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Title: Spinal Cord Injury Neuroprotection with Glyburide

(SCING)

Pilot Study: An Open-Label Prospective Evaluation of the Feasibility, Safety, Pharmacokinetics, and Preliminary Efficacy of Oral Glyburide in Patients with Acute Traumatic Spinal Cord Injury

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Study Protocol and Statistical Analysis Plan

Principal Investigator:

H. Francis Farhadi, M.D., Ph.D.
Phone: 614-366-4961
E-Mail: Francis.Farhadi@osumc.edu

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1.0 SYNOPSIS

1.1 Design

This will be a prospective multi-center single arm open-label pilot study of oral glyburide in patients with acute traumatic cervical spinal cord injuries (SCI). The study population consists of subjects with acute traumatic ASIA A, B or C SCI, age 18-80 years, and able to start study drug within 8 hours of injury. The study will enroll and treat up to a maximum of 10 patients who will be matched in a 1:3 ratio with historical controls collected from the North American Clinical Trials Network database.

1.2 Objectives

Primary Objectives

- To assess the feasibility of recruiting subjects with ASIA A, B, or ASIA C acute SCIs within the specified 8-hour time frame.
- To assess the preliminary safety of oral glyburide in subjects with ASIA A, B, or ASIA C acute ACIs

Secondary Objectives

- To study the pharmacokinetics of oral glyburide following acute SCI.
- To undertake a preliminary assessment of the effects of study drug on measures of neurologic outcome using a matched cohort group for comparison.
- To study the effects of study drug on serum biomarkers.
- To study the effects of study drug on intramedullary MR imaging changes related to SCI.

1.3 Interventions and Duration

Standard of care treatment will be instituted for all patients including management of respiratory and hemodynamic parameters in a monitored setting for at least the first three days following SCI. All subjects meeting eligibility criteria will be approached as soon as possible following injury and informed consent obtained for enrollment. While all subjects will undergo standard of care computed tomography (CT) and magnetic resonance imaging (MRI) studies, only review of the CT studies will be required prior to enrollment.

As soon as feasible and if indicated, surgical intervention for spinal cord decompression and spinal stabilization will be undertaken. Safety labs and Adverse Events will be assessed through Day 14 or discharge (whichever is earlier). Serum biomarker levels will be assessed at baseline, and Days 1, 3, and 7. Adverse events will be further assessed, along with functional outcomes, at Day 28 (±7 days), Day 42 (±7 days), Day 84 (±14 days), Day 182 (±14 days), and Day 365 (±30 days). Study participation is expected to last 365 Days ± 30 days. Adverse Event and functional outcome assessments will be undertaken by ASIA-certified study personnel.

1.4 Statistical Considerations

Descriptive statistics will be generated for all variables of interest. Categorical measures will be reported with frequencies, percentages and continuous measures with means and standard deviations.

The primary outcomes of feasibility will be the rate of recruitment and the proportion of patients recruited versus screened.

All adverse events that occur during the initial hospitalization period will be summarized. The frequency of adverse events during this period will be compared to matched NACTN Registry historical controls in a 1:3 ratio (along with corresponding confidence intervals).

Matched tests will be utilized to compare neurologic outcomes and biomarker levels between enrolled subjects receiving oral glyburide and matched historical controls.

2.0 INTRODUCTION

In this initial phase open–label pilot study, we propose to enroll patients with defined inclusion/exclusion criteria at up to ten Level I/II trauma centers including Ohio State University Wexner Medical Center (Principal Site). The primary objectives are to assess the feasibility and safety of enrolling, evaluating, and treating acute cervical SCI patients with oral glyburide.

Oral glyburide is a widely used blood glucose-lowering drug that belongs to the sulfonylurea class. Blood glucose is lowered acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Oral Glyburide has been used successfully in the treatment of non-insulin-dependent diabetes mellitus (NIDDM) for more than 20 years. In treating NIDDM, the drug works by inhibiting ATP-sensitive potassium channels in pancreatic beta cells by antagonism of SUR1. This inhibition causes cell membrane depolarization, which causes voltage-dependent calcium channels to open, which in turn causes an increase in intracellular calcium in the beta cell, stimulating insulin release.

The Sur1-Trpm4 channel is selectively expressed in the central nervous system (including the spinal cord) under conditions of ischemia, hypoxia, and trauma [6, 8-10] leading to vasogenic and cytotoxic edema followed by oncotic cell death [11]. A double-blind, multicenter, randomized trial of an intravenous form of glyburide (Cirara^{TM}) in patients with large ischemic strokes likely to develop malignant cerebral edema (GAMES-RP study) identified the drug to be well-tolerated at 3 mg per day [2] with few treatment-related serious adverse events (SAEs) reported and reassuringly limited to hypoglycemia.

Neurotrauma patients, including those with spinal cord injuries, typically have elevated blood glucose levels over the first three days following their injury. For example, a large retrospective review of 528 patients with SCI [35] indicated that 53% of patients were hyperglycemic on admission (glucose concentration ≥126 mg/dl) and that hyperglycemia was a significant risk predictor of poor functional outcome. As such, oral glyburide administration for its potential neuroprotective effects in the SCI population appears unlikely to cause significant adverse events related to hypoglycemia and may indeed be beneficial independently given its blood glucose lowering effects.

Between August 2015 and August 2016, we screened patients with acute traumatic cervical SCIs (GOSCIP study; clinical trials NCT02524379) for potential treatment with Cirara^{TM}. Sixteen patients were screened during this period but none met the eligibility criteria. Given the ongoing enrolment difficulty with this intravenous drug within the 6 hr timeline, we have decided to amend several elements of the trial including some of the inclusion/exclusion

criteria. First, the route of administration will be changed to the oral form allowing for easier and streamlined drug administration. An extension of the window of administration to 8 hours from the time of injury will also be implemented. Several screened patients fell out of the eligibility due to this constrained time window, especially considering that Cirara™ preparation takes in the order of 1-2 hours.

