age, sex, severity and level of SCI.

2.2 Treatment

All patients enrolled in the study will receive riluzole (Rilutek®) according to the following administration protocol. The patients will receive riluzole 50mg PO or NG every 12 hours starting within 12 hours of injury and lasting for 14 days. The administration of riluzole will be one hour before or two hours after any oral or NG feeding.

All other treatment will be per standard of care at the hospital to which the patients are admitted.

2.3 Study Stoppage

Safety of the subjects will be continuously monitored. Every safety event will be reviewed by both the local and central Medical Monitor. The central Medical Monitor will be a single person, a clinical expert in the field of spine injury treatment and will not be involved as an investigator within the study.

The central Medical Monitor will advise the Study Steering Committee, consisting of core investigators. The Study Steering Committee will have the authority to stop the study for safety reasons.

3 Inclusion Criteria

- Age equal to or greater than 18 years and less than or equal to 70 years;
- Willing to give written informed consent to participate in the study. The informed consent may require proxy to sign if arm/hand function is compromised.
- No other life-threatening injury
- Spinal cord injury at the neurologic level from C4 to T12
- ASIA Impairment Scale level A, B or C
- No cognitive impairment which would preclude an informed consent (including moderate or severe traumatic brain injury)
- Less than 12 hours since injury

4 Exclusion Criteria

- Equal or more than 12 hours since injury
- Hypersensitivity to riluzole or any of its components
- Unable to receive riluzole orally or via NG tube
- History of liver or kidney disease (e.g. Hepatitis A, B or C, Cirrhosis, etc.)
- Has a recent history of regular substance abuse (illicit drugs, alcohol)
- Unconscious
- Penetrating spinal cord injury
- Pregnancy as established by urine pregnancy test
- Life expectancy less than 12 months
- Is currently involved in another therapeutic SCI research study that precludes or complicates participation in this study (e.g. study of another therapeutic drug aiming for spinal cord injury recovery, any study that substantially interferes with the f/u schedule, or any high risk study that complicates evaluation of safety outcomes. Types of studies that would not preclude participation are e.g. behavioral adaptation studies, mental health interventions)
- Has a mental disorder or other illness, which in the view of the site investigator, would preclude accurate evaluation (e.g. schizophrenia, severe cognitive disability, Parkinson disease)
- Unable to commit to the follow-up schedule
- Is a prisoner
- Unable to converse, read or write English at the elementary school level

5 Number of Sites, Investigators, Patients

5.1 Sites and investigators

This protocol is the sole description of a study being carried out by “North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury”. NACTN was organized in 2004 for the purpose of conducting clinical trials of new therapy for spinal cord injury in an effective manner that enrolls sufficient numbers of patients, defines and adheres to standard protocols with skilled personnel providing maximal safety to patients undergoing treatment of spinal cord injury. NACTN is supported by grants from the Christopher Reeve Foundation and the Department of Defense. NACTN currently comprises seven major hospital centers. Before initiating the study, each study site will submit this protocol for local IRB review and approval after receiving Office of Research (ORP), Human Research Protection Office (HRPO) approval.

Clinical Centers:

- 1. The Methodist Hospital, Houston**
Principal Investigator, Robert G. Grossman, M.D.
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- 2. The University of Toronto, Toronto**
Investigator, Michael Fehlings, M.D., Ph.D.
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- 3. The University of Texas-Memorial Hermann Hospital, Houston**
Investigator, John Crommett, M.D.
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- 4. The Rehabilitation Institute of Chicago, Chicago**
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- 5. The University of Virginia Hospital, Charlottesville**
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Contract Research Organization:

AO Clinical Investigation and Documentation (AOCID) of North America

Study Monitor, Elinor Cappuccio
609-375-2017, Elinor.Cappuccio@afoundation.org

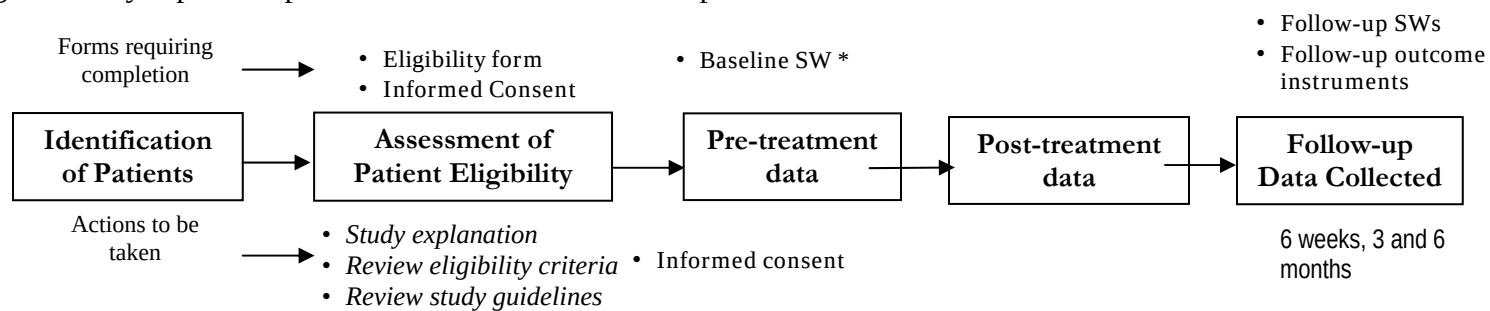
AO Clinical Investigation and Documentation (AOCID) of North America is a Contract Research Organization (CRO). AOCID is a non-profit organization that is supported by the AO Foundation. AOCID has extensive experience in conducting clinical trials in spinal surgery. AOCID will assume responsibility for the training of clinical coordinators at each clinical site in the use of the OPVerdi Electronic Data Capture (EDC) System, verifying data accuracy, data quality, data completeness and protocol adherence. No budget is requested by AOCID.

5.2 Patient Recruitment

A physician or a research nurse designated specifically for this study will approach each potential subject and inquire about their interest and eligibility in participating in this study. The approach will be performed as soon as possible upon arrival to the hospital and after emergency medical treatment has been performed and the patient's medical condition has been stabilized. This inquiry will include a series of screening questions to confirm eligibility, and will also provide a description of the study, and the responsibilities and risk/potential benefits for participating. If the subject wishes to participate, a member of the research team will explain the purpose of the study, the procedures, the risk/benefits, and the alternatives to participation according to the site-specific IRB regulations of the participating institution. An investigator or member of the research team will consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

Each subject choosing to participate will sign and date an informed consent and appropriate data release authorization (e.g. HIPAA authorization in the USA; PIPEDA in Canada). After the informed consent and the data release forms have been obtained, the study procedures will be initiated.

Figure 1. Key aspects of patient recruitment and follow-up



*SW = source worksheets

Each site will provide subjects with a telephone number for advice in case of complications or questions regarding follow-up visits.

5.3 Criteria for withdrawing a patient from the study

For analysis reasons, subjects who fail to follow-up according to the study plan will not be removed from the study (unless they formally withdraw their consent); they will be censored instead. Censoring refers to the inclusion in the analysis of the data contributed to the study up to the last available follow-up. The reasons for censoring patients from the study include (but are not limited to) refusal or loss to follow-up, complications that may or may not be related to the study which would preclude further participation and death.

6 Duration and Follow-up Schedule

This study will follow patients for 6 months. This will include baseline pre-treatment evaluation, post-treatment evaluation, planned follow-up visits at 6 weeks, and 3 and 6 months as well as all unplanned visits.

The main outcome of safety will be evaluated at 3 months F/U. Subjects will continue to be followed-up until 6 months in order to evaluate short-term neurological outcomes.

However, patients will be followed from the medical view point for as long as clinically indicated.

Upon study entry, the site will obtain the following information:

- The patient's mailing address, telephone number, and email address (when available)
- Alternate numbers such as cell phone numbers (when available)
- The name, address and phone number of primary caregiver
- The mailing address, telephone number, and email address (when available) of alternative contact provided by the patient

Patients will receive telephone reminders for upcoming study visits from a member of the research staff.

The principal investigator at each investigative site will be responsible for patient follow-up. The study coordinator will be the primary point of contact for data entry and data query issues. However, the principal investigator can delegate these duties to any member of the investigative team before the commencement of the study. This will allow all delegated staff to be instructed in data collection, Source Worksheets (SW) (Appendix 17.4), and the Electronic Case Report Forms (CRF) completion.

The staff will complete the adverse event section of the source worksheet and corresponding CRF in case there is an adverse event. These CRFs will be regularly monitored and collected by the study coordinator at each site as well as the local Medical Monitor and the central Medical Monitor for the study. The research staff will

notify the principal investigator about any serious adverse event (SAE) that occurs and will contact the designated study monitor within 24 hours of such events. The IRB will also be notified of any SAEs that occur according to the existing regulations.

7 Safety, Efficacy and Pharmacological Evaluation

7.1 Safety

Adverse events (AE) will be carefully recorded. Mild, moderate, severe and serious complications will be considered AEs and collected in the appropriate AE section of the source worksheet. These will be monitored during treatment and during the entire duration of each patient's follow-up, including all scheduled and unplanned visits.

The major adverse effects that have been reported following the administration of riluzole include:

- o Psychiatric disturbances
- o Liver damage - Liver damage has been primarily noted after prolonged administration of riluzole. It is not known if liver damage will occur in a course of treatment as short as the 14 days planned for the present study.

Other adverse effects that have been reported less frequently include:

- o Gastrointestinal disturbances
- o Neutropenia

In addition to recording adverse effects known to be associated with the administration of riluzole, there are specific morbidities that we will record that are related to spinal cord injury that might be worsened by the administration of riluzole. These morbidities are: infections (wound, pulmonary, bladder), cardiovascular disturbances, respiratory depression, DVT/pulmonary embolus, skin breakdown, and neuropathic pain. The NACTN database contains extensive data on the incidence of these morbidities. This database will be used as the standard for comparison with the riluzole treated patients to determine if the incidence of these complications is affected by the administration of riluzole.

Appropriate laboratory monitoring will be carried out to detect liver damage and/or neutropenia, and other disturbances of body chemistry and hematology. Baseline testing of liver function will be done to rule out preexisting liver disease. Baseline testing will include Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV). Baseline testing will also include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), bilirubin, prothrombin time (PT), international normalized ratio (INR), and hemogram. These tests will also be obtained at 3, 7, 10 and 14 days after the start of riluzole.

7.2 Neurological and Functional Outcome Measures

7.2.1 ASIA Motor Score

ASIA Motor Score (Appendix 17.1) is a standard, widely used instrument to evaluate motor function of the upper and lower extremities. The range of the score is from 0 to 100 (normal motor function in all 10 muscles examined bilaterally). More information is available at www.asia-spinalinjury.org.

7.2.2 ASIA Sensory Score

ASIA Sensory Score (Appendix 17.1) is a standard, widely used instrument to evaluate sensory function. The range of the score is from 0 (absence of sensory function) to 100 (no sensory disturbances). More information is available at www.asia-spinalinjury.org.

7.2.3 ASIA Impairment Score

ASIA Impairment Score (Appendix 17.1) is a standard, widely used instrument to evaluate impairment of function. The range of the scale is from A (no sensory and motor function) to E (normal).

7.2.4 Brief Pain Inventory (Short Form)

The Brief Pain Inventory (BPI) (Appendix 17.2) is a simple and easy to tool that provides information about the history, intensity, location, and quality of pain. Numeric scales (range from 0 to 10) indicate the intensity of pain in general, at its worst, at its least, and right now. A percentage scale quantifies relief from current therapies. A figure representing the body is provided for the patient to shade the area corresponding to his or her pain. Seven questions determine the degree to which pain interferes with function, mood, and enjoyment of life. The BPI is self-administered and easily understood. The copy of the instrument is available at <http://www.ohsu.edu/ahc/pain/paininventory.pdf>.

7.2.5 Spinal Cord Independence Measure

The Spinal Cord Independence Measure (SCIM) is a comprehensive rating scale that measures the ability of patients with spinal cord lesions (SCL) to perform everyday tasks according to their value for the patient (Appendix 17.13).

7.3 Pharmacokinetics and Pharmacodynamics

7.3.1 Rationale

Therapeutic drug monitoring (TDM) of riluzole is essential for the clinical trials in acute spinal cord injury patients for the following four reasons:

1. Riluzole is commonly used as a standard regimen of fixed oral doses of 50 mg twice daily for treatment in patients with amyotrophic lateral sclerosis (ALS),

since it received FDA approval in 1995. However, a high intersubject variability of riluzole serum concentrations among ALS patients has been documented (Groeneveld et al. 2001).

2. Riluzole is cleared by extensive metabolism, mainly by CYP 1A2, with only 2% of the dose recovered unchanged in the urine. Smoking is known to induce CYP 1A2. In addition, the standard care of SCI patients includes administration of MPSS (methylprednisolone) which is a substrate and inducer of CYP 3A4 and 2C19, which may indirectly affect the hepatic clearance of riluzole. Therefore, smoking history and other concomitant medications of CYP 1A2 substrates or inducers may affect the serum/plasma of riluzole concentrations.
3. Riluzole is highly protein bound, 97%, to serum albumin and to lipoproteins which also poses potential concerns on drug-drug interaction with other medications which compete for protein binding.
4. Riluzole serum concentrations in patients with ALS were found to be associated with side effects and symptoms of ALS (Groeneveld et al. 2003).

7.3.2 Specific Aims

1. To determine the individual peak/trough concentrations of riluzole at a steady state after 14-day treatment of 50 mg twice daily by oral or NG administration.
2. To derive individual pharmacokinetic parameters of half-life ($t_{1/2}$), systemic exposure (AUC_{0-24}), volume of distribution (V_d) and clearance (CL) by one-compartment model, using Bayesian iterative two-stage procedure.
3. To correlate pharmacokinetics and pharmacodynamics of riluzole in patients by attempting the correlation of the riluzole concentrations with laboratory measures including, AST, ALT, WBC count, and the incidence of AE and SAE, as well as with efficacy scores, namely, ASIA motor score, ASIA sensory score, ASIA impairment score and SCIM.

7.3.3 Methodologies

1. Sampling schedules for blood plasma and CSF

- 1.1 Blank control: A blood sample (5 ml) will be drawn and placed in a heparinized tube prior to the riluzole treatment, and plasma samples are collected as the blank control.

1.2 Blood samples for determinations of peak and trough concentrations:

Patients will receive riluzole 50 mg orally twice daily for 14 days (Section 2.2). On the 3rd and 14th days, blood samples will be taken for the trough and peak concentrations, respectively. One sample (2 ml) will be drawn before the riluzole dose is given and another blood sample (2 ml) will be drawn at 2 hr post dose. The research staff will record the exact sampling time for all four blood samples (two on day 3 and two on day 14).

The plasma samples will be separated from the blood immediately by centrifugation in the laboratory at 2,700 g for 10 min, and stored at -80°C (at least as low as -20°C) prior to the shipment with dry ice to Dr. Diana Chow at 1441 Moursund Street, University of Houston, College of Pharmacy at Texas Medical Center. Samples from each site will be shipped in complete sets of 7 samples for each patient collected over time. The plasma samples Dr. Chow receives will be labeled with a study code stripped of patient identifiers. Dr. Chow will not have the ability to link the samples to the patient.

Note: The plasma, instead of serum, samples will be collected, because it has been established that riluzole concentrations in plasma and serum are comparable at concentration < 500 ng/ml (van Kan et al. 2004). With a standard drug regimen of 50 mg twice daily, riluzole serum concentrations are in the range of 60 – 250 ng/ml (Groeneveld et al., 2003). The plasma samples retaining clotting factors will have one less variability than serum samples.

	Day 1	Day 3		Day 14	
	Pre-treatment – before the beginning of riluzole treatment	Before administration of riluzole	Two hours after the administration of riluzole	Before administration of riluzole	Two hours after the administration of riluzole
Amount of blood	5 ml	2 ml	2 ml	2 ml	2 ml

1.3 Blank plasma sample (30-50 ml) for assay development and validation.

The assay of van Kan et al (2004) will be adopted. The lower limit of quantification (LLOQ) and linearity will be established. The assay will be validated with within-day and between-day variations, as well as the precision and accuracy with quality control (QC) samples of low, medium and high concentrations, respectively.

1.4 CSF samples

The assay developed is also capable of quantifying the riluzole concentration in CSF, whenever the sample is available. CSF withdrawal is indicated if there is a suspicion of meningitis or if there is a need for myelography.

2. HPLC assay of riluzole plasma concentrations

Riluzole will be extracted from plasma samples (0.5 ml) with 5 ml of dichloromethane after the addition of 1 ml borax buffer at pH 9. The internal standard (I.S.) is 5-methoxy-psoralen [20 µl, 10 µg/ml in methanol-water 1:1 (v/v)]. The riluzole will be quantified using the HPLC assay with C18 column, eluted with a mobile phase of methanol:0.065 M ammonium acetate buffer (6:4) with 0.5 ml of triethylamine, adjusted to pH 4.0 with 50% acetic acid, detected at $UV_{\max}$ of 260 nm.

3. Pharmacokinetic analysis and modeling

Pharmacokinetic parameters of half-life ($t_{1/2}$), systemic exposure ($AUC_{0 \rightarrow 24}$), volume of distribution (V_d) and clearance (CL) will be derived, using Bayesian iterative two-stage procedure. The reference parameters will be derived based on the one-compartment model reported (Bruno et al. 1997). The area under the plasma concentration–time curve will be calculated over a 24 hour period, expressed as per kilogram of body weight ($AUC_{0 \rightarrow 24}/kg$), and used as a measure of total riluzole systemic exposure.

4. Statistical analysis

- 4.1 The impacts of age, gender, smoking history, and concomitant medications on the plasma concentration of riluzole and pharmacokinetics parameters will be evaluated with multivariate linear regression analysis.
- 4.2 The correlations between plasma concentrations and $AUC_{0 \rightarrow 24}/kg$ with the occurrence of side effects or efficacy measurement in SCI patients will be determined with logistic regression analysis.

Relationships between plasma concentrations and $AUC_{0 \rightarrow 24}/kg$ with AST, ALT and WBC count will be determined with linear regression analysis.

8 Demographics and Prognostic Variables

Recording information about the prognostic factors and demographic characteristics that may be associated with the outcomes of interest will be important to gain initial understanding of the impact of these variables on patient outcomes. The demographics will capture all items from the North American Clinical Trial Network Dataset. Further, we will capture the information about the treatment using the same forms. For details see attached SW forms (Appendix 17.4).

9 Blinding

This is an open-label study.

10 Complications and Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have a causal relationship with the study treatment. It can therefore be any unfavorable and unintended event (including an abnormal laboratory finding), symptom, or disease temporally associated with research participation, whether or not related to research participation.

Adverse events occurring during each patient's follow-up period will be recorded on the AE section of the source worksheets. Such information will include, at a minimum, the date of the event, event seriousness, event treatment, event outcome, and the relation (if any) of the event to the treatment procedure. Therefore, all AEs will be followed until resolved.

Each adverse event will be classified as serious or non-serious. Serious adverse events (SAE) will be reported to the Study Monitor within 24 hours of becoming aware of the event. As some local IRBs may have different SAE reporting requirements, SAEs are to be reported to the IRB within the established guidelines of their local IRB, or within 48 hours of becoming aware of the event.

Serious adverse event (SAE) is defined as the one that:

- Results in death.
- Is life-threatening, (Note: the term life-threatening in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.).
- Requires inpatient hospitalization or prolongation of existing hospitalization or transfer to a higher level of care (i.e. Floor to ICU).
- Results in persistent or significant disability/incapacity.
- Necessitates surgical intervention.
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a SAE when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

RELATIONSHIP TO RESEARCH PARTICIPATION:

- Unrelated - This causal relationship is assigned when the AE is definitely not associated with the research participation/treatment.
- Unlikely - This causal relationship is assigned when there is no temporal relationship to the administration of the investigational material or other factors which are more likely to have caused the event.

- Possibly related - This causal relationship is assigned when the AE starts at a reasonable time after study participation, but could have been produced by the subject's clinical state or other modes of therapy administered to the subject.
- Probably related - This causal relationship is assigned when the adverse event starts at a reasonable time after study participation, stops/improves when study participation/treatment has been stopped, and cannot be reasonably explained by known characteristics of the clinical state.
- Definitely related - This causal relationship is assigned when the adverse event starts at a reasonable time after study participation/treatment, stops/improves when study participation/treatment has been stopped, can reasonably be explained by known characteristics of the study participation/treatment.

Pain, neurological, or functional symptoms should be considered AEs in the following circumstances:

- When a patient's complaint for any of these symptoms resulted in an unscheduled visit or
- When a patient presents with new or worsening pain, neurological and/or function symptoms of clinical significance as compared to a previous visit.

Patients may require additional spine surgery as treatment for an AE. Since surgery creates additional risk for the patient, events leading to subsequent surgical intervention are to be captured on the Adverse Event section of the source worksheets.

Anticipated AEs are those which might reasonably be expected to occur as a result of the spinal cord injury and/or the administration of riluzole can include, but are not necessarily limited to:

Unanticipated Problems: All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

Neurological Complications

- Loss of neurological function
- Neuropathic pain

Systemic Medical Complications

- o Allergic reaction to riluzole
- o Cardiac arrest
- o Respiratory depression

- o Skin breakdown
- o DVT/Pulmonary embolus
- o Jaundice
- o GI effects: nausea, vomiting, diarrhea
- o Infection

- **Death**

Adverse events will be evaluated in accordance with the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) published August 9, 2006. Adverse events (AE) will be graded as mild, moderate, severe, and life-threatening.

Hepatic and hematological values are most likely to be affected by riluzole. The table below grades the severity of the adverse events based on CTCAE general guidelines:

Adverse Event	Short Name	Mild	Moderate	Severe	Life Threatening
Hepatic					
Alkaline phosphatase	ALP	>ULN-2.5 x ULN *	>2.5-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN
ALT, (SGPT) Alanine aminotransferase (serum-glutamic-pyruvic transaminase)	ALT	>ULN-2.5 x ULN	>2.5-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN
AST (SGOT) Aspartate aminotransferase (serum-glutamic oxaloacetic transaminase)	AST	>ULN-2.5 x ULN	>2.5-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN
GGT (γ-Glutamyl transpeptide)	GGT	>ULN-2.5 x ULN	>2.5-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN
Bilirubin	Bilirubin	>ULN-1.5 x ULN	>1.5-3.0 x ULN	>3.0-10.0 x ULN	>10.0 x ULN
Renal					
Creatinine	Creatinine	>ULN-1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 x ULN
Hematological					
Leukocytes (Total WBC)	Leukocytes	<LLN-3000/mm ³ * < LLN-3.0 x 10 ⁹ /L	<3000-2000/mm ³ <3.0-2.0 x 10 ⁹ /L	<2000-1000/mm ³ <2.0-1.0 x 10 ⁹ /L	<1000/mm ³ <1.0 x 10 ⁹ /L

Lymphopenia	Lymphopenia	<LLN-800/mm ³ < LLN-0.8 x 10 ⁹ /L	<800-500/mm ³ <0.8-0.5 x 10 ⁹ /L	<500-200/mm ³ <0.5-0.2 x 10 ⁹ /L	<200/mm ³ <0.2 x 10 ⁹ /L
Neutrophils/ Granulocytes (ANC/AGC)	Neutrophils	<LLN-1500/mm ³ < LLN-1.5 x 10 ⁹ /L	<1500-1000/mm ³ <1.5-1.0 x 10 ⁹ /L	<1000-500/mm ³ <1.0-0.5 x 10 ⁹ /L	<500/mm ³ <0.5 x 10 ⁹ /L

* ULN, LLN – Upper and Lower Limits of Normal

* See Appendix 17.4 Source Worksheet forms for units of measurement

Medical Monitor

The Medical Monitor will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor will comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor will also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the ORP HRPO.

11 Statistical Planning

11.1 Sample Size

This study will enroll 36 subjects. Based on current NACTN registry data, we expect the incidence rates of complications in the case series of 36 patients will range from 0.15 to 0.30. Using a one-sided exact binomial test with a Type I error of 5%, the case series of 36 will have approximate power of 0.80 to 0.99 to detect the doubling of a complication rate in the case series.

11.2 Statistical Analysis

Demographic and baseline data will be summarized in tabular form with appropriate descriptive statistics. Safety data will be summarized by Blyth-Still-Casella confidence intervals. NACTN Registry complication rates will be used as referent complication rates to test hypotheses that the complication rates in the case series exceed those expected from the registry data. Since a large number of comparisons will be computed, the False-Discovery-Rate testing procedure will be used to control the problem of multiple testing.

Liver chemistries at baseline 3, 7, 10, and 14 days after the start of riluzole will be summarized by linear regressions fitted to each patient. Linear random-intercept and random-coefficient (slope) models will be developed to examine if the liver chemistry profiles exhibit a non-zero, positive slope.

An overview of pharmacokinetic analyses and modeling is given in Section 7.3 (Pharmacokinetics and Pharmacodynamics).

Exploratory analyses of neurological outcomes and adverse events will be made by comparison with cases enrolled in the existing NACTN database. Prediction models based on the NACTN database will be developed taking into account relevant stratifying variables and these will then be used to calibrate the experience of the case series. These analyses will be performed by the Data Management and Statistical Coordinating Center (DMC) at the University of Texas, School of Public Health, Houston (Investigator, Ralph Frankowski, Ph.D.). The DMC has developed data gathering forms, quality monitoring and statistical-analytical tools for studies that involve the network of centers and are collecting extensive data on the acute and recovery phases of spinal cord injury.

12 Risk Analysis

The majority of procedures in this study correspond to the standard of care procedures. Risks associated with the standard of care procedures will be present regardless of any study participation.

Trial-specific risks include risks associated with trial-related investigational treatment, trial-related investigations and data collection.

Investigational drug (riluzole) is an approved drug for the treatment of amyotrophic lateral sclerosis (ALS). The safety profile in this indication is acceptable and well described. The listed side effects include nausea, vomiting, stomach pain, loss of appetite, dizziness, drowsiness, weakness, diarrhea, constipation and tingling or numbness around the mouth. Possible reactions include breathing trouble, cough, fever, chills, sore throat, swelling of the hands or feet, skin rash, and muscle aches.

There is no documented experience of riluzole treatment in patients with acute traumatic spinal cord injury. While current knowledge does not suggest that the administration of riluzole to patients with SCI would result in serious adverse events, the safety of the administration of riluzole in patients with SCI is unknown. The purpose of this study is to establish an initial safety profile.

Clinical research investigations performed in this trial include physical examinations, blood testing, cerebrospinal fluid testing (only if cerebrospinal fluid is obtained as a part of the routine clinical process) and interview questionnaires as referenced on page 12 (Appendix 17.12). Physical examinations that will be performed for the research purposes are non-invasive neurologic examinations to be performed as a part of the ASIA testing. Questionnaires applied in this investigation are standard research instruments and have been applied in a large number of studies. Blood samples for determination of riluzole plasma levels will be obtained by needle venipuncture or through arterial line (if present). Cerebrospinal fluid will be obtained from a lumbar puncture if clinically indicated during the management of the patient.

The majority of risks for patients arise from general treatment related risks of the standard of care procedures and will occur to patients regardless of any study participation.

All adverse events will be reported and recorded according to the current regulations.

13 Subject Confidentiality

The anonymity of participating subjects will be maintained. Subjects will be identified by their initials and assigned a subject number on Source Worksheets and Electronic Case Report Forms (CRF) and other documents submitted to the central investigative site. All record (hard copy and electronic) will be protected by the PI's and access will be granted to authorized personnel only. Each individual's data will be protected by study codes and passwords to ensure confidentiality. Documents that will not be submitted to the study monitor and that identify the subject (e.g., the signed informed consent document) will be maintained in strict confidence by the local investigator, except to the extent necessary to allow auditing by the appropriate ethical/legal authorities and the study monitor. Records at each study location will be maintained in a locked designated area. These exact procedures will follow standard routines at each investigative site.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

14 Study Conduct Issues

14.1 Data Entry, Database Management, & Quality Control

Source data includes all information in original records, observations or other activities in this research study necessary for the reconstruction and evaluation of the research. Samples of source data include, but are not limited to, medical history information, lab results, demographics, subject identification number, concomitant medications, informed consent, IRB approval and surgery reports. Examples of source documents include, but are not limited to, hospital records, lab reports, subject diaries, source worksheets, MRI reports and CT reports.

For this study, source worksheets (SW) will be developed consistently with all variables outlined in the study protocol. These worksheets, in combination with other relevant source documents (e.g., x-ray, MRI and CT reports), will serve as source data. These data from these assorted source documents will be entered electronically directly into the CRFs by using the electronic data capture system known as OPVerdi.

The OPVerdi study database will act as a repository for all collected data and will be inaccessible by anyone without pre-assigned confidential password access. The individuals who will be assigned password access to the database will be site study

coordinators, site investigators and the central and local monitors. The passwords will be site specific (i.e. sites will have access only to their own data but not to the data from other sites). An aggressive database backup schedule will be implemented and closely administered.

Prior to the initiation of the study, a site visit will be made by the study monitor to each investigative site. This visit will include a detailed discussion of the protocol, performance of study procedures, source worksheet and CRF completion, as well as the operations of the OPVerdi system.

14.2 Data Coordination

In collaboration with Dr. Ralph Frankowski, Ph.D., Professor of Biostatistics at the University of Texas School of Public Health (UTSPH)-Data Management and Statistical Coordinating Center (DMC), Dr. Robert Grossman will oversee all data evaluation and coordination between NACTN clinical centers, University of Houston, College of Pharmacy and University of Washington. All pharmacokinetic data from the University of Houston and all data entered electronically into the OPVerdi system will be provided to UTSPH for statistical analysis.

14.3 Study Monitoring

A dedicated Study Monitor from the AOCID will oversee this study in accordance with the applicable regulations, Good Clinical Practices (GCPs), and standard operating procedures. The monitor will contact the site prior to study initiation to schedule a site initiation visit to review the protocol and data collection procedures with the site staff. A study close-out visit will take place after the last subject attends his/her last follow-up at each institution. The monitor will have frequent communication with each of the investigative sites. During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data is authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

Both on-site and distance monitoring will be employed during the course of the study. The study monitor's primary day-to-day responsibility will be to ensure that all subjects initially enrolled are adhering to the study protocol. This responsibility will include: ensuring that all data entered into the electronic CRF system is complete and consistent; all scheduled and unscheduled visits are documented; and conducting the visits to each of the investigative sites. In addition, the study monitor will regularly check the study database to identify missing data or unrealistic values. Inconsistencies will be resolved by contacting the individual site and asking for clarification and verification against the subject's source documents. On-site monitoring will involve validating a random sample of source documents against the study database.

14.4 Reporting Requirements

14.4.1 Protocol Modifications

Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the ORP HRPO for acceptance.

14.4.2 Protocol Deviations

Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the ORP HRPO as soon as the deviation is identified.

14.4.3 ORP HRPO Final Approval

The protocol will be conducted in accordance with the protocol submitted to and approved by the ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the ORP HRPO.

14.4.4 Continuing Review and Final Study Report

A copy of the continuing review report for the research study will be submitted to the local IRB of Record. A copy of the approved continuing review report and the local IRB of Record approval notification must be submitted to the ORP HRPO as soon as these documents become available. The PI will report progress of the approved research to the local IRB of Record and the ORP HRPO as often as requested, but not less frequently than once per year.

A copy of the final study report will be submitted to the local IRB of Record. A copy of the approved/accepted final study report and the local IRB of Record approval/acceptance notification will be submitted to the ORP HRPO as soon as these documents become available.

14.4.5 Compliance

The knowledge of any pending compliance inspection/visit by the FDA, DHHS-OHRP, or other government agency concerning clinical investigation or research, the issuance

of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to ORP HRPO.

15 Timeline and Informed Consent Form

15.1 Timeline



15.2 Sample Informed Consent Form

Consent and Authorization Form	MED. REC. NO. _____
IRB#: _____	NAME _____
Protocol Approval Date: _____	BIRTHDATE _____

University of (NAME) Consent and Authorization Form

TITLE: Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

PRINCIPAL SITE INVESTIGATOR: Name and phone number

SUB-INVESTIGATORS: Name and phone number

SPONSOR: Department of Defense (DOD) - Telemedicine and Advanced Technology Research Center (TATRC) and the Christopher Reeve Foundation

PURPOSE

You are invited to participate in this research study because you have sustained acute spinal cord injury.

This research study has been designed to determine if the use of the drug **riluzole** is safe in patients with acute spinal cord injury. Your injury affects your neurologic function due to destruction in your spinal cord. **Riluzole** is a drug that is approved and has shown to be effective for another neurologic condition called amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). Laboratory studies have shown that **riluzole** can reduce the extent of spinal cord injury in animals. The present study is a trial of the use of **riluzole** to limit the damage to the spinal cord after spinal cord injury.

Inclusion Criteria

- Age equal to or greater than 18 years and less than or equal to 70 years;
- Willing to give written informed consent to participate in the study. The informed consent may require proxy to sign if arm/hand function is compromised.
- No other life-threatening injury
- Spinal cord injury at the neurologic level from C4 to T12
- ASIA Impairment Scale level A, B or C

- No cognitive impairment which would preclude an informed consent (including moderate or severe traumatic brain injury)
- Less than 12 hours since injury

Exclusion Criteria

- Equal or more than 12 hours since injury
- Hypersensitivity to riluzole or any of its components
- Unable to receive riluzole orally or via NG tube
- History of liver or kidney disease (e.g. Hepatitis A, B or C, Cirrhosis, etc.)
- Has a recent history of regular substance abuse (illicit drugs, alcohol)
- Unconscious
- Penetrating spinal cord injury
- Pregnancy as established by urine pregnancy test
- Life expectancy less than 12 months
- Is currently involved in another therapeutic SCI research study that precludes or complicates participation in this study (e.g. study of another therapeutic drug aiming for spinal cord injury recovery, agent, any study that substantially interferes with the f/u schedule, or any high risk study that complicates evaluation of safety outcomes. Types of studies that would not preclude participation are e.g. behavioral adaptation studies, mental health interventions)
- Has a mental disorder or other illness, which in the view of the site investigator, would preclude accurate evaluation (e.g. schizophrenia, severe cognitive disability, Parkinson disease)
- Unable to commit to the follow-up schedule
- Is a prisoner
- Unable to converse, read or write English at the elementary school level

Your participation in this study will begin when you sign this form agreeing to participate in this study. This has to be within 12 hours of injury, as there is evidence currently suggests **riluzole** acts to protect the spinal cord if given within 12 hours after injury. Data about you will be collected starting immediately after you sign the informed consent. You will be required to return for follow-up visits at 6 weeks, 3 and 6 months after the treatment. You may be asked to return for follow up visit at 12 months, as well. Additional visits may also be required. About 36 patients will take part in this study throughout the United States and Canada.

You will receive **riluzole** 50mg orally every 12 hours, starting within 12 hours after your injury, for 14 days.

STANDARD OF CARE TREATMENT OF SPINAL CORD INJURY

You will receive the standard of care treatment of your spinal cord injury, which includes the cardiac, pulmonary and surgical decompressive and stabilization procedures that are indicated for your particular injury.

ADDITIONAL AND ALTERNATIVE TREATMENTS

The only specific drug therapy that is generally accepted as having a possible benefit for spinal cord injury is methylprednisolone (methylprednisolone is also known as Solu-Medrol). In this study you may be given methylprednisolone in addition to riluzole.

The alternative to taking part in the study is to decline to participate in the study. Your participation in the study is entirely voluntary. If you do not participate in this study, it will not affect your care. You will receive the standard of care that patients with spinal cord injury receive at INSTITUTION. Your treatment may include receiving methylprednisolone but if you choose not to participate in the study you will not receive riluzole.

RISKS AND DISCOMFORTS

Riluzole is generally well tolerated. However, there is risk of a reaction to riluzole. The reactions that have been observed include the following symptoms: nausea, vomiting, stomach pain, loss of appetite, dizziness, drowsiness, weakness, diarrhea, constipation and tingling or numbness around the mouth. Other symptoms include: breathing trouble, cough, fever, chills, sore throat, swelling of the hands or feet, skin rash, and muscle aches. Changes may occur in your liver function and in your blood cells. Your blood will be monitored for evidence of changes of function of your liver (increase of liver enzymes) and changes in your blood cells (decrease of white blood cells also known as neutropenia). Five blood draws of approximately 2 tablespoons of blood or less will be obtained within 14 days to monitor your blood. Risks associated with blood draws may include a feeling of light headedness, bruising, pain or infection. If a significant reaction to riluzole is observed in your physical state or in your blood the administration of riluzole will be stopped. Physical symptoms and changes in the blood caused by riluzole usually return to normal when riluzole is stopped.

Severe allergic reactions to riluzole are rare but may occur. A severe reaction might worsen your neurologic function, affect your heart or breathing, or might lead to death.

You may decline to do any of the study tasks that you do not wish to do.

BENEFITS

By participating in this study you may make a better recovery from your injury and benefit from improved neurologic function. You may help determine beneficial treatment for future patients.

CONFIDENTIALITY AND PRIVACY OF YOUR PROTECTED HEALTH INFORMATION

Release of Health Information – If you decide to participate in this study, information about your health may be used or disclosed for the purposes of conducting this study. This information may include information from your medical record that is relevant to this study, such as your medical history, medications, test results, diagnoses, treatments, operative reports (reports from operations that you have undergone), and discharge summaries. It may also include information relating to: Human Immunodeficiency Virus (“HIV”) infection or Acquired Immunodeficiency Syndrome (“AIDS”); treatment for or history of drug or alcohol abuse; or mental or behavioral health or psychiatric care. Information collected by the study doctor and/or research staff specifically for this study, such as test results, blood samples, physical examinations, information about possible side effects, and surveys you might be asked to complete could also be used or disclosed.

Individuals that may use or release this information include: physicians, physicians’ office staff, hospital staff, the study doctor, and authorized members of the study doctor’s research staff. These individuals may release this information to the study doctor, authorized members of the study doctor’s staff, the funding agency of the study (Department of Defense and Christopher Reeve Foundation) as well as its agents or contractors, other researchers, the Institutional Review Board (IRB), the United States Food and Drug Administration (FDA) and its representatives, and other government agencies.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Material Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner as to protect the confidentiality of subject information.

In most cases, the information released to the above listed individuals or entities will not contain your name, social security number, or any other personal information. However, authorized representatives of your study doctor, IRB, FDA, or other government agencies may review records containing personal information to make sure that the study information is correct. Because of the need to provide information to these parties, absolute confidentiality cannot be guaranteed.

Use of Information – This information may be used to determine whether you meet all requirements for participation in the study, to monitor your healthcare during the study, to enable the sponsor to answer the scientific questions for which the study was designed, and to ensure that the study has been done properly. Examples of the use of this information are as follows: the sponsor may use the information in submissions to government agencies throughout the world, to request approval of the study drug or device; the sponsor may use the information for reporting adverse events to government agencies, such as the FDA; the sponsor may also transfer the information to business partners or companies it hires to provide study-related services; the sponsor

may also provide overall study results, including your information, to other study doctors. The data from this study may be used in the future studies evaluating use of riluzole in patients with spinal cord injury. In addition, this data will become a part of the North American Clinical Trials Network (NACTN) database. It will be used for comparison with the data received from the future studies which will be carried out by NACTN concerning the treatment of patients with spinal cord injuries.

In addition, both the sponsor and the study doctor may use the information to prepare reports or publications of the study results. However, when results of the research study are reported in medical journals or at scientific meetings, the people who were in the study are not named and identified. Therefore, your names would not be disclosed in any presentation or publication.

You need to understand that once your information has been released, it may no longer be protected by US federal regulations relating to data privacy and could be used or re-disclosed in ways other than those listed in this section of the consent form.

You have the right to see and copy your medical records but information relating to this study may be withheld until the end of this study. You must contact the Principal Investigator, listed on page one of the research consent (Name, phone number and address of Principal Investigator), if you desire to gain access to your records. Dr. (Principal Investigator) will maintain a current list of individuals requesting a copy of their records at this site.

Authorization to Disclose – By signing this consent form, you authorize disclosure of personal information to, and review of your medical records by, the people and entities described above. You do not have to authorize this disclosure of information. However, if you do not, you will not be able to participate in this study.

Expiration of Authorization – Because this information is being disclosed for research use, there is no specific expiration date for the authorization to disclose and use this information. The sponsor may keep and continue to use your study information for several years. Your study doctor may need to add to or correct information about you even after your study participation is over; including providing updates of your health status if that is important to the purpose of the study. The time period when review of your medical records can be used or disclosed under this authorization ends when all activities related to this study are completed. This authorization will remain in effect unless you revoke it.

Revoking Authorization to Disclose – If you stop participating in this study, you also have the right to revoke (withdraw) your authorization to disclose and use your information. Revoking your authorization means taking back the permission you gave the study doctor to send information about you to the sponsor or other people and entities. If you revoke your authorization, your doctor will not use or release any more information about you after receiving your request, except to tell the sponsor that you have stopped early and have revoked your authorization. However, the sponsor and the study doctor can still keep and use any information that it has already received to the extent necessary to preserve the integrity of the research study.

If you want to revoke your authorization, you must do so in writing to the study doctor. You can get a revocation form from your study doctor or you can write a letter to the study doctor at the address below:

Name and address of Principal Investigator

You may revoke your authorization at any time. However, once you do so, you can no longer continue to participation in the study.

COSTS

The procedures in this study that are associated with your clinical care or surgery care are part of your regular treatment. These would be performed even if you were not in this study. The costs associated with your clinical care or surgery will be billed to your insurance. If you are uninsured, you will be billed for them. You will be responsible for any costs your insurance does not cover.

There are no costs associated with participation in the research study itself. The experimental drug used in this study will be provided at no cost to you.

LIABILITY

If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact a member of the research staff at (phone number). After hours or in case of emergency, you may call (phone number of Hospital Operator) and ask the operator to page Dr. (Principal Investigator).

If you require medical treatment as a result of participation in this study, your treatment will be provided. All reasonable and necessary medical expenses you receive, including hospitalization, to treat adverse reactions to study participation that would not be expected from the standard treatment using currently approved therapies for your condition will be provided at no cost to you or your insurance company by the study sponsor. You, or your medical insurance, will be responsible for other medical expenses resulting from your medical condition. You have not waived your legal rights by signing this form. For clarification on this subject, or if you have further questions, please call the XXXXXX.

EXPENSES FOR MEDICAL CARE RELATED TO THIS RESEARCH

If you are hurt or get sick because of this research study, you can receive medical care at an Army hospital or a clinic free of charge. You will only be treated for injuries that are directly caused by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study, (name and telephone number of Principal Investigator). If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at (301) 619-7663/2221.