The feasibility of screening, consenting, enrolling, and administering oral glyburide in the acute setting following spinal cord trauma (≤8 hours from injury) will be assessed at the participating centers. Further, a comprehensive assessment of all-cause AEs will be undertaken in this study for spinal cord trauma patients.

The data obtained from this pilot study should inform the design of further multicenter phase II/III clinical studies evaluating the efficacy and safety of oral glyburide in improving functional outcomes following SCI.

2.1 SCI Background

There are currently no standard of care neuro-protective strategies for the treatment of acute traumatic SCI. Methylprednisolone is no longer considered standard of care based on its dubious clinical benefit combined with its demonstrated adverse effect on immune function [3]. The sodium-channel blocker, Riluzole, was recently evaluated in a phase 1/2a trial of 36 patients by the North American Clinical Trials Network (NACTN) group [4]. While safety data appeared favorable, a larger phase 2/3 study is currently underway to assess for efficacy in improving neurologic outcomes. Other potential therapies are either at the pre-clinical or early pilot stage [33]

Progressive hemorrhagic necrosis (PHN) represents an increasingly well-characterized mechanism of secondary injury that negatively impacts neurologic outcomes. Structural failure of the integrity of intramedullary capillaries, so called ‘capillary fragmentation’ is thought to underlie this acute and dynamic secondary injury process. Animal studies modeling contusional SCIs across different laboratories have revealed a 2-2.5-fold increase in extravasated intramedullary blood within the first 12-24 hours following blunt impact trauma [5-7]. The formation of distinct microscopic

hemorrhages within the cord in turn is linked to the progressive secondary injury and neurologic deterioration following SCI.

2.2 Glyburide and Signaling Background

Glyburide (also known as Glibenclamide; 5-chloro-N-(4-[N-(cyclohexylcarbamoyl) sulfamoyl]phenethyl)-2-methoxybenzamide) is an anti-diabetic medication in a class of medications known as sulfonylureas. In treating NIDDM, the drug works by inhibiting ATP-sensitive potassium channels in pancreatic beta cells by antagonism of SUR1. This inhibition causes cell membrane depolarization, which causes voltage-dependent calcium channels to open, which in turn causes an increase in intracellular calcium in the beta cell, stimulating insulin release.

The Sur1-Trpm4 channel is selectively expressed in the central nervous system (including the spinal cord) under conditions of ischemia, hypoxia, and trauma [6, 8-10], leading to vasogenic and cytotoxic edema followed by oncotic cell death [11]. With respect to micro vascular endothelial cells, this process leads to the formation of space- occupying edema and secondary hemorrhage. Spinal cord edema and micro hemorrhage formation through this mechanism is a critical secondary injury process that progressively exacerbates mechanical compression, ischemia, and neuronal/glial cell death following trauma [12].

Numerous pharmacokinetic studies of oral glyburide have assessed single-dose administrations in normal subjects and have demonstrated significant absorption within one hour, peak drug levels at about four hours, and low but detectable levels at twenty-four hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Multiple-dose studies with glyburide (a widely available oral glyburide formulation) in diabetic patients demonstrate drug level concentration-time curves similar to single-dose studies, indicating no build-up of drug in tissue depots. The decrease of glyburide in the serum of normal healthy individuals is biphasic, the terminal half-life being about 10 hours [34].

In a phase 1 study of intravenous glyburide (Cirara^{TM}), the drug was administered as a bolus dose followed by a 3-day continuous infusion maintenance dose. Five groups of patients were dosed, totaling 26 patients on drug (4 dosing groups, with doses ranging from 0.4 to 10 mg/day) and 8 on placebo. There were no SAEs during the study. Two subjects (one in the 6 mg/day treatment group and one in the 10 mg/day treatment group) were discontinued from the study due to persistent hypoglycemia. The subject in the 6 mg/day treatment group who was discontinued from the study also experienced transient increases in ALT and AST levels beginning 3 days after study drug discontinuation, which returned to normal by Day 22. There were no other clinically significant drug-related AEs [1]. Based on this work, Phase 2a pilot and exploratory randomized trials were undertaken by Remedy Pharmaceuticals (GAMES-RP) wherein a total of 93 stroke patients were dosed at 3 mg/day for 3 days. There were no new safety concerns raised in these patients [36].

2.3 Rationale for Glyburide following SCI

Emerging evidence implicates the Sur1 – Trpm4 channel as the molecular precursor of PHN [6, 13-15]. Up-regulation and co-association of the regulatory and pore forming subunits of this ion channel have been demonstrated to occur in endothelial and other cells only after SCI, as demonstrated in rodents and humans [6, 16, 17]. PHN-associated secondary micro hemorrhage formation in turn is specifically associated with channel up- regulation and activation in micro vessels [6, 16, 18]. Following trauma, spinal cord edema and micro hemorrhage formation through this mechanism is a critical secondary injury process that exacerbates mechanical compression and ischemia, and contributes to neuronal/glial cell death.

Glyburide-mediated blockade of the Sur1 – Trpm4 channel in rodent models of SCI leads to minimal secondary micro hemorrhage formation and the absence of capillary fragmentation, the pathologic hallmark of PHN. Lesion volumes and hind limb locomotor functional outcome measures, measured up to 6 weeks, are significantly improved in animals treated with Glyburide shortly after the time of injury [6, 13-16]. Delayed treatment at 3 hours following SCI in rats, a more clinically-relevant time frame, also yielded significant functional benefit [19]. While the magnitude of

Glyburide-mediated neurological benefit appears to correlate with the magnitude of the initial experimental injury, significant treatment effects have been consistently demonstrated for both lesion volume and functional scores in all studies to date [14, 16, 19].