PARTICIPATION:

If you have any questions regarding your rights as a research subject, you may contact this institution with the Research Integrity Office at (phone number). You do not have to join this or any other research study. If you join, and later change your mind, you may withdraw at any time, for any reason, and you do not need to disclose your reason. If you refuse to join or if you withdraw early from the study, there will be no penalty or loss of any benefits to which you are otherwise entitled.

You may be removed from the study if the investigator or study sponsor stops the study, if you develop serious side effects, or if you do not follow instructions.

You will be told about any new information that might change your decision to be in this study.

If you leave the study before all the study procedures are completed, we may ask you to complete some of the end of study procedures to be sure all safety monitoring is finished.

We will give you a copy of this signed form.

SIGNATURES

Your signature below indicates that you have read this entire form and that you agree to be in this study.

Printed Name of Subject

Date

Signature of Subject

Date

Signature of Legally Authorized Representative

Date

Signature of Person Obtaining Consent

Date

If you have any questions regarding this study now or in the future, contact Dr. (Principal Investigator) or members of the study team at (phone number).

16 References

Reference List

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17 Appendix

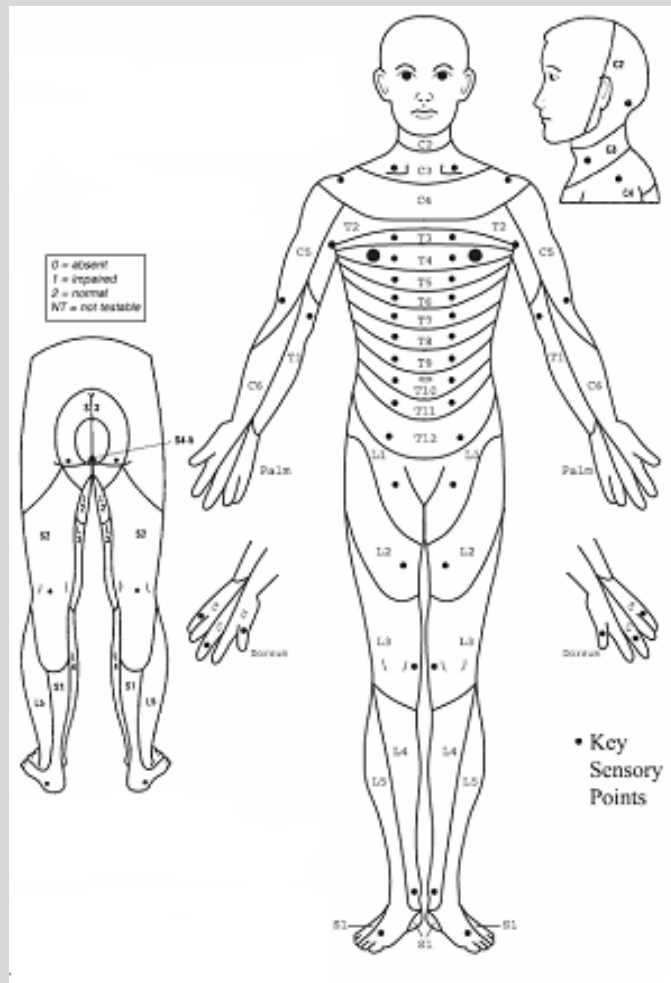
17.1 ASIA Assessment

ASIA Motor Scale			
Key muscles MUSCLE GRADING	Upper limb:		
	R	L	
0 = No contraction/ total paralysis	☐	☐	C5 Elbow flexors
1 = Palpable or visible contraction			
2 = Active movement, full range of motion, gravity eliminated	☐	☐	C6 Wrist extensors
3 = Active movement, full range of motion, against gravity			
4 = Active movement, full range of motion, against gravity and provides some resistance	☐	☐	C7 Elbow extensors
5 = Normal or active movement, full range of motion, against gravity and provides normal resistance	☐	☐	C8 Finger flexors (distal phalanx of middle finger)
5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present			
NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture	☐	☐	T1 Finger abductors (little finger)
	Lower limb:		
	R	L	
	☐	☐	L2 Hip flexors
	☐	☐	L3 Knee extensors
	☐	☐	L4 Ankle dorsiflexors
	☐	☐	L5 Long toe extensors
	☐	☐	S1 Ankle plantar flexors

ASIA Sensory Scale

	Light Touch		Pin Prick	
	R	L	R	L
C2	☐	☐	☐	☐
C3	☐	☐	☐	☐
C4	☐	☐	☐	☐
C5	☐	☐	☐	☐
C6	☐	☐	☐	☐
C7	☐	☐	☐	☐
C8	☐	☐	☐	☐
T1	☐	☐	☐	☐
T2	☐	☐	☐	☐
T3	☐	☐	☐	☐
T4	☐	☐	☐	☐
T5	☐	☐	☐	☐
T6	☐	☐	☐	☐
T7	☐	☐	☐	☐
T8	☐	☐	☐	☐
T9	☐	☐	☐	☐
T10	☐	☐	☐	☐
T11	☐	☐	☐	☐
T12	☐	☐	☐	☐
L1	☐	☐	☐	☐
L2	☐	☐	☐	☐
L3	☐	☐	☐	☐
L4	☐	☐	☐	☐
L5	☐	☐	☐	☐
S1	☐	☐	☐	☐
S2	☐	☐	☐	☐
S3	☐	☐	☐	☐
S45	☐	☐	☐	☐

Any anal sensation (Yes/No)

☐


Key Sensory Points:

0=Absent 2= Normal
1= Impaired NT- Not testable

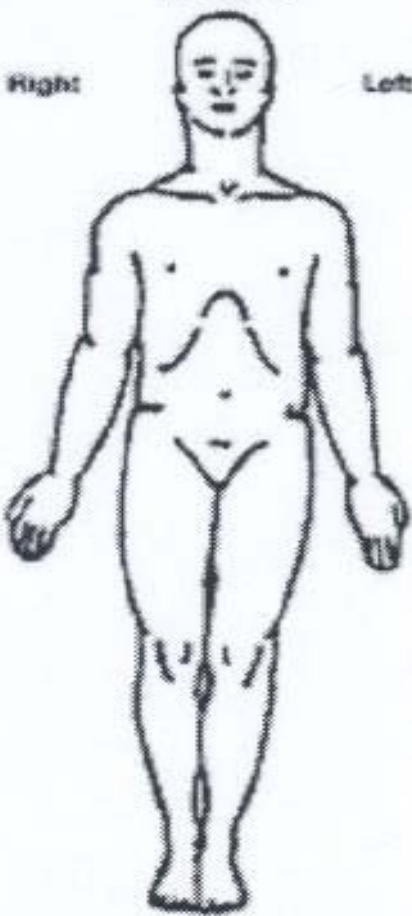
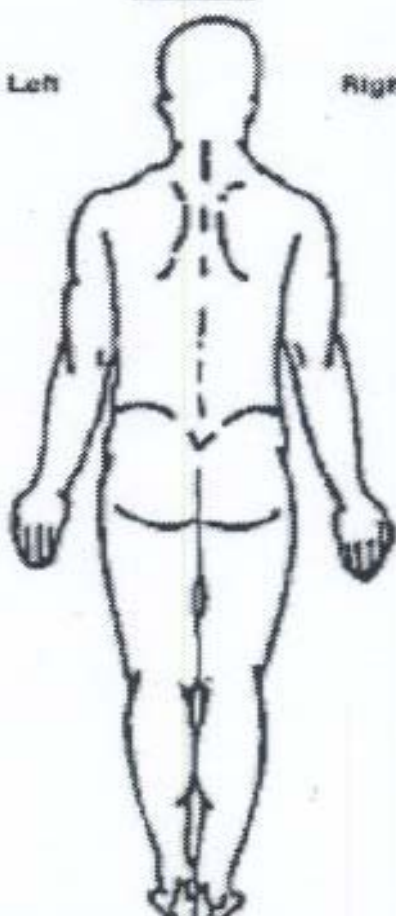
ASIA Impairment Scale

	Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
	Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
	Grade C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
	Grade D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
	Grade E	Normal	Motor and sensory function are normal.

Performed by (please initial):**Date:** __/__/__
 dd/mm/yyyy

American Spinal Injury Association:
International Standards for Neurological Classification of Spinal Cord Injury, revised 2002; Chicago, IL

17.2 Brief Pain Inventory

Brief Pain Inventory (Short Form)	
1 Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these everyday kinds of pain today? ☐ Yes ☐ No	
2 On the diagram shade in the areas where you feel pain. Put an X on the area that hurts the most.	
Front right left	Back left right
<u>Front</u>  <u>Back</u> 	
3 Please rate your pain by circling the one number that best describes your pain at its <i>worst</i> in the last 24 hours. 0 1 2 3 4 5 6 7 8 9 10 No pain Pain as bad as you can imagine	

4 Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

No pain

Pain as bad
as you can imagine

5 Please rate your pain by circling the one number that best describes your pain on the average.

No pain

Pain as bad
as you can imagine

6 Please rate your pain by circling the one number that tells how much pain you have right now.

No pain

Pain as bad
as you can imagine

**7 What treatments or medications are you receiving for your pain?
(Please write the name of the treatments or medications below.)**

8 In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows much relief you have received.

No relief

Complete
Relief

9 Circle the one number that describes best how, during the past 24 hours, pain has interfered with your:

a) general activity

Does not
interfere

Completely interferes

b) mood

Does not
interfere

Completely interferes

c) walking ability

Does not
interfere

Completely interferes

d) normal work (includes both work outside the home and housework)

Does not
interfere

Completely interferes

e) relations with other people

Does not
interfere

Completely interferes

f) sleep										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere									Completely interferes	
g) enjoyment of life										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere									Completely interferes	
Copyright 1991 Charles S. Cleeland, PhD Pain Research Group All rights reserved										

17.3 Spinal Cord Independence Measure (SCIM)

Spinal Cord Independence Measure (SCIM) Version 1, May 1996	
Self-Care	
1 Feeding (cutting, opening containers, bringing food to mouth, holding cup with fluid)	
0. Needs parenteral, gastrostomy or fully assisted oral feeding	
1. Eats cut food using several adaptive devices for hand and dishes	
2. Eats cut food using only one adaptive device for hand; unable to hold cup	
3. Eats cut food with one adaptive device; holds cup	
4. Eats cut food without adaptive devices; needs a little assistance (e.g., to open containers)	
5. Independent in all tasks without any adaptive device	
2 Bathing (soaping, manipulating water tap, washing)	
0. Requires total assistance	
1. Soaps only small part of body with or without adaptive device	
2. Soaps with adaptive device; cannot reach distant parts of the body or cannot operate a tap	
3. Soaps without adaptive devices; needs a little assistance to reach distant parts of body	
4. Washes independently with adaptive devices or in specific environmental setting	
5. Washes independently without adaptive devices	
Self-Care (continued)	
3 Dressing (preparing clothes, dressing upper and lower body, undressing)	
0. Requires total assistance	
1. Dresses upper body partially (e.g., without buttoning) in special setting (e.g., back support)	
2. Independent in dressing and undressing upper body. Needs much assistance for lower body	
3. Requires little assistance in dressing upper or lower body	
4. Dresses and undresses independently, but requires adaptive devices and/or special setting	
5. Dresses and undresses independently, without adaptive devices	

4 Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup)

0. Requires total assistance

1. Performs only one task (e.g., washing hands and face)

2. Performs some tasks using adaptive devices; needs help to put on/take off devices

3. Performs some tasks using adaptive devices; puts on/takes off devices independently

4. Performs all tasks with adaptive devices or most tasks without devices

5. Independent in all tasks without adaptive devices

Respiration and Sphincter Management

5 Respiration

0. Requires assisted ventilation

2. Required tracheal tube and partially assisted ventilation

4. Breaths independently but requires much assistance in tracheal tube management

6. Breaths independently and requires little assistance in tracheal tube management

8. Breaths without tracheal tube, but sometimes requires mechanical assistance for breathing

10. Breaths independently without any device

6 Sphincter management - Bladder

0. Indwelling catheter

5. Assisted intermittent catheterization or no catheterization, residual urine volume > 100cc

10. Intermittent self-catheterization

15. No catheterization required, residual urine volume < 100cc

Respiration and Sphincter Management (continued)

7 Sphincter management - Bowel

0. Irregularity, improper timing or very low frequency (less than once in 3 days) of bowel movements

5. Regular bowel movements, with proper timing, but with assistance (e.g., for applying suppository)

10. Regular bowel movements, with proper timing, without assistance

8 Use of toilet (perineal hygiene, clothes adjustment before/after, use of napkins or diapers)

0. Requires total assistance

1. Undresses lower body, needs assistance in all the remaining tasks

2. Undresses lower body and partially clean self (after); needs assistance in adjusting clothes and/or diapers

- 3. Undresses and cleans self (after); needs assistance in adjusting clothes and/or diapers
- 4. Independent in all tasks but needs adaptive devices or special setting (e.g., grab-bars)
- 5. Independent without adaptive devices or special setting

Mobility (room and toilet)

9 Mobility in bed and action to prevent pressure sores

- 0. Requires total assistance
- 1. Partial mobility (turns in bed to one side only)
- 2. Turns to both sides in bed but does not fully release pressure
- 3. Releases pressure when lying only
- 4. Turns in bed and sits up without assistance
- 5. Independent in bed mobility; performs push-ups in sitting position without full body elevation
- 6. Performs push-ups in sitting position

10 Transfers: bed-wheelchair (locking wheelchair, lifting footrests, removing and adjusting transferring, lifting feet)

- 0. Requires total assistance
- 1. Needs partial assistance and/or supervision
- 2. Independent

Mobility (room and toilet) (Continued)

11 Transfers: wheelchair-toilet-tub (if uses toilet wheelchair – transfers to and from; if uses wheelchair – locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet)

- 0. Requires total assistance
- 1. Needs partial assistance and/or supervision, or adaptive device (e.g., grab-bars)
- 2. Independent

Mobility (indoors and outdoors)

12 Mobility indoors (short distances)

- 0. Requires total assistance
- 1. Needs electric wheelchair or partial assistance to operate manual wheelchair
- 2. Moves independently in manual wheelchair
- 3. Walks with a walking frame

- 4. Walks with crutches
- 5. Walks with two canes
- 6. Walks with one cane
- 7. Needs leg orthosis only
- 8. Walks without aids

13 Mobility for moderate distances (10 – 100 meters)

- 0. Requires total assistance
- 1. Needs electric wheelchair or partial assistance to operate manual wheelchair
- 2. Moves independently in manual wheelchair
- 3. Walks with a walking frame
- 4. Walks with crutches
- 5. Walks with two canes
- 6. Walks with one cane
- 7. Needs leg orthosis only
- 8. Walks without aids

Mobility (indoors and outdoors) (Continued)

14 Mobility outdoors (more than 100 meters)

- 0. Requires total assistance
- 1. Needs electric wheelchair or partial assistance to operate manual wheelchair
- 2. Moves independently in manual wheelchair
- 3. Walks with a walking frame
- 4. Walks with crutches
- 5. Walks with two canes
- 6. Walks with one cane
- 7. Needs leg orthosis only
- 8. Walks without aids

15 Stair management

- 0. Unable to climb or descend stairs
- 1. Climbs 1 or 2 steps only, in a training setup
- 2. Climbs and descends at least 3 steps with support or supervision of another person
- 3. Climbs and descends at least 3 steps with support of handrail and/or crutch and/or cane
- 4. Climbs and descends at least 3 steps without any support or supervision

16 Transfers: wheelchair-car (approaching car, locking wheelchair, removing arm and foot transferring to and from car, bringing wheelchair into and out of car)

0. Requires total assistance

1. Needs partial assistance and/or supervision, and/or adaptive devices

2. Independent without adaptive devices

Loewenstein Rehabilitation Hospital, Raana, Israel. Reproduced with permission.

17.4 Source Worksheets (SW)

See Attachment

17.5 Riluzole Label

See Attachment

17.6 Sanofi-Aventis documents on Hypersensitivity to Riluzole

See attachment

17.7 IND EXEMPT LETTER FROM FDA

See attachment

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

Baseline

Version 1, 11 June 2008

Follow-up Site:

FU 6-weeks

FU 3-months

FU 6-months

FU unscheduled

SAE-Form

Patient-Trial-Number

Patient Initials: last name, first

Created by:

Zoya Bauer, MD, PhD

Jerika Robles, Project Manager

(University of Washington, USA)

(AOCID NA)

Reviewed by:

Branko Kopjar, MD, PhD

(University of Washington, USA)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

Patient Trial Number

Riluzole Investigator Baseline Fi.doc

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

Baseline

Pre-Treatment Data (Day 1)

1. Informed consent														GENERIC DATA	
1.1 I informed the patient about the nature, objective and risks of this clinical trial. She / he declared her / his voluntarily informed consent to participate in this study in writing (Informed consent form).															
Yes ☐ No ☐															
Remember to provide the patient with a copy of the signed informed consent															
1.2 Date signed		Day												Year	
		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec		
			☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

Patient Trial Number

Riluzole Investigator Baseline Fi.doc

2. Inclusion Criteria		GENERIC DATA	
2.1	Subject ≥ 18 and ≤ 70 years of age	☐ Yes	☐ No $\rightarrow$ Exclusion
2.2	Subject is able and willing to give written informed consent to participate in the study. (If arm/hand function is compromised, the informed consent will be signed by proxy.)	☐ Yes	☐ No $\rightarrow$ Exclusion
2.3	Subject has no other life-threatening injury	☐ Yes	☐ No $\rightarrow$ Exclusion
2.4	Subject has spinal cord injury at the neurologic level from C4 to T12	☐ Yes	☐ No $\rightarrow$ Exclusion
2.5	Subject has ASIA Impairment Scale level A, B or C	☐ Yes	☐ No $\rightarrow$ Exclusion
2.6	Subject has no cognitive impairment which would preclude an informed consent (including moderate or severe traumatic brain injury)	☐ Yes	☐ No $\rightarrow$ Exclusion
2.7	Subject is <12 hours since injury	☐ Yes	☐ No $\rightarrow$ Exclusion
If any INCLUSION CRITERIA question is answered NO , this subject CANNOT enter the study.			

3. Exclusion Criteria		GENERIC DATA	
3.1	Subject is ≥ 12 hours since injury	☐ No	☐ Yes $\rightarrow$ Exclusion
3.2	Subject has hypersensitivity to riluzole or any of its components	☐ No	☐ Yes $\rightarrow$ Exclusion
3.3	Subject is unable to receive riluzole orally or via NG tube	☐ No	☐ Yes $\rightarrow$ Exclusion
3.4	Subject has history of liver or kidney disease (e.g. Hepatitis A, B or C, Cirrhosis,)	☐ No	☐ Yes $\rightarrow$ Exclusion
3.5	Subject has a recent history (<12 months) of regular substance abuse (recreational drugs, alcohol)	☐ No	☐ Yes $\rightarrow$ Exclusion
3.6	Subject is unconscious	☐ No	☐ Yes $\rightarrow$ Exclusion
3.7	Subject has penetrating spinal cord injury	☐ No	☐ Yes $\rightarrow$ Exclusion
3.8	Subject is pregnant	☐ No	☐ Yes $\rightarrow$ Exclusion
3.9	Subject has life expectancy <12 months	☐ No	☐ Yes $\rightarrow$ Exclusion
3.10	Subject is currently involved in another study that precludes or complicates participation in this study	☐ No	☐ Yes $\rightarrow$ Exclusion
3.11	Subject has a disease or condition that would preclude accurate evaluation (e.g. significant psychiatric disease)	☐ No	☐ Yes $\rightarrow$ Exclusion
3.12	Subject is a prisoner	☐ No	☐ Yes $\rightarrow$ Exclusion
3.13	Subject is unable to converse, read or write English at the elementary school level	☐ No	☐ Yes $\rightarrow$ Exclusion

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

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3.14 Unable to commit to follow-up schedule ☐ No ☐ Yes → Exclusion

If any EXCLUSION CRITERIA question is answered YES, this subject CANNOT enter the study.

4. Subject eligibility - Waiver

GENERIC DATA

4.1 Was a waiver granted for any deviations from the inclusion/exclusion criteria? ☐ N/A ☐ No ☐ Yes, specify:

If a waiver was granted for subject's enrolment into the study, document reason for deviation, date, and who granted the waiver

Reason:

Date (mm/dd/yyyy):

Granted by:

5. Case identification data

GENERIC DATA

5.1 Patient trial number: (eg: ABC-123)

5.2 Date of birth

Day

Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec

Year

5.3 Date of current hospital admission

5.4 Time of clinical evaluation:

hrs. min. AM PM

5.5 Gender:

☐ female (♀) ☐ male (♂)

5.6 Weight:

lbs.

5.7 Height:

ft.

in.

5.8 Marital status

☐ Married

☐ Single

(never married)

☐ Divorced

☐ Widowed

☐ Separated

Only single selection is allowed

5.9 Ethnicity

☐ Hispanic

☐ Non Hispanic

☐ Unknown

☐ Other, please specify:

Only single selection is allowed

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

Patient Trial Number

Riluzole Baseline Investigator

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

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5.10 Race:

- ☐ White
 ☐ Native Hawaiian or Other Pacific Islander
☐ Black or African American
 ☐ American Indian or Alaska Native
☐ Asian
 ☐ Other, please specify:

5.11 If you are of Asian ancestry, please specify your country of origin: ☐ N/A

- ☐ Japan
 ☐ Taiwan
☐ China
 ☐ Philippine
☐ Vietnam
 ☐ Other

Only single selection is allowed

5.12 Current employment status:

- ☐ Employed
 ☐ Unemployed
 ☐ Retired
 ☐ Disability

Only single selection is allowed

5.13 Education level:

- ☐ Less than high school
 ☐ High school graduate
 ☐ Some college
 ☐ Associate's degree
☐ Bachelor's degree
 ☐ Master's degree
 ☐ Professional degree
 ☐ Doctoral degree
 ☐ NA

Only single selection is allowed

6. Co-morbidities

GENERAL HEALTH

6.1 Cardiovascular System ☐ No ☐ Yes → please specify

Myocardial Infarct	☐ No	☐ Yes
Angina / Coronary Artery Disease	☐ No	☐ Yes
Congestive Heart Failure (CHF)	☐ No	☐ Yes
Arrhythmias	☐ No	☐ Yes
Hypertension	☐ No	☐ Yes
Venous Disease	☐ No	☐ Yes
Peripheral Arterial Disease	☐ No	☐ Yes

6.2 Respiratory System ☐ No ☐ Yes

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

Patient Trial Number

Riluzole Baseline Investigator

5/35

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

- 6 -

6.3 Gastrointestinal System	☐ No	☐ Yes → <i>please specify</i>
Hepatic	☐ No	☐ Yes
Stomach / Intestine	☐ No	☐ Yes
Pancreas	☐ No	☐ Yes
6.4 Endocrine System	☐ No	☐ Yes → <i>please specify</i>
Diabetes Mellitus	☐ No	☐ Yes
6.5 Psychiatric/Mental health	☐ No	☐ Yes
6.6 Rheumatologic	☐ No	☐ Yes
6.7 Neurological System	☐ No	☐ Yes → <i>please specify</i>
Stroke	☐ No	☐ Yes
Paralysis	☐ No	☐ Yes
Neuromuscular conditions	☐ No	☐ Yes

7. Other general health items		GENERAL HEALTH
7.1 Does the subject currently smoke cigarettes, or has smoked in the past?	☐ Yes	☐ No (If No, proceed to Question #7.2)
7.1.1 How long has the subject smoked cigarettes? (years)		
7.1.2 How many cigarettes does the subject smoke/ has smoked per day? (packs per day)		
7.1.3. If smoked in the past, when did the subject stop smoking? (years)		
7.2 Do you drink alcohol?	☐ Yes	☐ No (if No, proceed to Section #8)
7.2.1 If yes, how many drinks do you have each day?		

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

Spinal Cord Injury Information

8. Spinal Cord Injury: Date and Cause												PRE-TREATMENT DATA	
8.1 Date when the traumatic acute spinal cord injury has occurred:													
Day												Year	
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec <td colspan="2" style="border: 1px solid black; width: 60px; height: 30px;"></td>													
8.2 Time when the traumatic acute spinal cord injury has occurred (hours and minutes):													
hrs. min. AM PM													
8.3 The traumatic acute spinal cord injury was caused by:													
☐ Assault (GSW/stabbing/blunt trauma)				☐ Motor vehicle occupant				☐ Motorcycle/Motocross rider				☐ Off-road vehicle/ATV	
☐ Bicycle rider				☐ Pedestrian				☐ Diving				☐ Other sport	
☐ Fall				☐ Unknown				☐ Other, please specify:					
Only single selection is allowed													
8.4 Type of acute spinal cord injury													
☐ Blunt				☐ Crush				☐ Other, please specify:					
Only single selection is allowed													

9. Vertebral Column Injury: Affected level(s) and Stability											
PRE-TREATMENT DATA											
9.1 Cervical spine:						9.2 Thoracic spine:					
☐ No C4 ☐ Yes ☐ No C5 ☐ Yes ☐ No C6 ☐ Yes ☐ No C7 ☐ Yes						☐ No T1 ☐ Yes ☐ No T2 ☐ Yes ☐ No T3 ☐ Yes ☐ No T4 ☐ Yes ☐ No T5 ☐ Yes ☐ No T6 ☐ Yes ☐ No T7 ☐ Yes ☐ No T8 ☐ Yes ☐ No T9 ☐ Yes ☐ No T10 ☐ Yes ☐ No T11 ☐ Yes ☐ No T12 ☐ Yes					
9.3 Stability of the spine:											
☐ Stable ☐ Unstable ☐ Imminent instability											
Only single selection is allowed											

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

10. Spinal Cord Injury: Severity and Clinical Syndromes		PRE-TREATMENT DATA
10.1 Severity of Spinal Cord Injury:		
☐ Complete tetraplegia ☐ Incomplete tetraplegia ☐ Complete paraplegia ☐ Incomplete paraplegia		
Only single selection is allowed		
10.2 Clinical Syndromes of Incomplete Spinal Cord Injury:		
☐ None ☐ Anterior cord syndrome ☐ Posterior cord syndrome ☐ Central cord syndrome		
☐ Brown-Séquard syndrome ☐ Other, please specify: 		
Level of Injury: Lowest Normal Motor Level		
Only single selection is allowed		

11. Spinal Cord Injury: ASIA SCALE		PRE-TREATMENT DATA																																										
Standard Neurological Classification of Spinal Cord Injury																																												
11.1 ASIA Motor Scale																																												
Key muscles MUSCLE GRADING 0 = No contraction/ total paralysis 1 = Palpable or visible contraction 2 = Active movement, full range of motion, gravity eliminated 3 = Active movement, full range of motion, against gravity 4 = Active movement, full range of motion, against gravity and provides some resistance 5 = Normal or active movement, full range of motion, against gravity and provides normal resistance 5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture	<table style="width: 100%; border-collapse: collapse;"> <tr> <th colspan="2" style="text-align: left; padding: 5px;">Upper limb:</th> <th></th> </tr> <tr> <th style="text-align: center; padding: 5px;">R</th> <th style="text-align: center; padding: 5px;">L</th> <th></th> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">C5 Elbow flexors</td> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">C6 Wrist extensors</td> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">C7 Elbow extensors</td> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">C8 Finger flexors (distal phalanx of middle finger)</td> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">T1 Finger abductors (little finger)</td> </tr> <tr> <th colspan="2" style="text-align: left; padding: 5px;">Lower limb:</th> <th></th> </tr> <tr> <th style="text-align: center; padding: 5px;">R</th> <th style="text-align: center; padding: 5px;">L</th> <th></th> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">L2 Hip flexors</td> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">L3 Knee extensors</td> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">L4 Ankle dorsiflexors</td> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">L5 Long toe extensors</td> </tr> <tr> <td style="text-align: center; padding: 5px;">☐</td> <td style="text-align: center; padding: 5px;">☐</td> <td style="padding: 5px;">S1 Ankle plantar flexors</td> </tr> </table>		Upper limb:			R	L		☐	☐	C5 Elbow flexors	☐	☐	C6 Wrist extensors	☐	☐	C7 Elbow extensors	☐	☐	C8 Finger flexors (distal phalanx of middle finger)	☐	☐	T1 Finger abductors (little finger)	Lower limb:			R	L		☐	☐	L2 Hip flexors	☐	☐	L3 Knee extensors	☐	☐	L4 Ankle dorsiflexors	☐	☐	L5 Long toe extensors	☐	☐	S1 Ankle plantar flexors
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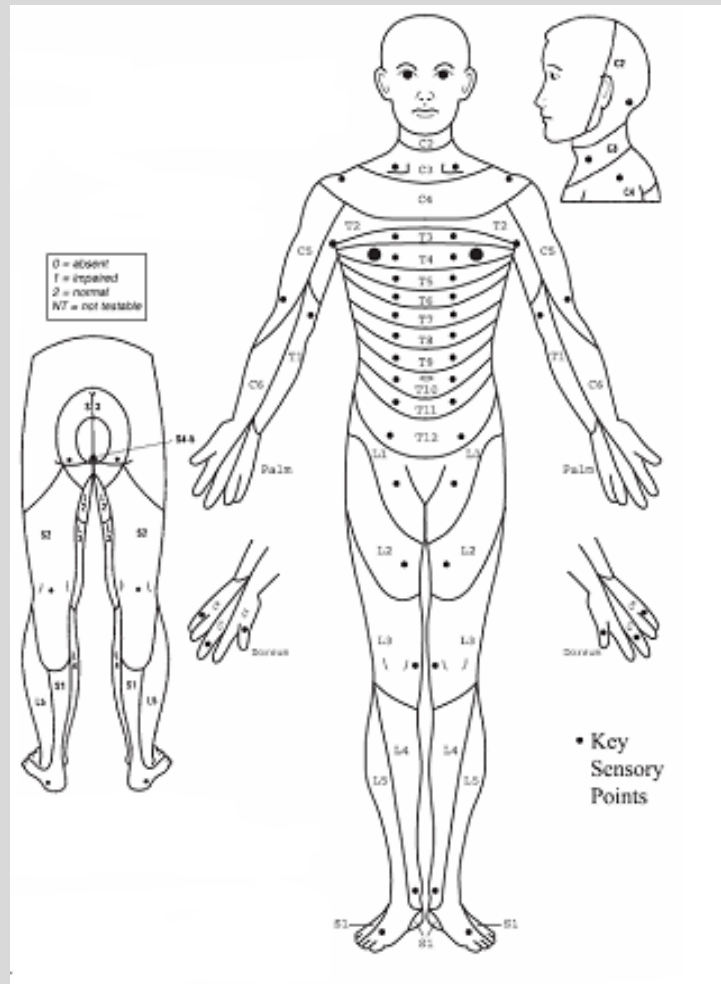
Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

Patient Trial Number _____
Riluzole Baseline Investigator _____

11.2 ASIA Sensory Scale

	Light Touch		Pin Prick	
	R	L	R	L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S45				



Any anal sensation (Yes/No)

Key Sensory Points:

0=Absent

2= Normal

1= Impaired

NT- Not testable

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Baseline Investigator

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

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11.3 ASIA Impairment Scale			
	Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
	Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
	Grade C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
	Grade D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
	Grade E	Normal	Motor and sensory function are normal.

11.4 Performed by (please initial):	
11.5 Date: <u> </u> / <u> </u> / <u> </u> mm/ dd /yyyy	

American Spinal Injury Association:
International Standards for Neurological Classification of Spinal Cord Injury, revised 2002; Chicago, IL

12. Lab Results. Baseline. < 12 hours since injury			PRE-TREATMENT DATA
Test	Result	Unit of Measurement	
HBV (Hepatitis B Virus)		HBsAg	
HCV (Hepatitis C Virus)		Anti-HCV (EIA)	
ALT (Alanine aminotransferase)		IU/L	
AST (Aspartate aminotransferases)		IU/L	
ALP (Alkaline phosphatase)		IU/L	
GGT (Gamma glutamyl transpeptidase)		IU/L	
Bilirubin		µmol/L	
Creatinine		µmol/L	
RBC (Red blood cells)		x 10¹²/L	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Baseline Investigator

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North American Clinical Trials (NACTN)
Riluzole Source Worksheet – Baseline

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Hgb (Hemoglobin)		g/L
Hct (Hematocrit)		%
MCV (Mean cell volume)		fl
Leukocytes (Total WBC)		$\times 10^9/L$
Neutrophils		$\times 10^9/L$ (%)
Lymphocytes		$\times 10^9/L$ (%)
Monocytes		$\times 10^9/L$ (%)
Eosinophiles		$\times 10^9/L$ (%)
Basophiles		$\times 10^9/L$ (%)
Platelets		$\times 10^9/L$ (%)
PT (Prothrombin time)		S
INR (International normalized ratio)		Ratio
Plasma sample	Preformed ☐ Yes ☐ No	

13. Pre-treatment Medications

PRE- TREATMENT DATA

13.1 Has the patient taken any medications prior to the spinal cord injury (including over-the-counter)?

☐ NO

☐ YES If YES, *fill out the Medication form*

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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 Riluzole Baseline Investigator

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Riluzole Source Worksheet – Baseline

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14. Signature (Pre-treatment information)

PRE-TREATMENT DATA

14.1 Pre-treatment data obtained by:

Name (Signature)

Date

DAY #1 - Day #14 Riluzole Treatment Data

15. Riluzole Treatment Details

TREATMENT DATA

15.1 Start date of riluzole treatment

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Day

Year

15.2 End date of riluzole treatment

Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

15.3 Time of beginning riluzole treatment (hours and minutes):

hrs. min. AM PM

15.4 Time frame between the occurrence of the injury and the first dose of riluzole:

hrs. min. AM PM

16. Riluzole Administration

TREATMENT DATA

Day #	Dose #	Date mm/dd/yyyy	Time	Dose (mg) (e.g. 50 mg or 100 mg)	Mode
1	1		hrs. min. AM PM		☐ PO* ☐ NG**
	2		hrs. min. AM PM		☐ PO ☐ (NG
2	3		hrs. min. AM PM		☐ PO ☐ NG
	4		hrs. min. AM PM		☐ PO ☐ NG

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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3	5	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
	6	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
4	7	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
	8	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
5	9	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
	10	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
6	11	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
	12	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
7	13	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
	14	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
8	15	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
	16	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
9	17	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
	18	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG
10	19	<u> / / </u>	hrs. min. AM PM		☐ PO ☐ NG

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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North American Clinical Trials (NACTN)

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	20	____/____/____	hrs. min. AM PM		☐ PO ☐ NG
11	21	____/____/____	hrs. min. AM PM		☐ PO ☐ NG
	22	____/____/____	hrs. min. AM PM		☐ PO ☐ NG
12	23	____/____/____	hrs. min. AM PM		☐ PO ☐ NG
	24	____/____/____	hrs. min. AM PM		☐ PO ☐ NG
13	25	____/____/____	hrs. min. AM PM		☐ PO ☐ NG
	26	____/____/____	hrs. min. AM PM		☐ PO ☐ NG
14	27	____/____/____	hrs. min. AM PM		☐ PO ☐ NG
	28	____/____/____	hrs. min. AM PM		☐ PO ☐ NG

PO* - Oral

NG** - Nasogastric tube

17. Skipped dose

☐ None skipped, all doses administered per protocol
(For each skipped dose indicate day #, dose #, date (mm/ dd /yyyy) and the reason why the drug was not administered)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number _____

Riluzole Baseline Investigator

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18. Signature (Riluzole Treatment information)		TREATMENT DATA
18.1 Treatment data obtained by:		
Name (Signature)	Date	

Day #3. Lab Tests and ASIA Scale

19. Lab Results. Day 3 after the start of riluzole		TREATMENT DATA
Test	Result	Unit of Measurement
ALT (Alanine aminotransferase)		IU/L
AST (Aspartate aminotransferases)		IU/L
ALP (Alkaline phosphatase)		IU/L
GGT (Gamma glutamyl transpeptidase)		IU/L
Bilirubin		μmol/L
Creatinine		μmol/L
RBC (Red blood cells)		x 10 ¹² /L
Hgb (Hemoglobin)		g/L
Hct (Hematocrit)		%
MCV (Mean cell volume)		fl

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number _____
Riluzole Baseline Investigator

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

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Leukocytes (Total WBC)		$\times 10^9/L$
Neutrophils		$\times 10^9/L$ (%)
Lymphocytes		$\times 10^9/L$ (%)
Monocytes		$\times 10^9/L$ (%)
Eosinophiles		$\times 10^9/L$ (%)
SBasophiles		$\times 10^9/L$ (%)
Platelets		$\times 10^9/L$ (%)
PT (Prothrombin time)		S
INR (International normalized ratio)		Ratio
Plasma sample	Before riluzole administration Preformed ☐ Yes ☐ No	2 hrs. after riluzole administration Preformed ☐ Yes ☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Baseline Investigator

20. Spinal Cord Injury: ASIA SCALE

TREATMENT DATA

Standard Neurological Classification of Spinal Cord Injury

20.1 ASIA Motor Scale

Key muscles

MUSCLE GRADING

0 = No contraction/ total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion, gravity eliminated

3 = Active movement, full range of motion, against gravity

4 = Active movement, full range of motion, against gravity and provides some resistance

5 = Normal or active movement, full range of motion, against gravity and provides normal resistance

5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present

NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture

Upper limb:

R

L

☐
☐

C5 Elbow flexors

☐
☐

C6 Wrist extensors

☐
☐

C7 Elbow extensors

☐
☐

C8 Finger flexors (distal phalanx of middle finger)

☐
☐

T1 Finger abductors (little finger)

Lower limb:

R

L

☐
☐

L2 Hip flexors

☐
☐

L3 Knee extensors

☐
☐

L4 Ankle dorsiflexors

☐
☐

L5 Long toe extensors

☐
☐

S1 Ankle plantar flexors

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

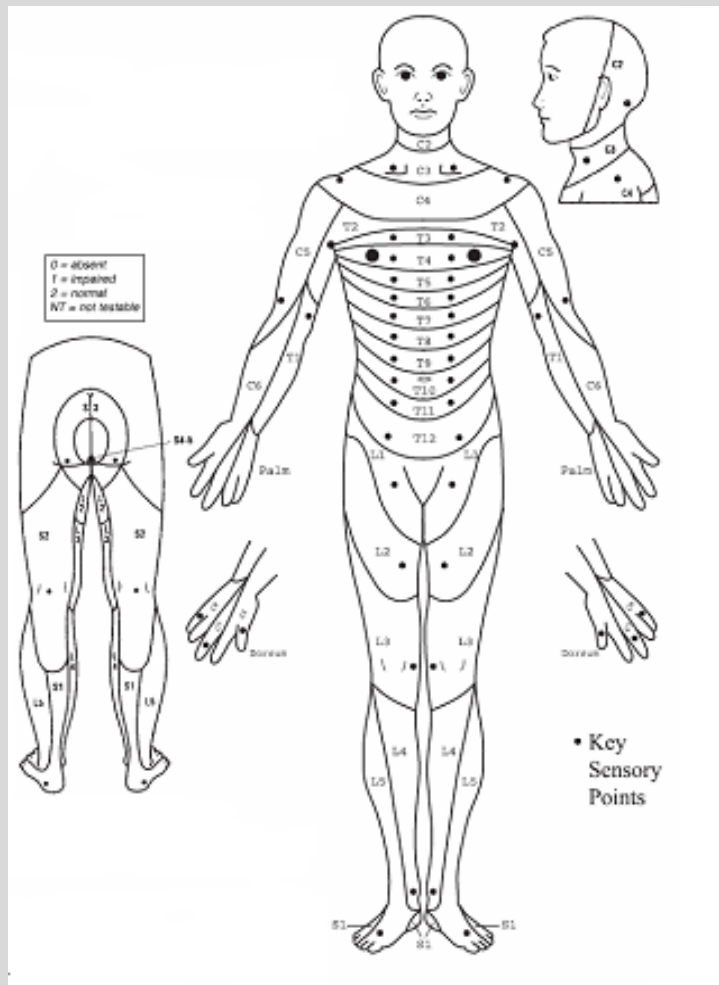
Riluzole Baseline Investigator

North American Clinical Trials (NACTN) Riluzole Source Worksheet – Baseline

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20.2 ASIA Sensory Scale

	Light Touch		Pin Prick	
	R	L	R	L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S45				



Any anal sensation (Yes/No)

Key Sensory Points:

0=Absent

2= Normal

1= Impaired

NT- Not testable

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Baseline Investigator

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North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

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20.3 ASIA Impairment Scale			
	Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
	Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
	Grade C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
	Grade D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
	Grade E	Normal	Motor and sensory function are normal.
20.4 Performed by (please initial):			
20.5 Date: <u> </u> / <u> </u> / <u> </u> mm/dd/yyyy			
American Spinal Injury Association: International Standards for Neurological Classification of Spinal Cord Injury, revised 2002; Chicago, IL			

21. Signature (Lab Tests information and ASIA)		TREATMENT DATA
21.1 Data obtained by:		
Name (Signature) _____		Date _____

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Baseline Investigator

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Day #7. Lab Tests

22. Lab Results. Day 7 after the start of riluzole		TREATMENT DATA
Test	Result	Unit of Measurement
ALT (Alanine aminotransferase)		IU/L
AST (Aspartate aminotransferases)		IU/L
ALP (Alkaline phosphatase)		IU/L
GGT (Gamma glutamyl transpeptidase)		IU/L
Bilirubin		µmol/L
Creatinine		µmol/L
RBC (Red blood cells)		$\times 10^{12}/L$
Hgb (Hemoglobin)		g/L
Hct (Hematocrit)		%
MCV (Mean cell volume)		fL
Leukocytes (Total WBC)		$\times 10^9/L$
Neutrophils		$\times 10^9/L$ (%)
Lymphocytes		$\times 10^9/L$ (%)
Monocytes		$\times 10^9/L$ (%)
Eosinophiles		$\times 10^9/L$ (%)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

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Basophiles		$\times 10^9/L$ (%)
Platelets		$\times 10^9/L$ (%)
PT (Prothrombin time)		S
INR (International normalized ratio)		Ratio

23. Signature (Lab Tests information)

TREATMENT DATA

23.1 Data obtained by:

Name (Signature)

Date

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Baseline Investigator

Day #10. Lab Tests

24. Lab Results. Day 10 after the start of riluzole		TREATMENT DATA
Test	Result	Unit of Measurement
ALT (Alanine aminotransferase)		IU/L
AST (Aspartate aminotransferases)		IU/L
ALP (Alkaline phosphatase)		IU/L
GGT (Gamma glutamyl transpeptidase)		IU/L
Bilirubin		µmol/L
Creatinine		µmol/L
RBC (Red blood cells)		$\times 10^{12}/L$
Hgb (Hemoglobin)		g/L
Hct (Hematocrit)		%
MCV (Mean cell volume)		fL
Leukocytes (Total WBC)		$\times 10^9/L$
Neutrophils		$\times 10^9/L$ (%)
Lymphocytes		$\times 10^9/L$ (%)
Monocytes		$\times 10^9/L$ (%)
Eosinophils		$\times 10^9/L$ (%)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

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Basophiles		x 10 ⁹ /L (%)
Platelets		x 10 ⁹ /L (%)
PT (Prothrombin time)		S
INR (International normalized ratio)		Ratio

25. Signature (Lab Tests information)

TREATMENT DATA

25.1 Data obtained by:

Name (Signature)

Date

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Baseline Investigator

Day #14. Lab Tests and ASIA Scale

26. Lab Results. Day 14 after the start of riluzole		TREATMENT DATA
Test	Result	Unit of Measurement
ALT (Alanine aminotransferase)		IU/L
AST (Aspartate aminotransferases)		IU/L
ALP (Alkaline phosphatase)		IU/L
GGT (Gamma glutamyl transpeptidase)		IU/L
Bilirubin		µmol/L
Creatinine		µmol/L
RBC (Red blood cells)		$\times 10^{12}/L$
Hgb (Hemoglobin)		g/L
Hct (Hematocrit)		%
MCV (Mean cell volume)		fl
Leukocytes (Total WBC)		$\times 10^9/L$
Neutrophils		$\times 10^9/L$ (%)
Lymphocytes		$\times 10^9/L$ (%)
Monocytes		$\times 10^9/L$ (%)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number _____
Riluzole Baseline Investigator

North American Clinical Trials (NACTN) Riluzole Source Worksheet – Baseline

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Eosinophiles		x 10 ⁹ /L (%)
Basophiles		x 10 ⁹ /L (%)
Platelets		x 10 ⁹ /L (%)
PT (Prothrombin time)		S
INR (International normalized ratio)		Ratio
Plasma sample	Before riluzole administration Preformed ☐ Yes ☐ No	2 hrs. after riluzole administration Preformed ☐ Yes ☐ No

27. Spinal Cord Injury: ASIA SCALE

TREATMENT DATA

Standard Neurological Classification of Spinal Cord Injury

27.1 ASIA Motor Scale

Key muscles

MUSCLE GRADING

0 = No contraction/ total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion, gravity eliminated

3 = Active movement, full range of motion, against gravity

4 = Active movement, full range of motion, against gravity and provides some resistance

5 = Normal or active movement, full range of motion, against gravity and provides normal resistance

5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present
NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture

Upper limb:

R

L

C5 Elbow flexors

C6 Wrist extensors

C7 Elbow extensors

C8 Finger flexors (distal phalanx of middle finger)

T1 Finger abductors (little finger)

Lower limb:

R

L

L2 Hip flexors

L3 Knee extensors

L4 Ankle dorsiflexors

L5 Long toe extensors

S1 Ankle plantar flexors

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

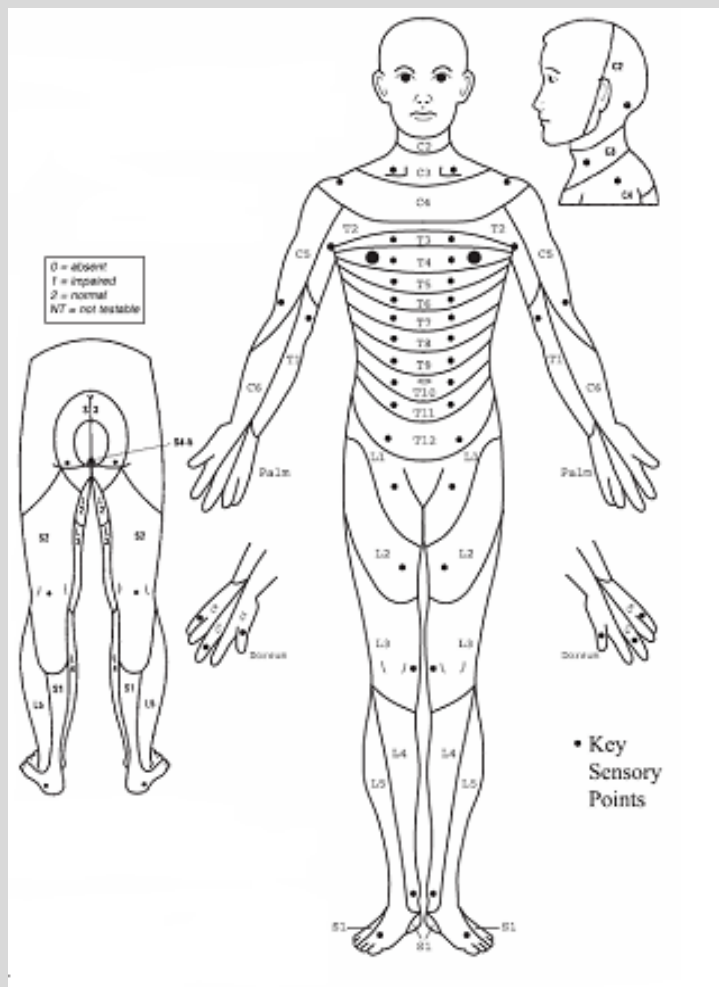
Patient Trial Number

Riluzole Baseline Investigator

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27.2 ASIA Sensory Scale

	Light Touch		Pin Prick	
	R	L	R	L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S45				



Any anal sensation (Yes/No)

Key Sensory Points:

0=Absent 2= Normal
1= Impaired NT- Not testable

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

11 Jun. 08

Patient Trial Number

Riluzole Baseline Investigator

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – Baseline

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27.3 ASIA Impairment Scale			
	Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
	Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
	Grade C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
	Grade D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
	Grade E	Normal	Motor and sensory function are normal.
27.4 Performed by (please initial):			
27.5 Date: _/_/_/ mm/ dd /yyyy			
American Spinal Injury Association: International Standards for Neurological Classification of Spinal Cord Injury, revised 2002; Chicago, IL			

28. Signature (ASIA and Lab Tests information)	TREATMENT DATA
28.1 Data obtained by:	
<u>Name (Signature)</u>	<u>Date</u>

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number
Riluzole Baseline Investigator

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Discharge Data

29. Spinal Cord Injury: Steroids Treatment		TREATMENT DATA
29.1 Were steroids administered to the patient? ☐ Yes ☐ No (skip to section 30 "Surgery treatment")		
29.2 Steroid name: ☐ NA		
☐ Methylprednisolone/Sulomedrol ☐ Dexamethasone/Decadron		
☐ Other, please specify:		
29.3 Loading Dose (Bolus): mg or mg/kg		
29.4 Bolus Date: / / mm/ dd /yyyy	29.5 Bolus time: hrs. min. AM PM	
29.6 Maintenance Dose : mg/hr or mg/kg/hr		
Only single selection is allowed		

30. Spinal Cord Injury: Surgery and Traction Treatment		TREATMENT DATA
30.1 Were surgical procedures performed to the patient? ☐ Yes ☐ No (skip to question 30.18 "Traction")		
30.2 Surgery Date of First surgery: / / mm/ dd /yyyy	30.3 Time of incision: hrs. min. AM PM Time of closure: hrs. min. AM PM	
30.4 Was a second surgical procedure performed on the subject? ☐ Yes ☐ No (skip to question 30.7)		
30.5 Surgery Date of Second surgery: / / mm/ dd /yyyy	30.6 Time of incision: hrs. min. AM PM Time of closure: hrs. min. AM PM	
30.7 Time of decompression of neural elements: hrs. min. AM PM ☐ Achieved prior to surgery ☐ Not achieved ☐ Achieved time unknown		
30.8 Spinal surgical approach: ☐ Anterior ☐ Posterior ☐ Both Anterior and Posterior		

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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30.9 Spinal surgical progression:

☐ Initial surgery ☐ Subsequent surgery planned/staged ☐ Subsequent surgery unplanned

30.10 Was the surgery done in stages:

☐ No ☐ Yes, 2 Stages ☐ Yes, 3 Stages

30.11 Estimated blood loss: ml/cc

30.12 Intraoperative Complications (check all that applies):

☐ No complications ☐ Hypotension (systolic <85 mmHG for 15 min)
☐ CSF leak ☐ Cord injury
☐ Vascular injury ☐ Nerve root injury
☐ Visceral injury ☐ Cardiac arrest
☐ Respiratory distress ☐ Other, please specify:

30.13 Post Operative Bracing (check all that applies):

☐ No post operative bracing ☐ LSO
☐ Collar ☐ TLSO
☐ Halo ☐ Other, please specify:
☐ CTO

30.14 Listhesis BEFORE surgical reduction:

☐ No listhesis ☐ Unknown or ☐ I ☐ II ☐ III ☐ IV or mm

30.15 Imaging of listhesis BEFORE surgical reduction:

☐ CT ☐ Fluoroscopy ☐ MRI ☐ X-Ray

30.16 Listhesis AFTER surgical reduction:

☐ No listhesis ☐ Unknown or ☐ I ☐ II ☐ III ☐ IV or mm

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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30.17 Imaging of listhesis AFTER surgical reduction:	
☐ CT	☐ Fluoroscopy ☐ MRI ☐ X-Ray
30.18 Was traction performed to the patient? ☐ Yes ☐ No (skip to section 31 "ASIA Scale")	
30.19 Date traction was INITIATED: ____/____/____ mm/ dd /yyyy	30.16 Time traction was INITIATED: hrs. min. AM PM
30.17 Date traction was COMPLETED: ____/____/____ mm/ dd /yyyy	30.18 Time traction was COMPLETED: hrs. min. AM PM

31. Spinal Cord Injury: ASIA SCALE		POST-TREATMENT DATA																								
Standard Neurological Classification of Spinal Cord Injury																										
31.1 ASIA Motor Scale																										
Key muscles MUSCLE GRADING 0 = No contraction/ total paralysis 1 = Palpable or visible contraction 2 = Active movement, full range of motion, gravity eliminated 3 = Active movement, full range of motion, against gravity 4 = Active movement, full range of motion, against gravity and provides some resistance 5 = Normal or active movement, full range of motion, against gravity and provides normal resistance 5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture	Upper limb: <table border="1"> <thead> <tr> <th>R</th> <th>L</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> </tbody> </table> Lower limb: <table border="1"> <thead> <tr> <th>R</th> <th>L</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> </tbody> </table>	R	L											R	L											C5 Elbow flexors C6 Wrist extensors C7 Elbow extensors C8 Finger flexors (distal phalanx of middle finger) T1 Finger abductors (little finger) L2 Hip flexors L3 Knee extensors L4 Ankle dorsiflexors L5 Long toe extensors S1 Ankle plantar flexors
R	L																									
R	L																									

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number _____
Riluzole Baseline Investigator

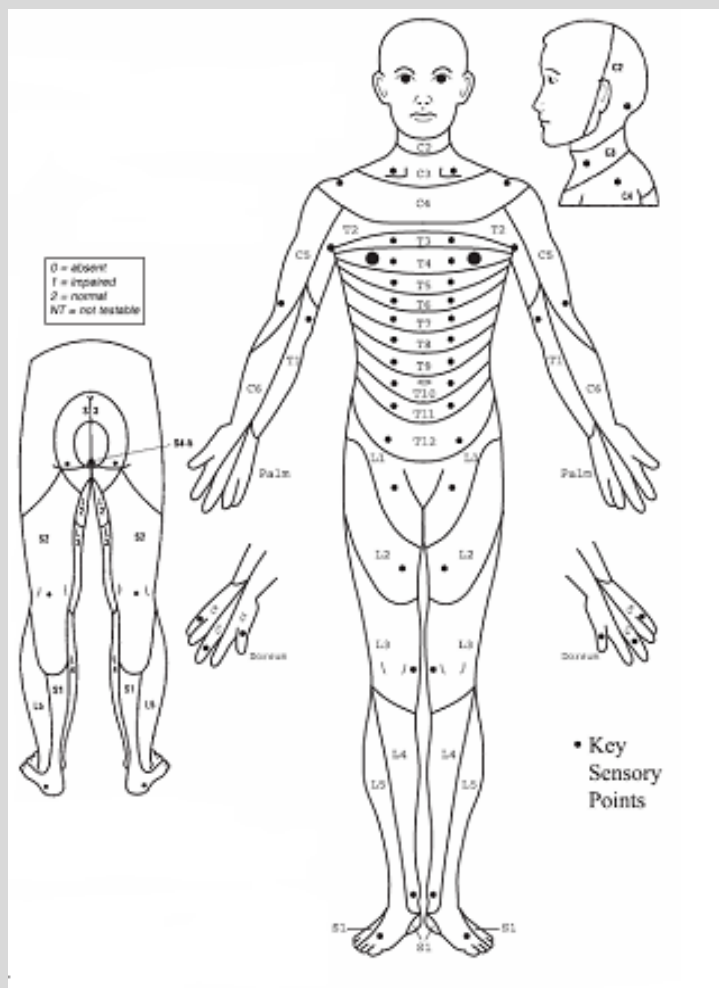
30/35

North American Clinical Trials (NACTN) Riluzole Source Worksheet – Baseline

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31.2 ASIA Sensory Scale

	Light Touch		Pin Prick	
	R	L	R	L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S45				



Any anal sensation (Yes/No)

Key Sensory Points:

0=Absent 2= Normal
1= Impaired NT- Not testable

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Source Worksheet – Baseline

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31.3 ASIA Impairment Scale

☐	Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
☐	Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
☐	Grade C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
☐	Grade D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
☐	Grade E	Normal	Motor and sensory function are normal.

31.4 Performed by (please initial):

31.5 Date:

__/__/__
mm/ dd /yyyy

American Spinal Injury Association:

International Standards for Neurological Classification of Spinal Cord Injury, revised 2002; Chicago, IL

32. Complications

TREATMENT DATA

32.1 Have any complications/adverse events been experienced since study entry?

☐ NO

☐ YES If YES, please *fill out the Complication Form*.

List of possible complications (check all that applied)

1.	Liver Disease: a. Acute liver failure b. Hepatitis c. Jaundice d. Elevations in blood levels of liver enzymes (ALT, AST, GGT) e. Other	☐ Yes	☐ No
2.	Hematology: a. Neutropenia b. DVT c. Anemia d. Thrombocytopenia e. Coagulopathy f. Other	☐ Yes	☐ No
3.	Neurological: a. Loss of neurological function b. Neuropathic pain c. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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4.	Cardiac: a. Bradycardia b. Other dysrhythmia c. Cardiac Arrest d. MI e. Shock (BP < 80 Systolic) f. CHF/cardiogenic pulmonary edema g. Other	☐ Yes	☐ No
5.	Pulmonary: a. ALI/ARDS (Acute lung injury/Acute respiratory distress syndrome) b. Respiratory Failure c. PE (Pulmonary Embolus) d. Other	☐ Yes	☐ No
6.	GI/GU: a. GI Hemorrhage b. Hematuria c. Ileus d. Diarrhea e. Nausea, vomiting, f. Pancreatitis g. Cholecystitis h. Acute renal failure (<i>creatinine >1.0 above baseline</i>) i. Other	☐ Yes	☐ No
7.	Infections: a. UTI b. Pneumonia c. Infectious diarrhea d. Sepsis e. CNS infections f. Abscess - <i>Note Location:</i> _____ g. Wound Infection h. Other	☐ Yes	☐ No
8.	Skin: a. Sacral b. Heel c. Scapular d. Occipital f. Trochanter g. Operative wound h. Other	☐ Yes	☐ No
9.	Failure of Stabilization: a. Loss of reduction b. Construct breakage c. Failure of orthosis d. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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10.	Neuropsychiatric: a. Depression/adjustment disorder b. Psychosis c. Seizure d. Cognitive deterioration e. Other	☐ Yes	☐ No
11.	Allergic Reaction to riluzole: a. Skin reaction: rash, hives, itching b. Difficulty breathing c. Tightness in the chest d. Swelling of the mouth, face, lips, or tongue e. Other	☐ Yes	☐ No
12.	Death	☐ Yes	☐ No
13.	Other, please specify:	☐ Yes	☐ No

33. Discharge medications

POST-TREATMENT DATA

33.1 Has the patient been prescribed any medications at discharge?

☐ NO

☐ YES If YES, please *fill out the Medication form*

34. Discharge from hospital

POST-TREATMENT DATA

34.1 Date of final patient's discharge:

Day

☐
☐
☐
☐
☐
☐
☐
☐
☐
☐
☐
☐
☐
☐

Year

Jan

Feb

Mar

Apr

May

Jun

Jul

Aug

Sep

Oct

Nov

Dec

35. General comments

GENERAL COMMENTS

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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36. Signature (Discharge information)

POST-TREATMENT DATA

36.1 Discharge data obtained by:

Name (Signature)

Date

37. Investigator's signature

I have assessed/reviewed all the information obtained for the Baseline and confirm it is accurate and complete.

Investigator's Name:

Investigator's Signature:

Date:

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Baseline Investigator

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

Follow-up

Version 1, 22 April 2008

Follow-up Site:

FU 6-weeks

FU 3-months

FU 6-months

FU unscheduled

SAE-Form

Patient-Trial-Number

Patient Initials: last name, first name

Created by:

Zoya Bauer, MD, PhD

Jerika Robles, Project Manager

(University of Washington, USA)

(AOCID NA)

Reviewed by:

Branko Kopjar, MD, PhD

(University of Washington, USA)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 WEEKS F

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

6 Week Follow-up

Post-Treatment Data

1. Case identification data													GENERIC DATA		
1.1 Patient trial number:		(eg: ABC-123)													
1.2 Date of birth			☐	☐	☐	☐	☐	☐	☐	☐	☐	☐			
		Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year
1.3 Date of examination			☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
1.4 Gender:		☐ female (♀) ☐ male (♂)													

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

2. Spinal Cord Injury: ASIA SCALE

POST-TREATMENT DATA

Standard Neurological Classification of Spinal Cord Injury

2.1 ASIA Motor Scale

Key muscles

MUSCLE GRADING

0 = No contraction/ total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion, gravity eliminated

3 = Active movement, full range of motion, against gravity

4 = Active movement, full range of motion, against gravity and provides some resistance

5 = Normal or active movement, full range of motion, against gravity and provides normal resistance

5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present

NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture

Upper limb:

R

L

☐
☐

C5 Elbow flexors

☐
☐

C6 Wrist extensors

☐
☐

C7 Elbow extensors

☐
☐

C8 Finger flexors (distal phalanx of middle finger)

☐
☐

T1 Finger abductors (little finger)

Lower limb:

R

L

☐
☐

L2 Hip flexors

☐
☐

L3 Knee extensors

☐
☐

L4 Ankle dorsiflexors

☐
☐

L5 Long toe extensors

☐
☐

S1 Ankle plantar flexors

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

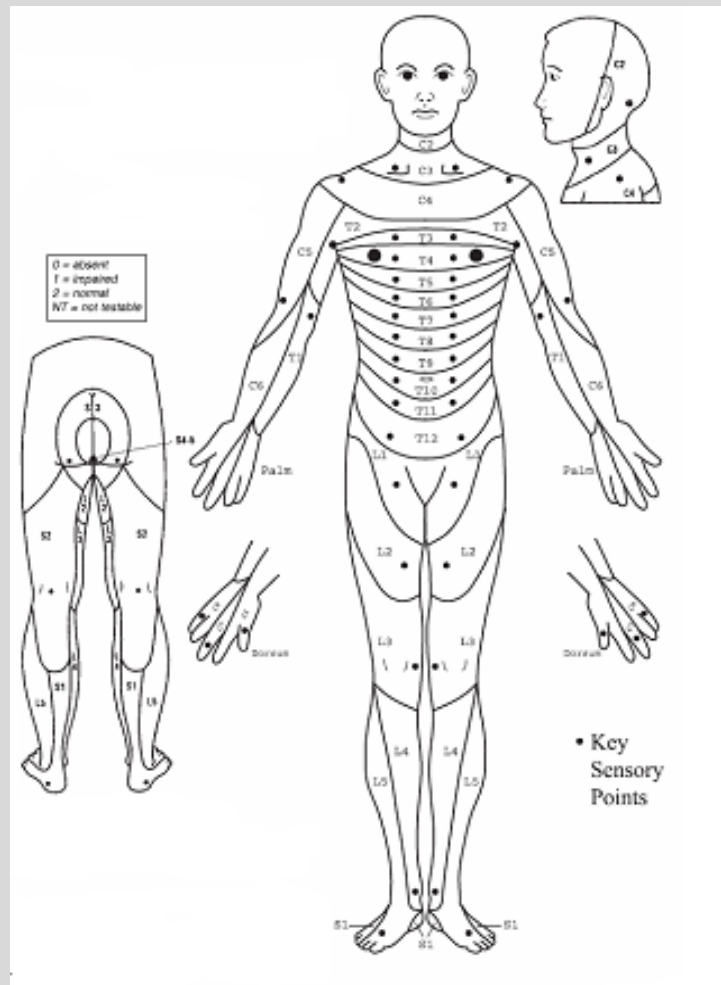
Riluzole Investigator F.U 6 WEEKS F

North American Clinical Trials (NACTN) Riluzole Source Worksheet – 6 Weeks F/U

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2.2 ASIA Sensory Scale

	Light Touch		Pin Prick	
	R	L	R	L
C2	☐	☐	☐	☐
C3	☐	☐	☐	☐
C4	☐	☐	☐	☐
C5	☐	☐	☐	☐
C6	☐	☐	☐	☐
C7	☐	☐	☐	☐
C8	☐	☐	☐	☐
T1	☐	☐	☐	☐
T2	☐	☐	☐	☐
T3	☐	☐	☐	☐
T4	☐	☐	☐	☐
T5	☐	☐	☐	☐
T6	☐	☐	☐	☐
T7	☐	☐	☐	☐
T8	☐	☐	☐	☐
T9	☐	☐	☐	☐
T10	☐	☐	☐	☐
T11	☐	☐	☐	☐
T12	☐	☐	☐	☐
L1	☐	☐	☐	☐
L2	☐	☐	☐	☐
L3	☐	☐	☐	☐
L4	☐	☐	☐	☐
L5	☐	☐	☐	☐
S1	☐	☐	☐	☐
S2	☐	☐	☐	☐
S3	☐	☐	☐	☐
S45	☐	☐	☐	☐



Any anal sensation (Yes/No)

☐

Key Sensory Points:

0=Absent 2= Normal
1= Impaired NT- Not testable

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 6 WEEKS F

4/15

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 6 Weeks F/U

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2.3 ASIA Impairment Scale

	Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
	Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
	Grade C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
	Grade D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
	Grade E	Normal	Motor and sensory function are normal.

2.4 Performed by (please initial):

2.5 Date:

__/__/__
mm/ dd /yyyy

American Spinal Injury Association:

International Standards for Neurological Classification of Spinal Cord Injury, revised 2002; Chicago, IL

3. Spinal Cord Independence Measure (SCIM)

Version 1, May 1996

POST-TREATMENT DATA

Self-Care

3.1 Feeding (cutting, opening containers, bringing food to mouth, holding cup with fluid)

0. Needs parenteral, gastrostomy or fully assisted oral feeding

1. Eats cut food using several adaptive devices for hand and dishes

2. Eats cut food using only one adaptive device for hand; unable to hold cup

3. Eats cut food with one adaptive device; holds cup

4. Eats cut food without adaptive devices; needs a little assistance (e.g., to open containers)

5. Independent in all tasks without any adaptive device

3.2 Bathing (soaping, manipulating water tap, washing)

0. Requires total assistance

1. Soaps only small part of body with or without adaptive device

2. Soaps with adaptive device; cannot reach distant parts of the body or cannot operate a tap

3. Soaps without adaptive devices; needs a little assistance to reach distant parts of body

4. Washes independently with adaptive devices or in specific environmental setting

5. Washes independently without adaptive devices

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Investigator F.U 6 WEEKS F

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Self-Care (continued)

3.3 Dressing (preparing clothes, dressing upper and lower body, undressing)

- 0. Requires total assistance
- 1. Dresses upper body partially (e.g., without buttoning) in special setting (e.g., back support)
- 2. Independent in dressing and undressing upper body. Needs much assistance for lower body
- 3. Requires little assistance in dressing upper or lower body
- 4. Dresses and undresses independently, but requires adaptive devices and/or special setting
- 5. Dresses and undresses independently, without adaptive devices

3.4 Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup)

- 0. Requires total assistance
- 1. Performs only one task (e.g., washing hands and face)
- 2. Performs some tasks using adaptive devices; needs help to put on/take off devices
- 3. Performs some tasks using adaptive devices; puts on/takes off devices independently
- 4. Performs all tasks with adaptive devices or most tasks without devices
- 5. Independent in all tasks without adaptive devices

Respiration and Sphincter Management

3.5 Respiration

- 0. Requires assisted ventilation
- 2. Required tracheal tube and partially assisted ventilation
- 4. Breaths independently but requires much assistance in tracheal tube management
- 6. Breaths independently and requires little assistance in tracheal tube management
- 8. Breaths without tracheal tube, but sometimes requires mechanical assistance for breathing
- 10. Breaths independently without any device

3.6 Sphincter management - Bladder

- 0. Indwelling catheter
- 5. Assisted intermittent catheterization or no catheterization, residual urine volume > 100cc
- 10. Intermittent self-catheterization
- 15. No catheterization required, residual urine volume < 100cc

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Respiration and Sphincter Management (continued)	
3.7 Sphincter management - Bowel	
0. Irregularity, improper timing or very low frequency (less than once in 3 days) of bowel movements 5. Regular bowel movements, with proper timing, but with assistance (e.g., for applying suppository) 10. Regular bowel movements, with proper timing, without assistance	
3.8 Use of toilet (perineal hygiene, clothes adjustment before/after, use of napkins or diapers)	
0. Requires total assistance 1. Undresses lower body, needs assistance in all the remaining tasks 2. Undresses lower body and partially clean self (after); needs assistance in adjusting clothes and/or diapers 3. Undresses and cleans self (after); needs assistance in adjusting clothes and/or diapers 4. Independent in all tasks but needs adaptive devices or special setting (e.g., grab-bars) 5. Independent without adaptive devices or special setting	

Mobility (room and toilet)	
3.9 Mobility in bed and action to prevent pressure sores	
0. Requires total assistance 1. Partial mobility (turns in bed to one side only) 2. Turns to both sides in bed but does not fully release pressure 3. Releases pressure when lying only 4. Turns in bed and sits up without assistance 5. Independent in bed mobility; performs push-ups in sitting position without full body elevation 6. Performs push-ups in sitting position	
3.10 Transfers: bed-wheelchair (locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet)	
0. Requires total assistance 1. Needs partial assistance and/or supervision 2. Independent	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Mobility (room and toilet) (Continued)	
3.11 Transfers: wheelchair-toilet-tub (if uses toilet wheelchair – transfers to and from; if uses regular wheelchair – locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet)	
0. Requires total assistance 1. Needs partial assistance and/or supervision, or adaptive device (e.g., grab-bars) 2. Independent	
Mobility (indoors and outdoors)	
3.12 Mobility indoors (short distances)	
0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Walks with a walking frame 4. Walks with crutches 5. Walks with two canes 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without aids	
3.13 Mobility for moderate distances (10 – 100 meters)	
0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Walks with a walking frame 4. Walks with crutches 5. Walks with two canes 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without aids	

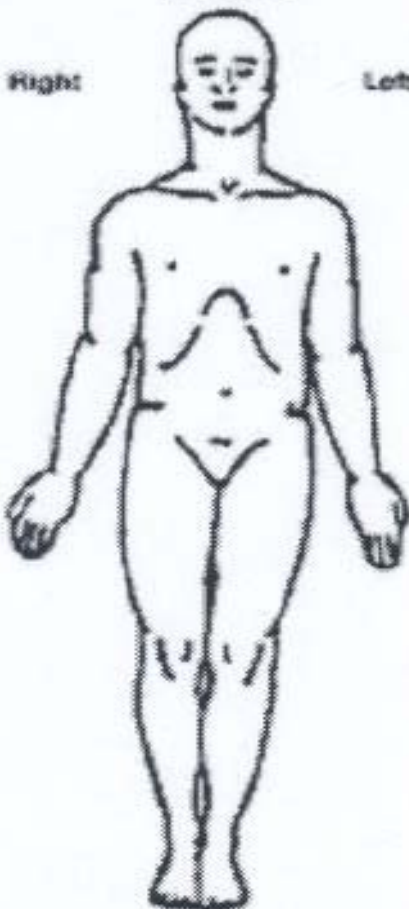
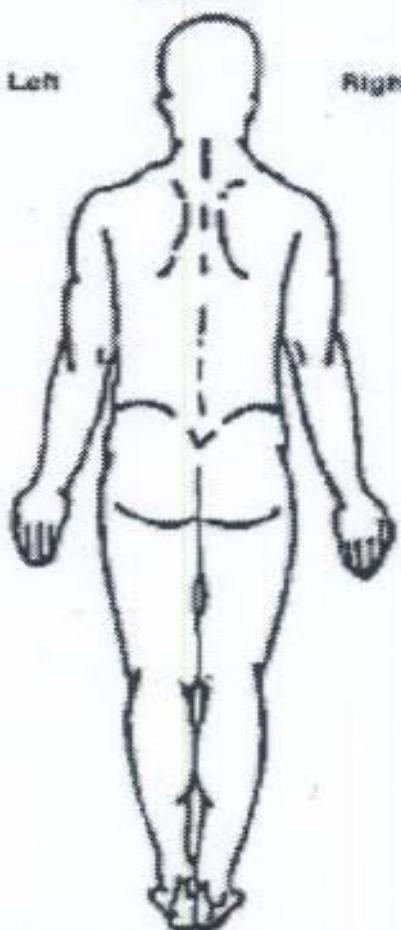
Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Mobility (indoors and outdoors) (Continued)	
3.14 Mobility outdoors (more than 100 meters)	
0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Walks with a walking frame 4. Walks with crutches 5. Walks with two canes 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without aids	
3.15 Stair management	
0. Unable to climb or descend stairs 1. Climbs 1 or 2 steps only, in a training setup 2. Climbs and descends at least 3 steps with support or supervision of another person 3. Climbs and descends at least 3 steps with support of handrail and/or crutch and/or cane 4. Climbs and descends at least 3 steps without any support or supervision	
3.16 Transfers: wheelchair-car (approaching car, locking wheelchair, removing arm and foot rests, transferring to and from car, bringing wheelchair into and out of car)	
0. Requires total assistance 1. Needs partial assistance and/or supervision, and/or adaptive devices 2. Independent without adaptive devices	
Loewenstein Rehabilitation Hospital, Raana, Israel. Reproduced with permission	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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4. Brief Pain Inventory (Short Form)		POST-TREATMENT DATA
4.1 Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these everyday kinds of pain today? ☐ Yes ☐ No		
4.2 On the diagram shade in the areas where you feel pain. Put an X on the area that hurts the most.		
right Front left	left Back right	
<u>Front</u>  <u>Back</u> 		
4.3 Please rate your pain by circling the one number that best describes your pain at its <i>worst</i> in the last 24 hours. 0 No pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine		
Please complete all appropriate items. Missing or inconsistent data will result in additional queries.		

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Riluzole Source Worksheet – 6 Weeks F/U

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4.4 Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

No
pain

Pain as bad
as you can imagine

4.5 Please rate your pain by circling the one number that best describes your pain on the average.

No
pain

Pain as bad
as you can imagine

4.6 Please rate your pain by circling the one number that tells how much pain you have right now.

No
pain

Pain as bad
as you can imagine

**4.7 What treatments or medications are you receiving for your pain?
(Please write the name of the treatments or medications below.)**

4.8 In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows much relief you have received.

No relief

Complete
Relief

4.9 Circle the one number that describes best how, during the past 24 hours, pain has interfered with your:

a) general activity

Does not
interfere

Completely
interferes

b) mood

Does not
interfere

Completely
interferes

c) walking ability

Does not
interfere

Completely
interferes

d) normal work (includes both work outside the home and housework)

Does not
interfere

Completely
interferes

e) relations with other people

Does not
interfere

Completely
interferes

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 6 WEEKS F

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North American Clinical Trials (NACTN)

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f) sleep										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does not interfere					Completely interferes					
g) enjoyment of life										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does not interfere					Completely interferes					

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Pain Research Group
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5 Complications		POST-TREATMENT DATA	
5.1 Have any complications/adverse events been experienced since the Baseline visit?			
☐ NO			
☐ YES If YES, please <i>fill out the Complication Form</i> .			
List of possible complications (check all that applied)			
1.	Liver Disease: a. Acute liver failure b. Hepatitis c. Jaundice d. Elevations in blood levels of liver enzymes (ALT, AST, GGT) e. Other	☐ Yes	☐ No
2.	Hematology: a. Neutropenia b. DVT c. Anemia d. Thrombocytopenia e. Coagulopathy f. Other	☐ Yes	☐ No
3.	Neurological: a. Loss of neurological function b. Neuropathic pain c. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 WEEKS F

12/15

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 6 Weeks F/U

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4.	Cardiac: a. Bradycardia b. Other dysrhythmia c. Cardiac Arrest d. MI e. Shock (BP < 80 Systolic) f. CHF/cardiogenic pulmonary edema g. Other	☐ Yes	☐ No
5.	Pulmonary: a. ALI/ARDS (Acute lung injury/Acute respiratory distress syndrome) b. Respiratory Failure c. PE (Pulmonary Embolus) d. Other	☐ Yes	☐ No
6.	GI/GU: a. GI Hemorrhage b. Hematuria c. Ileus d. Diarrhea e. Nausea, vomiting, f. Pancreatitis g. Cholecystitis h. Acute renal failure (<i>creatinine >1.0 above baseline</i>) i. Other	☐ Yes	☐ No
7.	Infections: a. UTI b. Pneumonia c. Infectious diarrhea d. Sepsis e. CNS infections f. Abscess - <i>Note Location:</i> _____ g. Wound Infection h. Other	☐ Yes	☐ No
8.	Skin: a. Sacral b. Heel c. Scapular d. Occipital f. Trochanter g. Operative wound h. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number _____

Riluzole Investigator F.U 6 WEEKS F

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 6 Weeks F/U

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9.	Failure of Stabilization: a. Loss of reduction b. Construct breakage c. Failure of orthosis d. Other	☐ Yes	☐ No
10.	Neuropsychiatric: a. Depression/adjustment disorder b. Psychosis c. Seizure d. Cognitive deterioration e. Other	☐ Yes	☐ No
11.	Allergic Reaction to riluzole: a. Skin reaction: rash, hives, itching b. Difficulty breathing c. Tightness in the chest d. Swelling of the mouth, face, lips, or tongue e. Other	☐ Yes	☐ No
12.	Death	☐ Yes	☐ No
13.	Other, please specify:	☐ Yes	☐ No

6. Current medications	TREATMENT DATA
6.1 Have there been any changes or new medications taken since the Baseline visit? ☐ NO ☐ YES If YES, fill out the Medication Form.	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 6 WEEKS F

14/15

7. General comments

GENERAL COMMENTS

8. Signature

8.1 Information for this visit obtained and completed by:

Name (Signature)

Date

9. Investigator's signature

I have assessed/reviewed all the information obtained for this visit and confirm it is accurate and complete.

Investigator's Name:

Investigator's Signature:

Date:

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 WEEKS F

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

Follow-up

Version 1, 22 April 2008

Follow-up Site:

FU 6-weeks

FU 3-months

FU 6-months

FU unscheduled

SAE-Form

Patient-Trial-Number

Patient Initials: last name, first name

Created by:

Zoya Bauer, MD, PhD

Jerika Robles, Project Manager

(University of Washington, USA)

(AOCID NA)

Reviewed by:

Branko Kopjar, MD, PhD

(University of Washington, USA)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 3 months F

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

3 Month Follow-up

Post-Treatment Data

1. Case identification data													GENERIC DATA		
1.1 Patient trial number:		(eg: ABC-123)													
1.2 Date of birth			☐	☐	☐	☐	☐	☐	☐	☐	☐	☐			
		Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year
1.3 Date of examination			☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
1.4 Gender:		☐ female (♀) ☐ male (♂)													

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 3 months F

2. Spinal Cord Injury: ASIA SCALE		POST-TREATMENT DATA																																					
Standard Neurological Classification of Spinal Cord Injury																																							
2.1 ASIA Motor Scale																																							
Key muscles MUSCLE GRADING 0 = No contraction/ total paralysis 1 = Palpable or visible contraction 2 = Active movement, full range of motion, gravity eliminated 3 = Active movement, full range of motion, against gravity 4 = Active movement, full range of motion, against gravity and provides some resistance 5 = Normal or active movement, full range of motion, against gravity and provides normal resistance 5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture		Upper limb: <table border="1"> <thead> <tr> <th>R</th> <th>L</th> <th></th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td>C5 Elbow flexors</td> </tr> <tr> <td> </td> <td> </td> <td>C6 Wrist extensors</td> </tr> <tr> <td> </td> <td> </td> <td>C7 Elbow extensors</td> </tr> <tr> <td> </td> <td> </td> <td>C8 Finger flexors (distal phalanx of middle finger)</td> </tr> <tr> <td> </td> <td> </td> <td>T1 Finger abductors (little finger)</td> </tr> </tbody> </table> Lower limb: <table border="1"> <thead> <tr> <th>R</th> <th>L</th> <th></th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td>L2 Hip flexors</td> </tr> <tr> <td> </td> <td> </td> <td>L3 Knee extensors</td> </tr> <tr> <td> </td> <td> </td> <td>L4 Ankle dorsiflexors</td> </tr> <tr> <td> </td> <td> </td> <td>L5 Long toe extensors</td> </tr> <tr> <td> </td> <td> </td> <td>S1 Ankle plantar flexors</td> </tr> </tbody> </table>		R	L				C5 Elbow flexors			C6 Wrist extensors			C7 Elbow extensors			C8 Finger flexors (distal phalanx of middle finger)			T1 Finger abductors (little finger)	R	L				L2 Hip flexors			L3 Knee extensors			L4 Ankle dorsiflexors			L5 Long toe extensors			S1 Ankle plantar flexors
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Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

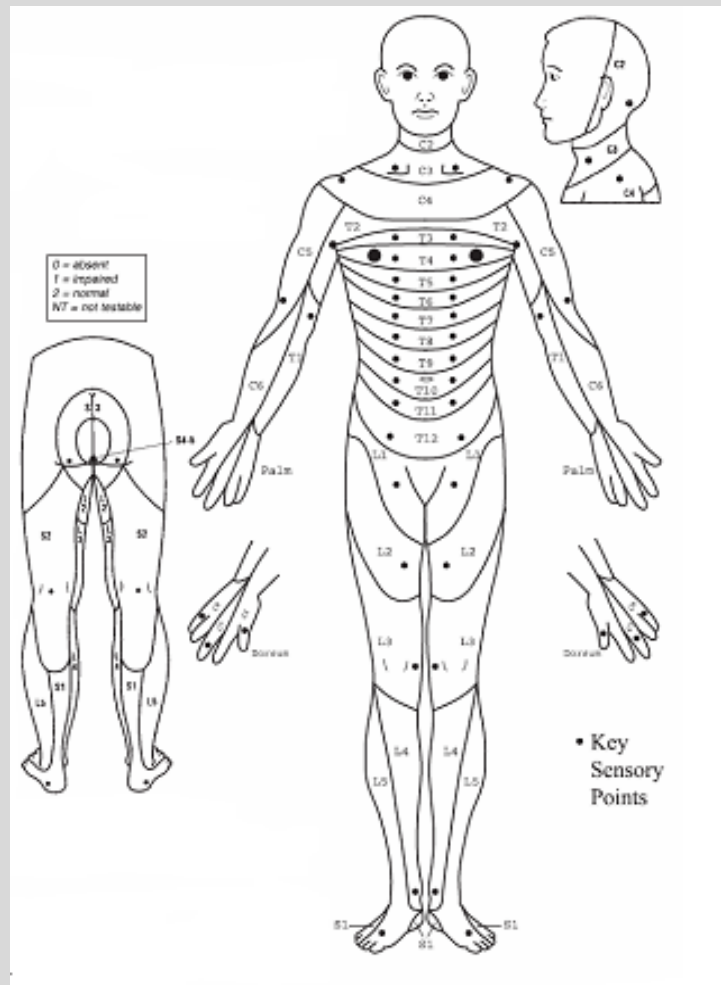
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North American Clinical Trials (NACTN) Riluzole Source Worksheet – 3 Month F/U

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2.2 ASIA Sensory Scale

	Light Touch		Pin Prick	
	R	L	R	L
C2	☐	☐	☐	☐
C3	☐	☐	☐	☐
C4	☐	☐	☐	☐
C5	☐	☐	☐	☐
C6	☐	☐	☐	☐
C7	☐	☐	☐	☐
C8	☐	☐	☐	☐
T1	☐	☐	☐	☐
T2	☐	☐	☐	☐
T3	☐	☐	☐	☐
T4	☐	☐	☐	☐
T5	☐	☐	☐	☐
T6	☐	☐	☐	☐
T7	☐	☐	☐	☐
T8	☐	☐	☐	☐
T9	☐	☐	☐	☐
T10	☐	☐	☐	☐
T11	☐	☐	☐	☐
T12	☐	☐	☐	☐
L1	☐	☐	☐	☐
L2	☐	☐	☐	☐
L3	☐	☐	☐	☐
L4	☐	☐	☐	☐
L5	☐	☐	☐	☐
S1	☐	☐	☐	☐
S2	☐	☐	☐	☐
S3	☐	☐	☐	☐
S45	☐	☐	☐	☐



Any anal sensation (Yes/No) ☐

Key Sensory Points:

0=Absent 2= Normal
1= Impaired NT- Not testable

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 3 months F

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 3 Month F/U

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2.3 ASIA Impairment Scale

	Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
	Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
	Grade C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
	Grade D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
	Grade E	Normal	Motor and sensory function are normal.