3.0 OBJECTIVES

3.1 Primary Objectives

- Feasibility: To assess the feasibility of running a larger phase II or III study among this population of patients where treatment must begin within a defined time frame. The number of patients who would otherwise be eligible for the study but did not receive study treatment within the 8-hour time frame will be recorded (ratio of recruited versus screened). The rate of recruitment will also be recorded.
- Safety: Vital signs, clinical exams, ECG, and clinical laboratory results will be carefully and continuously monitored during the course of hospitalization. Adverse events (AEs) will be assessed throughout the course of hospitalization through Day 28. In addition to presenting a summary of all AEs, where possible, a comparison of AEs occurring in study subjects vs. those occurring in matched historical controls (as captured in the NACTN registry) will be made. To facilitate this comparison, AEs will be grouped into one of 10 systems according to a modified NACTN chart [20, 21] (see appendix 1): cardiac, pulmonary, hematology, gastrointestinal/genitourinary, infections, skin, failure of stabilization, neuropsychiatric, hypoglycemia/other metabolic, and other. These AEs will be described further with respect to the specific name of the event (that is, the "type" of event; for example, for cardiac events, the type could be bradycardia or other dysrhythmia, cardiac arrest, etc.). Severity ("intensity", as per the NACTN chart) as well as relatedness to glyburide will also be assessed. The frequency of AEs, as well as mortality (all-cause and cardiac-related), will be compared to that of a matched cohort from the NACTN registry [20, 21].

Specific outcome variables related to assessing blood glucose (BG)-related safety of glyburide are:

- Hypoglycemia (i.e. Blood Glucose (BG) < 55 mg/dL
- Symptomatic hypoglycemia i.e. hypoglycemia with investigator-identified hypoglycemic symptoms.

The following table defines which BG values should be reported as AEs:

Table 1: Blood Glucose Values and AE reporting

BG Value	Report as AE?
70-79 mg/dL	Mandatory AE reporting not required; may be reported as an AE (and coded appropriately in terms of severity) if the event meets the protocol-defined definitions.
55- 69 mg/dL	Must be reported as an AE, if confirmed by a point-of-care or lab value retest (and coded appropriately in terms of severity)
< 55 mg/dL	Must be reported as a SAE (appendix 2), if confirmed by either a point-of-care or lab value retest (and coded appropriately in terms of severity)

Specific outcome variables related to assessing cardiac-related safety of glyburide are:

- Incidence/severity of cardiac AEs and cardiac mortality
- Incidence of QTc of > 500 ms
- Mean QTc and mean change in QTc from baseline.

3.2 Secondary Objectives

- Pharmacokinetics of glyburide following acute cervical SCI: Plasma concentrations will be serially quantified through day 3 following SCI. Comparisons will be made to reported levels achieved healthy patient cohorts
- Neurologic recovery following SCI: The neurologic status of patients will be assessed using the ASIA Impairment Scale (as assessed by ISNCSCI criteria) and the Spinal Cord Independence Measure (SCIM version III) [22]. The motor and sensory sub scores of the ASIA assessment will be determined on first contact,

every day until Day 4, at 1-2-4-6 weeks, and at 3-6-12 months of follow-up. The SCIM version III will be assessed at 3, 6 and 12 months of follow-up. Comparisons will be made to control subjects (with a 1:3 matching ratio in the NACTN registry matched based on age, co-morbidities, initial injury severity, and injury level.

- Serum biomarker levels: Standard enzyme-linked immunosorbent assay (ELISA) techniques will be used to measure blood levels of neurofilament light chain, neuron- specific enolase, tau, S100b, and glial fibrillary acidic protein levels on admission, at 24 hours and on days 3, and 7following SCI. Comparisons will be made to (i) matched control serum values of non-treated subjects with acute cervical SCIs [23] and (ii) previously published values observed in non-treated control patients [24-26].
- Spinal cord lesion volumetric analysis: Standard sequences (T1, T2, FLAIR, SWI) at 3T field strength will be used to assess the extent of the hemorrhagic lesion and surrounding edema. Patients will be imaged on the day of admission and on day 2 following injury (standard-of-care studies). Volumetric assessments of lesion size (based on manual outlines) will be performed and compared at the two time-points by the study neuroradiologist to assess for the progression of intrinsic cord signal changes [27].

4.0 STUDY DESIGN

4.1 Inclusion/Exclusion Criteria

All patients with ASIA A, B or C acute traumatic spinal cord injuries will be assessed for suitability and prospectively enrolled in the study. Only cervical level (C2-C8) level injuries in patients aged 18 to 80 years old will be included. Detailed eligibility criteria are listed below.

The use of immunosuppressive therapy (including methylprednisolone and other corticosteroids) will be discouraged; however, use of such therapy will not require exclusion or discontinuation from the study. While once considered as an option for patients with acute SCI, it is noteworthy that more recent recommendations have all re-

evaluated the routine use of methylprednisolone [28]. The most recent guidelines published by a panel convened by the Joint Section on Spine and Peripheral Nerves of the American Association of Neurological Surgeons and Congress of Neurological Surgeons has in fact recommended against its use following acute SCI given its negative risk- benefit profile [3]. In the words of the panel: "Administration of methylprednisolone for the treatment of acute SCI is not recommended. Clinicians considering methylprednisolone therapy should bear in mind that the drug is not approved by the Food and Drug Administration for this application. There is no Class I or Class II medical evidence supporting the clinical benefit of methylprednisolone in the treatment of acute SCI. Scattered reports of Class III evidence claim inconsistent effects likely related to random chance or selection bias. However, Class I, II, and III evidence exists that high-dose steroids are associated with harmful side effects, including death." Of note, the recent phase 1/2a riluzole study reported that corticosteroids were administered at the time of admission to only 39% of the patients (while 58% of historic NACTN registry patients had received this treatment) [4].