2.4 Performed by (please initial):

2.5 Date:

__/__/__
mm/ dd /yyyy

American Spinal Injury Association:

International Standards for Neurological Classification of Spinal Cord Injury, revised 2002; Chicago, IL

3. Spinal Cord Independence Measure (SCIM)

Version 1, May 1996

POST-TREATMENT DATA

Self-Care

3.1 Feeding (cutting, opening containers, bringing food to mouth, holding cup with fluid)

0. Needs parenteral, gastrostomy or fully assisted oral feeding

1. Eats cut food using several adaptive devices for hand and dishes

2. Eats cut food using only one adaptive device for hand; unable to hold cup

3. Eats cut food with one adaptive device; holds cup

4. Eats cut food without adaptive devices; needs a little assistance (e.g., to open containers)

5. Independent in all tasks without any adaptive device

3.2 Bathing (soaping, manipulating water tap, washing)

0. Requires total assistance

1. Soaps only small part of body with or without adaptive device

2. Soaps with adaptive device; cannot reach distant parts of the body or cannot operate a tap

3. Soaps without adaptive devices; needs a little assistance to reach distant parts of body

4. Washes independently with adaptive devices or in specific environmental setting

5. Washes independently without adaptive devices

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Investigator F.U 3 months F

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Self-Care (continued)

3.3 Dressing (preparing clothes, dressing upper and lower body, undressing)

- 0. Requires total assistance
- 1. Dresses upper body partially (e.g., without buttoning) in special setting (e.g., back support)
- 2. Independent in dressing and undressing upper body. Needs much assistance for lower body
- 3. Requires little assistance in dressing upper or lower body
- 4. Dresses and undresses independently, but requires adaptive devices and/or special setting
- 5. Dresses and undresses independently, without adaptive devices

3.4 Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup)

- 0. Requires total assistance
- 1. Performs only one task (e.g., washing hands and face)
- 2. Performs some tasks using adaptive devices; needs help to put on/take off devices
- 3. Performs some tasks using adaptive devices; puts on/takes off devices independently
- 4. Performs all tasks with adaptive devices or most tasks without devices
- 5. Independent in all tasks without adaptive devices

Respiration and Sphincter Management

3.5 Respiration

- 0. Requires assisted ventilation
- 2. Required tracheal tube and partially assisted ventilation
- 4. Breaths independently but requires much assistance in tracheal tube management
- 6. Breaths independently and requires little assistance in tracheal tube management
- 8. Breaths without tracheal tube, but sometimes requires mechanical assistance for breathing
- 10. Breaths independently without any device

3.6 Sphincter management - Bladder

- 0. Indwelling catheter
- 5. Assisted intermittent catheterization or no catheterization, residual urine volume > 100cc
- 10. Intermittent self-catheterization
- 15. No catheterization required, residual urine volume < 100cc

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Respiration and Sphincter Management (continued)	
3.7 Sphincter management - Bowel	
0. Irregularity, improper timing or very low frequency (less than once in 3 days) of bowel movements 5. Regular bowel movements, with proper timing, but with assistance (e.g., for applying suppository) 10. Regular bowel movements, with proper timing, without assistance	
3.8 Use of toilet (perineal hygiene, clothes adjustment before/after, use of napkins or diapers)	
0. Requires total assistance 1. Undresses lower body, needs assistance in all the remaining tasks 2. Undresses lower body and partially clean self (after); needs assistance in adjusting clothes and/or diapers 3. Undresses and cleans self (after); needs assistance in adjusting clothes and/or diapers 4. Independent in all tasks but needs adaptive devices or special setting (e.g., grab-bars) 5. Independent without adaptive devices or special setting	

Mobility (room and toilet)	
3.9 Mobility in bed and action to prevent pressure sores	
0. Requires total assistance 1. Partial mobility (turns in bed to one side only) 2. Turns to both sides in bed but does not fully release pressure 3. Releases pressure when lying only 4. Turns in bed and sits up without assistance 5. Independent in bed mobility; performs push-ups in sitting position without full body elevation 6. Performs push-ups in sitting position	
3.10 Transfers: bed-wheelchair (locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet)	
0. Requires total assistance 1. Needs partial assistance and/or supervision 2. Independent	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Mobility (room and toilet) (Continued)	
3.11 Transfers: wheelchair-toilet-tub (if uses toilet wheelchair – transfers to and from; if uses regular wheelchair – locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet) 0. Requires total assistance 1. Needs partial assistance and/or supervision, or adaptive device (e.g., grab-bars) 2. Independent	
Mobility (indoors and outdoors)	
3.12 Mobility indoors (short distances) 0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Walks with a walking frame 4. Walks with crutches 5. Walks with two canes 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without aids	
3.13 Mobility for moderate distances (10 – 100 meters) 0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Walks with a walking frame 4. Walks with crutches 5. Walks with two canes 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without aids	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Mobility (indoors and outdoors) (Continued)	
3.14 Mobility outdoors (more than 100 meters)	
0. Requires total assistance	
1. Needs electric wheelchair or partial assistance to operate manual wheelchair	
2. Moves independently in manual wheelchair	
3. Walks with a walking frame	
4. Walks with crutches	
5. Walks with two canes	
6. Walks with one cane	
7. Needs leg orthosis only	
8. Walks without aids	
3.15 Stair management	
0. Unable to climb or descend stairs	
1. Climbs 1 or 2 steps only, in a training setup	
2. Climbs and descends at least 3 steps with support or supervision of another person	
3. Climbs and descends at least 3 steps with support of handrail and/or crutch and/or cane	
4. Climbs and descends at least 3 steps without any support or supervision	
3.16 Transfers: wheelchair-car (approaching car, locking wheelchair, removing arm and foot rests, transferring to and from car, bringing wheelchair into and out of car)	
0. Requires total assistance	
1. Needs partial assistance and/or supervision, and/or adaptive devices	
2. Independent without adaptive devices	

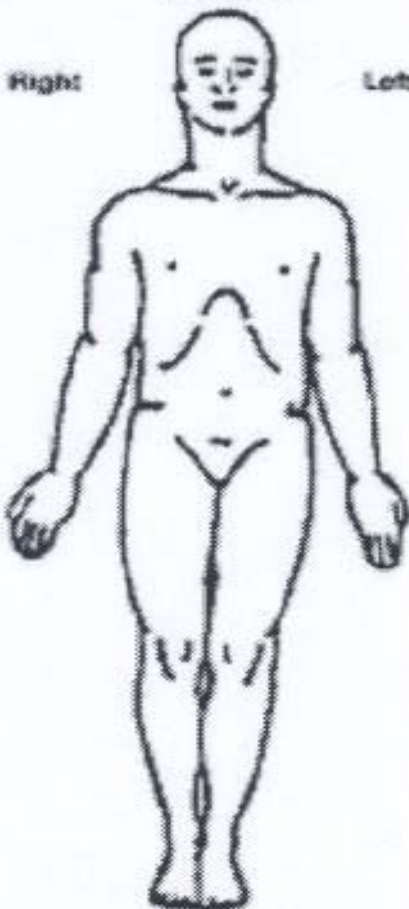
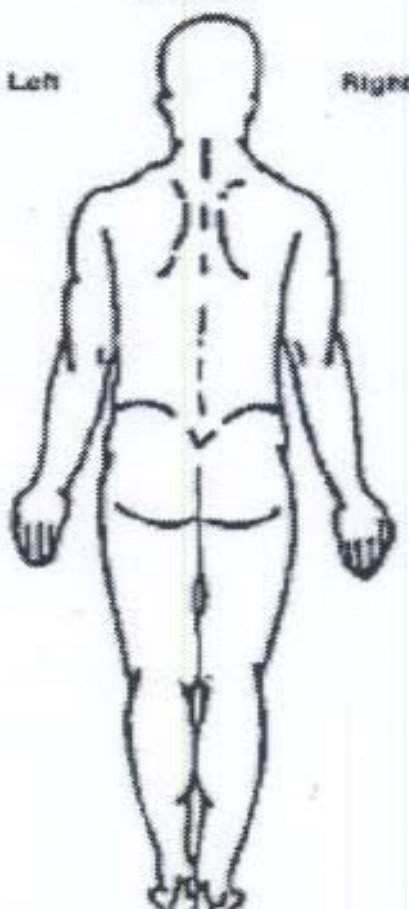
Loewenstein Rehabilitation Hospital, Raana, Israel. Reproduced with permission.

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 3 months F

4. Brief Pain Inventory (Short Form)		POST-TREATMENT DATA
4.1 Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these everyday kinds of pain today? ☐ Yes ☐ No		
4.2 On the diagram shade in the areas where you feel pain. Put an X on the area that hurts the most.		
Front right left	Back left right	
<u>Front</u>  <u>Back</u> 		
4.3 Please rate your pain by circling the one number that best describes your pain at its <i>worst</i> in the last 24 hours. 0 No pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine		

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 3 Month F/U

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4.4 Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

No
pain

Pain as bad
as you can imagine

4.5 Please rate your pain by circling the one number that best describes your pain on the average.

No
pain

Pain as bad
as you can imagine

4.6 Please rate your pain by circling the one number that tells how much pain you have right now.

No
pain

Pain as bad
as you can imagine

**4.7 What treatments or medications are you receiving for your pain?
(Please write the name of the treatments or medications below.)**

4.8 In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows much relief you have received.

No relief

Complete
Relief

4.9 Circle the one number that describes best how, during the past 24 hours, pain has interfered with your:

a) general activity

Does not
interfere

Completely
interferes

b) mood

Does not
interfere

Completely
interferes

c) walking ability

Does not
interfere

Completely
interferes

d) normal work (includes both work outside the home and housework)

Does not
interfere

Completely
interferes

e) relations with other people

Does not
interfere

Completely
interferes

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 3 months F

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North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 3 Month F/U

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f) sleep										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does not interfere					Completely interferes					
g) enjoyment of life										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does not interfere					Completely interferes					

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Pain Research Group
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5 Complications		POST-TREATMENT DATA	
5.1 Have any complications/adverse events been experienced since the Baseline visit?			
☐ NO			
☐ YES If YES, please <i>fill out the Complication Form</i> .			
List of possible complications (check all that applied)			
1.	Liver Disease: a. Acute liver failure b. Hepatitis c. Jaundice d. Elevations in blood levels of liver enzymes (ALT, AST, GGT) e. Other	☐ Yes	☐ No
2.	Hematology: a. Neutropenia b. DVT c. Anemia d. Thrombocytopenia e. Coagulopathy f. Other	☐ Yes	☐ No
3.	Neurological: a. Loss of neurological function b. Neuropathic pain c. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 3 months F

12/15

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 3 Month F/U

- 13 -

4.	Cardiac: a. Bradycardia b. Other dysrhythmia c. Cardiac Arrest d. MI e. Shock (BP < 80 Systolic) f. CHF/cardiogenic pulmonary edema g. Other	☐ Yes	☐ No
5.	Pulmonary: a. ALI/ARDS (Acute lung injury/Acute respiratory distress syndrome) b. Respiratory Failure c. PE (Pulmonary Embolus) d. Other	☐ Yes	☐ No
6.	GI/GU: a. GI Hemorrhage b. Hematuria c. Ileus d. Diarrhea e. Nausea, vomiting, f. Pancreatitis g. Cholecystitis h. Acute renal failure (<i>creatinine >1.0 above baseline</i>) i. Other	☐ Yes	☐ No
7.	Infections: a. UTI b. Pneumonia c. Infectious diarrhea d. Sepsis e. CNS infections f. Abscess - <i>Note Location:</i> _____ g. Wound Infection h. Other	☐ Yes	☐ No
8.	Skin: a. Sacral b. Heel c. Scapular d. Occipital f. Trochanter g. Operative wound h. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number _____

Riluzole Investigator F.U 3 months F

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 3 Month F/U

- 14 -

9.	Failure of Stabilization: a. Loss of reduction b. Construct breakage c. Failure of orthosis d. Other	☐ Yes	☐ No
10.	Neuropsychiatric: a. Depression/adjustment disorder b. Psychosis c. Seizure d. Cognitive deterioration e. Other	☐ Yes	☐ No
11.	Allergic Reaction to riluzole: a. Skin reaction: rash, hives, itching b. Difficulty breathing c. Tightness in the chest d. Swelling of the mouth, face, lips, or tongue e. Other	☐ Yes	☐ No
12.	Death	☐ Yes	☐ No
13.	Other, please specify:	☐ Yes	☐ No

6. Current medications	TREATMENT DATA
6.1 Have there been any changes or new medications taken since the Baseline visit? ☐ NO ☐ YES If YES, fill out the Medication Form.	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 3 months F

7. General comments

GENERAL COMMENTS

8. Signature

8.1 Information for this visit obtained and completed by:

Name (Signature)

Date

9. Investigator's signature

I have assessed/reviewed all the information obtained for this visit and confirm it is accurate and complete.

Investigator's Name:

Investigator's Signature:

Date:

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 3 months F

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

Follow-up

Version 1, 22 April 2008

Follow-up Site:

FU 6-weeks

FU 3-months

FU 6-months

FU unscheduled

SAE-Form

Patient-Trial-Number

Patient Initials: last name, first name

Created by:

Zoya Bauer, MD, PhD

Jerika Robles, Project Manager

(University of Washington, USA)

(AOCID NA)

Reviewed by:

Branko Kopjar, MD, PhD

(University of Washington, USA)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 months F

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

6 Month Follow-up

Post-Treatment Data

1. Case identification data													GENERIC DATA		
1.1 Patient trial number:		(eg: ABC-123)													
1.2 Date of birth			☐	☐	☐	☐	☐	☐	☐	☐	☐	☐			
		Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year
1.3 Date of examination			☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
1.4 Gender:		☐ female (♀) ☐ male (♂)													

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 months F

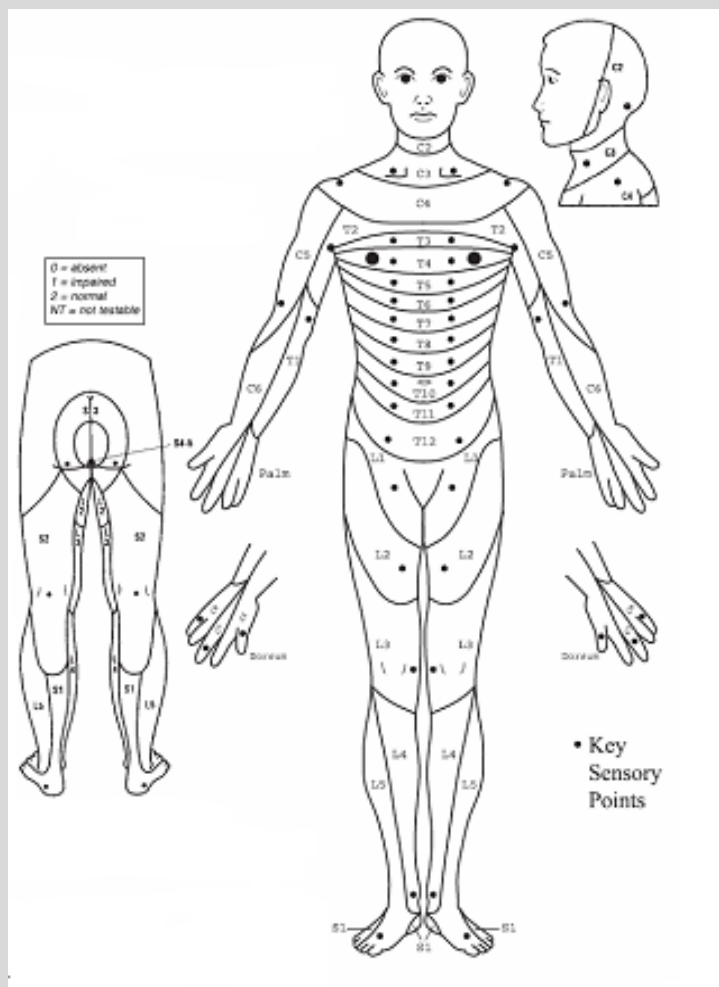
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Standard Neurological Classification of Spinal Cord Injury																																							
2.1 ASIA Motor Scale																																							
Key muscles MUSCLE GRADING 0 = No contraction/ total paralysis 1 = Palpable or visible contraction 2 = Active movement, full range of motion, gravity eliminated 3 = Active movement, full range of motion, against gravity 4 = Active movement, full range of motion, against gravity and provides some resistance 5 = Normal or active movement, full range of motion, against gravity and provides normal resistance 5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture		Upper limb: <table border="1"> <thead> <tr> <th>R</th> <th>L</th> <th></th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td>C5 Elbow flexors</td> </tr> <tr> <td> </td> <td> </td> <td>C6 Wrist extensors</td> </tr> <tr> <td> </td> <td> </td> <td>C7 Elbow extensors</td> </tr> <tr> <td> </td> <td> </td> <td>C8 Finger flexors (distal phalanx of middle finger)</td> </tr> <tr> <td> </td> <td> </td> <td>T1 Finger abductors (little finger)</td> </tr> </tbody> </table> Lower limb: <table border="1"> <thead> <tr> <th>R</th> <th>L</th> <th></th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td>L2 Hip flexors</td> </tr> <tr> <td> </td> <td> </td> <td>L3 Knee extensors</td> </tr> <tr> <td> </td> <td> </td> <td>L4 Ankle dorsiflexors</td> </tr> <tr> <td> </td> <td> </td> <td>L5 Long toe extensors</td> </tr> <tr> <td> </td> <td> </td> <td>S1 Ankle plantar flexors</td> </tr> </tbody> </table>		R	L				C5 Elbow flexors			C6 Wrist extensors			C7 Elbow extensors			C8 Finger flexors (distal phalanx of middle finger)			T1 Finger abductors (little finger)	R	L				L2 Hip flexors			L3 Knee extensors			L4 Ankle dorsiflexors			L5 Long toe extensors			S1 Ankle plantar flexors
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		L5 Long toe extensors																																					
		S1 Ankle plantar flexors																																					

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

2.2 ASIA Sensory Scale

	Light Touch		Pin Prick	
	R	L	R	L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S45				



Any anal sensation (Yes/No)

Key Sensory Points:

0=Absent 2= Normal
1= Impaired NT- Not testable

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 6 months F

2.3 ASIA Impairment Scale

	Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
	Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
	Grade C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
	Grade D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
	Grade E	Normal	Motor and sensory function are normal.

2.4 Performed by (please initial):

2.5 Date:

__/__/__
mm/dd/yyyy

American Spinal Injury Association:

International Standards for Neurological Classification of Spinal Cord Injury, revised 2002; Chicago, IL

3. Spinal Cord Independence Measure (SCIM)

Version 1, May 1996

POST-TREATMENT DATA

Self-Care

3.1 Feeding (cutting, opening containers, bringing food to mouth, holding cup with fluid)

0. Needs parenteral, gastrostomy or fully assisted oral feeding

1. Eats cut food using several adaptive devices for hand and dishes

2. Eats cut food using only one adaptive device for hand; unable to hold cup

3. Eats cut food with one adaptive device; holds cup

4. Eats cut food without adaptive devices; needs a little assistance (e.g., to open containers)

5. Independent in all tasks without any adaptive device

3.2 Bathing (soaping, manipulating water tap, washing)

0. Requires total assistance

1. Soaps only small part of body with or without adaptive device

2. Soaps with adaptive device; cannot reach distant parts of the body or cannot operate a tap

3. Soaps without adaptive devices; needs a little assistance to reach distant parts of body

4. Washes independently with adaptive devices or in specific environmental setting

5. Washes independently without adaptive devices

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 6 months F

Self-Care (continued)

3.3 Dressing (preparing clothes, dressing upper and lower body, undressing)

- 0. Requires total assistance
- 1. Dresses upper body partially (e.g., without buttoning) in special setting (e.g., back support)
- 2. Independent in dressing and undressing upper body. Needs much assistance for lower body
- 3. Requires little assistance in dressing upper or lower body
- 4. Dresses and undresses independently, but requires adaptive devices and/or special setting
- 5. Dresses and undresses independently, without adaptive devices

3.4 Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup)

- 0. Requires total assistance
- 1. Performs only one task (e.g., washing hands and face)
- 2. Performs some tasks using adaptive devices; needs help to put on/take off devices
- 3. Performs some tasks using adaptive devices; puts on/takes off devices independently
- 4. Performs all tasks with adaptive devices or most tasks without devices
- 5. Independent in all tasks without adaptive devices

Respiration and Sphincter Management

3.5 Respiration

- 0. Requires assisted ventilation
- 2. Required tracheal tube and partially assisted ventilation
- 4. Breaths independently but requires much assistance in tracheal tube management
- 6. Breaths independently and requires little assistance in tracheal tube management
- 8. Breaths without tracheal tube, but sometimes requires mechanical assistance for breathing
- 10. Breaths independently without any device

3.6 Sphincter management - Bladder

- 0. Indwelling catheter
- 5. Assisted intermittent catheterization or no catheterization, residual urine volume > 100cc
- 10. Intermittent self-catheterization
- 15. No catheterization required, residual urine volume < 100cc

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 months F

Respiration and Sphincter Management (continued)	
3.7 Sphincter management - Bowel	
0. Irregularity, improper timing or very low frequency (less than once in 3 days) of bowel movements 5. Regular bowel movements, with proper timing, but with assistance (e.g., for applying suppository) 10. Regular bowel movements, with proper timing, without assistance	
3.8 Use of toilet (perineal hygiene, clothes adjustment before/after, use of napkins or diapers)	
0. Requires total assistance 1. Undresses lower body, needs assistance in all the remaining tasks 2. Undresses lower body and partially clean self (after); needs assistance in adjusting clothes and/or diapers 3. Undresses and cleans self (after); needs assistance in adjusting clothes and/or diapers 4. Independent in all tasks but needs adaptive devices or special setting (e.g., grab-bars) 5. Independent without adaptive devices or special setting	

Mobility (room and toilet)	
3.9 Mobility in bed and action to prevent pressure sores	
0. Requires total assistance 1. Partial mobility (turns in bed to one side only) 2. Turns to both sides in bed but does not fully release pressure 3. Releases pressure when lying only 4. Turns in bed and sits up without assistance 5. Independent in bed mobility; performs push-ups in sitting position without full body elevation 6. Performs push-ups in sitting position	
3.10 Transfers: bed-wheelchair (locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet)	
0. Requires total assistance 1. Needs partial assistance and/or supervision 2. Independent	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Mobility (room and toilet) (Continued)	
3.11 Transfers: wheelchair-toilet-tub (if uses toilet wheelchair – transfers to and from; if uses regular wheelchair – locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet) 0. Requires total assistance 1. Needs partial assistance and/or supervision, or adaptive device (e.g., grab-bars) 2. Independent	
Mobility (indoors and outdoors)	
3.12 Mobility indoors (short distances) 0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Walks with a walking frame 4. Walks with crutches 5. Walks with two canes 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without aids	
3.13 Mobility for moderate distances (10 – 100 meters) 0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Walks with a walking frame 4. Walks with crutches 5. Walks with two canes 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without aids	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

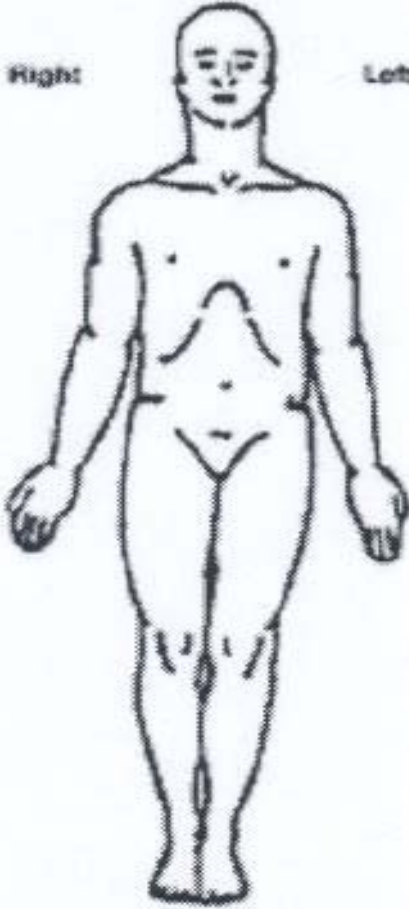
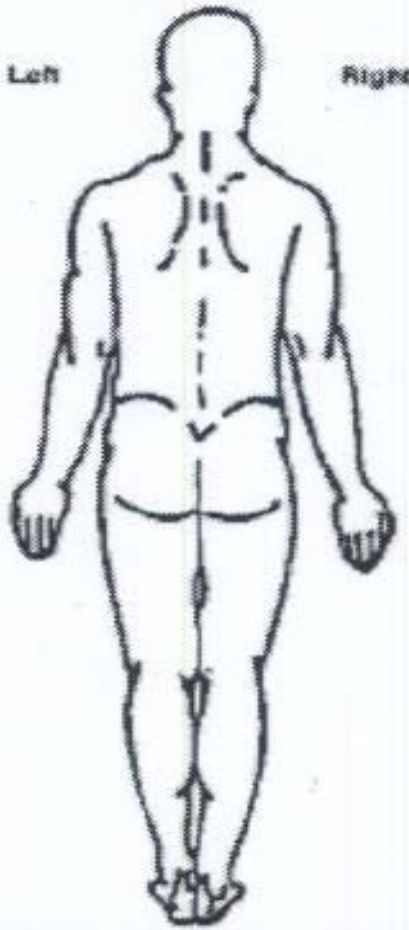
Mobility (indoors and outdoors) (Continued)	
3.14 Mobility outdoors (more than 100 meters)	
0. Requires total assistance	
1. Needs electric wheelchair or partial assistance to operate manual wheelchair	
2. Moves independently in manual wheelchair	
3. Walks with a walking frame	
4. Walks with crutches	
5. Walks with two canes	
6. Walks with one cane	
7. Needs leg orthosis only	
8. Walks without aids	
3.15 Stair management	
0. Unable to climb or descend stairs	
1. Climbs 1 or 2 steps only, in a training setup	
2. Climbs and descends at least 3 steps with support or supervision of another person	
3. Climbs and descends at least 3 steps with support of handrail and/or crutch and/or cane	
4. Climbs and descends at least 3 steps without any support or supervision	
3.16 Transfers: wheelchair-car (approaching car, locking wheelchair, removing arm and foot rests, transferring to and from car, bringing wheelchair into and out of car)	
0. Requires total assistance	
1. Needs partial assistance and/or supervision, and/or adaptive devices	
2. Independent without adaptive devices	
Loewenstein Rehabilitation Hospital, Raana, Israel. Reproduced with permission.	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 months F

4. Brief Pain Inventory (Short Form)		POST-TREATMENT DATA
4.1 Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these everyday kinds of pain today? ☐ Yes ☐ No		
4.2 On the diagram shade in the areas where you feel pain. Put an X on the area that hurts the most.		
right Front left	left Back right	
<u>Front</u>  <u>Back</u> 		
4.3 Please rate your pain by circling the one number that best describes your pain at its <i>worst</i> in the last 24 hours. 0 1 2 3 4 5 6 7 8 9 10 No pain Pain as bad as you can imagine		

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number _____
Riluzole Investigator F.U 6 months F

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 6 Month F/U

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4.4 Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

No
pain

Pain as bad
as you can imagine

4.5 Please rate your pain by circling the one number that best describes your pain on the average.

No
pain

Pain as bad
as you can imagine

4.6 Please rate your pain by circling the one number that tells how much pain you have right now.

No
pain

Pain as bad
as you can imagine

**4.7 What treatments or medications are you receiving for your pain?
(Please write the name of the treatments or medications below.)**

4.8 In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows much relief you have received.

No relief

Complete
Relief

4.9 Circle the one number that describes best how, during the past 24 hours, pain has interfered with your:

a) general activity

Does not
interfere

Completely
interferes

b) mood

Does not
interfere

Completely
interferes

c) walking ability

Does not
interfere

Completely
interferes

d) normal work (includes both work outside the home and housework)

Does not
interfere

Completely
interferes

e) relations with other people

Does not
interfere

Completely
interferes

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 6 months F

11/15

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 6 Month F/U

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f) sleep										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does not interfere					Completely interferes					
g) enjoyment of life										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does not interfere					Completely interferes					

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Pain Research Group
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5 Complications		POST-TREATMENT DATA	
5.1 Have any complications/adverse events been experienced since the Baseline visit?			
☐ NO			
☐ YES If YES, please <i>fill out the Complication Form</i> .			
List of possible complications (check all that applied)			
1.	Liver Disease: a. Acute liver failure b. Hepatitis c. Jaundice d. Elevations in blood levels of liver enzymes (ALT, AST, GGT) e. Other	☐ Yes	☐ No
2.	Hematology: a. Neutropenia b. DVT c. Anemia d. Thrombocytopenia e. Coagulopathy f. Other	☐ Yes	☐ No
3.	Neurological: a. Loss of neurological function b. Neuropathic pain c. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number

Riluzole Investigator F.U 6 months F

12/15

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 6 Month F/U

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4.	Cardiac: a. Bradycardia b. Other dysrhythmia c. Cardiac Arrest d. MI e. Shock (BP < 80 Systolic) f. CHF/cardiogenic pulmonary edema g. Other	☐ Yes	☐ No
5.	Pulmonary: a. ALI/ARDS (Acute lung injury/Acute respiratory distress syndrome) b. Respiratory Failure c. PE (Pulmonary Embolus) d. Other	☐ Yes	☐ No
6.	GI/GU: a. GI Hemorrhage b. Hematuria c. Ileus d. Diarrhea e. Nausea, vomiting, f. Pancreatitis g. Cholecystitis h. Acute renal failure (<i>creatinine >1.0 above baseline</i>) i. Other	☐ Yes	☐ No
7.	Infections: a. UTI b. Pneumonia c. Infectious diarrhea d. Sepsis e. CNS infections f. Abscess - <i>Note Location:</i> _____ g. Wound Infection h. Other	☐ Yes	☐ No
8.	Skin: a. Sacral b. Heel c. Scapular d. Occipital f. Trochanter g. Operative wound h. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number _____

Riluzole Investigator F.U 6 months F

North American Clinical Trials (NACTN)

Riluzole Source Worksheet – 6 Month F/U

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9.	Failure of Stabilization: a. Loss of reduction b. Construct breakage c. Failure of orthosis d. Other	☐ Yes	☐ No
10.	Neuropsychiatric: a. Depression/adjustment disorder b. Psychosis c. Seizure d. Cognitive deterioration e. Other	☐ Yes	☐ No
11.	Allergic Reaction to riluzole: a. Skin reaction: rash, hives, itching b. Difficulty breathing c. Tightness in the chest d. Swelling of the mouth, face, lips, or tongue e. Other	☐ Yes	☐ No
12.	Death	☐ Yes	☐ No
13.	Other, please specify:	☐ Yes	☐ No

6. Current medications	TREATMENT DATA
6.1 Have there been any changes or new medications taken since the Baseline visit? ☐ NO ☐ YES If YES, <i>fill out the Medication Form.</i>	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 months F

7. General comments

GENERAL COMMENTS

8. Signature

8.1 Information for this visit obtained and completed by:

Name (Signature)

Date

9. Investigator's signature

I have assessed/reviewed all the information obtained for this visit and confirm it is accurate and complete.

Investigator's Name:

Investigator's Signature:

Date:

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U 6 months F

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

Unscheduled Follow-Up Visit

Version 1, 22 April 2008

Follow-up Site:

FU 6-weeks

FU 3-months

FU 6-months

SAE-Form

Patient-Trial-Number

Patient Initials: last name, first name

Created by:

Zoya Bauer, MD, PhD

Jerika Robles, Project Manager

(University of Washington, USA)

(AOCID NA)

Reviewed by:

Branko Kopjar, MD, PhD

(University of Washington, USA)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U. Unscheduled F

North American Clinical Trials (NACTN)
Riluzole Source Worksheet – Unscheduled Visit

- 2 -

1. Case identification data												GENERIC DATA		
1.1 Patient trial number:	. . — . .										(eg: ABC-123)			
1.2 Date of birth:		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		Year	
	Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
1.3 Date of examination:		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
1.4 Gender:	☐ female (♀) ☐ male (♂)													

2. Complications		POST-TREATMENT DATA	
2.1 Have any complications/adverse events been experienced since the last visit?			
☐ NO			
☐ YES If YES, please <i>fill out the Complication Form.</i>			
List of possible complications (check all that applied)			
1.	Liver Disease: a. Acute liver failure b. Hepatitis c. Jaundice d. Elevations in blood levels of liver enzymes (ALT, AST, GGT) e. Other	☐ Yes	☐ No
2.	Hematology: a. Neutropenia b. DVT c. Anemia d. Thrombocytopenia e. Coagulopathy f. Other	☐ Yes	☐ No
3.	Neurological: a. Loss of neurological function b. Neuropathic pain c. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number
 Riluzole

Investigator

F.U.

Unscheduled

F

North American Clinical Trials (NACTN)
Riluzole Source Worksheet – Unscheduled Visit

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4.	Cardiac: a. Bradycardia b. Other dysrhythmia c. Cardiac Arrest d. MI e. Shock (BP < 80 Systolic) f. CHF/cardiogenic pulmonary edema g. Other	☐ Yes	☐ No
5.	Pulmonary: a. ALI/ARDS (Acute lung injury/Acute respiratory distress syndrome) b. Respiratory Failure c. PE (Pulmonary Embolus) d. Other	☐ Yes	☐ No
6.	GI/GU: a. GI Hemorrhage b. Hematuria c. Ileus d. Diarrhea e. Nausea, vomiting, f. Pancreatitis g. Cholecystitis h. Acute renal failure (<i>creatinine >1.0 above baseline</i>) i. Other	☐ Yes	☐ No
7.	Infections: a. UTI b. Pneumonia c. Infectious diarrhea d. Sepsis e. CNS infections f. Abscess - <i>Note Location:</i> _____ g. Wound Infection h. Other	☐ Yes	☐ No
8.	Skin: a. Sacral b. Heel c. Scapular d. Occipital f. Trochanter g. Operative wound h. Other	☐ Yes	☐ No

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number _____

Riluzole Investigator F.U. Unscheduled F

North American Clinical Trials (NACTN)
Riluzole Source Worksheet – Unscheduled Visit

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9.	Failure of Stabilization: a. Loss of reduction b. Construct breakage c. Failure of orthosis d. Other	☐ Yes	☐ No
10.	Neuropsychiatric: a. Depression/adjustment disorder b. Psychosis c. Seizure d. Cognitive deterioration e. Other	☐ Yes	☐ No
11.	Allergic Reaction to riluzole: a. Skin reaction: rash, hives, itching b. Difficulty breathing c. Tightness in the chest d. Swelling of the mouth, face, lips, or tongue e. Other	☐ Yes	☐ No
12.	Death	☐ Yes	☐ No
13.	Other, please specify:	☐ Yes	☐ No

3. Current medications	TREATMENT DATA
3.1 Since the last visit, have there been any new or changes in medications used to treat current complication(s)? ☐ NO ☐ YES If YES, <i>fill out the Medication Form.</i>	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

4. General comments

GENERAL COMMENTS

5. Signature

5.1 Information for this visit obtained and completed by:

Name (Signature)

Date

6. Investigator's signature

I have assessed/reviewed all the information obtained for this visit and confirm it is accurate and complete.

Investigator's Name:

Investigator's Signature:

Date:

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

22 Apr. 08

Patient Trial Number

Riluzole Investigator F.U. Unscheduled F

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

Medication Form

Version 1.0, 28 April 2008

Patient-Trial-Number

Patient Initials: First name, Last name

Created by:

Zoya Bauer, MD, PhD
Jerika Robles, Project Manager

(University of Washington, USA)
(AOCID NA)

Reviewed by:

Branko Kopjar, MD, PhD

(University of Washington, USA)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

28 Apr. 08

Patient Trial Number

Riluzole Medication SW Form F.doc

North American Clinical Trials (NACTN)
Riluzole Source Worksheet – Medication Form

- 2 -

1. Case identification data														GENERIC DATA		
1.1 Patient trial number: . . – . . (eg: ABC-123)										1.2 Gender: ☐ female (♀) ☐ male (♂)						
1.3 Date of birth:		DAY	Jan ☐	Feb ☐	Mar ☐	Apr ☐	May ☐	Jun ☐	Jul ☐	Aug ☐	Sep ☐	Oct ☐	Nov ☐	Dec ☐	YEAR	

2. Medications								TREATMENT DATA
<u>Term of Medication</u> Please indicate (use letter): P = Pre-treatment medication D = Post- Treatment / Discharge medication C= Concomitant medications	<u>Generic Name</u> [If combination, list trade name]	<u>Route</u> [e.g. PO, PR, IV]	<u>Daily dose</u> (mg)	<u>Date started</u> _/_/_/ MM/DD/YYYY (e.g. 04/07/2007)	<u>Date stopped</u> _/_/_/ MM/DD/YYYY * If continues – leave blank	<u>* At Final Visit -</u> write "C" if continuing	<u>Indication for Use</u>	

28 Apr. 08

- 3 -

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

Patient Trial Number

3. Investigator's Signature

I have carefully assessed/ reviewed all the information noted for the specified visit and confirm that it is accurate and complete.

Visit	Investigator's Initials	Date ____/____/____ (MM/DD/YYYY e.g. 04/07/2007)
Baseline Pre-Treatment		
Day 1		
Day 2		
Day 3		
Day 4		
Day 5		
Day 6		
Day 7		
Day 8		
Day 9		
Day 10		
Day 11		
Day 12		
Day 13		
Day 14		
Discharge		
FU 6 Weeks		
FU 3 Months		
FU 6 Months		
FU Unscheduled Visit		
FU Unscheduled Visit		
FU Unscheduled Visit		
FU Unscheduled Visit		
FU Unscheduled Visit		
FU Unscheduled Visit		

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

28 Apr. 08

STUDY FLOW CHART – “Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury”

Study Nominal Time	Screening (<12hrs from Injury)	Treatment Period									
Study Timeframe From Injury	Initial Data	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Study Visit Number	Baseline	1	2	3	4	5	6	7	8	9	10
Study Procedures List											
Informed Consent	X										
Eligibility Criteria Review	X										
Medical History	X										
Case Identification Data	X										
Injury Detail	X										
ASIA Scale	X			X							
BPI (Short Form)											
SCIM											
Clinical Lab Test/ Blood Draw	X			X				X			X
Blood Plasma test for determination of riluzole concentration	X			X*							
CSF test for determination of riluzole activity**											
Riluzole Treatment Details	X										
Riluzole Administration		X	X	X	X	X	X	X	X	X	X
Surgery Data											
Adverse Event/Complications (SAE Form)		X	X	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X	X	X

****CSF test for determination of riluzole concentration at any day when CSF withdrawal is clinically indicated**

X* Blood plasma must be collected twice on day 3: before riluzole administration and 2 hours after riluzole administration.

STUDY FLOW CHART – “Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury”
(Continuation)

Study Nominal Time	Treatment Period				Post Treatment	Follow-up			
Study Timeframe From Injury	Day 11	Day 12	Day 13	Day 14	Discharge from Acute	6 Week F/U	3 Month F/U	6 Month F/U	Unscheduled
Study Visit Number	11	12	13	14	15	16	17	18	-----
Study Procedures List									
Informed Consent									
Eligibility Criteria Review									
Medical History									
Case Identification Data									
Injury Detail									
ASIA Scale				X	X	X	X	X	
BPI (Short Form)						X		X	
SCIM						X	X	X	
Clinical Lab Test/ Blood Draw				X					
Blood Plasma test for determination of riluzole activity				*X*					
CSF test for determination of riluzole activity**									
Riluzole Treatment Details									
Riluzole Administration	X	X	X	X					
Surgery Data					X				
Adverse Event/Complications (SAE Form)	X	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X

****CSF test for determination of riluzole activity at any day when CSF withdrawal is clinically indicated**

***X* Blood plasma must be collected twice on day 14: before riluzole administration and 2 hours after riluzole administration.**

Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury

Source Worksheet

Version 1, 28 April 2008

Complications/Adverse Events

This form is used to record acute medical complications occurring during the hospitalization of the patient. For each system, record the date of the complication and specify the type of complication as well as a determination of whether that complication was mild, moderate, or severe (**Code intensity as 1, 2, or 3 respectively.**) Space is provided for multiple occurrences of complications. If the patient experiences more than five occurrences of complications of a system submit an additional Complications Form.

Patient-Trial-Number

Patient Initials: last name, first name

Created by:

Zoya Bauer, MD, PhD
Jerika Robles, Project Manager

(University of Washington, USA)
(AOCID NA)

Reviewed by:

Branko Kopjar, MD, PhD

(University of Washington, USA)

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

28 Apr. 08

Patient Trial Number

Riluzole Investigator Complication form F.doc

North American Clinical Trials (NACTN)

Riluzole Source Worksheet–Complication/Adverse Event Form

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1. Case identification data

GENERIC DATA

1.1 Patient trial number: (eg: ABC-123)

1.2 Gender: ☐ female (♀) ☐ male (♂)

1.3 Date of birth:

DAY

Jan

Feb

Mar

Apr

May

Jun

Jul

Aug

Sep

Oct

Nov

Dec

YEAR

ACUTE CARE COMPLICATIONS

1.Liver Disease	1 st Occurrence	2 nd Occurrence	3 rd Occurrence	4 th Occurrence	5 th Occurrence
☐ No liver complications during acute care hospitalization. A) Acute liver failure B) Hepatitis C) Jaundice D) Elevations in blood levels of liver enzymes (ALT, AST, GGT) E) Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Medication ☐ Other ____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Medication ☐ Other ____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Medication ☐ Other ____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Medication ☐ Other ____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Medication ☐ Other ____

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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North American Clinical Trials (NACTN)
Riluzole Source Worksheet – Complication/Adverse Event Form

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2. Hematology	1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence	5th Occurrence
☐ No hematology complications during acute care hospitalization. A)Neutropenia B)DVT C)Anemia D)Thrombocytopenia E)Coagulopathy F) Other	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Anticoagulation ☐ IVC filter ☐ Transfusion <= 4units ☐ Transfusion >4units ☐ Transfusion platelets ☐ Transfusion FFP ☐ Vitamin K ☐ Other _____	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Anticoagulation ☐ IVC filter ☐ Transfusion <= 4units ☐ Transfusion >4units ☐ Transfusion platelets ☐ Transfusion FFP ☐ Vitamin K ☐ Other _____	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Anticoagulation ☐ IVC filter ☐ Transfusion <= 4units ☐ Transfusion >4units ☐ Transfusion platelets ☐ Transfusion FFP ☐ Vitamin K ☐ Other _____	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Anticoagulation ☐ IVC filter ☐ Transfusion <= 4units ☐ Transfusion >4units ☐ Transfusion platelets ☐ Transfusion FFP ☐ Vitamin K ☐ Other _____	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Anticoagulation ☐ IVC filter ☐ Transfusion <= 4units ☐ Transfusion >4units ☐ Transfusion platelets ☐ Transfusion FFP ☐ Vitamin K ☐ Other _____
3. Neurological	1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence	5th Occurrence
☐ No neurological complications during acute care hospitalization. A) Loss of neurological function B)Neuropathic pain C)Other	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Operation ☐ Other _____

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Investigator Complication form F.doc

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Riluzole Source Worksheet – Complication/Adverse Event Form

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4. Cardiac	1 st Occurrence	2 nd Occurrence	3 rd Occurrence	4 th Occurrence	5 th Occurrence
☐ No cardiac complications during acute care hospitalization. A) Bradycardia B) Other dysrhythmia C) Cardiac Arrest D) MI E) Shock (BP < 80 Systolic) F) CHF/ cardiogenic pulmonary edema G) Other	Date ____ / ____ / ____	Date ____ / ____ / ____	Date ____ / ____ / ____	Date ____ / ____ / ____	Date ____ / ____ / ____
	Type ____ Intensity ____	Type ____ Intensity ____	Type ____ Intensity ____	Type ____ Intensity ____	Type ____ Intensity ____
	Therapy Required	Therapy Required	Therapy Required	Therapy Required	Therapy Required
	☐ None	☐ None	☐ None	☐ None	☐ None
	☐ Atropine	☐ Atropine	☐ Atropine	☐ Atropine	☐ Atropine
	☐ Epinephrine	☐ Epinephrine	☐ Epinephrine	☐ Epinephrine	☐ Epinephrine
	☐ Pacemaker	☐ Pacemaker	☐ Pacemaker	☐ Pacemaker	☐ Pacemaker
	☐ Antiarrhythmic	☐ Antiarrhythmic	☐ Antiarrhythmic	☐ Antiarrhythmic	☐ Antiarrhythmic
	☐ Rate-control med	☐ Rate-control med	☐ Rate-control med	☐ Rate-control med	☐ Rate-control med
	☐ Cardioversion	☐ Cardioversion	☐ Cardioversion	☐ Cardioversion	☐ Cardioversion
☐ CPR	☐ CPR	☐ CPR	☐ CPR	☐ CPR	
☐ Defibrillation	☐ Defibrillation	☐ Defibrillation	☐ Defibrillation	☐ Defibrillation	
☐ Intubation	☐ Intubation	☐ Intubation	☐ Intubation	☐ Intubation	
☐ Fibrinolytics	☐ Fibrinolytics	☐ Fibrinolytics	☐ Fibrinolytics	☐ Fibrinolytics	
☐ Cardiac cath.	☐ Cardiac cath.	☐ Cardiac cath.	☐ Cardiac cath.	☐ Cardiac cath.	
☐ Surgical treatment (CABG)	☐ Surgical treatment (CABG)	☐ Surgical treatment (CABG)	☐ Surgical treatment (CABG)	☐ Surgical treatment (CABG)	
☐ PA cath.	☐ PA cath.	☐ PA cath.	☐ PA cath.	☐ PA cath.	
☐ Volume expansion	☐ Volume expansion	☐ Volume expansion	☐ Volume expansion	☐ Volume expansion	
☐ Vasoactive med.	☐ Vasoactive med.	☐ Vasoactive med.	☐ Vasoactive med.	☐ Vasoactive med.	
☐ Antibiotics	☐ Antibiotics	☐ Antibiotics	☐ Antibiotics	☐ Antibiotics	
☐ Other _____	☐ Other _____	☐ Other _____	☐ Other _____	☐ Other _____	

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Source Worksheet – Complication/Adverse Event Form

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5. Pulmonary	1 st Occurrence	2 nd Occurrence	3 rd Occurrence	4 th Occurrence	5 th Occurrence
☐ No pulmonary complications during acute care hospitalization. A)ALI/ARDS (Acute lung injury/Acute respiratory distress syndrome) B)Respiratory Failure C)PE (Pulmonary Embolus) D)Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Intubation ☐ NIPPV ☐ Change vent. mode ☐ Bronchoscopy ☐ Antibiotics ☐ Pronation ☐ Anticoagulation ☐ Fibrinolytics ☐ IVC filter ☐ Thrombectomy/Embolectomy ☐ Chest tube ☐ Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Intubation ☐ NIPPV ☐ Change vent. mode ☐ Bronchoscopy ☐ Antibiotics ☐ Pronation ☐ Anticoagulation ☐ Fibrinolytics ☐ IVC filter ☐ Thrombectomy/Embolectomy ☐ Chest tube ☐ Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Intubation ☐ NIPPV ☐ Change vent. mode ☐ Bronchoscopy ☐ Antibiotics ☐ Pronation ☐ Anticoagulation ☐ Fibrinolytics ☐ IVC filter ☐ Thrombectomy/Embolectomy ☐ Chest tube ☐ Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Intubation ☐ NIPPV ☐ Change vent. mode ☐ Bronchoscopy ☐ Antibiotics ☐ Pronation ☐ Anticoagulation ☐ Fibrinolytics ☐ IVC filter ☐ Thrombectomy/Embolectomy ☐ Chest tube ☐ Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Intubation ☐ NIPPV ☐ Change vent. mode ☐ Bronchoscopy ☐ Antibiotics ☐ Pronation ☐ Anticoagulation ☐ Fibrinolytics ☐ IVC filter ☐ Thrombectomy/Embolectomy ☐ Chest tube ☐ Other
6. GI/GU	1 st Occurrence	2 nd Occurrence	3 rd Occurrence	4 th Occurrence	5 th Occurrence
☐ No GI/GU complications during acute care hospitalization. A)GI Hemorrhage B)Hematuria C)Ileus D)Diarrhea E)Nausea, vomiting, F)Pancreatitis G)Cholecystitis H)Acute renal failure (creatinine >1.0 above baseline) I)Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Transfusion PRBCs ☐ EGD ☐ Dialysis ☐ Colonoscopy ☐ Surgical intervention ☐ TPN ☐ Exploratory laparotomy ☐ Neostigmine ☐ Bladder irrigation ☐ Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Transfusion PRBCs ☐ EGD ☐ Dialysis ☐ Colonoscopy ☐ Surgical intervention ☐ TPN ☐ Exploratory laparotomy ☐ Neostigmine ☐ Bladder irrigation ☐ Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Transfusion PRBCs ☐ EGD ☐ Dialysis ☐ Colonoscopy ☐ Surgical intervention ☐ TPN ☐ Exploratory laparotomy ☐ Neostigmine ☐ Bladder irrigation ☐ Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Transfusion PRBCs ☐ EGD ☐ Dialysis ☐ Colonoscopy ☐ Surgical intervention ☐ TPN ☐ Exploratory laparotomy ☐ Neostigmine ☐ Bladder irrigation ☐ Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Transfusion PRBCs ☐ EGD ☐ Dialysis ☐ Colonoscopy ☐ Surgical intervention ☐ TPN ☐ Exploratory laparotomy ☐ Neostigmine ☐ Bladder irrigation ☐ Other

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Patient Trial Number _____

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7. Infections	1 st Occurrence	2 nd Occurrence	3 rd Occurrence	4 th Occurrence	5 th Occurrence
☐ No infections during acute care hospitalization. A)UTI B)Pneumonia C)Infectious diarrhea D)Sepsis E)CNS infections F)Abscess - Note Location: _____ G)Wound Infection H)Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Antibiotics ☐ Bladder irrigation ☐ Intubation ☐ NIPPV ☐ Diversion colostomy ☐ Change vent. mode ☐ Bronchoscopy ☐ TPN ☐ Antimotility agents ☐ Remove hardware ☐ Remove central line ☐ Surgical drainage ☐ I&D ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Antibiotics ☐ Bladder irrigation ☐ Intubation ☐ NIPPV ☐ Diversion colostomy ☐ Change vent. mode ☐ Bronchoscopy ☐ TPN ☐ Antimotility agents ☐ Remove hardware ☐ Remove central line ☐ Surgical drainage ☐ I&D ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Antibiotics ☐ Bladder irrigation ☐ Intubation ☐ NIPPV ☐ Diversion colostomy ☐ Change vent. mode ☐ Bronchoscopy ☐ TPN ☐ Antimotility agents ☐ Remove hardware ☐ Remove central line ☐ Surgical drainage ☐ I&D ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Antibiotics ☐ Bladder irrigation ☐ Intubation ☐ NIPPV ☐ Diversion colostomy ☐ Change vent. mode ☐ Bronchoscopy ☐ TPN ☐ Antimotility agents ☐ Remove hardware ☐ Remove central line ☐ Surgical drainage ☐ I&D ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Antibiotics ☐ Bladder irrigation ☐ Intubation ☐ NIPPV ☐ Diversion colostomy ☐ Change vent. mode ☐ Bronchoscopy ☐ TPN ☐ Antimotility agents ☐ Remove hardware ☐ Remove central line ☐ Surgical drainage ☐ I&D ☐ Other _____
8. Skin	1 st Occurrence	2 nd Occurrence	3 rd Occurrence	4 th Occurrence	5 th Occurrence
☐ No skin complications during acute care hospitalization. A)Sacral B)Heel C)Scapular D)Occipital E)Trochanter F)Operative wound Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Surgical debridement ☐ Wound VAC ☐ Antibiotics ☐ Amputation ☐ Dressing Change ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Surgical debridement ☐ Wound VAC ☐ Antibiotics ☐ Amputation ☐ Dressing Change ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Surgical debridement ☐ Wound VAC ☐ Antibiotics ☐ Amputation ☐ Dressing Change ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Surgical debridement ☐ Wound VAC ☐ Antibiotics ☐ Amputation ☐ Dressing Change ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Surgical debridement ☐ Wound VAC ☐ Antibiotics ☐ Amputation ☐ Dressing Change ☐ Other _____

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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9.Failure of Stabilization	1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence	5th Occurrence
☐ No failure of stabilization during acute care hospitalization. A) Loss of reduction B) Construct breakage C) Failure of orthosis D) Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Orthosis ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Orthosis ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Orthosis ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Orthosis ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Orthosis ☐ Operation ☐ Other _____
10. Neuropsychiatric	1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence	5th Occurrence
☐ No neuropsychiatric complications during acute care hospitalization. A) Depression/adjustment disorder B) Psychosis C) Seizure D) Cognitive deterioration E) Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Psychiatric consultation ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Psychiatric consultation ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Psychiatric consultation ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Psychiatric consultation ☐ Operation ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Medication ☐ Psychiatric consultation ☐ Operation ☐ Other _____

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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11. Allergic Reaction to Riluzole	1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence	5th Occurrence
☐ No allergic reaction to Riluzole during acute care hospitalization. A) Skin reaction: rash, hives, itching B) Difficulty breathing C) Tightness in the chest D) Swelling of the mouth, face, lips, or tongue E) Other	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Epinephrine ☐ Steroids ☐ Antihistamines ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Epinephrine ☐ Steroids ☐ Antihistamines ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Epinephrine ☐ Steroids ☐ Antihistamines ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Epinephrine ☐ Steroids ☐ Antihistamines ☐ Other _____	Date ____ / ____ / ____ Type ____ Intensity ____ Therapy Required ☐ None ☐ Stop administering riluzole ☐ Epinephrine ☐ Steroids ☐ Antihistamines ☐ Other _____

12. Death

12.1 Date of death (mm/dd/yyyy): ____ / ____ / ____

12.2 Primary cause of death: _____

12.3 Contributing causes of death: _____

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

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Riluzole Source Worksheet–Complication/Adverse Event Form

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3. Investigator's Signature

I have carefully assessed/ reviewed all the information noted for the specified visit and confirm that it is accurate and complete.

Visit	Investigator's Initials	Date ____/____/____ (MM/DD/YYYY e.g. 04/07/2007)
Baseline Pre-Treatment		
Day 1		
Day 2		
Day 3		
Day 4		
Day 5		
Day 6		
Day 7		
Day 8		
Day 9		
Day 10		
Day 11		
Day 12		
Day 13		
Day 14		
Discharge		
FU 6 Weeks		
FU 3 Months		
FU 6 Months		
FU Unscheduled Visit		
FU Unscheduled Visit		
FU Unscheduled Visit		
FU Unscheduled Visit		
FU Unscheduled Visit		
FU Unscheduled Visit		

Please complete all appropriate items. Missing or inconsistent data will result in additional queries.

28 Apr. 08

Patient Trial Number

Riluzole

Investigator

Complication

form

F.doc

 AO Foundation Clinical Investigation AO Clinical Investigation and Documentation Clavadelerstrasse 8 CH-7270 Davos	F03.001.002.001	Valid from: 01.04.2008
	Adverse Event Form North America	Revision: 001 Version: 002 Replaces: Version 001

Please send / fax this Adverse Event Form along with fax coversheet (indicating protocol number) to: AO Clinical Investigation and Documentation of North America 100 Overlook Center, 2nd floor Princeton, NJ 08540/ USA Fax: +1 609 375 2683 Phone: +1 609 375 2018	Sender: Investigator: Hospital: Phone:

1. Case Identification Data														GENERIC DATA	
Site Number:											Patient trial number:		-		
	To be determined by participating hospital														
Patient Initials:	/														
	First Name Last Name														
Date of Birth:															
	Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year	
Date of Adverse Event:															
	Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year	
Date SAE Form Completed:															
	Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year	
Date Site Became Aware of Event :															
	Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year	
Type of Report:	☐ Initial ☐ Follow-up														

2. Description of Adverse Event		ADVERSE EVENT
2.1 Please describe the severity of the adverse event:		
☐ Serious AE	Event results in death or is life-threatening or requires inpatient hospitalization or prolongation of hospitalization or results in permanent impairment or led to foetal distress, foetal death congenital abnormality or birth defect. It contains also all events that could have been led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune Please note: When a serious adverse event occurs during the study an AE form must be completed by the investigator and sent to AOCID and IRB/EC immediately or within 24 hours. ➤ Attach a copy of the subject's Medical History form to this form in order to have additional information about the patient!!	
☐ Unexpected AE	Adverse device or treatment effect that has previously not been observed or is not described in the investigators brochure	
☐ Anticipated AE	AE that has been addressed in the investigators brochure	
2.2. If Serious AE, please provide the following: (Check all that apply)		
☐ Death	☐ Disability or Permanent Damage	
☐ Life-Threatening	☐ Intervention required to prevent one of the listed outcomes	
☐ Hospitalization – initial or prolonged	☐ Other serious medical event	☐ Congenital anomaly/ birth defect

Please complete all appropriate items. Missing or inconsistent data will require additional queries.

Patient Trial Number

Date

Signature of investigator for completeness and correctness of data

 AO Foundation Clinical Investigation AO Clinical Investigation and Documentation Clavadelstrasse 8 CH-7270 Davos	F03.001.002.001	Valid from: 01.04.2008
	Adverse Event Form North America	Revision: 001 Version: 002 Replaces: Version 001

2.3 Adverse Event:

Relationship of the adverse event to the study procedure/ treatment: or investigational drug/device:

- ☐ Definite
 ☐ Probable
 ☐ Possible
 ☐ Unlikely
☐ Unrelated

2.4 Please describe the adverse event:

Please give details of the event:

3. Suspect product

☐ N/A

Indicate all the following for each suspect product: Product name, dose, frequency, route, usage dates, indication for use, lot #, Expiration Date.

- ☐ Event discontinued after use of product stopped
☐ Event discontinued after reduction of dose
☐ Event reappeared after product reintroduced

Please complete all appropriate items. Missing or inconsistent data will require additional queries.

Patient Trial Number

Date

Signature of investigator for completeness and correctness of data

 AO Foundation Clinical Investigation AO Clinical Investigation and Documentation Clavadelstrasse 8 CH-7270 Davos	F03.001.002.001	Valid from: 01.04.2008 Revision: 001 Version: 002 Replaces: Version 001
	Adverse Event Form North America	

4. Suspect medical device

☐ N/A

Indicate all the following for each suspect product: Brand name, device name, manufacturer's name/city/state, model#, lot #, catalog #, serial #, expiration date, indicate device operator's relationship to subject, date of implantation if applicable, date of explantation if applicable, single-use device that was reprocessed and reused on the subject? – if yes, indicate reprocessor's name and address

5. Actions taken due to the occurrence of the event

ADVERSE EVENT

Was any action taken as a result of the event?

☐ Yes

☐ No (Skip to Section 6)

Start Date of Action
Taken:

Day

Jan

Feb

Mar

Apr

May

Jun

Jul

Aug

Sep

Oct

Nov

Dec

Year

Stop Date of Action
Taken:

☐ N/A - Continues

Specify action taken (i.e., treatment for event, temporary or permanent discontinuation of treatment, any reduction in dose, etc.):

Please complete all appropriate items. Missing or inconsistent data will require additional queries.

Patient Trial Number

Date

Signature of investigator for completeness and correctness of data

 AO Foundation Clinical Investigation AO Clinical Investigation and Documentation Clavadelstrasse 8 CH-7270 Davos	F03.001.002.001	Valid from: 01.04.2008
	Adverse Event Form North America	Revision: 001 Version: 002 Replaces: Version 001

6. Outcome to date ADVERSE EVENT

☐ Patient recovered without persistent damage
☐ Patient recovered with persistent damage

Please specify damage:

Date Event Resolved:

Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year

☐ Not known, if further information becomes available, please send ASAP
☐ Patient died, please specify:
 Cause of death:

Date of death:

Day	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year

7. Concomitant medication

Include concomitant medications (product names and dates of therapy; do not include treatment for event here)
 ➤ Attach copy of subject's Medication Form

8. Additional Relevant History

Any additional relevant history (to include history of smoking, alcohol use, allergies, race, pregnancy, etc.) Include dates.

Please complete all appropriate items. Missing or inconsistent data will require additional queries.

 AO Foundation Clinical Investigation AO Clinical Investigation and Documentation Clavadelstrasse 8 CH-7270 Davos	F03.001.002.001	Valid from: 01.04.2008
	Adverse Event Form North America	Revision: 001 Version: 002 Replaces: Version 001

9. Test / Laboratory data

Record below or attach *any laboratory results* providing relevant information related to the AE. Include dates.

☐ Copies of lab results attached

10. General comments

GENERAL COMMENTS

Any additional comments, information relevant for the event

11. Reporter

Reporter's Name:

Reporter's Signature:

Title:

Phone:

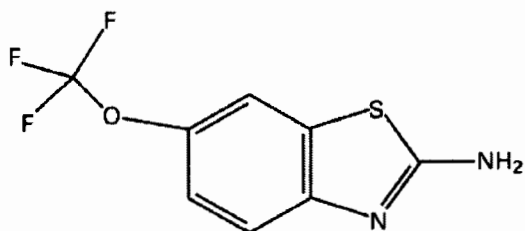
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Please complete all appropriate items. Missing or inconsistent data will require additional queries.

RILUTEK®
(riluzole) Tablets
Rx only

DESCRIPTION

RILUTEK® (riluzole) is a member of the benzothiazole class. Chemically, riluzole is 2-amino-6-(trifluoromethoxy)benzothiazole. Its molecular formula is $C_8H_5F_3N_2OS$ and its molecular weight is 234.2. Its structural formula is as follows:



Riluzole is a white to slightly yellow powder that is very soluble in dimethylformamide, dimethylsulfoxide and methanol, freely soluble in dichloromethane, sparingly soluble in 0.1 N HCl and very slightly soluble in water and in 0.1 N NaOH. RILUTEK is available as a capsule-shaped, white, film-coated tablet for oral administration containing 50 mg of riluzole. Each tablet is engraved with "RPR 202" on one side.

Inactive Ingredients:

Core: anhydrous dibasic calcium phosphate, USP; microcrystalline cellulose, NF; anhydrous colloidal silica, NF; magnesium stearate, NF; croscarmellose sodium, NF.

Film coating: hypromellose, USP; polyethylene glycol 6000; titanium dioxide, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

The etiology and pathogenesis of amyotrophic lateral sclerosis (ALS) are not known, although a number of hypotheses have been advanced. One hypothesis is that motor neurons, made vulnerable through either genetic predisposition or environmental factors, are injured by glutamate. In some cases of familial ALS the enzyme superoxide dismutase has been found to be defective.

The mode of action of RILUTEK is unknown. Its pharmacological properties include the following, some of which may be related to its effect: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage-dependent sodium channels, and 3) ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors.

Riluzole has also been shown, in a single study, to delay median time to death in a transgenic mouse model of ALS. These mice express human superoxide dismutase bearing one of the mutations found in one of the familial forms of human ALS.

It is also neuroprotective in various *in vivo* experimental models of neuronal injury involving excitotoxic mechanisms. In *in vitro* tests, riluzole protected cultured rat motor neurons from the excitotoxic effects of glutamic acid and prevented the death of cortical neurons induced by anoxia.

Due to its blockade of glutamatergic neurotransmission, riluzole also exhibits myorelaxant and sedative properties in animal models at doses of 30 mg/kg (about 20 times the recommended human daily dose) and anticonvulsant properties at a dose of 2.5 mg/kg (about 2 times the recommended human daily dose).

Pharmacokinetics

Riluzole is well-absorbed (approximately 90%), with average absolute oral bioavailability of about 60% (CV=30%). Pharmacokinetics are linear over a dose range of 25 to 100 mg given every 12 hours. A high fat meal decreases absorption, reducing AUC by about 20% and peak blood levels by about 45%. The mean elimination half-life of riluzole is 12 hours (CV=35%) after repeated doses. With multiple-dose administration, riluzole accumulates in plasma by about twofold and steady-state is reached in less than 5 days. Riluzole is 96% bound to plasma proteins, mainly to albumin and lipoproteins over the clinical concentration range.

The 50 mg market tablet was equivalent, with respect to AUC, to the tablet used in the dose ranging clinical trials, while the C_{max} was approximately 30% higher. Both tablets have been used in clinical trials. However, if doses greater than those recommended are given, it is likely that higher plasma levels will be achieved, the safety of which has not been established (see DOSAGE AND ADMINISTRATION).

Metabolism and Elimination

Riluzole is extensively metabolized to six major and a number of minor metabolites, not all of which have been identified. Some metabolites appear pharmacologically active in *in vitro* assays. The metabolism of riluzole is mostly hepatic and consists of cytochrome P450-dependent hydroxylation and glucuronidation.

There is marked interindividual variability in the clearance of riluzole, probably attributable to variability of CYP 1A2 activity, the principal isozyme involved in N-hydroxylation.

In vitro studies using liver microsomes show that hydroxylation of the primary amine group producing N-hydroxyriluzole is the main metabolic pathway in human, monkey, dog and rabbit. In humans, cytochrome P450 1A2 is the principal isozyme involved in N-hydroxylation. *In vitro* studies predict that CYP 2D6, CYP 2C19, CYP 3A4 and CYP 2E1 are unlikely to contribute significantly to riluzole metabolism in humans. Whereas direct glucuroconjugation of riluzole (involving the glucurotransferase isoform UGT-HP4) is very slow in human liver microsomes, N-hydroxyriluzole is readily conjugated at the hydroxylamine group resulting in the formation of O- (>90%) and N-glucuronides.

Following a single 150 mg dose of ^{14}C -riluzole to 6 healthy males, 90% and 5% of the radioactivity was recovered in the urine and feces respectively over a period of 7 days. Glucuronides accounted for more than 85% of the metabolites in urine. Only 2% of a riluzole dose was recovered in the urine as unchanged drug.

Special Populations

Hepatic Impairment:

The area-under-the-curve (AUC) of riluzole, after a single 50 mg oral dose, increases by about 1.7-fold in patients with mild chronic liver insufficiency (n=6; Child-Pugh's score A) and by about 3-fold in patients with moderate chronic liver insufficiency (n=6; Child-Pugh's score B) compared to healthy volunteers (n=12) (see WARNINGS and PRECAUTIONS). The pharmacokinetics of riluzole have not been studied in patients with severe hepatic impairment.

Renal Impairment:

There is no significant difference in pharmacokinetic parameters between patients with moderate ($n=5$; creatinine clearance 30-50 $\text{ml}\cdot\text{min}^{-1}$) and severe ($n=7$; creatinine clearance $<30 \text{ ml}\cdot\text{min}^{-1}$) renal insufficiency and healthy volunteers ($n=12$) after a single oral dose of 50 mg riluzole. The pharmacokinetics of riluzole have not been studied in patients undergoing hemodialysis.

Age:

The pharmacokinetic parameters of riluzole after multiple dose administration (4.5 days of treatment at 50 mg riluzole b.i.d.) are not affected in the elderly (≥ 70 years).

Gender:

No gender effect on riluzole pharmacokinetics has been found in young or elderly healthy subjects. However, in one placebo-controlled clinical trial with population pharmacokinetics, riluzole mean clearance was found to be 30% lower in female patients (corresponding to an approximate increase in AUC of 45%) as compared to male patients. No favorable or adverse effects of riluzole in relation to gender were seen in controlled trials, however.

Smoking:

Patients who smoke cigarettes eliminate riluzole 20% faster than non-smoking patients, based on a population pharmacokinetic analysis on data from 128 ALS patients, of whom 19 were smokers. However, there is no need for dosage adjustment in these patients.

Race:

Clearance of riluzole in Japanese subjects native to Japan was found to be 50% lower as compared to Caucasians after normalizing for body weight. Although it is not clear if this difference is due to genetic or environmental factors (e.g., smoking, alcohol, coffee, and dietary preferences), it is possible that Japanese subjects may possess a lower capacity (oxidative and/or conjugative) for metabolizing riluzole. There are no studies, however, of lower doses in Japanese subjects (see PRECAUTIONS).

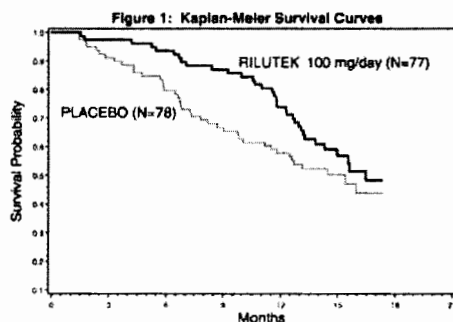
Clinical Trials

The efficacy of RILUTEK as a treatment of ALS was established in two adequate and well-controlled trials in which the time to tracheostomy or death was longer for patients randomized to RILUTEK than for those randomized to placebo.

These studies admitted patients with either familial or sporadic ALS, a disease duration of less than 5 years, and a baseline forced vital capacity greater than or equal to 60%.

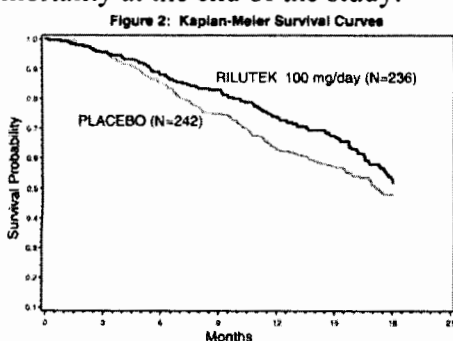
In one study, performed in France and Belgium, 155 ALS patients were followed for at least 13 months (maximum duration 18 months) after being randomized to either 100 mg/day (given 50 mg BID) of RILUTEK or placebo.

Figure 1, which follows, displays the survival curves for time to death or tracheostomy. The vertical axis represents the proportion of individuals alive without tracheostomy at various times following treatment initiation (horizontal axis). Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test $p=0.12$), the difference was found to be significant by another appropriate analysis (Wilcoxon test $p=0.05$). As seen, the study showed an early increase in survival in patients given riluzole. Among the patients in whom treatment failed during the study (tracheostomy or death) there was a difference between the treatment groups in median survival of approximately 90 days. There was no statistically significant difference in mortality at the end of the study.



In the second study, performed in both Europe and North America, 959 ALS patients were followed for at least 1 year (North American centers) and up to 18 months (European centers) after being randomized to either 50, 100, 200 mg/day of RILUTEK or placebo.

Figure 2, which follows, displays the survival curves for time to death or tracheostomy for patients randomized to either 100 mg/day of RILUTEK or placebo. Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test $p = 0.076$), the difference was found to be significant by another appropriate analysis (Wilcoxon test $p = 0.05$). Not displayed in Figure 2 are the results of 50 mg/day of RILUTEK which could not be statistically distinguished from placebo and the results of 200 mg/day which are essentially identical to 100 mg/day. As seen, the study showed an early increase in survival in patients given riluzole. Among the patients in whom treatment failed during the study (tracheostomy or death) there was a difference between the treatment groups in median survival of approximately 60 days. There was no statistically significant difference in mortality at the end of the study.



Although riluzole improved early survival in both studies, measures of muscle strength and neurological function did not show a benefit.

INDICATIONS AND USAGE

RILUTEK is indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS). Riluzole extends survival and/or time to tracheostomy.

CONTRAINDICATIONS

RILUTEK is contraindicated in patients who have a history of severe hypersensitivity reactions to riluzole or any of the tablet components.

WARNINGS

Liver Injury / Monitoring Liver Chemistries

RILUTEK should be prescribed with care in patients with current evidence or history of abnormal liver function indicated by significant abnormalities in serum transaminase (ALT/SGPT; AST/SGOT), bilirubin, and/or gamma-glutamyl transferase (GGT) levels (see PRECAUTIONS and DOSAGE AND ADMINISTRATION sections). Baseline elevations of several LFTs (especially elevated bilirubin) should preclude the use of RILUTEK.

RILUTEK, even in patients without a prior history of liver disease, causes serum aminotransferase elevations. Experience in almost 800 ALS patients indicates that about 50% of riluzole-treated patients will experience at least one ALT/SGPT level above the upper limit of normal, about 8% will have elevations > 3 X ULN, and about 2% of patients will have elevations > 5 X ULN. A single non-ALS patient with epilepsy treated with concomitant carbamazepine and phenobarbital experienced marked, rapid elevations of liver enzymes with jaundice (ALT 26 X ULN, AST 17 X ULN, and bilirubin 11 X ULN) four months after starting RILUTEK; these returned to normal 7 weeks after treatment discontinuation.

Maximum increases in serum ALT usually occurred within 3 months after the start of riluzole therapy and were usually transient when < 5 times ULN. In trials, if ALT levels were < 5 times ULN, treatment continued and ALT levels usually returned to below 2 times ULN within 2 to 6 months. Treatment in studies was discontinued, however, if ALT levels exceeded 5 X ULN, so that there is no experience with continued treatment of ALS patients once ALT values exceed 5 times ULN. Treatment should be discontinued if ALT levels are ≥ 5 X ULN or if clinical jaundice develops (see PRECAUTIONS: Laboratory Tests). There were rare instances of jaundice and hepatitis. Serum aminotransferases including ALT levels should be measured before and during riluzole therapy. Serum ALT levels should be evaluated every month during the first 3 months of treatment, every 3 months during the remainder of the first year, and periodically thereafter. Serum ALT levels should be evaluated more frequently in patients who develop elevations. (see PRECAUTIONS).

Neutropenia

Among approximately 4000 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than $500/\text{mm}^3$), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case was more complex, with marked anemia as well as neutropenia and the etiology of both is uncertain. Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt treating physicians to check white blood cell counts.

PRECAUTIONS

Use in Patients with Concomitant Disease

RILUTEK should be used with caution in patients with concomitant liver insufficiency (see WARNINGS, CLINICAL PHARMACOLOGY). In particular, in cases of RILUTEK-induced hepatic injury manifested by elevated liver enzymes, the effect of the hepatic injury on RILUTEK metabolism is unknown.

Special Populations

Riluzole should be used with caution in elderly patients whose hepatic function may be compromised due to age. Also, female patients and Japanese patients may possess a lower metabolic capacity to eliminate riluzole compared to males and Caucasian subjects, respectively (see CLINICAL PHARMACOLOGY: Special Populations).

Information for the Patient

Patients should be advised to report any febrile illness to their physicians (see WARNINGS: Neutropenia).

Patients and caregivers should be advised that RILUTEK should be taken on a regular basis and at the same time of the day (*e.g.*, in the morning and evening) each day. If a dose is missed, take the next tablet as originally planned (see DOSAGE AND ADMINISTRATION).

Patients should be warned about the potential for dizziness, vertigo, or somnolence and advised not to drive or operate machinery until they have gained sufficient experience on RILUTEK to gauge whether or not it affects their mental and/or motor performance adversely.

Whether alcohol increases the risk of serious hepatotoxicity with RILUTEK is unknown; therefore, patients being treated with RILUTEK should be discouraged from drinking excessive amounts of alcohol.

Patients should also be made aware that RILUTEK should be stored at temperatures between 20°-25°C (68°-77°F) and protected from bright light.

RILUTEK must be kept out of the reach of children.

Laboratory Tests

As noted in the WARNINGS Section, there is no experience with continued treatment of patients once ALT exceeds 5 X ULN. Treatment should be discontinued if ALT levels are ≥ 5 X ULN or if clinical jaundice develops. Because there is no experience with rechallenge of patients who have had RILUTEK discontinued for ALT > 5 X ULN, no recommendations about restarting RILUTEK can be made.

In the two controlled trials in patients with ALS, the frequency with which values for hemoglobin, hematocrit, and erythrocyte counts fell below the lower limit of normal was greater in RILUTEK-treated patients than in placebo-treated patients; however, these changes were mild and transient. The proportions of patients observed with abnormally low values for these parameters showed a dose-response relationship. Only one patient was discontinued from treatment because of severe anemia. The significance of this finding is unknown.

Drug Interactions

There have been no clinical studies designed to evaluate the interaction of riluzole with other drugs.

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Hepatotoxic Drugs:

The clinical trials in ALS excluded patients on concomitant medications which were potentially hepatotoxic, (*e.g.*, allopurinol, methyldopa, sulfasalazine). Accordingly, there is no information about the safety of administering RILUTEK in conjunction with such medications. If the practitioner chooses to prescribe such a combination, caution should be exercised.

Drugs Highly Bound To Plasma Proteins:

Riluzole is highly bound (96%) to plasma proteins, binding mainly to serum albumin and to lipoproteins. The effect of riluzole (up to 5 mcg/mL) on warfarin (5 mcg/mL) binding did not show any displacement of warfarin. Conversely, riluzole binding was unaffected by the addition of warfarin, digoxin, imipramine and quinine at high therapeutic concentrations.

Effect of Other Drugs On Riluzole Metabolism:

In vitro studies using human liver microsomal preparations suggest that CYP 1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole and, therefore, potential interactions may occur when riluzole is given concurrently with agents that affect CYP 1A2 activity. Potential inhibitors of CYP 1A2 (e.g., caffeine, phenacetin, theophylline, amitriptyline, and quinolones) could decrease the rate of riluzole elimination, while inducers of CYP 1A2 (e.g., cigarette smoke, charcoal-broiled food, rifampicin, and omeprazole) could increase the rate of riluzole elimination.

Effect of Riluzole On the Metabolism of Other Drugs:

CYP 1A2 is the principal isoenzyme involved in the initial oxidative metabolism of riluzole; potential interactions may occur when riluzole is given concurrently with other agents which are also metabolized primarily by CYP 1A2 (e.g., theophylline, caffeine, and tacrine). Currently, it is not known whether riluzole has any potential for enzyme induction in humans.

Drug Laboratory Test Interactions: None known

Carcinogenesis, Mutagenesis, Impairment of Fertility

Riluzole was not carcinogenic in mice or rats when administered for 2 years at daily oral doses up to 20 mg/kg and 10 mg/kg, respectively, which are approximately equivalent to the maximum human dose on a mg/m² basis.

The genotoxic potential of riluzole was evaluated in the bacterial mutagenicity (Ames) test, the mouse lymphoma mutation assay in L5178Y cells, the *in vitro* chromosomal aberration assay in human lymphocytes and the *in vivo* rat cytogenetic assay and *in vivo* mouse micronucleus assay in bone marrow. There was no evidence of mutagenic or clastogenic potential in the Ames test, the mouse lymphoma assay, or the *in vivo* assays in the mouse and rat. There was an equivocal clastogenic response in the *in vitro* human lymphocyte chromosomal aberration assay, which was not reproduced in a second assay performed at equal or higher concentrations; riluzole was therefore considered non-clastogenic in the human lymphocyte assay.

N-hydroxyriluzole, the major active metabolite of riluzole, caused chromosomal damage in the *in vitro* mammalian mouse lymphoma assay and in the *in vitro* micronucleus assay that used the same mouse lymphoma cell line, L5178Y. N-hydroxyriluzole was not mutagenic in this cell line when tested in the HPRT gene mutation assay, and was negative in the Ames bacterial gene mutation assay (with and without rat or hamster S9), the *in vitro* UDS assay in rat hepatocytes, the chromosomal aberration test in human lymphocytes, and the *in vivo* mouse bone marrow micronucleus test.

Riluzole impaired fertility when administered to male and female rats prior to and during mating at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m² basis (see PRECAUTIONS: "Pregnancy" for effects on fertility).

Pregnancy

Pregnancy category C:

Oral administration of riluzole to pregnant animals during the period of organogenesis caused embryotoxicity in rats and rabbits at doses of 27 mg/kg and 60 mg/kg, respectively, or 2.6 and 11.5 times, respectively, the recommended maximum human daily dose on a mg/m² basis. Evidence of maternal toxicity was also observed at these doses.

When administered to rats prior to and during mating (males and females) and throughout gestation and lactation (females), riluzole produced adverse effects on pregnancy (decreased implantations, increased intrauterine death) and offspring viability and growth at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m² basis.

There are no adequate and well-controlled studies in pregnant women. Riluzole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

In rat studies, ¹⁴C-riluzole was detected in maternal milk. It is not known whether riluzole is excreted in human breast milk. Because many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants from RILUTEK® is unknown, women should be advised not to breast-feed during treatment with RILUTEK.

Geriatric Use

Age-related compromised renal and hepatic function may cause a decrease in clearance of riluzole (see CLINICAL PHARMACOLOGY: Special Populations). In controlled clinical trials, about 30% of patients were over 65. There were no differences in adverse effects between younger and older patients.

Pediatric Use

The safety and the effectiveness of RILUTEK in pediatric patients have not been established.

ADVERSE REACTIONS

The most commonly observed AEs associated with the use of RILUTEK more frequently than placebo treated patients were: asthenia, nausea, dizziness, decreased lung function, diarrhea, abdominal pain, pneumonia, vomiting, vertigo, circumoral paresthesia, anorexia, and somnolence. Asthenia, nausea, dizziness, diarrhea, anorexia, vertigo, somnolence, and circumoral paresthesia were dose related.

Approximately 14% (n = 141) of the 982 individuals with ALS who received RILUTEK in pre-marketing clinical trials discontinued treatment because of an adverse experience. Of those patients who discontinued due to adverse events, the most commonly reported were: nausea, abdominal pain, constipation, and ALT elevations. In a dose response study in ALS patients, the rates of discontinuation of RILUTEK for asthenia, nausea, abdominal pain, and ALT elevation were dose related.

Incidence in Controlled ALS Clinical Studies

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients with ALS treated with RILUTEK (n=794) participating in placebo-controlled trials and were numerically greater in the patients treated with RILUTEK 100 mg/day than with placebo or for which a dose response relationship is suggested.

The prescriber should be aware that these figures cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the AE incidences in the population studied.

Table 1
Adverse Events Occurring in Placebo-Controlled Clinical Trials

Body System / Adverse Event†	†Percentage of patients reporting events			
	Riluzole 50 mg/day (N=237)	Riluzole 100 mg/day (N=313)	Riluzole 200 mg/day (N=244)	Placebo (N=320)
Body as a Whole				
Asthenia	14.8	19.2	20.1	12.2
Headache	8.0	7.3	7.0	6.6
Abdominal pain	6.8	5.1	7.8	3.8
Back pain	1.7	3.2	4.1	2.5
Aggravation reaction	0.4	1.3	2.0	0.9
Malaise	0.4	0.6	1.2	0.0
Digestive				
Nausea	12.2	16.3	20.5	10.6
Vomiting	4.2	4.2	4.5	1.6
Dyspepsia	2.5	3.8	6.1	5.0
Anorexia	3.8	3.2	8.6	3.8
Diarrhea	5.5	2.9	9.0	3.1
Flatulence	2.5	2.6	2.0	1.9
Stomatitis	0.8	1.0	1.2	0.0
Tooth disorder	0.0	1.0	1.2	0.3
Oral Moniliasis	0.4	0.6	1.2	0.3
Nervous				
Hypertonia	5.9	6.1	5.3	5.9
Depression	4.2	4.5	6.1	5.0
Dizziness	5.1	3.8	12.7	2.5
Dry mouth	3.0	3.5	2.0	3.4
Insomnia	2.1	3.5	2.9	3.4
Somnolence	0.8	1.9	4.1	1.3
Vertigo	2.5	1.9	4.5	0.9
Circumoral paresthesia	1.3	1.6	3.3	0.0
Skin and Appendages				
Pruritus	3.8	3.8	2.5	3.1
Eczema	0.8	1.6	1.6	0.6
Alopecia	0.0	1.0	1.2	0.6
Exfoliative dermatitis	0.0	0.6	1.2	0.0
Respiratory				
Decreased lung function	13.1	10.2	16.0	9.4
Rhinitis	8.9	6.4	7.8	6.3
Increased cough	2.1	2.6	3.7	1.6
Sinusitis	0.4	1.0	1.6	0.9
Cardiovascular				
Hypertension	6.8	5.1	3.3	4.1
Tachycardia	1.3	2.6	2.0	1.3
Phlebitis	0.4	1.0	0.8	0.3
Palpitation	0.4	0.6	1.2	0.9
Postural hypotension	0.8	0.0	1.6	0.6
Metabolic and Nutritional Disorders				

Body System / Adverse Event†	Riluzole 50 mg/day (N=237)	Riluzole 100 mg/day (N=313)	Riluzole 200 mg/day (N=244)	Placebo (N=320)
Weight loss	4.6	4.8	3.7	4.7
Peripheral edema	4.2	2.9	3.3	2.2
Musculoskeletal System				
Arthralgia	5.1	3.5	1.6	3.4
Urogenital System				
Urinary tract infection	2.5	2.6	4.5	2.2
Dysuria	0.0	1.0	1.2	0.3

Other Adverse Events Observed

Other events which occurred in more than 2% of patients treated with RILUTEK 100 mg/day but equally or more frequently in the placebo group included: accidental injury, apnea, bronchitis, constipation, death, dysphagia, dyspnea, flu syndrome, heart arrest, increased sputum, pneumonia, and respiratory disorder.

The overall adverse event profile for RILUTEK was similar between females and males, and was independent of age. Because the largest non-white racial subgroup was only 2% of patients exposed to RILUTEK (18/794) in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse experience reports by race. In ALS studies, dizziness did occur more commonly in females (11%) than in males (4%). There was not a difference between females and males in the rates of discontinuation of RILUTEK for individual adverse experiences.

Other Adverse Events Observed During All Clinical Trials

RILUTEK has been administered to 1713 individuals during all clinical trials, some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 1713 individuals exposed to RILUTEK who experienced an event of the type cited on at least one occasion while receiving RILUTEK. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000 patients.