- **Inclusion Criteria:**
  1. Age: ≥ 18 years and ≤ 80 years
  2. Written informed consent by patient or legal authorized representative
  3. No other life-threatening injury
  4. No evidence of sepsis
  5. Acute cervical SCI with ASIA Impairment Scale grade A, B or C on admission
  6. Non-penetrating SCI at neurologic level from C2 to C8
  7. Initiation of study drug within 8 hours of injury
- **Exclusion Criteria**
  1. Unconsciousness or other mental impairment that prevents neurological assessment within the first 8 hours
  2. Acute SCI with ASIA Impairment Scale grade D or E
  3. Currently involved in another non-observational SCI research study or receiving another investigational drug
  4. History of hypersensitivity to sulfonylureas, in particular glyburide, or any of its components

5. Other illness (including mental disorder) that could preclude accurate medical and neurological evaluation (at discretion of the site investigator)
6. Unable to commit to the follow-up schedule
7. A recent history of regular substance abuse (illicit drugs, alcohol), which in the opinion of the investigator would interfere with the subject's participation in the study
8. Any condition likely to result in the patient's death within the next 12 months
9. Prisoner
10. Severe renal disorder from the patient's history (e.g. dialysis) or baseline eGFR of < 30 mL/min/1.73 m^2
11. Known severe liver disease, or ALT > 3 times upper limit of normal or bilirubin > 2 times upper limit normal. Subjects may be randomized if liver function tests have been drawn but are not yet available and the subject has no known history of liver disease; however, treatment with glyburide will be discontinued prior to the second dose if liver function tests indicate ALT > 3 times upper limit of normal or bilirubin > 2 times upper limit of normal
12. Blood glucose <55 mg/dL at enrollment or immediately prior to administration of glyburide, or a clinically significant history of hypoglycemia
13. Acute ST elevation myocardial infarction, and/or acute decompensated heart failure, and/or QTc > 520 ms, and/or known history of cardiac arrest (PEA, VT, VF, asystole), and/or admission for an acute coronary syndrome, myocardial infarction, or coronary intervention (percutaneous coronary intervention or coronary artery surgery) within the past 3 months
14. Known treatment with Bosentan within past 7 days
15. Known G6PD enzyme deficiency
16. Pregnancy: Women must be either post-menopausal, permanently sterilized or, if ≤ 50 years old, must have a negative test for pregnancy obtained before enrollment
17. Breast-feeding women who do not agree to stop breast-feeding during and for 7 days following the end of oral glyburide administration
18. Subjects who in the opinion of the investigator are not suitable for inclusion in the study (reason to be documented).

4.2 Number of Patients

To assess the feasibility of recruitment and of the protocol procedures (specifically the ≤ 8 hr injury-to-drug timeframe), the study will plan to enroll and treat 10 patients across all study sites.

4.3 Study-related Management (standard-of-care)

The following items will be performed as standard-of-care:

- Vital signs (Temperature, Blood Pressure, Pulse, Respiration Rate, O2 saturation)
- Blood work; CT scans of the spine and head (as indicated); pre- and post-operative (Day 2) MRI of the cervical spine

Cervical CT studies will reveal the nature of the associated spinal fracture and/or misalignment. Subjects with bilateral cervical facet dislocations or with fracture patterns associated with > 75% canal compromise will be excluded from the study given that a significant component of their underlying SCI likely involves direct parenchymal and/or ischemic mechanisms [29]. Adherence to acute SCI management guidelines most recently revised by a consensus panel in 2013 [3] will be strongly encouraged. These guidelines include avoidance of hypoxia and hypotension with induced hypertension as needed to keep mean arterial pressure ≥ 85mmHg for 7 days. Early intervention with surgical decompression and stabilization within 24-48 hrs (when medically feasible) will be encouraged for all patients [30] but will ultimately be left to the discretion of the treating surgeon.

4.4 Study-related management (non-standard of care)

Non-standard-of-care blood work will be obtained at the following time points following the SCI:

- Pharmacokinetic Analysis: Daily, baseline through Day 3
- Biomarkers Levels: Enrollment/Baseline, 24 hours, Day 3, and Day 7

Clinical, imaging, and safety assessments will be performed throughout the study period:

- Patients will be closely monitored clinically for all AEs during the first 28 days of the study. SAEs will be monitored for the entire duration of the study. For the initial hospitalization period, the incidence of AEs will be compared where possible to that of matched controls obtained from the NACTN registry (1:3 ratio with respect to age, co-morbidities, injury level, and injury severity). The 1:3 patient matching will be undertaken by the study statistician.
- Neurological evaluation will be carried out at specific time-points up to one year following SCI to assess for changes in neurological status. The 3, 6, and 12-month ISNCSCI motor/sensory and SCIM vIII scores of the patients will also be compared where possible to that of matched controls from the literature and from the NACTN registry.

5.0 STUDY ASSESSMENT AND PROCEDURES

5.1 Screening

Patients with suspected acute cervical SCI will be screened upon arrival to hospital. These evaluations will occur prior to enrolment:

- Vital signs (Temperature, Blood Pressure, Respiration rate, Pulse, O2 saturation, Height, Weight)
  - Note: Height and Weight can be estimated if patient cannot be measured.
- Physical examination and Medical History
- Cervical SCI Time, Cause, and Level of injury
- Demographics and Clinical Variables (age, race, gender, and BMI)
- Neurological examination including ISNCSCI motor and sensory assessments
- ECG (12-lead), read within 12 hours and recorded as clinically significant or non- clinically significant by study team member
- Clinical laboratory tests:
  - Pregnancy test for women of child-bearing potential
  - Hematology: complete blood count
  - Chemistry: electrolytes (sodium, potassium, chloride, bicarbonate), BUN, creatinine, glucose

- Liver Function Tests: AST, ALT, bilirubin (total and direct), and alkaline phosphatase.
  - Glyburide can commence if liver function tests are not yet available but will be discontinued if ALT > 3 times upper limit or bilirubin > 2 times upper limit of normal.

Because pertinent patient information will already be collected as part of the standard of care, and to reduce additional study-specific procedures, screening and baseline information may be taken from the patient's medical records prior to obtaining informed consent. However, informed consent will be obtained prior to performing any study-specific procedures.

Once study eligibility has been confirmed (inclusion/exclusion criteria are met) and informed consent obtained, the patient will be enrolled into the study.

5.2 Registration Procedures

General Guidelines

Primary health care personnel (residents, attending staff, and nurse practitioners) at participating centers will identify potential subjects and will then contact the site coordinator who will then verify eligibility and register the patient using the electronic data capture system (REDCap)

Following registration, patients should begin protocol treatment within 8 hours of the injury. Issues that would cause treatment delays should be discussed with the Study Principal Investigator.