* = AE frequency ≤ to placebo

Body as a Whole:

Frequent: Hostility*. *Infrequent:* Abscess*, sepsis*, photosensitivity reaction*, cellulitis, face edema*, hernia, peritonitis, attempted suicide, injection site reaction, chills*, flu syndrome, intentional injury, enlarged abdomen, neoplasm. *Rare:* Acrodynia, hypothermia, moniliasis*, rheumatoid arthritis.

Digestive System: *Infrequent:* Increased appetite, intestinal obstruction*, fecal impaction, gastrointestinal hemorrhage, gastrointestinal ulceration, gastritis*, fecal incontinence, jaundice, hepatitis, glossitis, gum hemorrhage*, pancreatitis, tenesmus, esophageal stenosis. *Rare:*

Cheilitis*, cholecystitis, hematemesis, melena*, biliary pain, proctitis, pseudomembranous enterocolitis, enlarged salivary gland, tongue discoloration, tooth caries.

Nervous System: *Frequent:* Agitation*, tremor. *Infrequent:* Hallucinations, personality disorder*, abnormal thinking*, coma, paranoid reaction*, manic reaction, ataxia, extrapyramidal syndrome, hypokinesia, urinary retention, emotional lability, delusions, apathy, hypesthesia, incoordination, confusion*, convulsion, leg cramps, amnesia, dysarthria, increased libido, stupor, subdural hematoma, abnormal gait, delirium, depersonalization, facial paralysis, hemiplegia, decreased libido, myoclonus. *Rare:* Abnormal dreams, acute brain syndrome, CNS depression, dementia, cerebral embolism, euphoria*, hypotonia, ileus*, peripheral neuritis, psychosis*, psychotic depression, schizophrenic reaction, trismus, wristdrop.

Skin and Appendages: *Infrequent:* Skin ulceration, urticaria, psoriasis, seborrhea*, skin disorder, fungal dermatitis*. *Rare:* Anaphylactoid reaction, angioedema, contact dermatitis, erythema multiforme, furunculosis*, skin moniliasis, skin granuloma, skin nodule.

Respiratory System: *Infrequent:* Hiccup, pleural disorder*, asthma, epistaxis, hemoptysis, yawn, hyperventilation*, lung edema*, hypoventilation*, lung carcinoma, hypoxia, laryngitis, pleural effusion, pneumothorax*, respiratory moniliasis, stridor.

Cardiovascular System: *Infrequent:* Syncope*, hypotension, heart failure, migraine, peripheral vascular disease, angina pectoris*, myocardial infarction*, ventricular extrasystoles, cerebral hemorrhage, atrial fibrillation*, bundle branch block, congestive heart failure, pericarditis, lower extremity embolus, myocardial ischemia*, shock*. *Rare:* Bradycardia, cerebral ischemia, hemorrhage, mesenteric artery occlusion, subarachnoid hemorrhage, supraventricular tachycardia*, thrombosis, ventricular fibrillation, ventricular tachycardia.

Metabolic and Nutritional Disorders: *Infrequent:* Gout*, respiratory acidosis, edema, thirst*, hypokalemia, hyponatremia, weight gain*. *Rare:* Generalized edema, hypercalcemia, hypercholesteremia.

Endocrine System: *Infrequent:* Diabetes mellitus, thyroid neoplasia. *Rare:* Diabetes insipidus, parathyroid disorder.

Hemic and Lymphatic System: *Infrequent:* Anemia*, leukocytosis, leukopenia, ecchymosis. *Rare:* Neutropenia, aplastic anemia, cyanosis, hypochromic anemia, iron deficiency anemia, lymphadenopathy, petechiae*, purpura.

Musculoskeletal System: *Infrequent:* Arthrosis, myasthenia*, bone neoplasm. *Rare:* Bone necrosis, osteoporosis, tetany.

Special Senses: *Infrequent:* Amblyopia, ophthalmitis. *Rare:* Blepharitis, cataract, deafness, diplopia*, ear pain, glaucoma, hyperacusis, photophobia, taste loss, vestibular disorder.

Urogenital System: *Infrequent:* Urinary urgency, urine abnormality, urinary incontinence, kidney calculus, hematuria, impotence, prostate carcinoma, kidney pain, metrorrhagia, priapism. *Rare:* Amenorrhea, breast abscess, breast pain, nephritis*, nocturia, pyelonephritis, enlarged uterine fibroids, uterine hemorrhage, vaginal moniliasis.

Laboratory Tests: *Infrequent:* Increased gamma glutamyl transferase, abnormal liver function/tests, increased alkaline phosphatase, positive direct Coombs test, increased gamma globulins. *Rare:* increased lactic dehydrogenase.

OVERDOSAGE

No specific antidote or information on treatment of overdosage with RILUTEK is available. In the event of overdose, RILUTEK therapy should be discontinued immediately. Experience with riluzole overdose in humans is limited. Neurological and psychiatric symptoms, acute toxic

encephalopathy with stupor, coma, and methemoglobinemia have been observed in isolated cases. Treatment should be supportive and directed toward alleviating symptoms. Severe methemoglobinemia may be rapidly reversible after treatment with methylene blue. The estimated oral median lethal dose is 94 mg/kg and 39 mg/kg for male mice and rats, respectively.

DOSAGE AND ADMINISTRATION

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RILUTEK tablets should be taken at least an hour before, or two hours after, a meal to avoid a food-related decrease in bioavailability.

Special Populations

Patients with Impaired Hepatic Function: see WARNINGS, PRECAUTIONS, CLINICAL PHARMACOLOGY.

HOW SUPPLIED

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Hypersensitivity pneumonitis possibly caused by riluzole therapy in ALS

David Cassiman, MD, PhD; Michiel Thomeer, MD;
Erik Verbeke, MD, PhD; and Wim Robberecht, MD, PhD

A 69-year-old man with sporadic amyotrophic lateral sclerosis (ALS) presented with complaints of increasing and disabling shortness of breath and dry cough for 3 months. A chest X-ray, taken for routine purposes 6 months before the start of symptoms, was normal.

The patient was diagnosed with ALS 33 months before presentation. Riluzole^{1,2} 50 mg twice daily was started 1 year later. He was treated with omeprazole 20 mg per day for more than 10 years, for a grade IV esophagitis. Ten days before the respiratory complaints started, omeprazole was switched to lansoprazole 15 mg per day.

After receiving antibiotics for a total of 20 days, without effect, the patient consulted a pulmonologist, who diagnosed him with pulmonary fibrosis. He was treated with methylprednisolone for 8 weeks (32 mg per day tapered every fortnight). This improved his general condition, but had only a minor effect on the coughing and dyspnea. After methylprednisolone was stopped, the complaints soon recurred and the patient presented himself to our clinic.

Clinical examination revealed ALS with predominant lower limb involvement: the patient was capable of walking with a walker, but was restricted to a wheelchair due to his dyspnea. The patient manifested an increased respiratory rate and use of accessory respiratory muscles. Lung auscultation was normal. Arterial blood gas at room air showed hypoxia (pH 7.49, oxygen tension 57 mm Hg, carbon dioxide tension 37 mm Hg). Laboratory tests revealed normal blood counts, normal liver and renal function and electrolytes, and increased erythrocyte sedimentation rate (63 mm/hour [normal value, 1 to 10 mm/hour]) and lactate dehydrogenase (701 U/L [normal value, 240 to 480 U/L]); antinuclear and antineutrophil cytoplasmic antibodies were negative. A chest X-ray was suggestive of interstitial lung disease (figure, A). Lung function measurements showed restrictive lung disease (forced vital capacity of 65% and total lung capacity of 57% of the predicted value) and a severe decrease of carbon monoxide diffusion (26% of the predicted value). Chest CT showed enlargement of the interlobular septa and bronchial structures (figure, C). Bronchoscopy results were normal. Broncho-alveolar lavage fluid stained negative for tuberculosis and contained no pathogenic bacteria or malignant cells. It contained 358 leukocytes per μ L (normal value, 50 to 250 per μ L), 51.5% of which were lymphocytes (normal value, 0.0 to 20.0%).

Thoracoscopic lung biopsy was performed, because less invasive technical investigations yielded no definite diagnosis and the patient was deteriorating. Anatomopathology revealed a picture suggestive of hypersensitivity pneumonitis (HP) (figure, E and F).

On the diagnosis of HP and exclusion of other potential causes, mainly by taking a detailed history of past and present exposures, riluzole and lansoprazole were discontinued and methylprednisolone 32 mg per day was restarted.

Three weeks later, the patient showed recovery from dyspnea and was walking with his walker again; the cough had disappeared. Control arterial blood gas showed complete normalization, control chest X-ray and CT showed significant resolution (figure 1, B and D), lung function showed partial recuperation (forced vital capacity of 78%), and carbon monoxide diffusion showed a significant increase to 40%.

Discussion. Neither the adverse events database of the distributor of riluzole (Aventis) nor the literature revealed reports of adverse events similar to the one reported here.^{3,4}

Omeprazole compromises the effect of riluzole by enhancing its metabolism, via induction of cytochrome p450 1A2, as can be read in the instruction leaflet of riluzole, supplied by Aventis. Lansoprazole does not have this effect. We hypothesize that the deleterious effect of riluzole in this patient only became apparent

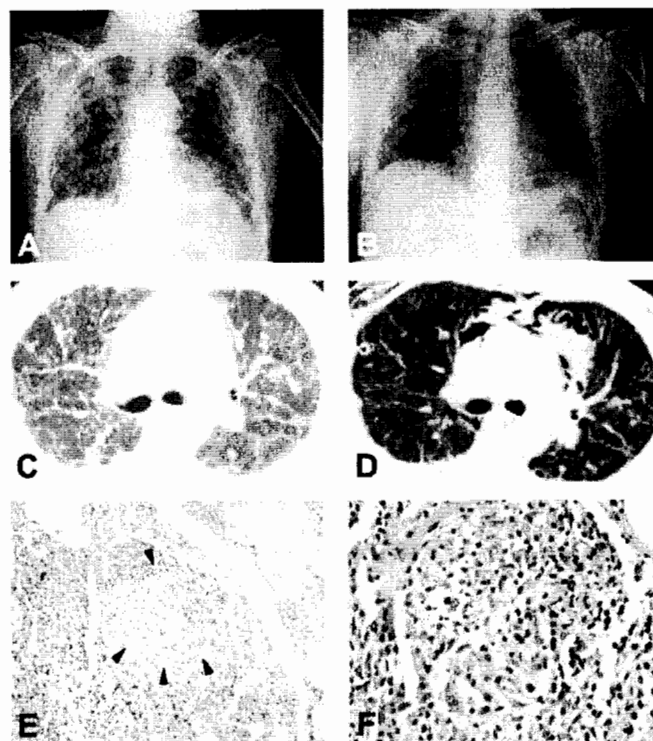


Figure. (A) Chest X-ray at presentation showed a normal mediastinum, normal lung hili, and a normal heart, but diffuse interstitial enhancement suggestive of interstitial lung disease. (B) Control chest X-ray, taken 3 weeks after cessation of riluzole therapy, showed resolution of the interstitial enhancement seen at presentation (see A). (C) Chest CT scan at presentation, at the level of the truncus pulmonalis, showed enlargement of the interlobular septa and bronchial structures (traction bronchiectasies). The lymph nodes are of normal size; there are no confluent alveolar infiltrates. (D) Control chest CT scan (level of the truncus pulmonalis), taken 3 months after cessation of riluzole, showed that the enlargement of interlobular septa and bronchial structures seen in C had diminished. (E) Pathologic examination of an open lung biopsy showed both the interstitial mononuclear infiltrate and loose epithelioid granulomas (a granuloma is delimited by the arrowheads), characteristic of hypersensitivity pneumonitis (hematoxylin-eosin [H-E], original magnification $\times 100$). (F) Detail of a loose epithelioid granuloma, as described in E (H-E, original magnification $\times 400$).

after switching omeprazole to lansoprazole, because this switch preceded the onset of symptoms in our patient by only 10 days. The prior 21 months of exposure to riluzole + omeprazole may have allowed the patient to develop a subclinical reaction to riluzole. That lansoprazole would be the cause of the HP is highly unlikely, in view of the short exposure to lansoprazole at the time of first symptoms (10 days) and the long-term widespread use of the compound without reports of similar adverse reactions.

The diagnosis of HP is supported by the biochemical, radio-

logic, and anatomopathologic data presented. Because the first steroid treatment, which was initiated while the patient was still on riluzole, had no lasting effect on his complaints, whereas discontinuation of riluzole combined with steroid treatment improved his condition, we consider the diagnosis of HP caused by riluzole to be probable.

The diagnosis of HP should be considered in patients with ALS taking riluzole and presenting with dyspnea, weight loss, and occasionally fever, in association with pulmonary infiltrates and a lymphocytic broncho-alveolar lavage fluid. The HP reaction does not depend on dosage, only on prior sensitization to the agent.

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Acute fatal stroke immediately following autologous fat injection into the face

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In cosmetic surgery, autologous fat injection into the face is generally considered safe.¹ However, cases of sudden visual loss or cerebral infarction after fat injection into the glabella have been reported.^{2,3} We report a patient with acute fatal cerebral infarction after autologous fat injection into the face.

Case report. Under local anesthesia, a 39-year-old woman underwent autologous fat injection into the glabella to correct frown lines. Her head was positioned supine during the procedure. Fat (5 mL) was injected into the glabella for over 4 minutes. There was no excessive bleeding or tension on the carotid arteries. One minute after fat injection, the patient developed mental change, aphasia, and right hemiplegia. Medical history showed no hypertension, diabetes mellitus, smoking, hyperlipidemia, heart disease, hypercoagulable state, arterial or venous occlusive disease, hematologic disease, previous surgery, or recent trauma. Physical examination immediately after symptom onset showed the blood pressure was 120/80 mm Hg, respiratory rate was 20 breaths/min, pulse rate was 58 beats/min, and body temperature was 36.8 °C. Physical examination at our emergency department showed surgical wounds on the glabella, left forehead, and periorbital area. Vital signs and the auscultation for neck vessels and heart were normal. Thirty minutes after symptom onset neurologic examination revealed drowsy mentality, global aphasia, and right complete sensorimotor hemiplegia. The left eye was midline fixed, and the pupil was dilated and unresponsive to direct light stimulation. Funduscopic examination showed severe corneal opacity in the

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left eye. Intraocular pressure of the left eye was zero. Brain CT done 50 minutes after symptom onset was normal including the signals suggesting air. Two hours after symptom onset, diffusion-weighted imaging revealed an acute infarction in the left hemisphere (figure, A). T2-weighted imaging showed high signal intensity within the left internal carotid artery (figure, B). Initial workups were normal including: complete blood count, prothrombin time, partial thromboplastin time, fibrinogen, fibrin degradation product, blood chemistries, chest radiographs, and EKG. Screening tests for vasculitis and coagulopathies were negative. Twelve hours later, she developed deep coma, central hyperventilation, and decorticate rigidity even with artificial ventilation and IV dexamethasone and saline. Two days later, the ophthalmologist revealed a necrotized left eye. The patient died 4 days later, and her family refused to grant permission for autopsy.

Discussion. Autologous fat injection is widely used in plastic surgery, and infection and sepsis are the main immediate complications.⁴ Sudden visual loss or cerebral infarction is rare but serious.^{2,3} Possible mechanisms for perioperative cerebral infarction during nonvascular surgery include: cerebral perfusion defect during general anesthesia; the increase of coagulability postoperatively; and air or fat embolism.⁵ Fat embolism is the presumed cause of stroke in this patient, but it is unclear if the patient had intracranial steno-occlusive diseases or carotid dissection because the patient's condition did not allow us to evaluate extracranial and intracranial vascular diseases. In addition, her family refused autopsy because of religious reasons. Because vascular imaging, echocardiography, and autopsy information were not obtained, the etiology could not be confirmed. However, the patient's symptoms developed 1 minute after the fat injection into the glabella, and there were no risk factors for stroke in this young patient. The operation was done using local anesthesia, and there was no evidence of a direct or indirect vessel injury during the procedure. The patient's left eye was totally necrotized. Considering the latency between the fat injection and the occurrence of symptoms, it is unclear whether the embolism to the internal carotid artery developed after the driven fatty particles entered the facial veins and passed the pulmonary circulation. The immediate onset of symptoms after fat injection may indicate the direct intravasation of fatty particles into the carotid artery system. The preconditions, local increase in pressure, and well-vascularized tissue have been proposed for the intravasation of fat resulting in fat embolism.⁶ Excessive force and velocity of injection may have caused the increase in local pressure. Functionally inactive anastomoses between the external and internal carotid arteries may become active if the pressure in the external carotid artery branches is increased.⁷ We propose that the fragments of fatty tissue reached the internal carotid artery by reversed flow through ocular and facial vessels and branches of the external carotid arteries after a local increase in pressure in highly vascularized tissue. In conclusion, fat injections into the glabella and periorbital areas should be done carefully to prevent intravasation of the fat.

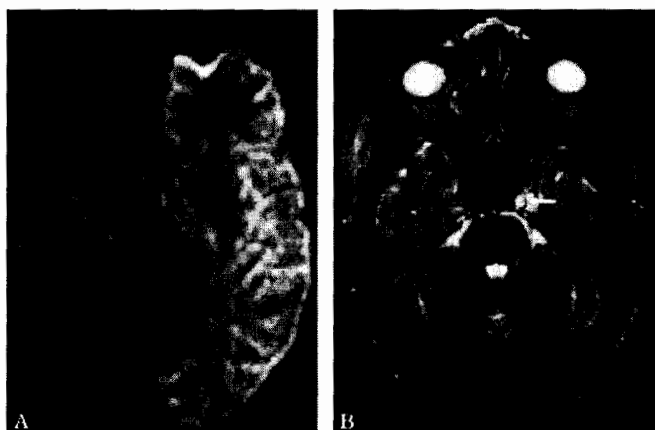


Figure. Diffusion-weighted imaging showed high signal intensities in the left cerebral hemisphere (A). T2-weighted imaging showed high signal intensities in the left carotid artery (arrow) (B).

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ALS in a patient with hereditary neuropathy with liability to pressure palsy

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Hereditary neuropathy with liability to pressure palsy (HNPP) is infrequently diagnosed, although epidemiologic data suggest the prevalence may be as high as 16/100,000.¹ HNPP is associated with a 1.5-Mb deletion on chromosome 17p11.2-12 bearing the peripheral myelin protein 22 (*PMP22*) gene. There is a possible association between HNPP and CNS demyelinating lesions. We present a patient with a 1.5-Mb deletion in the *PMP22* gene who presented with symptoms, signs, and electrophysiologic findings of ALS in addition to multiple mononeuropathies.

Case report. A 51-year-old woman presented in 2005 with a 4-month history of increasing weakness in the right upper limb and deteriorating gait due to a sensation of "heaviness" in her legs. There was no history of falls, incontinence, or visual symptoms. She had a previous diagnosis of left-sided carpal tunnel syndrome.

On examination, she had a mildly spastic gait and increased tone in four limbs. There was wasting evident in the muscles of the right hand, with fasciculations seen in the right triceps, biceps, and quadriceps muscles bilaterally. There were increased reflexes throughout, with patellar clonus and positive Hoffmann's sign. Our patient had pes cavus, and she informed us that her daughter and three sisters also had high-arched feet. No other relevant family history was known.

EMG revealed marked acute and chronic denervation changes in both upper limbs, involving the right more severely. Milder chronic neuropathic features were evident in both lower limbs, with no evidence of bulbar denervation. Nerve conduction studies demonstrated normal sural nerve sensory action potentials (SAPs), but reduced radial and median nerve SAPs bilaterally. There was marked slowing of the median motor nerve conduction velocities bilaterally at the wrist, with very severe slowing of the ulnar nerves bilaterally at the elbow and moderate slowing of the right common peroneal motor nerve conduction velocities at the fibular head. There was no evidence of proximal conduction blocks in the four limbs.

The conclusion from neurophysiologic studies was that these findings might represent dual pathology, consistent with widespread anterior horn cell disease, with a background compressive neuropathy such as HNPP.

MRI of the brain and spinal cord was normal. CSF analysis was normal, with no oligoclonal bands found. Other investigations included normal full blood count, routine biochemistry, serum lead levels, and negative HIV (1 and 2) and syphilis serology. Antineuronal antibodies, human peripheral nerve, and spinal cord antiganglioside antibodies were negative. Genetic analysis for HNPP was positive, demonstrating a deletion at the chromosome site 17p11.2.

Clinical follow-up at 6 months after our patient's initial presentation revealed progression of symptoms and signs. She is now markedly dysarthric, with prominent fasciculations and wasting in the muscles of all limbs. Her weakness has progressed, and the deep tendon reflexes remain brisk, with bilateral extensor plantar responses. She now fulfills the revised El Escorial research diagnostic criteria for definite ALS.² Muscle biopsy was not deemed necessary, given the clinical and neurophysiologic findings.

Discussion. HNPP is a demyelinating neuropathy, clinically characterized by recurrent painless focal neuropathies, which occur mainly at common entrapment sites.³ Prolonged neurologic deficits are uncommon, as symptoms tend to improve within days to weeks.³ Electrophysiologic examinations of patients with HNPP reveals two characteristic findings, namely, a generalized sensorimotor neuropathy and superimposed focal conduction abnormalities preferentially located at common entrapment or compression sites.⁴ The disease is autosomal dominantly inherited and is associated with a 1.5-Mb deletion on chromosome 17p11.2-12 bearing the peripheral myelin protein 22 (*PMP22*) gene.³ *PMP22* is localized in the compact part of peripheral nerve myelin and accounts for about 2 to 5% of the total myelin.⁵ *PMP22* has an essential role in the formation and maintenance of compact myelin, but its role outside the peripheral nervous system is uncertain.⁵ Previous case reports and a single larger family study have demonstrated that a possible association exists with HNPP and CNS lesions.^{5,6} The CNS lesions identified consisted of MRI findings of possible demyelination, with clinical evidence on history or examination consistent with CNS lesions in some patients.

Although cases of neuropathies such as motor neuropathy with conduction block have been shown to mimic ALS,⁷ to our knowledge there has been no description of HNPP associated with ALS to account for our patient's mixed upper and lower motor neuron signs and her electrophysiologic findings. Whether our patient's syndrome represents a coincidental co-occurrence of two uncommon conditions or a possibly new CNS manifestation of HNPP is unknown.

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An acute, life-threatening, hypersensitivity reaction to riluzole

Eric J. Sorenson, MD

Riluzole is the only Food and Drug Administration–approved treatment of ALS that has been shown to modestly prolong survival.¹ Riluzole is generally well tolerated. Serious drug-related side

effects occur in fewer than 2% of subjects.² Approximately half of these are attributable to elevations in liver transaminases.² Long-term follow-up studies have not suggested any long-term toxicity of this drug.³ Adverse events in general are thought to be minor and reversible with discontinuation of the drug. We report a severe, life-threatening systemic inflammatory reaction to riluzole in a patient with ALS.

Case report. A healthy 50-year-old man was diagnosed with ALS after presenting with 1 year of progressive asymmetrical hand weakness. He fulfilled the El Escorial Criteria for clinically definite ALS at the time of his presentation. He began riluzole therapy at 50 mg twice daily. Concurrently, he was started on zolpidem tartrate to assist with his sleep. Fourteen days later, he began to complain of myalgias and fevers to 40°C. His liver enzymes at that time demonstrated a modest elevation: AST of 92 (normal, 12 to 31), alanine aminotransferase of 166 (normal, 10 to 45), alkaline phosphatase of 140 (normal, 45 to 115). His baseline liver enzymes had been normal before starting the riluzole. His riluzole was held because of the elevated enzymes, but his zolpidem was continued. His symptoms continued to progress during the next 48 hours to include prominent nausea and diffuse pruritic rash. His admission examination revealed the diffuse rash, generalized lymphadenopathy, and atrial fibrillation. Evaluation included chest x-ray, demonstrating diffuse interstitial infiltrates; echocardiogram, demonstrating constrictive pericarditis; and a bone marrow biopsy, demonstrating hypercellular marrow with several granulomas. Infectious disease work-up was unremarkable. The patient's atrial fibrillation required rate control with metoprolol and amiodarone. He was otherwise treated supportively. His symptoms improved spontaneously and he was discharged after a 16-day hospitalization. By 3 months, his liver enzymes returned to normal and his skin rash resolved. His cardiac medications were discontinued, and he has remained in normal sinus rhythm. Follow-up echocardiogram demonstrated resolution of his pericarditis, and his lymphadenopathy was no longer apparent on clinical examination. The patient was not rechallenged with riluzole. He has continued to use the zolpidem intermittently as a sleep aid. He has now been observed for 1 year, and there has been no recurrence.

Discussion. A number of idiosyncratic reactions have been reported with the use of riluzole. The reported cases to date have demonstrated isolated organ involvement without a systemic reaction. These include case reports of acute hepatitis and pancreatitis caused by riluzole therapy.^{4,5} There have been two cases of hypersensitivity pneumonitis.^{6,7} These cases all had a focal inflammatory component. Liver biopsy in one case demonstrated an inflammatory reaction with the presence of mononuclear cells and plasmacytes.⁴ Lung biopsy in one of the cases of hypersensitivity pneumonitis also demonstrated a mononuclear infiltrate and loose epithelioid granulomas.⁷ In each of these cases, the inflammatory reaction was limited to a single organ and resolved with stoppage of riluzole. One case was rechallenged with riluzole after resolution of the patient's hepatitis with recurrence.⁴

The present case is an example of a rare idiosyncratic reaction that can occur with the riluzole in ALS. This is the first case report of a severe systemic inflammatory reaction occurring

within 2 weeks of beginning riluzole therapy. Secondly, this patient's reaction is atypical for the usual allergic hypersensitivity reaction. The previously reported adverse reactions have suggested a localized inflammatory component with involvement isolated to a single organ. Interestingly, in this case and in one previous case, there was a prominent granulomatous reaction. Finally, this is the first case to report life-threatening cardiac involvement as an acute reaction to riluzole.

Without a rechallenge with riluzole, one cannot conclude definitively that this reaction is caused by this medication. This was unlikely caused by zolpidem. The reaction resolved without stopping the zolpidem, and we are unaware of previous similar reactions attributable to zolpidem. Given the temporal onset within 2 weeks of the riluzole's initiation and the spontaneous resolution of the symptoms after the withdrawal of the medication, it is likely that riluzole was the cause. This case highlights the need to consider drug reaction with the occurrence of any single or multiorgan inflammatory reaction after the initiation of riluzole therapy. Although our case began acutely after the initiation of therapy, others have reported occurrences late as an idiosyncratic reaction.

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Ptosis as a feature of late-onset glycogenosis type II

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Glycogenosis type II, or acid maltase deficiency, is an autosomal recessive lysosomal storage disease caused by a deficiency of acid alpha-glucosidase. Diagnosis of glycogenosis type II is suspected in patients with a progressive proximal muscle weakness in combination with myopathic discharges on electromyogram and a raised serum creatine kinase. Diagnosis is confirmed by mutation analysis and muscle biopsy.¹

We investigated the association between glycogenosis type II and ptosis in a 37-year-old woman diagnosed with glycogenosis type II who initially presented to our neurologic center with unilateral ptosis and decreased levator function. Proximal,

truncal, and facial muscle weakness are common symptoms in glycogenosis type II. Weakness of the levator palpebrae muscle, however, is not a known feature of glycogenosis type II. Ptosis in patients with late-onset glycogenosis type II has incidentally been reported.^{2,3}

Methods. Twelve patients with biochemically proven late-onset glycogenosis type II were enrolled from the Dutch population: eight patients from the Radboud University Nijmegen Medical Centre and four patients from the Erasmus Medical Centre, Rotterdam. In all 12 patients, diagnosis of glycogenosis type II was confirmed by mutation analysis of the GAA gene, revealing compound heterozygosity for IVS1-(13T>G). Patients were excluded in cases of congenital ptosis or known comorbidity associated with ptosis, such as myasthenia gravis, mitochondrial myopathy, or cranial nerve III palsy. Patients underwent ophthalmologic examination including standardized photography of the eyes.

Ptosis is present when the upper eyelid is less than 2.0 mm from midpupil or when there is more than 2.0 mm of asymmetry between the left and right upper eyelid.⁴ Severity of ptosis is divided into mild (1.5 to 2.0 mm), moderate (0.5 to 1.5 mm), and severe (<0.5 to 0.5 mm) ptosis. The maximal upward deflection of the eyelid was measured to determine the levator palpebrae function. For statistical analysis, the Fisher exact test was used.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the December 26 issue to find the title link for this article.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 79,600

North American Clinical Trials Network
for Treatment of Spinal Cord Injury
(NACTN) of the Christopher Reeve Foundation
Attention: Robert G. Grossman, MD
Director, The Neurological Institute
6569 Fannin, Suite 944
Houston, TX 77030

Dear Dr. Grossman:

We acknowledge receipt of your Investigational New Drug Application (IND), submitted on October 17, 2007 and received on October 18, 2007, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rilutek® (riluzole) tablets.

After reviewing the information contained in your submission, we have concluded that your study meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.

The IND regulations [21 CFR 312.2(b)] state that clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements for an IND if all of the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.
2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.
3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.
4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.

In addition, 21 CFR 312.2(b)(5) exempts from the IND requirements a clinical investigation that involves use of a placebo if the investigation does not otherwise require submission of an IND.

We remind you that exemption from the requirements for an IND does not in any way exempt you from complying with the requirements for informed consent under 21 CFR 50.20 and initial and continuing Institutional Review Board review under 21 CFR Part 56.

For additional information, you can check our web site at <http://www.fda.gov/cder> for the IND regulations.

If you have any questions, please call Tamy Kim, PharmD, Regulatory Project Manager, at 301-796 -1125.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name

IND 79600

GROSSMAN ROBERT G
MD

RILUTEK (RILUZOLE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ

11/20/2007

NACTN National Training

Monday, June 2, 2008

Frazier Rehabilitation Institute, 220 Abraham Flexner Way
Fixed Auditorium, 1st Floor (near the cafeteria)

Monday, June 2, 2008

7:30 – 8:00 AM	Continental Breakfast
8:00 – 8:30 AM	Welcome - Opening Remarks and Introductions S. Howley, C. Shields, S. Harkema
8:30 – Noon	ASIA Lecture
Noon – 1:00 PM	Lunch
1:00 – 4:00 PM	ASIA Exam Practice <i>Frazier 11th floor South/Spinal Cord Medicine Clinic, Rooms 1113, 1114, 1115, 1116, 1120, 1121</i>
4:00 - 4:30 PM	Break
4:30 – 6:00 PM	Review of Manual of Operations (MOO) – Version 3.1 E. Toups <i>Frazier Boardroom, 15th floor</i> Review of Data Forms – Version 3.1 – E. Toups Review FIM, SCIM and WISCI Exams M. Schmidt
6:00 – 7:00 PM	Working Buffet Dinner
6:30 – 7:30 PM	Data Management Center (DMC) – R. Frankowski A. Sample Patient Summary B. Sample Output for Clinical Edit Checks C. NACTN Summary Data Letter to Co-Investigators and Coordinators regarding need for ASIA follow-up examinations (handout) - C. Shields DOD Regulatory Process – E. Toups OPVerdi Presentation – E. Cappuccio

NACTN National Training

Tuesday, June 3, 2008

Frazer Rehabilitation Institute, 220 Abraham Flexner Way

Fixed Auditorium, 1st Floor (near the cafeteria)

7:30 - 8:00AM

Continental Breakfast

8:00AM – Noon

ASIA Exams

Noon

Adjourn and Box Lunches

NACTN Training
June 2-3, 2008
Frazier Rehab, Louisville, KY

Name	Email	Address
Elizabeth Toups, RN, MS Senior Study Coordinator The Methodist Hospital	etoups@tmhs.org	6560 Fannin STE 944 Houston, TX 77030 713-441-3897
Deborah L. Pucci, PT, MPT, ATP Study Coordinator Rehabilitation Institute of Chicago	dpucci@irc.org	Wheelchair and Seating Center 345 E. Superior Chicago, IL 60611 312-238-6012
Rachel Scollon, BA Research Coordinator Thomas Jefferson University	Rachel.scollon@jefferson.edu	909 Walnut Street, 2nd Fl Philadelphia, PA 19107
Christopher Shields, MD Principal Investigator, NACTN Hospital Endowed Chair, Kentucky Spinal Cord Injury Research Center Clinical Director University of Louisville	cbshields1@gmail.com	210 East Gray Street, STE 1102 Louisville, KY 40205 502-583-1697
Susan Harkema, PhD Co-Principal Investigator, NACTN University of Louisville	Susan.harkema@jhs.org	Frazier Rehab Institute 220 Abraham Flexner Way 15 th Floor South Louisville, KY 40205 502-581-8747
Anne Watson, RN Study Coordinator University of Louisville	ajwats01@louisville.edu	210 East Gray Street, STE 1102 Louisville, KY 40205 502-629-5270
Belinda N. Coyle, RN, BSN Spinal Cord Medicine Nurse Coordinator University of Louisville	belinda.coyle@jhsmh.org	
Douglas P. Stevens, MD Assistant Clinical Professor Physical Medicine and Rehabilitation University of Louisville	dstevens@rehabmds.net	
Todd W. Vitaz, MD Assistant Professor, Director of Neurosurgical Oncology, Co-Director of Neurosciences Intensive Care University of Louisville	t.vitaz@louisville.edu	
Bizhan Aarabi, MD Principal Investigator, NACTN University of Maryland School of Medicine	BAARABI@smail.umaryland.edu	22 South Greene Street Suite S-12-D Baltimore, Maryland 21201 410 328 7371

NACTN Training
June 2-3, 2008
Frazier Rehab, Louisville, KY

Christina (Charlene) Aldrich, RN, MSN Senior Clinical Research Specialist University of Maryland, SOM	CALDRICH@smail.umaryland.edu	Dept. Neurosurgery 22 S. Greene St., Ste. S12D Baltimore, MD 21201 410-328-5332
Heather Thomas, BS, CPhT Clinical Research Assistant University of Maryland, SOM	hthomas@smail.umaryland.edu	Dept of Neurosurgery, 22 S. Greene Street, S12D Baltimore, MD 21201 410 328 14181
James D. Guest, MD, PhD Principal Investigator, NACTN University of Miami	JGuest@med.miami.edu	Neurosurgery & Miami Project to Cure Paralysis 1095 NW 14 th Terrace Miami, FL 33136 305-575-7059
Qing He, MD University of Miami	QHe2@med.miami.edu	305-243-4588
Ralph Frankowski, PhD Principal Investigator, NACTN Data Registry Management Center UT School of Public Health	Ralph.F.Frankowski@uth.tmc.edu	1200 Herman Pressler W1004 Houston, TX 77030 713-500-9320
Martha Powner, RN, MN Senior Research Nurse University of Texas at Houston	Martha.Powner@uth.tmc.edu	Health Science Center Dept. Neurosurgery, Suite 7.148 6431 Fannin Street Houston, TX 77030 713-500-6936
Georgene Hergenroeder, MHA, RN, CCRC, Research Manager, Research Dept. University of Texas at Houston	Georgene.W.Hergenroeder@uth.tmc.edu	Health Science Center Dept. Neurosurgery 6431 Fannin Street, MSB 7.156 Houston, TX 77030 713-500-6130
Joshua Baker, RN, MD Research Associate University of Texas at Houston	Thomas.J.Baker@uth.tmc.edu	Health Science Center Dept. Neurosurgery, Suite 7.148 6431 Fannin Street Houston, TX 77030 713-500-6145
Yuliya Petrenko, RN Clinical Research Coordinator (NACTN)	yuliya.petrenko@uhn.on.ca	University Health Network Toronto Western Hospital 399 Bathurst Street, Toronto 416-603-5285
Kayee Tung, RN, BScN Clinical Research Coordinator (SCI- TRN)	kayee.tung@uhn.on.ca	University Health Network Toronto Western Hospital 399 Bathurst Street, Toronto 416-716-7446 416-790-0830 (pager)
Rosalie Magtoto, RN	rosalie.magtoto@uhn.on.ca	University Health Network

Frazier Rehab, Louisville, KY

[illegible]

Frazier Rehab, Louisville, KY

[illegible]

Component I, Administrative Core
Christopher Reeve Foundation (CRF)

During the quarter just ended, the following tasks and/or objectives were addressed:

1. USAMRMC Animal Care and Use Review Office (ACURO) issued approval for the use of mice in project "Efficacy of Amnion Derived Multipotent Progenitor Cells (AMPCs) for Acute Treatment of Spinal Cord Injury (SCI)," Proposal Log #06059005, February 26, 2008.
2. One-year Research Agreement between the Christopher Reeve Foundation and the Regents of the University of California on behalf of its Irvine Campus (UCI) was executed on April 7, 2008. Total amount of the first-year award is \$96,974.00.
3. CRF has requisitioned a check in the amount of \$48,487.00, the first of two payments that will be made on the subject Agreement. It is anticipated the check will be sent to UCI Monday, April 21st.
4. As a consequence, CRF has not yet submitted a Request for Advance or Reimbursement for this modification-payment.

Component II – UCI Injury Core:

1. Contract No. modification P00001 to W81XWH-07-1-0361 2. Report Date 04-15-2008
=

3. Reporting period from 01-JAN-08 to 31-MAR-08

4. PI Grossman/Anderson 5. Telephone No. 949-824-6750

6. Institution Christopher and Dana Reeve Foundation

7. Project Title Efficacy of Amnion Derived Multipotent Progenitor Cells (AMPCs) for Acute Treatment of Spinal Cord Injury (SCI)

8. Current staff, with percent effort of each on project.

N/A %
%

N/A %
%

9. Contract expenditures to date (as applicable):

This Qtr/Cumulative	This Qtr/Cumulative
Personnel <u> N/A </u> / <u> </u>	Travel <u> </u> / <u> </u>
Fringe Benefits <u> N/A </u> / <u> </u>	Equipment <u> </u> / <u> </u>
Supplies <u> N/A </u> / <u> </u>	Other <u> </u> / <u> </u>

This Qtr/Cumulative
Subtotal <u> N/A </u> / <u> </u>
Indirect Costs <u> N/A </u> / <u> </u>
Fee <u> N/A </u> / <u> </u>
Total <u> N/A </u> / <u> </u>

10. Comments on administrative and logistical matters.

This contract received a late start due to gaining approval for human subjects and animal use through the appropriate DOD departments. After processing through DOD, the subcontract to UCI from CDRF was drafted and submitted on February 26th to UCI contracts and grants. The finalized subcontract between CDRF and UCI was executed on April 7th 2008.

11. Use additional page(s), as necessary, to describe scientific progress for the quarter in terms of the tasks or objectives listed in the statement of work for this contract.

Although finalizing the contract has been in progress as described above, there is indirect scientific progress on this project. Animals required for Aim A but funded directly by Stemnion received spinal cord injuries and cell transplants in January 2008. Animals received behavioral testing using weekly open-field scoring and terminal Catwalk, were sacrificed 28d post-transplant, and tissue from these animals harvested preparatory to MRI analysis of lesion volume (the DOD funded component of this Aim), and processing to test for cell survival. MRI analysis of these cords is scheduled to begin the week of April 21st.

12. Use additional page(s) to present a brief statement of plans or milestones for the next quarter.

Preliminary behavioral analysis (embedded in this project, but not DOD funded per se) has not revealed improvements in locomotor recovery similar to those observed in the case of delayed transplantation (9 days post-SCI). This may suggest reconsideration of Aims B and C: that is, it may be appropriate to test a side-by-side timepoint of transplantation, perhaps

focusing specifically on the epicenter group, prior to proceeding with selecting the optimal time post-SCI for conducting the additional experiments proposed.

As soon as MRI analysis is complete for these animals (noted above), sectioning and histology to assess the presence of surviving human cells will be initiated. This data will be integrated with the final BMS (open-field) behavioral data analysis, and evaluation of the Catwalk terminal testing locomotor kinematic data from these groups. Based on this data, we anticipate that it may be appropriate to request to deviate from the experimental plan to initiate an additional experiment, testing simultaneously epicenter transplants immediately and 9 days post-SCI, in order to replicate our original data and ensure appropriate selection of the optimal treatment timepoint for Aims B and C. Such a study would not require a 28d survival, but could be completed with a 2 week survival instead, which would be adequate for the locomotor behavioral recovery comparison required.

In the original 9d post-SCI transplantation paradigm we tested both epicenter and rostral-caudal parenchymal transplant locations, and only the epicenter transplants improved locomotor recovery. All experiments were conducted in a blinded fashion, and none of the technicians involved in behavioral testing had any access to coded animal data identifying the experimental groups. Because of difference between the epicenter and parenchymal transplant groups and the magnitude of the behavioral change observed, we believe it is unlikely that there is a false positive for recovery of function in that experiment. However, because the remainder of the experiments proposed essentially ride on this data, we feel that the side-by-side comparison proposed above would be prudent and result in the best science. Of additional note, we have identified a difference in cell preparation techniques in the AMPs provided by Stemnion - pursuant to preparing for clinical translation, Stemnion has instituted a change in culture techniques that allows exclusion of animal products. Accordingly, this change also supports the appropriateness of modifying the experimental plan to confirm our observations in the 9d post-SCI transplant paradigm with this altered cell population.