Patients may be registered by a participating site only after the initial IRB approval for the site has been forwarded to the Coordinating Center and the Coordinating Center has activated the site. Eligible patients who consent to participate in the study will be entered on the study by the local site.

5.3 Registration Process

To register a patient, the following documents should be completed and uploaded to the electronic data capture system (REDCap) by the research team:

- Copy of required clinical and radiologic tests
- Signed patient consent form
- HIPAA authorization form
- Eligibility Screening Worksheet
- Registration Form

Eligible patients will be enrolled within the first 8 hours after documented trauma, so that oral glyburide administration can begin no later than 8 hours after injury. This injury-to-drug timeframe appears feasible given the injury-to-admission times reported in recent SCI studies. For instance, in the phase 1/2a Riluzole study [4], the mean injury-to-admission time was 3.0 ± 1.8 hours (median 2.3 hours). The median injury-to-drug time of 8.5 hours in that study likely reflects the time taken for additional MRI studies (in addition to CT imaging).

5.4 On-Study: Baseline

These evaluations occur following subject enrollment, prior to the subject receiving glyburide

- Concomitant medications (including all medications taken within 7 days prior to screening)
- Medical procedures (performed since acute SCI)
- Baseline AEs (beginning at the time of enrollment)
- PK sample (serum)
- Biomarker sample (serum)
- CT and MRI studies
    - CT studies will be performed and reviewed prior to enrollment. Standard of care cervical MRI may be initiated prior to start of study drug but this is not a requirement. Study drug will be administered as soon as possible following enrollment irrespective of whether MRI has been performed.

5.5 Study Drug Description, Dose, and Administration

Enrolled patients will receive 12 doses of glyburide starting within 8 hours of SCI. The dosing regimen involves an initial dose of 1.25 mg followed by eleven consecutive doses of 0.625 mg every 6 hours. The total daily dose of glyburide on Day 1, Day 2 and Day 3 will be 3.125 mg, 2.5 mg, and 2.5 mg respectively (see Table 2).

Table 2: Study Dosing

	Day 1	**Day 2**	**Day 3**
Total Dose	3.125 mg	2.5 mg	2.5 mg
	First dose of 1.25 mg then 0.625 mg every 6 hours	0.625 mg every 6 hours	0.625 mg every 6 hours

This injury-to-drug timeframe will apply to patients managed non-operatively as well as to patients undergoing surgery (likely a majority of patients in the trial). Drug administration should not be stopped as the standard of care diagnostic studies and treatment is provided, including if the patient is transferred to the OR for decompression and stabilization. Hard stop rules for glyburide administration are listed below.

In the event a dose of glyburide is missed (beyond 2.5 hours from the expected administration time), the next dose should be administered at 1.25 mg followed by the usual 0.625 mg dose for subsequent administrations. If the missed dose is acknowledged within 2.5 hours of the expected administration time the dose should be given and the deviation noted.

5.6 Prohibited Interventions

No sulfonylurea agents may be administered during the first 4 days of admission. Subsequently, it is preferable that no sulfonylureas be administered through study completion. However, use of sulfonylureas starting beyond Day 4 will not result in study discontinuation.

The use of therapeutic steroids or hypothermia (cooling to below 36 Celsius) is discouraged for treatment of the patient's acute SCI. If the patient requires steroid therapy for the treatment of another condition, this is allowable.

No other investigational drugs may be administered during the study follow-up period. Decisions on whether to withdraw the patient from the study will be made on a case-by-case basis should another investigational drug nevertheless have been administered.

5.7 Interventions Related to Blood Glucose

- **Insulin**
  Insulin is not permitted during the period of study drug administration when BG < 120 mg/dL. "Tight" BG control (80 – 110 mg/dL) is not permitted during the period of study drug administration.

- **Supplemental Fluids**
  Supplemental fluids are to be standard of care except that during glyburide administration, D5NS or D10NS must be used instead of NS if necessary to maintain BG above 80 mg/dL. Total fluid volume should be consistent with site clinical practice and the clinical status of the subject.

- **Hypoglycemia treatment**
  Any BG of < 70 mg/dL must be promptly treated with a bolus of D50W at a volume (ml) of (100 – BG in mg/dL) x 0.4 as per Juneja et al. 2009 [31]. If supplemental fluids are NS, D5NS should be started. If supplemental fluids are D5NS, D10NS should be substituted. All BG < 70 mg/dL also should preferably be verified by laboratory testing, but repeat point-of-care tests may be used as well. To avoid false readings, blood for the repeat test must be drawn prior to treatment with D50W or switching supplemental fluids.

- **Glyburide Dose Reduction**
  Glyburide dosing must be reduced if subject is being administered D5NS or D10NS and (i) there is one confirmed BG < 55 mg/dL; or (ii) there are three confirmed BG < 70 mg/dL within a 12-hour period. If (i) or (ii) above occurs and the subject is on NS, D5NS or D10NS must first be started. If criteria (i) or (ii) are still met, then glyburide dosing should be adjusted to every 8 hours until three consecutive blood glucose readings of >70 are noted. If appropriate levels of BG are not reached within 8 hours of the first dose reduction, the next dose of glyburide should be skipped as an additional dose reduction. Glyburide dosage must only be adjusted based on verified laboratory or repeat point-of-care test values that are taken 15 minutes or more following the last administration of insulin.

- **Glyburide Discontinuation**
  The dosing regimen can only be reduced twice; if (i) or (ii) above occurs a third time, glyburide must be discontinued. Glyburide dosage must only be stopped based on verified laboratory test values or, if not available, a repeat point-of-care that are taken 15 minutes or more following the last administration of insulin. When glyburide is stopped as a result of low BG, D50W should be administered by bolus in order to maintain BG > 80 mg/dL. Multiple D50W boluses may be administered, the timing and volume of which are at the discretion of the clinician. BG monitoring is required every 15 (± 10) minutes until BG ≥ 80 for 3 consecutive readings without bolus glucose supplementation, then hourly (± 30 minutes) for the next 6 hours.

5.8 Days 1-7 (0-168 hours)

- The first dose of glyburide must be administered within 8 hours of injury and stopped after 72 hours. Hard stop rules for glyburide administration are listed below.
- As per recommended standard-of-care guidelines [3], subjects will be admitted to the intensive care unit following initial diagnostic testing where continuous respiratory, cardiac, and hemodynamic monitoring will be undertaken [32]. Maintenance of normal blood oxygenation and a mean arterial blood pressure of 85-90 mmHg will be emphasized in this monitored setting continuously over the first full 7 days following injury.

- The following assessments will be performed through day 7 following injury (during and after study drug regimen):
    - Safety labs: 24 hours (±12 hours), 48 hours (±12 hours) 72 hours (±12 hours) and 96 hours (±12 hours).
        - Hematology: complete blood count
        - Chemistry: electrolytes (sodium, potassium, chloride, bicarbonate), BUN, creatinine
        - Liver Function Tests: AST, ALT, bilirubin (total and direct), and alkaline phosphatase
    - Blood glucose (BG) monitoring will be hourly (± 30 minutes) for Hours 1-24, every 2 hours (± 30 minutes) for Hours 25-48 and every 4 hours (± 60 minutes) for Hours 49-88. If BG < 70 mg/dL, BG monitoring is required every 15 (± 10 minutes) minutes until BG ≥ 80 for 3 consecutive readings without exogenous bolus glucose supplementation, then hourly (± 30 minutes) for the next 12 hours and every 2 hours (± 30 minutes) thereafter.
    - Continuous bedside cardiac telemetry monitoring from Hour 0 through Hour 72
    - ECG (12-lead) at 4-6 hours, 24±6 hours, 48±6 hours and 60-72 hours (from the start of study drug regimen). The ECGs will be read within 12 hours, recorded as clinically significant or non-clinically significant, and signed off on by study team member.
    - Blood sampling for PK prior to dosing, at 4-6 hr (prior to the second study drug administration), 24±6 hours, 48±6 hours and 60-72 hours.
        - PK Samples to be drawn as close as possible to ECGs
    - Start time of drug and time of subsequent dosing. Record reason for any missed doses.
    - Concomitant medications and procedures/therapies
    - Review safety and AEs
    - ASIA Impairment Scale scoring at 24±12 hours, 48±12 hours, 72±12 hours, and 96±12 hours. In the event of spinal fracture reduction (closed or open with additional stabilization), an additional ASIA evaluation must be recorded as close to the start of the procedure as possible, preferably within

2 hours. Every attempt should be made to collect the ASIA grading free of the effects of sedating drugs.
    - Blood sampling for additional laboratory tests to identify biomarkers prior to dosing and at 1, 3 and 7 days
- Cervical MRI scans performed on admission and on Day 2 will be uploaded to REDCap.

5.9 Up to day of discharge (but no later than Day 14)

In addition to continuous review of safety and AEs during the second week of hospitalization (up until discharge, as applicable), the following evaluations and assessments will be performed prior to Day 14 or Discharge, whichever is earlier:

- ASIA Impairment Scale scoring. Every attempt will be made to collect scores free of the effects of sedating and/or paralytic drugs.
- Concomitant medications
- Safety labs:
    - Hematology: complete blood count
    - Chemistry: electrolytes (sodium, potassium, chloride, bicarbonate), BUN, creatinine, glucose
- Liver Function Tests: AST, ALT, bilirubin (direct and total), and alkaline phosphatase
- Concomitant procedures and therapies
- Contact information for the subject (home and cellular telephone numbers, email addresses, home addresses, rehabilitation or nursing home information including fax and phone numbers); LAR (home and cellular telephone numbers, email addresses, home addresses); family members (home and cellular telephone numbers, email addresses, home addresses); and personal physician (phone and fax numbers)

5.10 Post-treatment follow-up

- *Post-treatment follow-up: Day 28 (± 7 days)*
    - Review unresolved AEs
    - Record additional AEs
    - ASIA Impairment Scale

- *Post-treatment Follow-up: Day 42 (± 7 days)*
  - Review unresolved AEs
  - Record additional SAEs
  - ASIA Impairment Scale
- *Post-treatment Follow-up: Day 84 (± 14 days)*
  - Review unresolved AEs
  - Record additional SAEs
  - ASIA Impairment Scale
  - Spinal Cord Independence Measure (vIII)
- *Post-treatment Follow-up: Day 182 (± 14 days) and Day 365 (± 30 days)*
  - Review unresolved AEs
  - Record additional SAEs
  - ASIA Impairment Scale
  - Spinal Cord Independence Measure (vIII)

5.11 Study Calendar

Test and Observations	Screening / Enrollment (up to 6 hours prior to treatment)	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14 or D/C	Day 28 (+/- 7 days)	Day 42 (+/- 7 days)	Day 84 (+/- 14 days)	Day 182 (+/- 14 days)	Day 365 (+/- 30 days)
History &Physical	X											

Vital Signs [a]	X											
Consent	X											
Demographic [b]	X											
Operative Data [f]							X					
Length of Stay							X					
Adverse Events[k]	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test [d]	X											
SCI (Cervical) [e]	X											
Inclusion/Exclusion	X											
Concomitant Review	X	X	X	X	X	X	X	X				
Procedures	X											
MRI	X		X									
CT	X											
Labs [c]	X	X	X	X	X		X					
ECG(12-lead)	X	X	X	X								
Drug												
Drug Administration [i,j]	X	X	X	X								
Serum Biomarkers [h]	X	X		X		X						
Pharmacokinetic [g]	X	X	X	X								
Outcome Measures												
AIS	X	X	X	X	X	X	X	X	X	X	X	X
SCIM vIII										X	X	X