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Therapeutics*

**11 September
2007**

North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury

Dr. Robert Grossman, MD

Director, The Neurological Institute

Chairman, Department of Neurosurgery

The Methodist Hospital, Houston

May 2007 – May 2009

\$2,514,575

11 September 2007



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**11 September
2007**

Problem to be Solved

Improving the outcome of spinal cord injury (SCI)
in military and civilian situations

Goals

- Developing a clinical and biostatistical framework for:
 - Bringing the therapies through the regulatory process
 - Establishing the therapies as standards of care
 - Testing new pharmacological and surgical therapies for SCI



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Solution

- Creation of the North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN) to bring promising new therapies for SCI from the laboratory to clinical trials
- Expansion to include military, VA and additional civilian hospitals



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2007**

Project Description

NACTN Neurosurgical and Rehabilitation Centers :

- 1-Methodist Hospital, Houston
- 2-University of Texas Health Science Center, Houston
- 3-Northwestern University-Rehabilitation Institution of Chicago
- 4-University of Toronto, Toronto
- 5-University of Virginia, Charlottesville
- 6-University of Louisville-Kentucky Spinal Cord Injury Research Center
- 7-University of Maryland, Baltimore
- 8- Walter Reed Army Medical Center, Washington, DC

Biostatistics and Data Management Center:

- 9-University of Texas School of Public Health, Houston

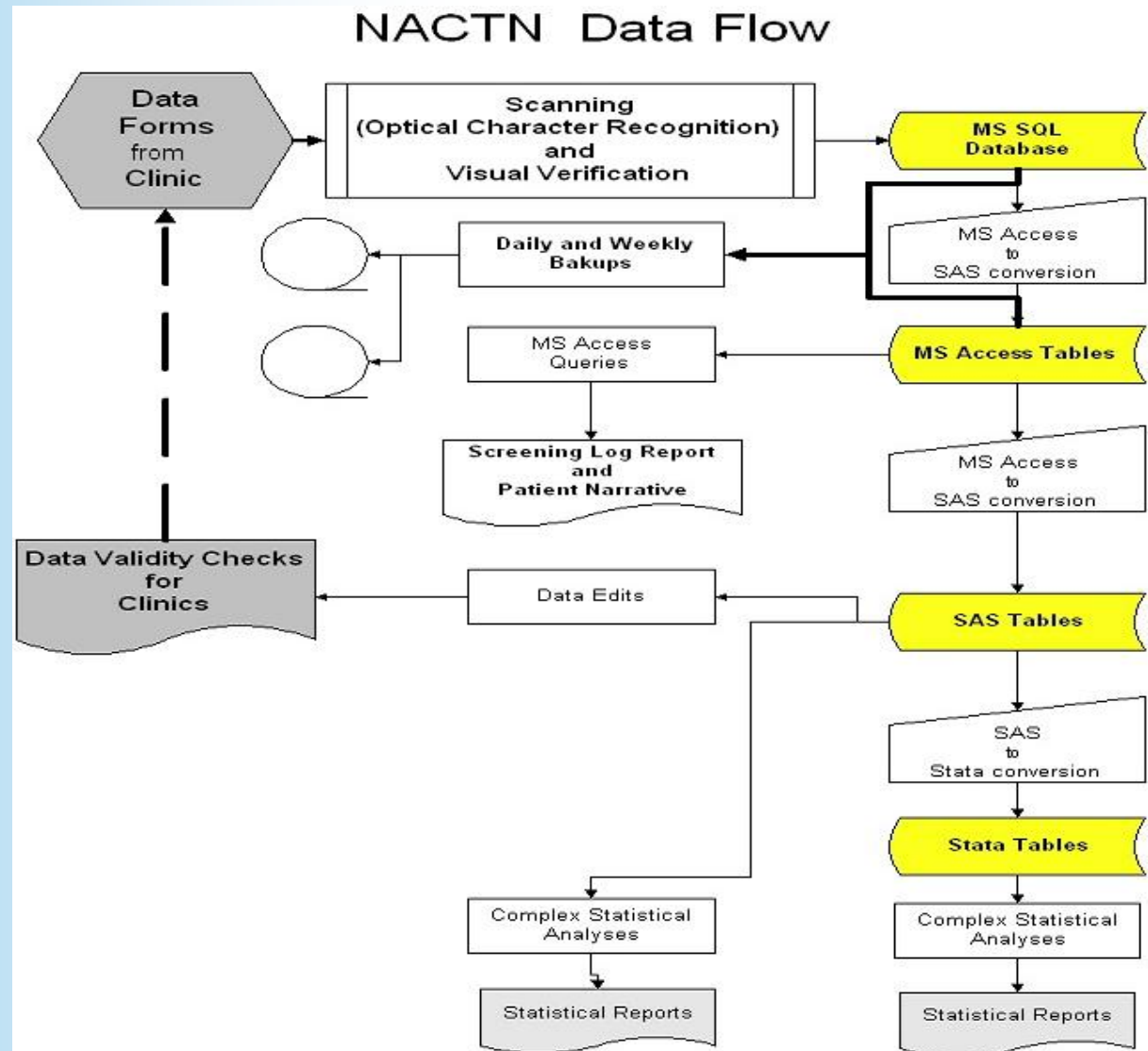


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Validation Strategy



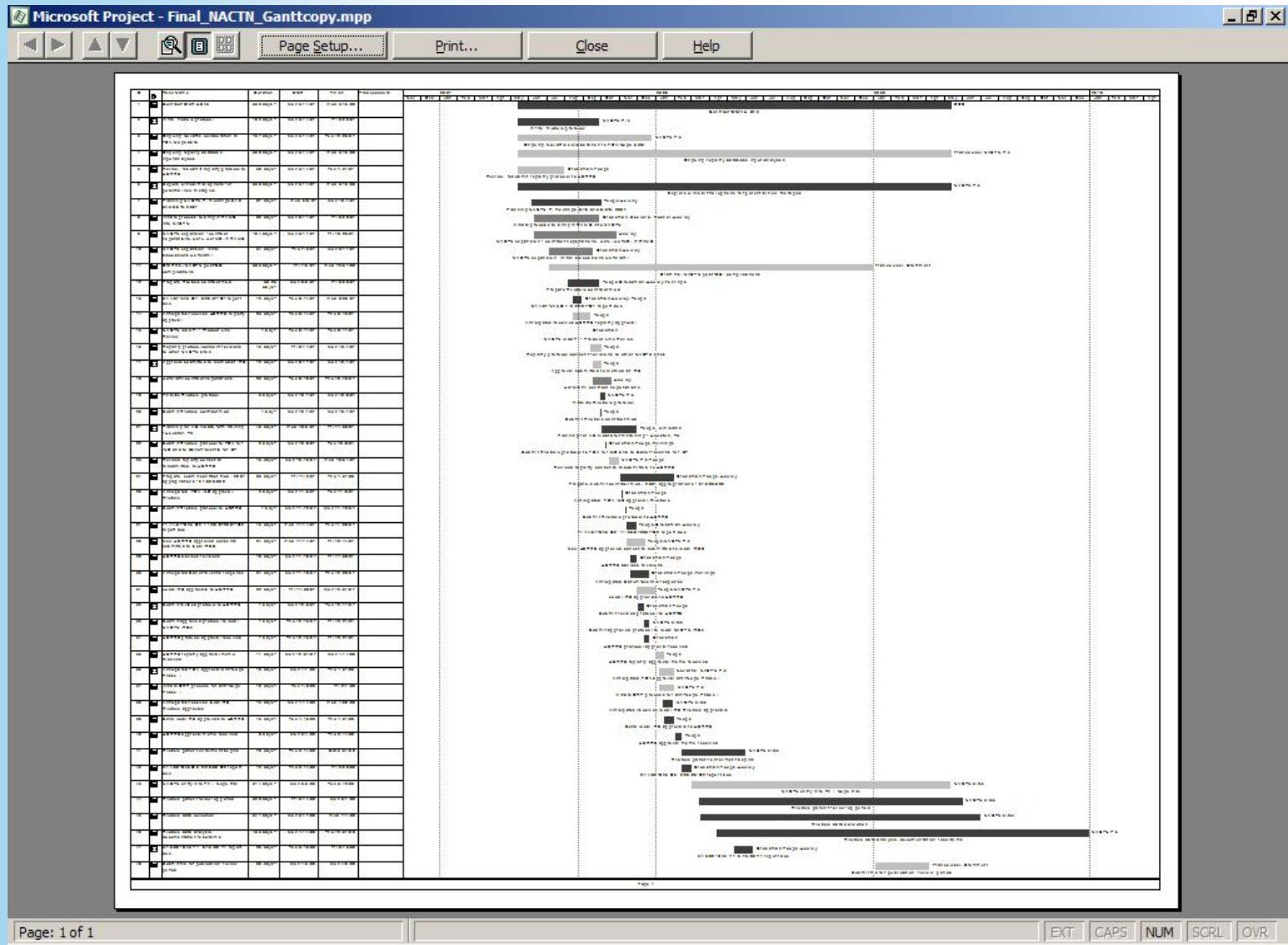


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Include detailed timeline/gantt chart Research/Development Timeline





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**11 September
2007**

Year One of the Study

- **May 14, 2007-** Grant Award Date
- **June – September 2007**
 - Incorporating WRAMC
 - Collaborating with Novartis for anti-Nogo Phase I trial in USA in response to FDA request for additional data
 - NACTN PI conference; August 10, 2007
 - Planning of Riluzole trial
- **July - October 2007**
 - NACTN Expansion with University of Louisville and University of Maryland
 - Preparing contract modification for Riluzole trial
- **July 2007 – January 2008**
 - Continual update of registry database to form control group



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**11 September
2007**

Year One of the Study

■ April – August 2007

- Incorporating changes to registry protocol & resubmitting to Human Subjects Research Review Board (HSRRB)
Submitted August 2, 2007.

■ August 14, 2007

- End of First Quarter; Report submitted August 23, 2007

■ July - October 2007

- Completion of Riluzole protocol
- Preparation and submission to FDA for IND application

■ September 11, 2007

- Product Line Review



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**11 September
2007**

Year One of the Study

■ **October 2007**

- Training meeting for clinicians in performance of the ASIA exam and use of the new NACTN data collection forms and new Manual of Operations (MOO)

■ **July – October 2007**

- Prepare and submit contract modification for Riluzole clinical trial

■ **July – December 2008**

- Prepare and submit Riluzole protocol to the IRBs and FDA

■ **November 14, 2007**

- End of Second Quarter; Report due November 29, 2007

■ **November 2007- January 2008**

- Prepare and submit contract modification for use of 2007 appropriations - \$1,680,000



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Successes to Date

Expansion of NACTN

- University of Louisville
- University of Maryland
- WRAMC agreed to join

Collaboration with Novartis Pharmaceuticals

- Anti-Nogo Phase I Clinical Trial in progress

Development of NACTN sponsored clinical trial

- Phase I Trial of Riluzole as a neuroprotective agent



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Challenges

Technical or programmatic

- Development of measurement of motor function and rate of recovery after injury
- Determination of clinical outcome endpoints
- Calculation of number of patients required to demonstrate efficacy of the therapy based upon reaching specific outcomes



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**11 September
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What Next

Phase I Trial of Riluzole in Patients with Acute Spinal Cord Injury

Riluzole

- A sodium channel blocker with anti-glutamatergic activity is neuroprotective in models of SCI
- Promotes functional recovery following SCI in rodents
- Safe and well tolerated in human trials of neuroprotection in Amyotrophic Lateral Sclerosis (ALS)
- Could be given at front line medical facilities



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**11 September
2007**

Compare Competing Solutions

What relevant ongoing solutions are being pursued by others?

There is no pharmacological therapy proven to be effective for SCI. The standard of care for SCI is supportive cardiovascular, pulmonary and nutritional therapy, and surgical therapy of decompression and stabilization of the spinal column.

There are no other large scale systematic trials of new therapies for SCI that are currently being carried out.



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**11 September
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Intellectual Property / Publications Deriving from this Project

List any Confidentiality Agreements - **N/A**

Patents Filed - **N/A**

❖ List any patent issued - **N/A**

List Invention Disclosures Submitted - **N/A**

List all Publications deriving from the project

1. Manual of Operations (MOO) - UTSPH
2. NACTN Data Forms - UTSPH
3. Medical problems post SCI – MS in preparation
4. Phase I Trial of Riluzole – Protocol in preparation



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**11 September
2007**

Transition/ Business/ Marketing/ Plan

Describe plan, if applicable

N/A at this time



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**11 September
2007**

Project Funding

<u>Current Budget</u>	<u>Expended Funds</u>	<u>%</u>
\$2,514,575	\$725,887	28.9



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Therapeutics*

11 September
2007

Additional Project Information

Lab/Company/Group: Christopher Reeve FDN

Principal Investigator: Robert Grossman, MD

Government COR: Ken Curley, MD

Government Project Officer: Heather White

Contract Instrument: Grant

Period of Performance: May 2007 – May 2009

Contract Specialist: Madeline Wahl

Date Initiated: 13- MAY-2007

EDMS# : 3204

Contract #: W81XWH-07-1-0361

CHRISTOPHER REEVE FOUNDATION

North American Clinical Trials Network (NACTN)

for Treatment of Spinal Cord Injury

NACTN was organized in 2004 for the purpose of conducting clinical trials of new therapy for spinal cord injury in an effective manner that enrolls sufficient numbers of patients, defines and adheres to standard protocols with skilled personnel providing maximal safety to patients undergoing treatment of spinal cord injury. NACTN is supported by grants from the Christopher Reeve Foundation and the Department of Defense. NACTN currently comprises eight hospital centers.

1. THE METHODIST HOSPITAL, HOUSTON

Investigator, Robert G. Grossman, M.D.

2. THE UNIVERSITY OF TEXAS-MEMORIAL HERMANN HOSPITAL, HOUSTON

Investigator, John Crommett, M.D.

3. THE UNIVERSITY OF VIRGINIA HOSPITAL, CHARLOTTESVILLE

Investigator, Christopher I. Shaffery, M.D.

4. THE REHABILITATION INSTITUTE OF CHICAGO

Investigator, David Chen, M.D.

5. THE UNIVERSITY OF TORONTO

Investigator, Michael Fehlings, M.D., Ph.D.

6. THE UNIVERSITY OF LOUISVILLE

Investigator, Christopher Shields, M.D.

7. UNIVERSITY OF MARYLAND, BALTIMORE

Investigator, Bizhan Aarabi, M.D.

8. WALTER REED ARMY MEDICAL CENTER

Investigator, Michael Rosner M.D.

DATA MANAGEMENT AND STATISTICAL COORDINATING CENTER (DMC)

THE UNIVERSITY OF TEXAS SCHOOL OF PUBLIC HEALTH, HOUSTON

Investigator, Ralph Frankowski, Ph.D.

1. REGISTRY SCREENING & ENROLLMENT

Status	Number
Screened	263
Enrolled	137
In Database	99

2. PATIENT DEMOGRAPHICS

Characteristic	Number (N=99)	Percent
Gender		
Male	77	77.8
Female	22	22.2
Age ¹ (yrs)		
< 20	9	9.1
20-39	33	33.3
40-59	28	28.3
60+	29	29.3
Race		
White	73	73.7
Other	26	26.3

¹Median age at injury = 45 yrs of age

4. INJURY TYPE & SCI REGION

Characteristic	Number (N=99)	Percent
Injury Type		
Blunt	87	87.9
Crush	7	7.1
Penetrating (Bulter/Missile)	3	3.0
Penetrating (Sharp Object)	1	1.0
Other	1	1.0
Injury Region ¹		
Cervical	75	75.8
Thoracic	15	15.2
Lumbar/Sacral	6	6.0
SCIWORA	3	3.0

¹Highest level reported when injury involved multiples levels

3. CIRCUMSTANCES OF INJURY

Cause of Injury	Number (N=99)	Percent
Fall	46	46.5
MVA	28	28.3
Motorcycle/Off-road	8	8.1
Diving	8	8.1
Assault	6	6.1
Other sport	3	3.0

5. PATIENT TRANSFER & STABILIZATION

Characteristic	Number (N=99)	Percent
Transfer		
From Scene ¹	52	52.5
Hospital Transfer ²	47	47.5
EMT Stabilization		
Collar	81	81.8
Board	68	68.7
Sandbags	0	0.0
Traction	0	0.0

¹Median time: Scene to Registry Hospital, 1.1 hrs

²Median time: Scene to Registry Hospital via Intermediate Hospital, 11.3 hrs

6. NON-SURGICAL TREATMENT

Orthosis	Number (N=99)	Percent
Traction	23	23.2
Collar	82	82.8
Halo	14	14.1
TLSO	14	14.1
DVT Prophylaxis		
Heparin	19	19.2
Low weight Heparin	44	44.4
IVC	3	3.0
SCDs/TEDs	72	72.7

7. SURGERY TYPE

Characteristic	Number (N=99)	Percent
Surgery		
Posterior only	45	45.4
Anterior only	15	15.2
Both	17	17.2
None	22	22.2

8. NUMBER OF ACUTE CARE PATIENTS WITH COMPLICATIONS

Complications	Patients	Percent
0	47	47.5
1	13	13.1
2	12	12.1
3 +	27	27.3
Total	99	100.0

9. MOST FREQUENT TYPES OF COMPLICATIONS BY SEVERITY

Complication	Type	Moderate	Severe
Cardiovascular	Bradycardia	1	3
	Cardiac Arrest	1	2
	Shock	2	2
Pulmonary	Ventilator Failure	9	8
Hematology	Anemia	6	1
Infection	Pneumonia	7	3
	Urinary Tract Infection	8	0
Skin	Sacral	6	1
NeuroPsychological	Depression	8	1

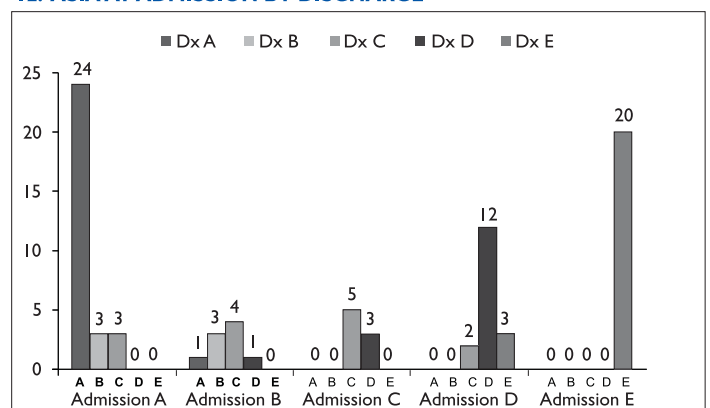
10. HOSPITAL STAY

Characteristic	Number (N=86)	Percent
Hospital Stay		
< 8 days	15	17.5
8-14	27	31.4
15-21	10	11.6
> 21	34	39.5

11. DISCHARGE STATUS

Characteristic	Number (N=96)	Percent
Discharge Status		
Rehab Hospital	57	59.4
Home Care	31	32.3
Long-Term Acute Care	2	2.1
Nursing home	3	3.1
Skilled nursing home	1	1.0
Unknown	2	2.1

12. ASIA AT ADMISSION BY DISCHARGE





CONSIDERATIONS IN THE DESIGN OF CLINICAL TRIALS IN SPINAL CORD INJURY

ROBERT G. GROSSMAN, M.D.
The Methodist Hospital

RALPH FRANKOWSKI, PH.D.
University of Texas School of Public Health

North American Clinical Trials Network

**Supported by the Christopher and Dana Reeve Foundation and
The Department of Defense**

All randomized prospective clinical trials of therapies for SCI that have been demonstrated to improve outcome in animals have failed to unequivocally demonstrate efficacy in man.

REVIEW OF TREATMENT TRIALS IN HUMAN SPINAL CORD INJURY: ISSUES, DIFFICULTIES, AND RECOMMENDATIONS

Charles H. Tator, M.D., Ph.D.

Division of Neurosurgery,
Toronto Western Hospital and
University of Toronto,
Toronto, Canada

Reprint requests:

Charles H. Tator, M.D., Ph.D.,
Toronto Western Hospital,
399 Bathurst Street,
Suite 4W-433,
Toronto, ON M5T 2S8, Canada.
Email: charles.tator@uhn.on.ca

Received, February 27, 2006.

Accepted, June 19, 2006.

OBJECTIVE: To provide a comprehensive review of the treatment trials in the field of spinal cord injury, emphasizing what has been learned about the effectiveness of the agents and strategies tested and the quality of the methodology. The review aims to provide useful information for the improvement of future trials. The review audience includes practitioners, researchers, and consumers.

METHODS: All publications describing organized trials since the 1960s were analyzed in detail, emphasizing randomized, prospective controlled trials and published Phase I and II trials. Trials were categorized into neuroprotection, surgery, regeneration, and rehabilitation trials. Special attention was paid to design, outcome measures, and case selection.

RESULTS: There are 10 randomized prospective control trials in the acute phase that have provided much useful information. Current neurological grading systems are greatly improved, but still have significant shortcomings, and independent, trained, and blinded examiners are mandatory. Other trial designs should be considered, especially those using adaptive randomization. Only methylprednisolone and thyrotropin-releasing hormone have been shown to be effective, but the results of the former are controversial, and studies involving the latter involved too few patients. None of the surgical trials has proven effectiveness. Currently, a multitude of cell-based Phase I trials in several countries are attracting large numbers of patients, but such treatments are unproven in effectiveness and may cause harm. Only a small number are being conducted in a randomized or blinded format. Several consortia have committed to a promise to improve the conduct of trials.

CONCLUSION: A large number of trials in the field of spinal cord injury have been conducted, but with few proven gains for patients. This review reveals several shortcomings in trial design and makes several recommendations for improvement.

KEY WORDS: Review, Human spinal cord injury, Treatment trials

Neurosurgery 59:957-987, 2006

DOI: 10.1227/01.NEU.0000245591.16087.89

www.neurosurgery-online.com

The field of spinal cord injury (SCI) is remarkable for the high number of treatment trials in humans. Unfortunately, none has produced a major improvement in neurological recovery or a meaningful increase in function, although much effort and resources have been expended. The high level of trial activity in this relatively small field, which encompasses only 11,000 new cases annually in North America (152), is likely related to the large personal and societal costs of these injuries with respect to loss of function and financial costs, and the fact that previous trials have not led to a breakthrough. Scientists are attracted to this field because of the high clinical need and the lack of effective therapy.

Although clinical trials in SCI have been reviewed before by the author and others (5, 49, 54, 73, 98, 124, 153), there is a need for a critical and comprehensive review of past and current trial methodology to determine the shortcomings. Indeed, there is considerable criticism and controversy about the methodology of some SCI trials, even those with hundreds of patients and well-defined protocols. Also, there has been a dramatic increase in the number of exploratory Phase I trials in human SCI since the late 1990s, and many of these have engendered further criticism and controversy. Furthermore, trials in other fields, such as cancer, have been experimenting with new trial designs, and much has been learned that is applicable to SCI.

SUMMARY

9 Neuroprotection Trials in Acute SCI -All RPCT

Effective ?

- MP - 3 Trials
- Controversy
- TRH – 20 patients

Not Effective

- Naloxone
- Tirilazad
- GM-1 – 760 patients
- Nimodipine
- Gacyclidine

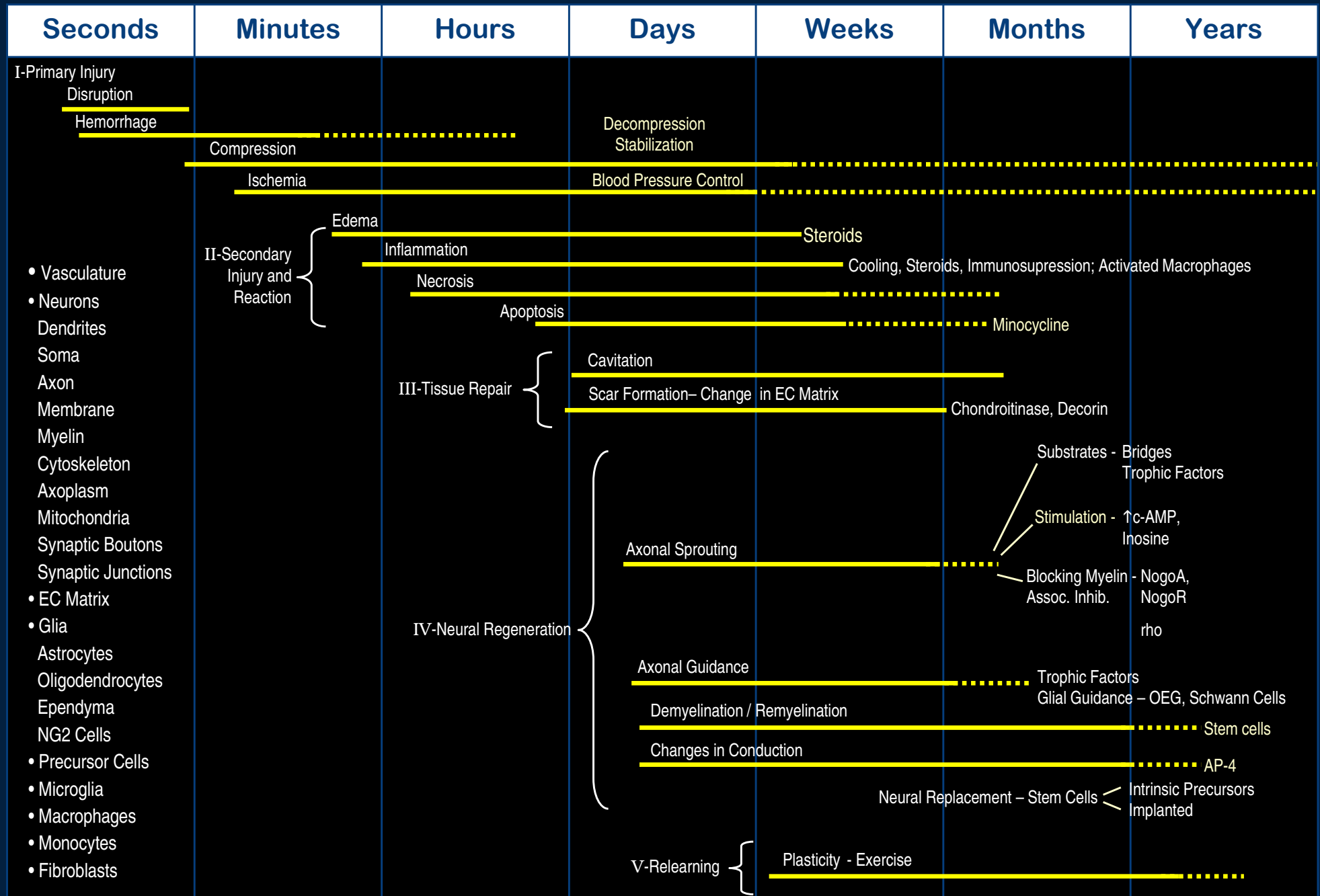
Were these therapies truly ineffective in man, or were there deficiencies in the design, execution and analysis of the clinical studies that prevented the detection of efficacy?

Causes of Failure - 1:

Degree of the efficacy of the therapy

- Weak effects of a single therapy acting on the multiple processes of the cascade of injury and repair
- Uncertainty of dosage - the problem of scaling up from animal to human studies
- The problem of the timing of delivery of therapy during the cascade of injury and repair

Mechanisms of SCI and Their Temporal Dimensions



Causes of Failure – 2:

Host variables

Differences between animal models and human injuries

TYPICAL ANIMAL MODEL

- Rodent
- Specific strain
- Female
- Age ~ 3 months - (normal life span = 24 months),
- Thoracic injury
- A transient impact without prolonged compression
- Delivery of therapy shortly after injury

TYPICAL HUMAN INJURY

- Median age ~ 41, (normal life span ~ 70 years)
- Male
- Cervical injury
- A prolonged period of compression
- Delivery of therapy after a delay of 12-24 hours

Differences in Animal Models and Human Injuries

- Proportions of structures injured, particularly motor neurons and axons of long tracts
- The distances over which axons must regenerate to reach their targets
- Degree of vascular injury and ischemia

Se:2
Im:7

[H]

Study Date
Study Time

MRN:

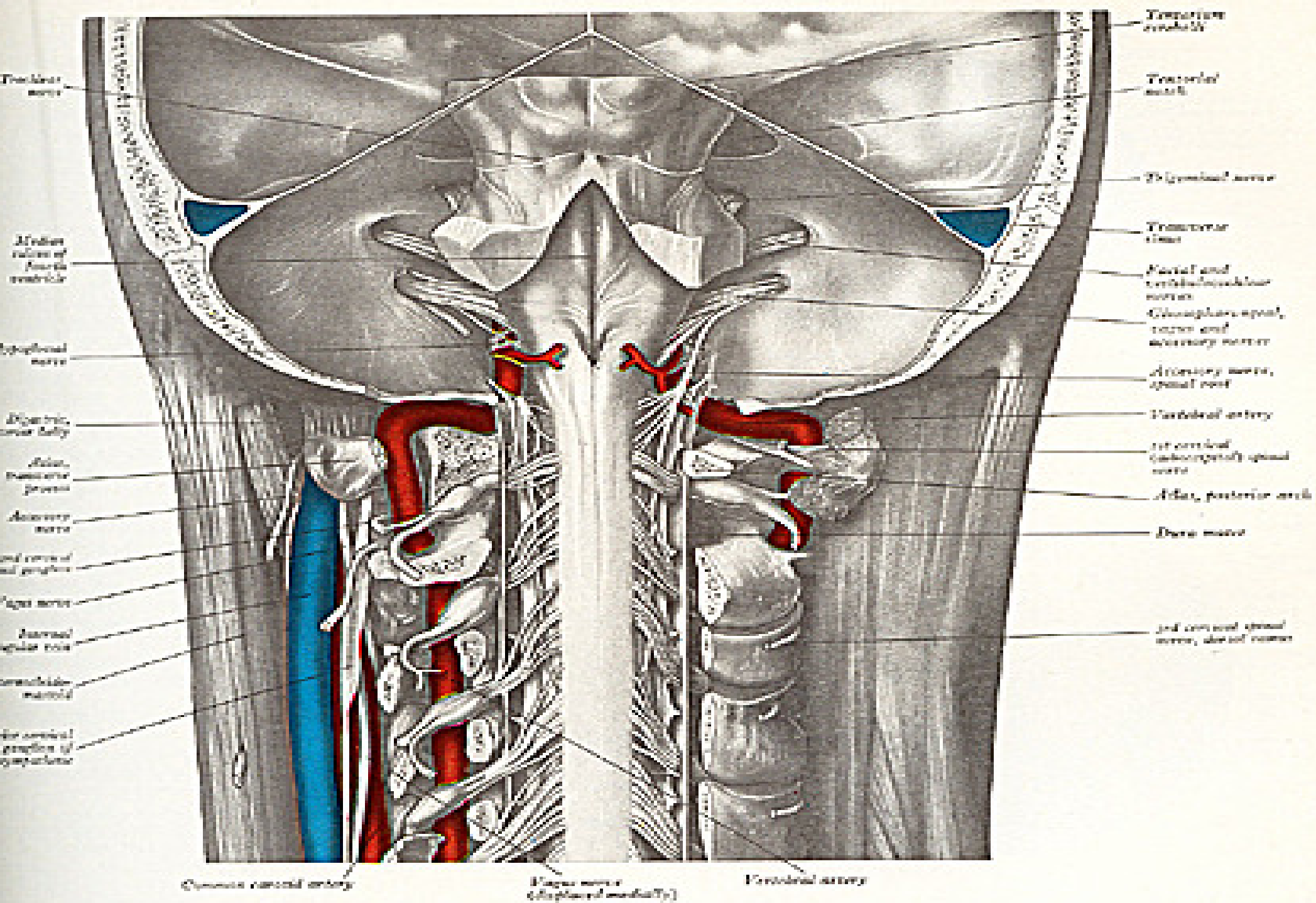
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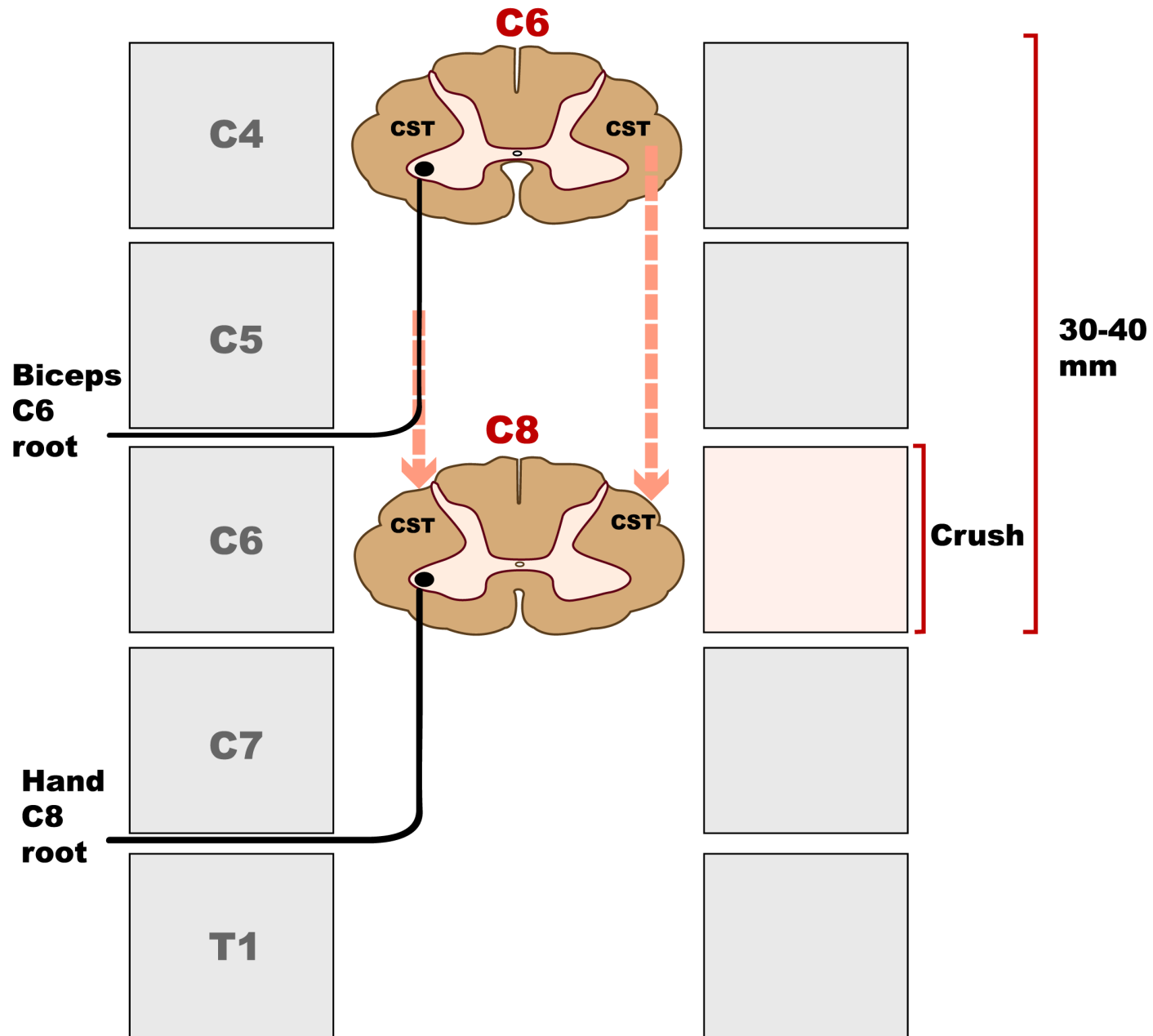
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Cervical Spine CORONAL SECTION



Se:7
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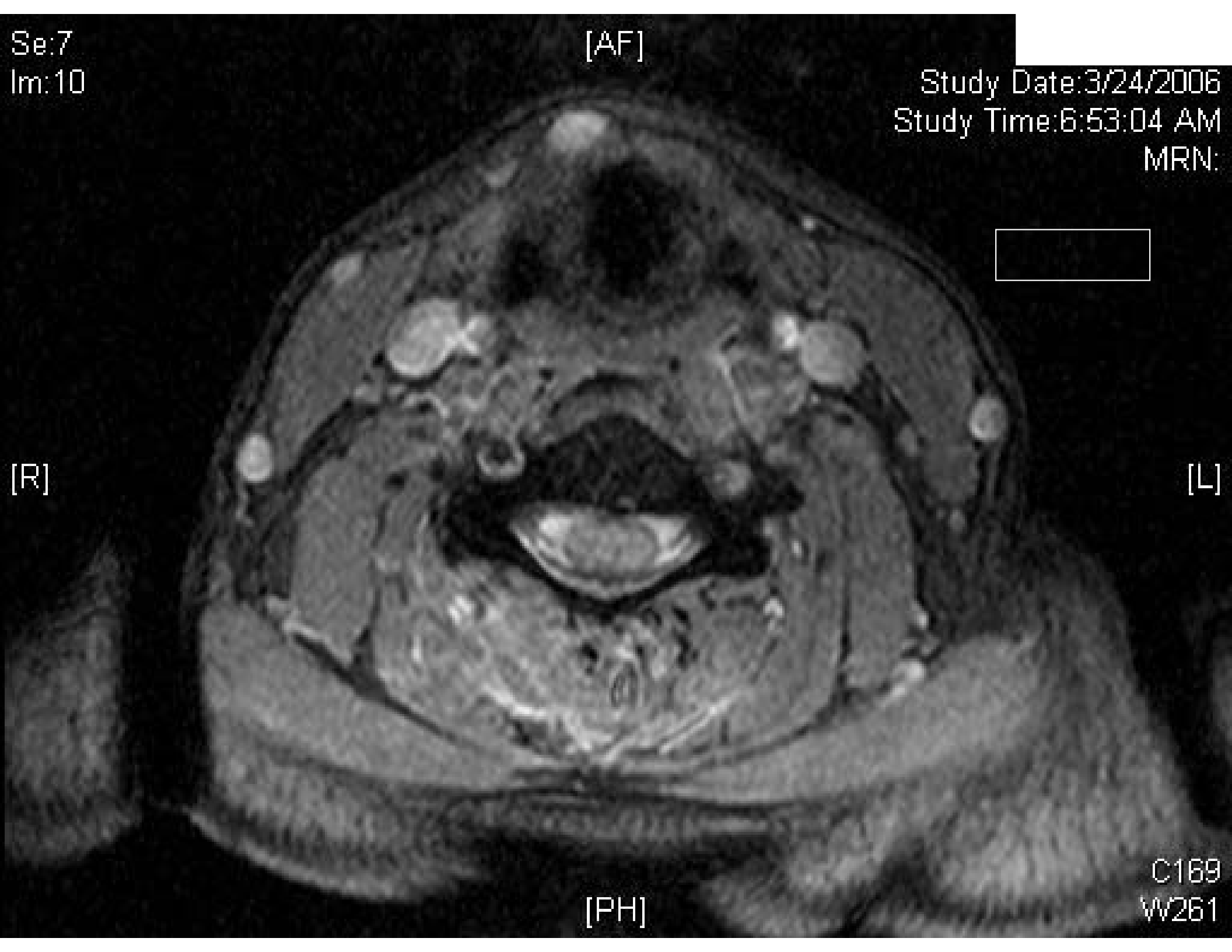
Study Date:3/24/2006
Study Time:6:53:04 AM
MRN:

[R]

[L]

[PH]

C169
WV261



Causes of Failure - 2

Biological and Clinical Variables that affect Outcome the Heterogeneity of Human SCI

1. Age of the patient
2. Pre-existing medical conditions
3. Genetic polymorphisms
4. Associated injuries, hypoxia, hypotension
5. Variations in the pathology and extent of injury – hematoma, compression
6. Medical and surgical therapy prior to and after the experimental therapy
7. Time to treatment
8. Medical complications that develop during treatment, particularly infections

North American Clinical Trials Network (NACTN)

Patient Demographics

<u>Characteristic</u>	<u>Number (N = 132)</u>	<u>Percent</u>
Gender		
Male	104	79.4
Female	27	20.6
Age ¹ (yrs)		
< 20	10	7.6
20-65	98	74.2
> 65	22	16.7
Unknown	2	1.5
Race		
White	96	72.7
Other	36	27.3

¹Median age at injury = 41.0 yrs of age

North American Clinical Trials Network (NACTN)

Circumstances of Injury

<u>Characteristic</u>	<u>Number (N=132)</u>	<u>Percent</u>
Cause of Injury		
Fall	53	40.2
MVA	39	29.5
Recreation	29	22.0
Assault	9	6.8
Other	2	1.5
Alcohol Involved		
Probable	36	27.3
Unlikely	89	67.4
Unknown	7	5.3

North American Clinical Trials Network (NACTN)

Injury Type and Level

<u>Characteristic</u>	<u>Number</u> (N=132)	<u>Percent</u>
Injury Type		
Closed	126	95.5
Open (bullet, sharp object)	6	4.5
Injury Level		
Cervical	99	75.0
Thoracic	23	17.4
Lumbar/Sacral	7	5.3
SCIWORA	3	2.3

¹Highest level reported when injury involved multiple levels

North American Clinical Trials Network (NACTN)

Patient Transfer and Stabilization

<u>Characteristic</u>	<u>Number (N=132)</u>	<u>Percent</u>
Transfer		
From Scene ¹	77	58.8
Hospital Transfer ²	54	41.2
EMT Stabilization		
Collar & Board	95	72.0
Collar Only	16	12.1
Board Only	4	3.0
None Reported	17	12.9

¹Median time: Scene to Registry Hospital, 1.4 hrs

²Median time: Intermediate Hospital to Registry Hospital, 14.4 hrs

North American Clinical Trials Network (NACTN)

Abbreviated Injury Scale for 54 SCI Admissions

Body Region	Severe AIS 4	Critical AIS 5	Total	Percent of 132
Head & Neck	33	21	54	40.9
Chest	6	17	23	17.4
Abdomen	2	2	4	3.0
Total	41	40	81	
Percent of 132	31.1	30.3	19.7	

North American Clinical Trials Network (NACTN)

Surgery Type

Surgery	<u>Number (N=132)</u>	<u>Percent</u>
Posterior	59	44.7
Anterior	23	17.4
Both	21	15.9
None	29	22.0
Decompression Achieved	89	67.4
Confirmed by MRI	48	36.4

North American Clinical Trials Network (NACTN)

Incidence of Complications

Complications	<u>Number (N=132)</u>	<u>Percent</u>
None	64	48.5
1	17	12.9
2	15	11.4
3+	36	27.2

North American Clinical Trials Network (NACTN)

Complications by Type

<u>Complication Type</u>	<u>Total (N = 256)</u>	<u>Percent of Total</u>
Pulmonary	56	21.9
Hematology	38	14.8
Skin	28	10.9
Cardiac	23	9.0
Infection	56	21.9
Spinal Instability	2	0.8
Neuropsychiatric	29	11.3
GI/GU	24	9.4

63 patients with complications
256 complications experienced by these 63 patients

North American Clinical Trials Network (NACTN)

Hospital Stay and Discharge Status

<u>Hospital Stay</u>	<u>Number (N=132)</u>	<u>Percent</u>
< 8 days	31	24.0
8-14	38	29.5
15-21	14	10.8
> 21	46	35.7
Discharge Status		
Rehab Hospital	84	63.6
Home Care	34	25.8
Long-Term Acute Care	2	1.5
Nursing Home	5	3.8
Death	5	3.8
NA	2	1.5