a. Temperature, blood pressure, pulse, O_2, respiration, BMI, height and weight (can be estimated if patient cannot be measured). Vitals are to be collected at screening (prior to enrolment).
b. Demographics: age, race, and gender.
c. Labs: hematology (complete blood count); chemistry (sodium, potassium, chloride, creatinine, electrolytes, bicarbonate, bun); liver function (AST, ALT, bilirubin total, bilirubin direct, and alkaline phosphatase); blood glucose (Blood glucose (BG) monitoring will be hourly (± 30 minutes) for Hours 1-24, every 2 hours (± 30 minutes) for Hours 25-48 and every 4 hours (± 60 minutes) for Hours 49-
88. If BG < 70 mg/dL, BG monitoring is required every 15 (± 10 minutes) minutes until BG ≥ 80 for 3 consecutive readings without exogenous bolus glucose supplementation, then hourly (± 30 minutes) for the next 12 hours and every 2 hours (± 30 minutes) thereafter)
d. Pregnancy test (only complete if woman is of childbearing potential). e. SCI (cervical): time, cause, and level of injury.
f. Optional: only required if patient has surgery.
g. Blood sampling for PK prior to dosing, at 4-6 hr. (prior to the second dose of glyburide (glyburide), 24±6 hours, 48±6 hours and 60-72 hours. PK samples to be drawn as close as possible to ECGs.
h. Serum biomarkers: enrollment/baseline, 24 hours, Day 3, and Day 7.
i. Cannot continue until enrollment liver function test are available and indicate ALT≤ 3 X upper limit of normal and Bilirubin ≤2 X upper limit of normal
j. Dosing regimen is 12 doses of glyburide; an initial dose of 1.25 mg followed by eleven consecutive doses of 0.625 mg every 6 hours. The total daily dose of glyburide on Day 1, Day 2 and Day 3 will be 3.125 mg, 2.5 mg, and 2.5 mg respectively (see table 2)
k. AEs/SAEs recorded through Day 28; new SAEs and unresolved AEs recorded through end of study.

6.0 ADVERSE EVENTS

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal, or
- is associated with a serious adverse event, or
- is associated with clinical signs or symptoms, or
- leads to additional treatment or to further diagnostic tests, or
- is considered by the investigator to be of clinical significance.

For this study, all AE's whether reported, observed, or elicited by direct or indirect questioning will be recorded from the time of study enrollment through study completion. Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to Study Drug, action taken, and outcome.

All unresolved AEs will be followed, whenever possible, until the events are resolved or stabilized, the subject is lost to follow-up, and/or it has been determined that the study treatment or participation in the study is not the cause. At the last scheduled assessment, the investigator should instruct each subject to report any subsequent event(s) that the subject or the subject's personal physician believes might reasonably be related to participation in this study.

Information on AEs should be recorded in the patient record, and also in the appropriate AE page of the REDCap database.

6.1 Adverse Event Reporting

Preexisting Condition

A preexisting condition is one that is present at the start of study drug administration. A preexisting condition should be reported as an adverse event if the frequency, severity, or the character of the condition worsens during the study period.

Abnormal Laboratory Values

A clinical laboratory abnormality should be reported as an adverse event if the following conditions are met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality, and
- The abnormality suggests a disease and/or organ toxicity, and
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

However:

- Electrolyte imbalances that are asymptomatic and not considered clinically significant by the investigator should not be reported as AEs even if they are treated; and
- Table 1 in Section 3.1 defines which blood glucose values should be reported as AEs.

Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization, according to the judgment of the clinical investigator, should be documented and reported as a Serious Adverse Event (SAE).

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are to be reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

6.2 Evaluating Adverse Events

All AEs must be evaluated by the Investigators for severity, seriousness, and relationship to Study Drug.

Adverse Event Severity and Seriousness

All AEs will be evaluated by the Investigators separately for both severity (mild, moderate, severe respectively coded as 1, 2, or 3; see appendix 1) and for seriousness (AE versus SAE).

Relationship to Study Drug

The relationship of the AE to glyburide will be specified by the Investigators as either Unrelated, Possibly/Probably related, and definitely related. When considering the potential relationship of an AE, the Study Investigators' assessment will include consideration of the incidence of complications anticipated in the SCI population in the absence of glyburide administration. For instance, in 485 subjects with acute SCIs recruited into the NACTN database, 1376 total complications were recorded during the initial hospitalization (Table 4) [21].

Table 4: Acute care complications: type, frequency, and incidence

Complication Type	Frequency (%)	Incidence Rate (%)
Pulmonary	348 (25.3)	36.7
Infection	285 (20.7)	33.2
Hematology	213 (15.5)	26.6
Cardiac	178 (12.9)	25.6
GI/GU	115 (8.4)	17.1
Skin	113 (8.2)	16.7
Neuropsychiatric	106 (7.7)	19.2
Death	18 (1.3)	3.7

Specifically, the following events are commonly anticipated in the SCI population in the absence of Study Drug (also see appendix 1):

- Abscess
- Acute Lung Injury and Acute Respiratory Distress Syndrome
- Adjustment disorder/depression
- Autonomic dysreflexia/dysregulation
- Bradycardia
- Acute renal failure
- Anemia
- Cardiac Arrest
- Cholecystitis
- Congestive heart failure/cardiogenic pulmonary edema
- CNS infections
- Coagulopathy
- Cognitive deterioration
- Construct failure
- Deep venous thrombosis
- Depression/Adjustment disorder
- Failure of orthosis
- GI hemorrhage
- Hematuria
- Ileus
- Infectious diarrhea
- Loss of reduction
- Myocardial infarction
- Other dysrhythmia
- Pancreatitis
- Neuropathic pain
- Pulmonary embolus
- Pneumonia
- Progressive neurologic decline (motor and/or sensory)
- Psychosis
- Respiratory failure
- Seizure
- Sepsis

- Shock
- Skin complication (e.g., sacral or operative wound)
- Spinal cord edema and hemorrhage
- Thrombocytopenia
- Urinary Tract Infection
- Wound infection

In this study, AEs will be continually monitored through Day 14 or up until discharge (whichever is earlier). AEs will be further reviewed and additional AEs recorded on Day 28 (±7 days); AEs will be followed for resolution through the end of the study. Beyond Day 28 through the end of the study, only new SAEs will be recorded.

6.3 Serious Adverse Event Collection and Expedited Reporting

A serious adverse event is any AE that is:

- fatal, or
- life-threatening, or
- requires or prolongs hospital stay, or
- results in persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or
- an important medical event. Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

<u>Reporting of Serious Adverse Events</u>

SAEs and unanticipated problems posing risks to subjects or others should be reported to the study PI using the SAE case report form (Appendix 2) by the study sites within 24 hours of occurrence.