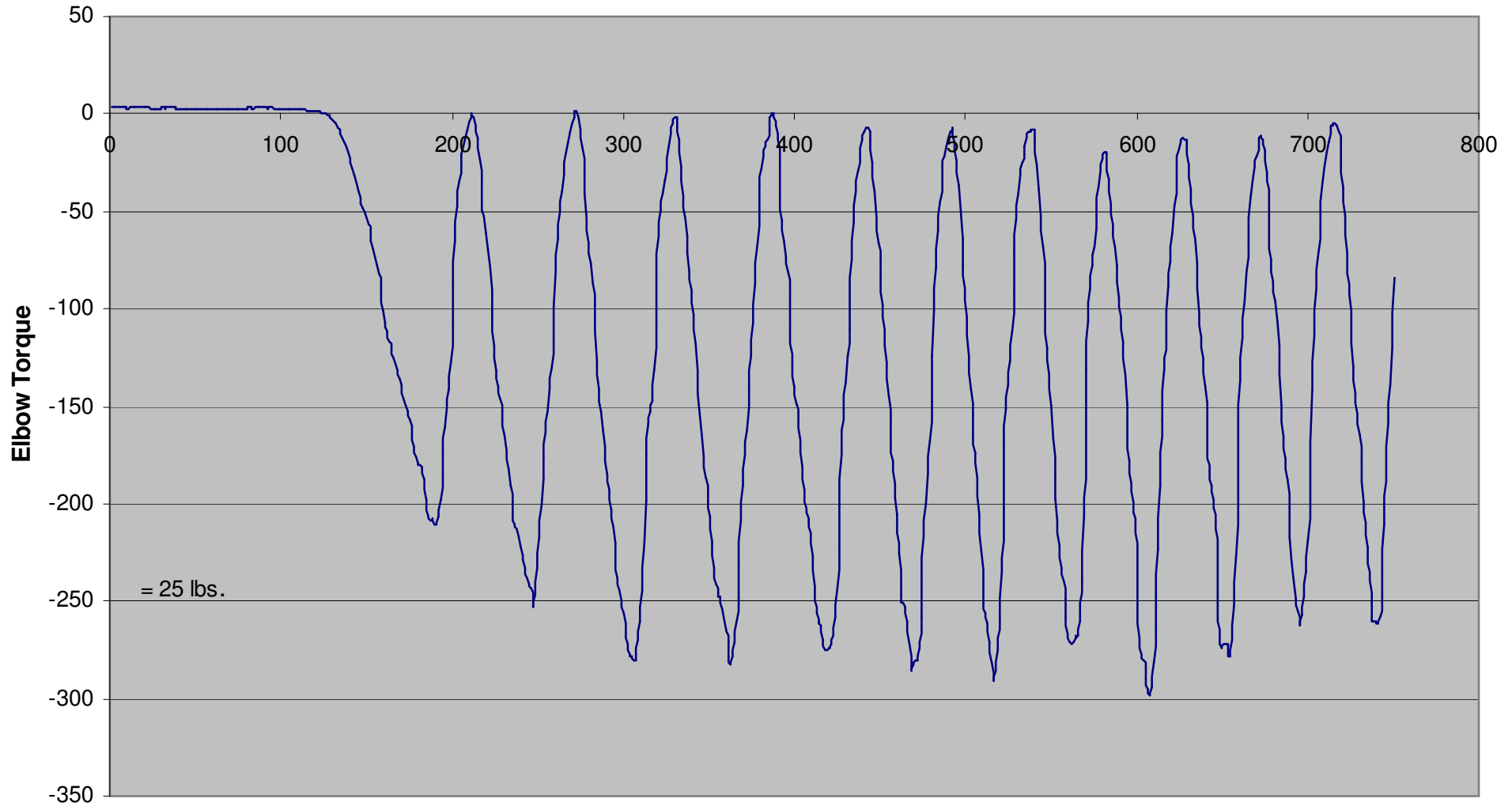
Urgent Problems in Clinical Trial Design

- Recognizing and controlling for biological and clinical variability
- Accurate and reproducible measurement of clinical outcomes, particularly the course of motor recovery
- Choosing outcome measures that can detect the effects of the therapy

Quantitative Measurement of Muscle Strength



Triceps Max Torque

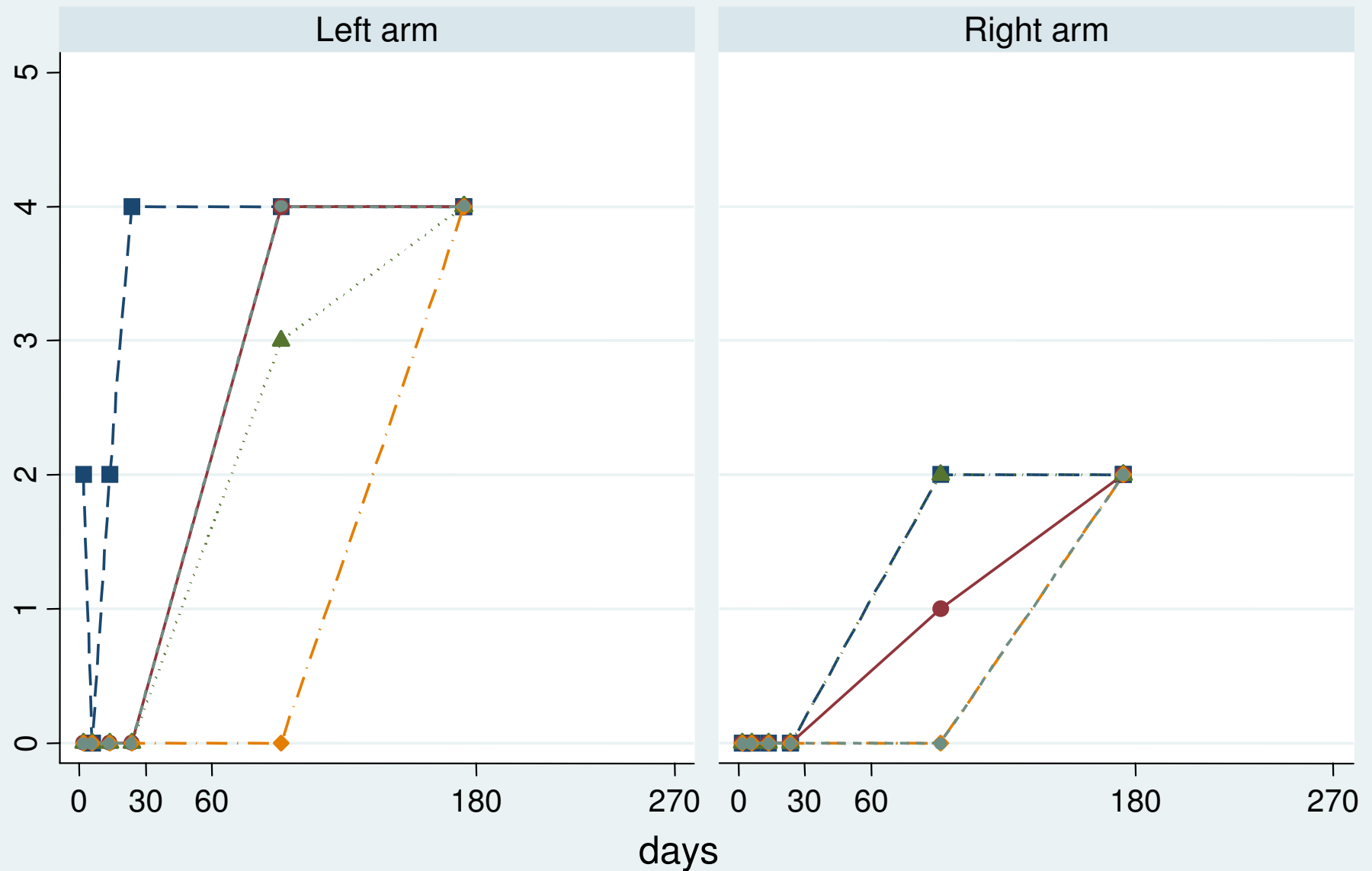


Total Time 15 sec

Construction of Trajectories of Recovery of Muscle Strength (Mean & SD) for Injuries at Specific Cord Levels

Highest Normal Motor Level = C4 (C5 Motor Injury)

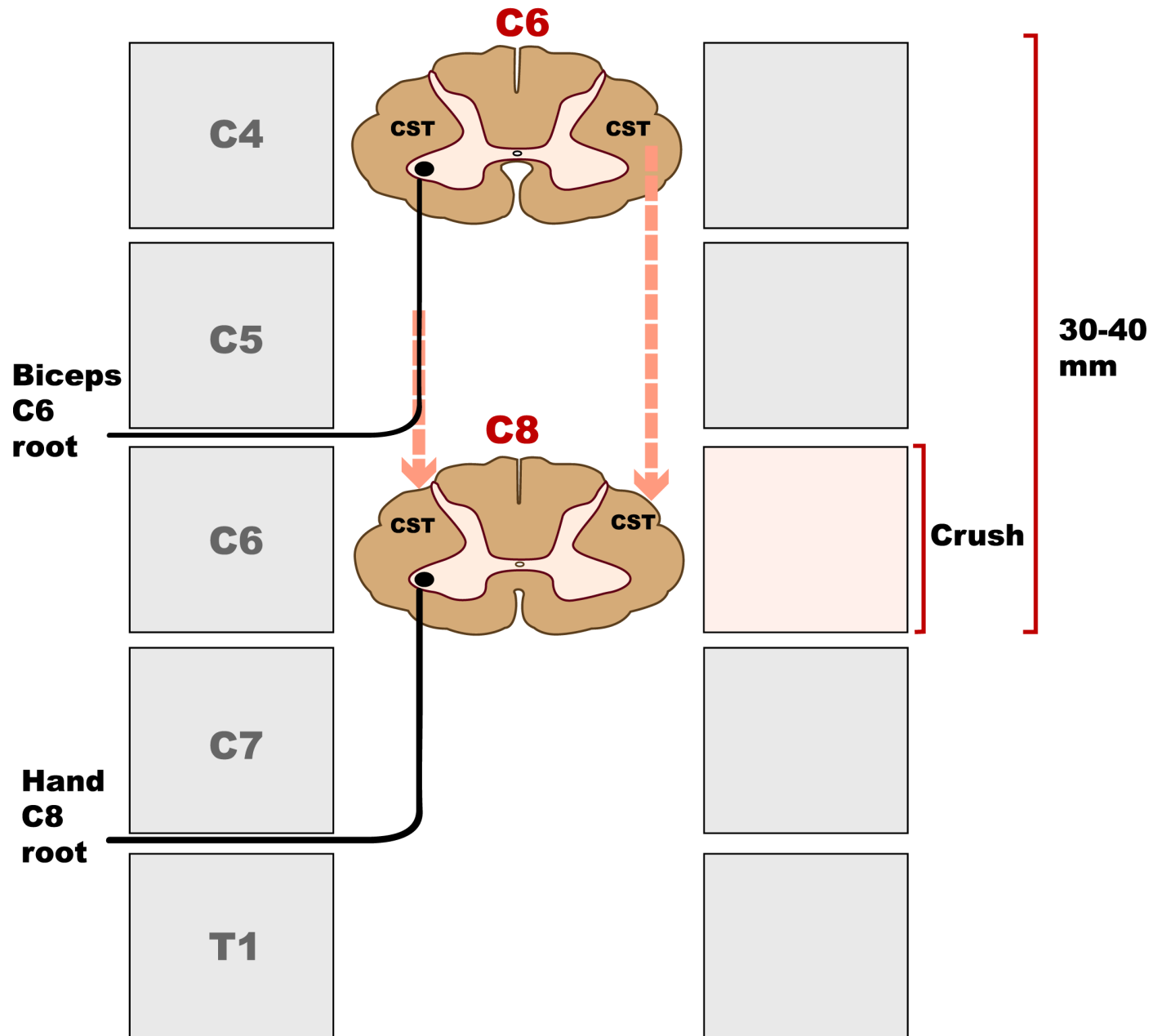
Subject: 0020014; Initial ASIA Grade = B, Level C4



Choosing Outcome Measures that are Sensitive to the Biological Effects of Specific Therapies

Problems with the Use of a Change in a Patient's ASIA Impairment Scale Grade from A to B as Measure of a Regenerative Therapy

Cervical Spine CORONAL SECTION



GRADED and REDEFINED ASSESSMENT of STRENGTH, SENSIBILITY and PREHENSION (GRASSP)



EUROPEAN CLINICAL TRIALS NETWORK

Collaboration: Armin Curt, Susan Duff, Michael Fehlings
Sukhvinder Kalsi-Ryan, Claudia Link, Molly Verrier
Lisa Ann Weurmser

Clinical Choice Trial Designs

Early Phase – Translational Clinical Trials (TCT) for proof of concept to evaluate if a therapy merits additional development.

- TCT's are a new development
- Generally, TCT's are quite small – less than 30 subjects

The primary outcome is:

- A biological measure derived from a well established paradigm of disease
- Represents an irrefutable signal regarding the intended therapeutic effect

The design and purposes of a translational design are to guide further experiments in the laboratory or clinic, inform treatment modifications, and validate the target, but not necessarily to provide reliable evidence regarding clinical outcomes. (Piantadosi, 2005)

Clinical Choice Trial Designs

Middle Phase – Frequentist or Bayesian phase II/IIb adaptive clinical seamless trial designs to develop preliminary evidence of efficacy and safety sufficient to justify a large scale

Late Phase - Comparative Randomized phase III clinical trial



Christopher Reeve and Dana Foundation

North American Clinical Trials Network for Spinal Cord Injury

NACTN

The Methodist Hospital

University of Texas Health Science Center, Memorial Hermann Hospital

University of Toronto, Toronto Western Hospital

University of Virginia Hospital

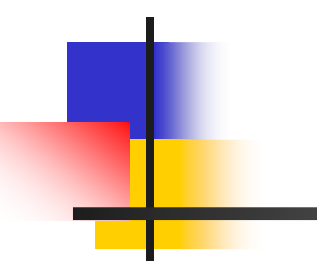
Rehabilitation Institute of Chicago

University of Louisville Hospital

University of Maryland Medical Center

Walter Reed Army Medical Center

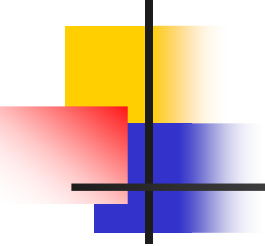
University of Texas School of Public Health - Data Management Center



Pharmacokinetics (PK) and Pharmacodynamics (PD) of Riluzole in Patients with Traumatic Acute SCI

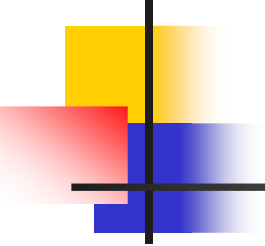
NACTN Meeting
February 18, 2008

Diana Shu-Lian Chow, Ph.D.
University of Houston



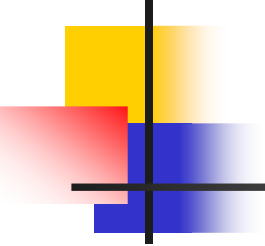
Rationale

- Therapeutic drug monitoring (TDM) of riluzole is essential
 - High intersubject variability in conc.
 - Riluzole conc. associated with side effects and efficacy in ALS patients



Rationale (Cont'd)

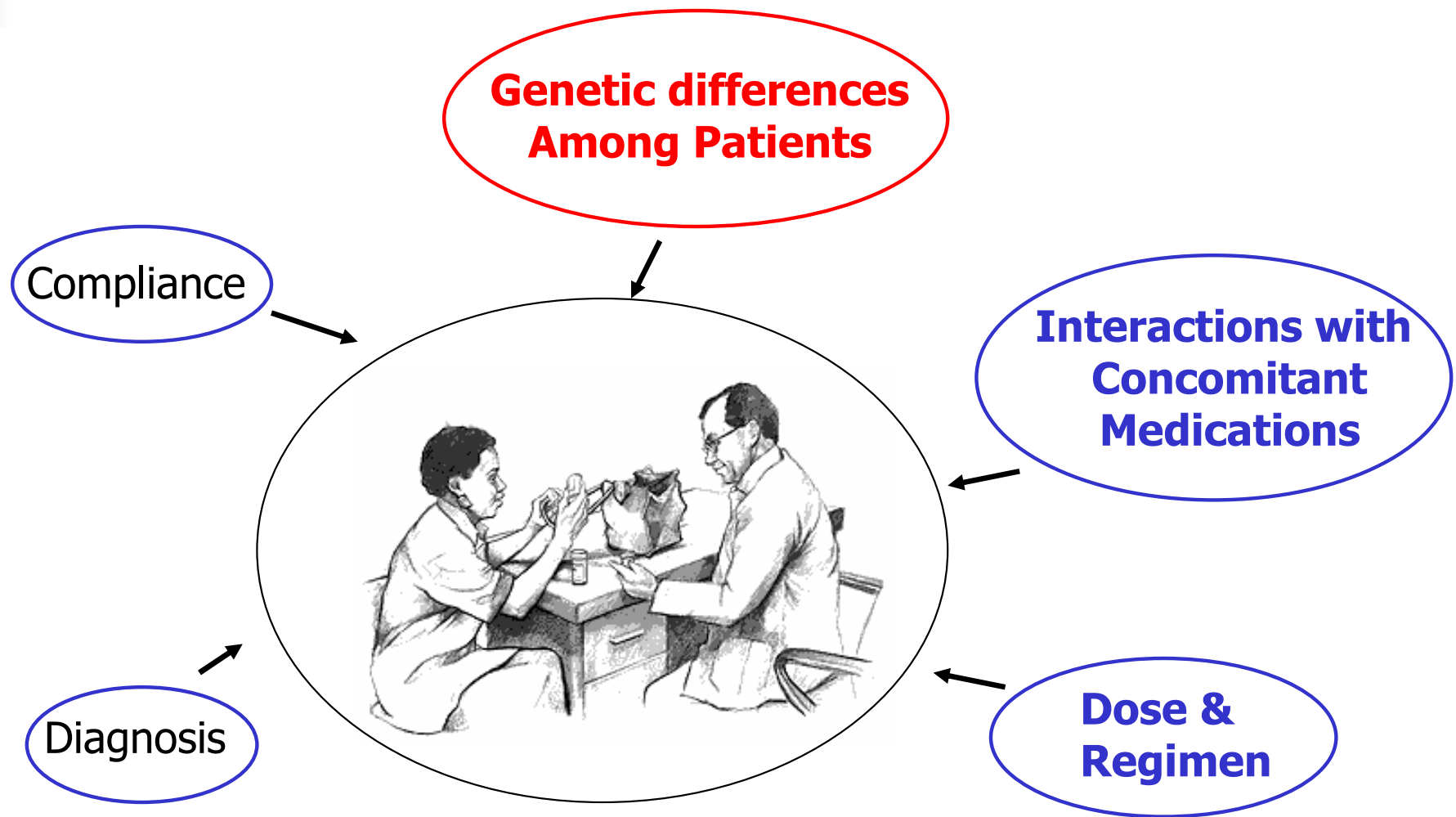
- Riluzole cleared by extensive metabolism, CYP 1A2
 - smoking
 - concomitant medications (substrate, inducer or inhibitor)
- Highly protein bound, 97%
 - Another potential drug-drug interaction

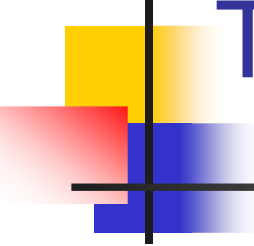


Few Equations

- Overall elimination rate constant
 - $k = CL / V$
- Half-life
 - $t_{1/2} = 0.693 V / CL$
- Accumulation Factor
 - $MDF = 1 / (1 - e^{-k\zeta})$
- Achieved Steady State Conc.
 - $C_{ss} = FD / CL \zeta$

Factors Influencing Patient's Response to Drug Therapy

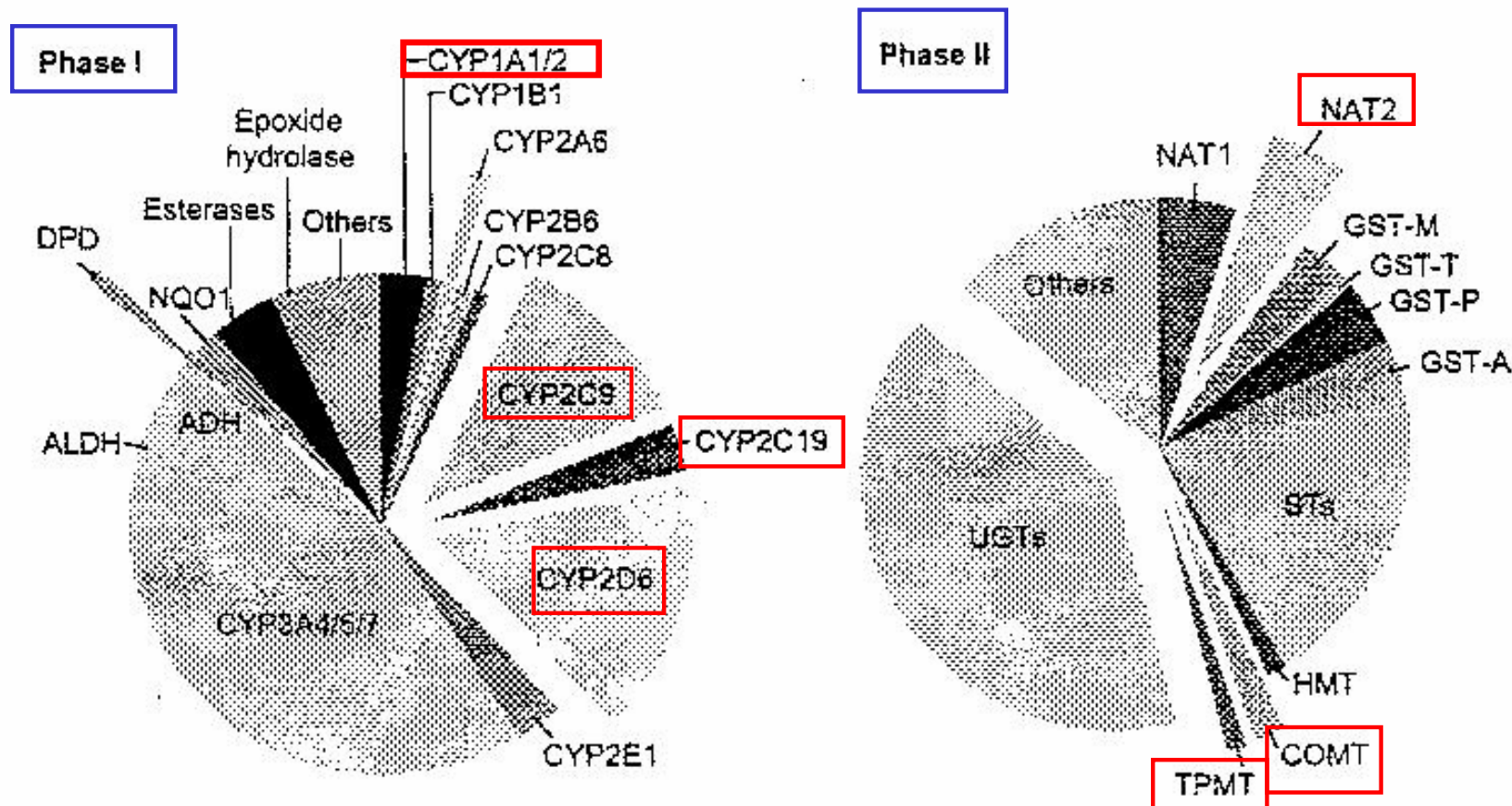




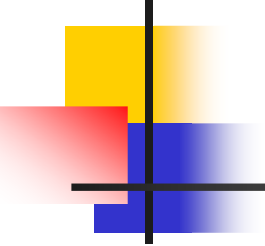
Mechanisms under Genomic Control That Can Alter Drug Efficacy or Toxicity

- Pharmacokinetics
 - Absorption
 - Distribution (Protein binding)
 - Metabolism
 - Excretion
- Pharmacodynamics
 - Mechanism of action
 - Upstream and downstream biological pathways related to mechanism of action
 - Unintended targets

Drug-Metabolizing Enzymes Exhibiting Clinically Relevant Genetic Polymorphisms

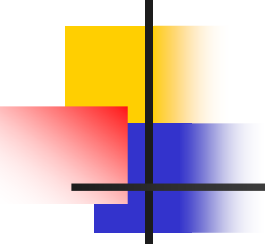


Not with CYP3A



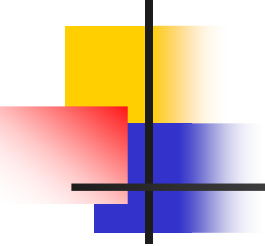
Significance of PK Study

- PK/PD correlations to relate plasma conc. of riluzole with the toxicity and efficacy of the treatment
 - Future TDM to individualize the dose
- May optimize the regimen for early onset (the first 12-24 hr) with a loading dose



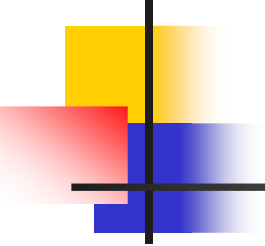
Loading Dose for Achieving Early Onset in First 12-24 hr?

- Rational approach
- Loading dose $D_L = (C_{ss}) (V)$
 - Where C_{ss} is steady state effective conc.
 - V is volume of distribution
- Is there any safety concern?
- PK/PD correlation data may better answer the question and guide the choice of D_L



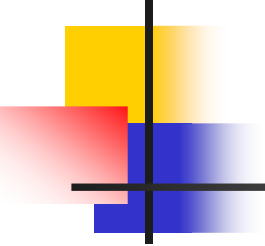
Specific Aims

- To determine individual peak and trough conc. at steady state
- To derive individual PK parameters
 - Half-life
 - Systemic exposure ($AUC_{0 \rightarrow 24}$)
 - Volume of distribution, V_d
 - Clearance, CL



Specific Aims (Cont'd)

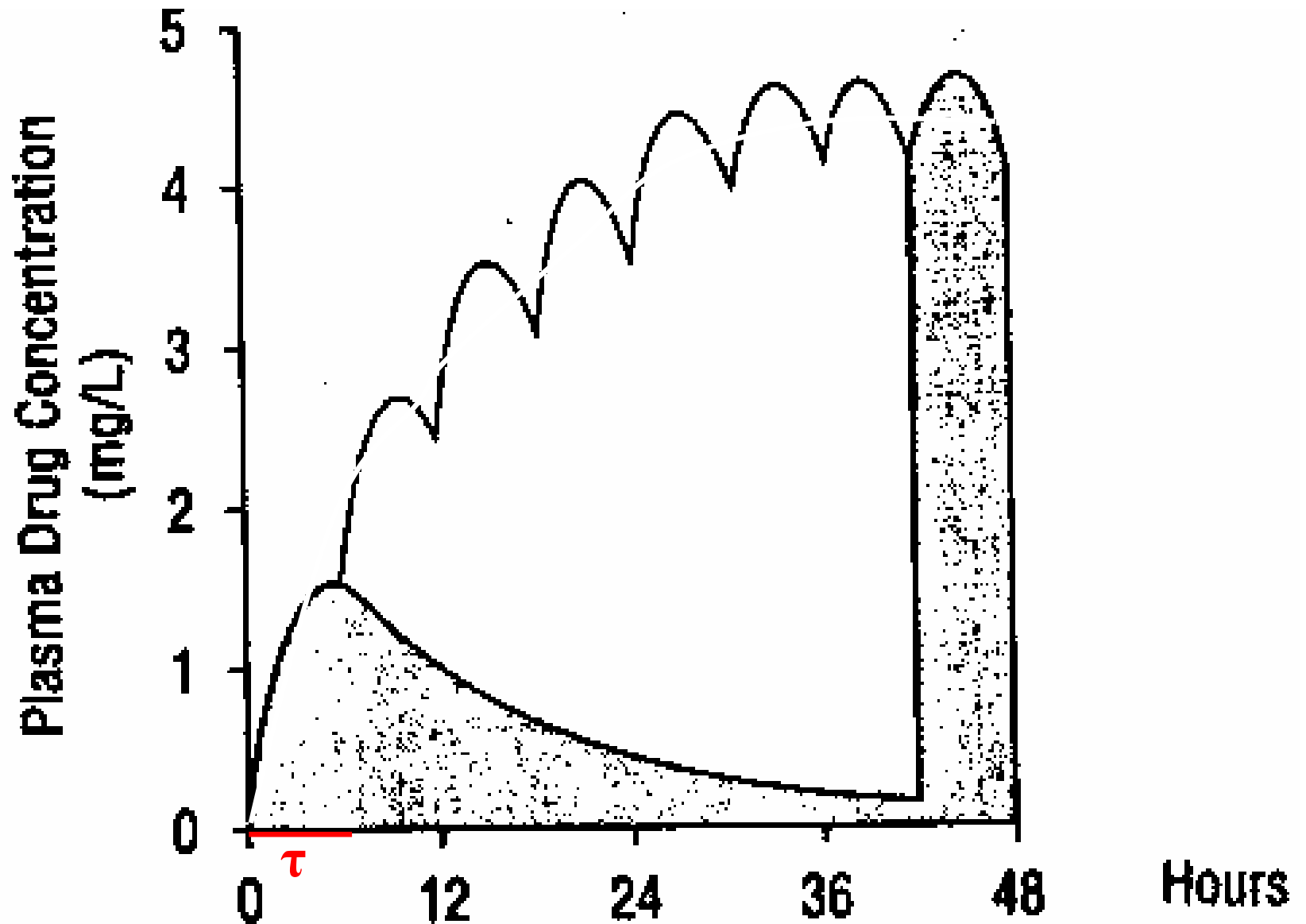
- To correlate PK and PD
 - C_{peak} , C_{trough} or $\text{AUC}_{0 \rightarrow 24}$
 - Lab measures, AST, ALT, WBC count
 - Incidence of AE and SAE
 - Efficacy scores, ASIA motor score, sensory score, impairment scale and SCIM

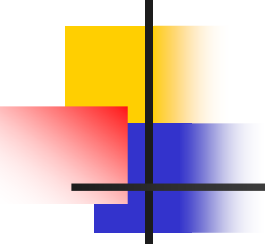


Plasma Samples

- Two plasma samples
 - Blank control (5 ml) prior to treatment
 - 2 ml, Before the 14th day dose (C_{trough})
 - 2 ml, 2 hr after the dose (C_{peak})
 - Blood samples in heparinized tube centrifuged at 2,700 g for 10 min to separate plasma
- Stored at -80°C (at least at -20°C) prior to shipment with dry ice to Dr. Diana Chow

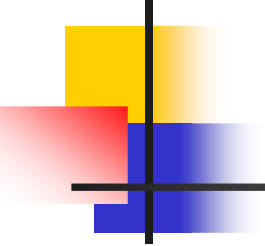
Plasma Profile





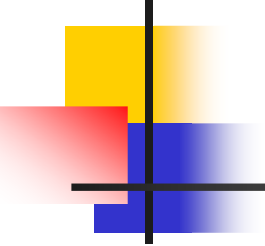
Plasma vs Serum Samples

- Riluzole conc < 500 ng/ml, drug conc. in plasma and serum are comparable.
- With 50 mg bid, riluzole concs are 60-250 ng/ml
- Using plasma sample retaining clotting factors that will have one less variability than using serum



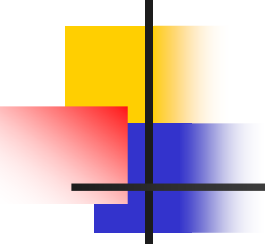
HPLC Assay is Ready

- Modified from assay of van Kan et al. (2004)
- LLOQ is 15 ng/ml [for samples at 60-250 ng/ml]
- Linearity in 10 – 1,000 ng/ml
- Precision < 5%
- Accuracy < 3% deviation



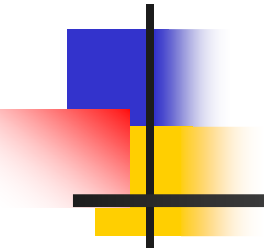
CSF Samples?

- HPLC assay is also capable of quantifying the conc in CSF.
- Whenever the sample is available.



Statistical Analyses

- Impacts of age, gender, smoking history and concomitant medications on riluzole conc and PK parameters
- Correlation of AUC /kg BW with side effects and efficacy



Questions?

The **CHRISTOPHER REEVE FOUNDATION (CRF)** is dedicated to curing spinal cord injury by funding innovative research, and improving the quality of life for people living with paralysis through grants, information and advocacy.

Christopher Reeve encouraged us all to be bold, to think outside the box, to **Go Forward**. In response to that mandate and to help fulfill its mission, the CRF has organized the **NORTH AMERICAN CLINICAL TRIALS NETWORK (NACTN) FOR TREATMENT OF SPINAL CORD INJURY** to bring promising therapies for spinal cord injury from the laboratory to clinical trials in an effective manner with maximum safety to patients undergoing treatment for their spinal cord injury.

NACTN is collaborating with a similar European clinical consortium to define the “natural history” of spinal cord injury, create an international database of carefully characterized spinal cord injuries, and refine outcome measures for treatment. In the process, the groups are building the foundation for a global effort that will help speed development of effective treatments for spinal cord injury and deliver them to people who need them.



NACTN DATA REGISTRY

The first step in reaching the NACTN goal is to build a data registry of spinal cord injuries. The data collected by the registry will be the foundation for building promising treatments for those with SCI. Initially the registry will be open only to acutely injured patients, that is, those who are admitted to a NACTN collaborating center hospital immediately after injury. It is intended that after an initial organizing period, both the registry and the number of collaborating centers will be expanded.

The NACTN centers contributing to the data registry will collect information from patients presenting with a new traumatic spinal cord and/or spinal column injury. Information will be collected on the natural history of SCI and treatment through the first 12 months following the date of injury.

The NACTN data registry is not intended to replace that of the Model Spinal Cord Injury Systems National SCI database. Rather it is intended to be the repository of the specific data needed to effectively test new therapies in clinical trials. Such data include imaging information from CT and MRI examinations, neurophysiological tests such as evoked potentials, and the changes that occur in the neurological and general medical status of the patient immediately following injury.



Role of Registry Participants:

As a participant, you will be asked to sign a consent form that will allow medical information to be sent to the NACTN data registry. This information will include the initial clinical assessment of the spinal cord injury, radiological imaging, neurophysiological tests, treatments (including stabilization, medication, and surgery), complications and hospital discharge summary. A standard neurological exam measuring movement and sensation will also be done at specific time points at the date of injury and beyond. In addition to information from the initial hospital stay, a patient will be followed during the first 12 months following the injury so that data on recovery and rehabilitation can be collected. The data registry will collect data from several standard evaluations that assess walking and functional independence. In most cases, this information may be available through the rehabilitation physician with a participant's written permission.

Participant Privacy:

The NACTN data registry will not maintain any personal identifying data such as names, addresses, social security number or medical record numbers. However, date of birth, date of injury and other pertinent treatment dates will be transmitted to the data registry. Each collaborating center will maintain its own contact and personal identifying information on participants to facilitate contacting them for follow up information. Data will be reported only in the aggregate form and data registry information will not be shared with unauthorized individuals, agencies, or companies.

COLLABORATING CENTERS OF THE NACTN

The Methodist Hospital, Houston, TX
Elizabeth Toups, RN, MS; 713-441-3897; EToups@tmh.tmc.edu

University of Texas Health Science Center, Houston, TX
John W. Crommett, MD; 713-500-6128

Northwestern University-Rehabilitation Institution of Chicago, Chicago, IL
Marianne Kaplan; 312-238-1524; mkaplan@ric.org

University of Toronto, Toronto, Canada
Yuriy Petrenko, MD; 416-603-5285; yuriy.petrenko@uhn.on.ca

University of Virginia, Charlottesville, VA
Gospova (Goga) Radakovic, MD; gr2p@virginia.edu

University of Louisville, Louisville, KY
Anne Watson, RN; 502-629-5270; ajwats01@louisville.edu

University of Maryland Medical System, Baltimore, MD
Carrie Byard, RN; 410-328-0939; cbyard@smail.umaryland.edu

University of Texas Health Science Center, Houston, TX
(Biostatistical Center)

Walter Reed Army Medical Center, Washington, D.C.
Thomas Maryniak; 202-782-9804; thomas.maryniak@amedd.army.mil



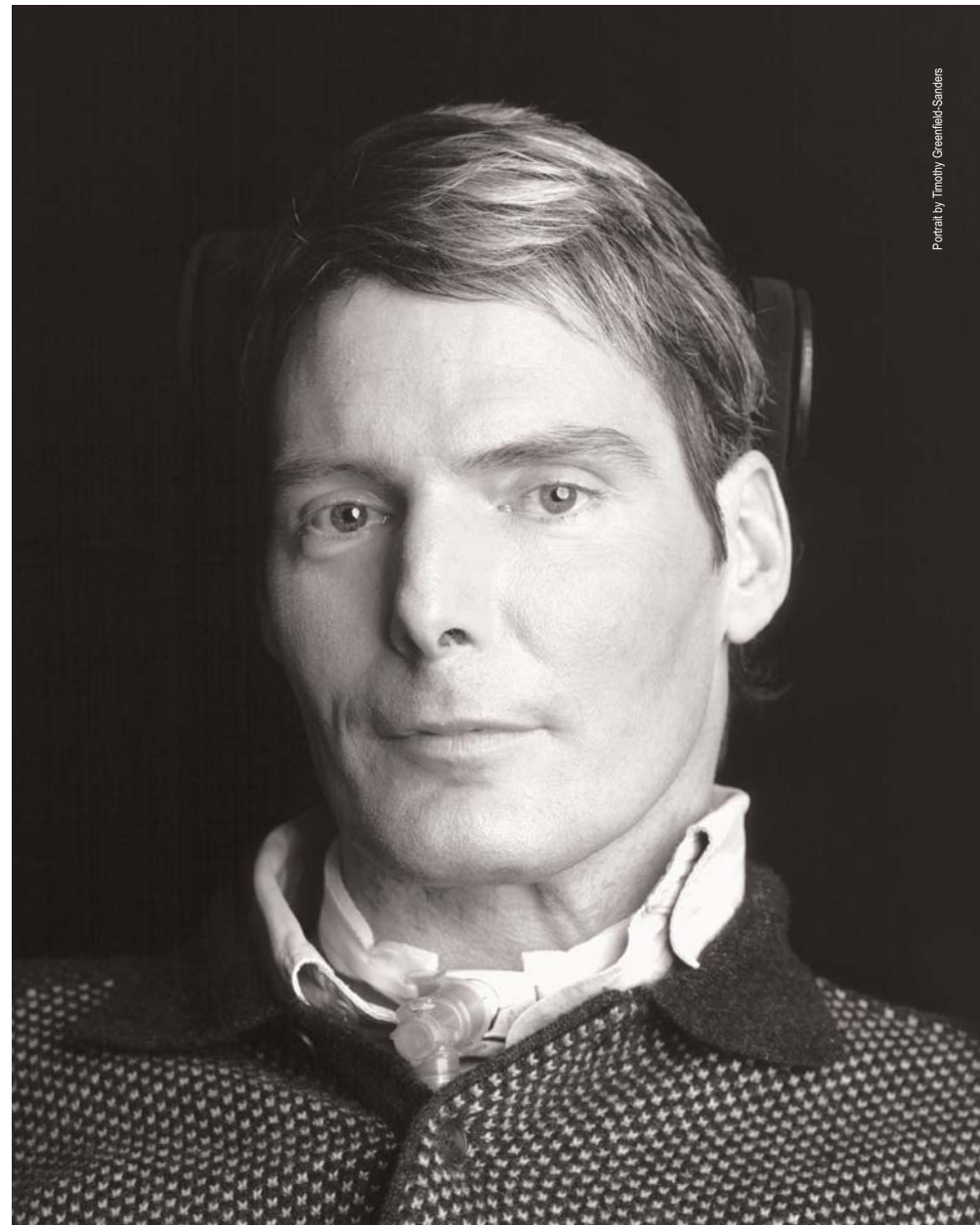
Christopher Reeve Foundation

The **Christopher Reeve Foundation (CRF)** is dedicated to curing spinal cord injury by funding innovative research, and improving the quality of life for people living with paralysis through grants, information and advocacy.

Christopher Reeve Foundation

636 Morris Turnpike, Suite 3A
Short Hills, NJ 07078
800.225.0292
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Fax: 973.912.9433
www.ChristopherReeve.org

Go Forward.



Portrait by Timothy Greenfield-Sanders



Christopher Reeve Foundation

**North American Clinical Trials Network
(NACTN) for Treatment of Spinal Cord Injury**

Quarterly Report Format

1. Award No. W81XWH-07-1-0361
2. Report Date: June 5, 2008
3. Reporting period February 14, 2008-May 13, 2008
4. Principal Investigator Dr. Robert Grossman
5. Telephone No.: 713-441-3810
6. Award Organization: Christopher Reeve Foundation
7. Project Title: North American Clinical Trials Network for Treatment of Spinal Cord Injury
8. Current staff, role and percent effort of each on project. **CONTINUED ON NEXT PAGE**

STAFF MEMBER	Role	% EFFORT
Robert Grossman MD	PI-Main	20
Susan Howley	Admin	20
Peter Wilderotter	Admin	5
Edward Jobst	Admin	5
Anne Homa	Admin	5.5
Bea Torre	Admin	5
Elizabeth Toups RN	Study Coordinator	80

9. Contract expenditures to date (as applicable):

COST ELEMENTS	THIS QUARTER	CUMULATIVE
Personnel	92,464	960,339
Fringe Benefits	26,352	275,548
Supplies		
Equipment		
Travel		
Other Direct Costs	22,558	70,071
Subtotal	141,374	1,305,958
Indirect Costs	13,953	130,413
Fee		
Total	155,327	1,436,671

10. Comments on administrative and logistical matters.
11. Use additional page(s), as necessary, to describe scientific progress for the quarter in terms of the tasks or objectives listed in the statement of work for this contract. Explain deviations where this isn't possible. Include data where possible.
12. Use additional page(s) to present a brief statement of plans or milestones for the next quarter.

8. Current staff, role and percent effort of each on project.

STAFF MEMBER	Role	% EFFORT
John Crommett MD	PI	20
Martha Power RN	Study Coordinator	80
David Chen MD	PI	20
Nurse RN	Study Coordinator	80
Michael Fehlings MD PhD	PI	20
Yuriy Petrenko MD	Study Coordinator	80
Christopher Shaffrey MD	PI	20
Michele Rehan MS	Study Coordinator	80
Christopher Shields MD	PI	20
Anne Watson	Study Coordinator	80
Bizhan Aarabi MD	PI	20
Carrie Byard RN	Study Coordinator	80
Michael K. Rosner MD	PI	20
TBD	Study Coordinator	100
Employees TBD	Nurse Clinician	100
Ralph Frankowski PhD	PI	3
Keith Bureau	Co PI	20
Christine Lusk	Res. Coordinator	25
Hyvan Dang	Analyst	66
Nina Newton	Res assoc	66
Colleen Moore	Specialist	30
Tim Pierce	Grants	5
Maria Grissom	Sr. Specialist	5