Investigators are responsible for complying with local IRB reporting requirements. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file. Participating sites will provide the coordinating site with the appropriate documentation of IRB SAE notification and receipt.

The PI will notify the FDA of any unexpected drug-related fatal or life- threatening experience as soon as possible but no later than 7 calendar days from original receipt of the information. All other unexpected drug-related SAEs will be reported no later than 15 calendar days after determination that the event qualifies for reporting.

If a previous AE that was not initially deemed reportable is later found to fit the criteria for reporting, the PI will submit the AE in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

6.4 Criteria for Intervention Discontinuation

A high incidence of medical complications occurs acutely following cervical SCI. As recently reported by Grossman and colleagues, overall complication rates range from 0.15 to 0.30 following SCI in the NACTN registry [20, 21].

- Blood Glucose

  Glyburide must be discontinued if the dose has already been reduced in accordance with the defined guidelines and following the reduction (i) there is one lab or repeat point-of-care confirmed BG < 55 mg/dL; OR (ii) there are three lab or repeat point-of-care confirmed BG < 70 mg/dL within a 12-hour period. When glyburide is stopped as a result of BG, D50W or an equivalent amount of dextrose using D5W, D10W, D25W, or D70W (or other concentration) should be administered by bolus in order to maintain BG > 80 mg/dL. Multiple such boluses may be administered, the timing and volume of which are at the discretion of the clinician. BG monitoring is required every 15 (± 10) minutes until BG ≥ 80 for 3 consecutive readings without bolus glucose supplementation, then hourly (± 30 minutes) for the next 6 hours.

- Cardiac

  Glyburide must be halted if:

1. A life threatening cardiac-related SAE occurs, whether or not believed by the clinician to be related to glyburide, and/or
2. Subject experiences QTc of > 550 ms (Bazett's formula) for 15 minutes, whether or not believed by the clinician to be related to glyburide. Before a decision to stop glyburide is made, ECG leads must be repositioned and must be confirmed to be in the correct position, following which the ECG must be repeated in order to confirm QTc > 550 ms.

- Hemolytic Anemia
  Glyburide must be discontinued if hemolytic anemia, which in the judgment of the investigator is severe, is detected. In the event of hemolytic anemia, a G6PD deficiency test should be performed following resolution of anemia. This test generally has a multi-day turnaround and will be used for information purposes only.
- Liver Function
  Glyburide must be discontinued if ALT raises to greater than 8-fold the upper limit of normal. Glyburide must be discontinued if the subject develops cholestatic jaundice or hepatitis.

7.0 STATISTICAL CONSIDERATIONS

Descriptive statistics will be generated for all variables of interest. Categorical measures will be reported with frequencies and percentages and continuous measures with means and standard deviations. The frequency of AEs will be reported (as captured on the modified NACTN form) and, where possible, will be compared to those of the matched controls (along with corresponding confidence intervals). We will match study patients and the historical NACTN cohort data on criteria including: age, co-morbidities, injury level, and injury severity (ASIA A, B or C SCI). Additionally, the number of patients who were otherwise eligible for the study but did not enroll due to lack of infusion within 6 hours will be reported. Secondarily, matched tests will be utilized to compare neurologic outcomes between those receiving glyburide and matched historical controls.

8.0 DATA SAFETY MONITORING PLAN

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of accrual and patient safety. The frequency and severity of AEs will be reviewed by the PI and compared to other sources, including published literature and scientific meetings. SAEs will also be reviewed by the Data and Safety Monitoring Committee (DSMC). The PI in conjunction with the DSMC will determine if the trial should be terminated early based on the AE reviews.

The DSMC will consist of an ethicist, an independent biostatistician and an independent clinician with specialty in neurologic surgery. The DSMC will meet prior to study initiation and on accrual of every 3 patients (but at a minimum of twice a year). DSMC meetings will be scheduled within a month of every 3rd patient being enrolled in the study. Prior to each scheduled DSMC meeting, the PI will prepare a progress report that will be reviewed by the DSMC.

9.0 STUDY CONDUCT CONSIDERATIONS

9.1 Regulatory and Ethical Consideration (including the informed consent process)

Subject Withdrawal

Subjects may voluntarily withdraw from the study at any time for any reason, and without prejudice to further treatment. Subject participation in the study may be terminated at any time at the discretion of the Investigator.

Possible reasons for discontinuation include, but are not limited to, the following:

- The subject's health would be jeopardized by continued participation (e.g., the patient required restricted medication, or alternative treatment seems to be in the subject's best interest.)
- Occurrence of a significant or intolerable clinical or laboratory AE that, in the opinion of the investigator, requires early termination.

- Withdrawal of subject consent. Subject withdrawal may occur any time the subject wishes to no longer continue with the study. Every attempt must be made to obtain information about the reason(s) for discontinuation, and any possible adverse events.
- Subject is enrolled but does not receive study drug, due (for example) to insufficient time to prepare and administer study drug, or elevated liver enzymes at screening.

The date the subject is discontinued from the clinical investigation and the reason for discontinuation will be recorded in the case report form (CRF). Subjects whose study therapy is discontinued for any reason should be treated and followed according to established medical practice.

Note that if a site learns, while a patient is receiving Study Drug, that the patient had taken sulfonylureas within 7 days of study enrollment, this will not be a cause for automatic discontinuation of Study Drug, or of withdrawal from the study.

Project Management

OSU Coordinating Center will be responsible for project management of the Study.

Data Management

Data entry will occur at the enrolling sites using the electronic data capture system (REDCap). Data quality assurance and analyses will be performed by the OSU Coordinating Center.

Data Monitoring

All aspects of the study will be monitored at regular intervals by qualified individuals from the OSU Coordinating Center. Monitoring will be conducted in accordance with FDA and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and will be described in a Data Monitoring Plan. The investigators must agree to allow monitors, FDA, or other relevant health authorities to inspect facilities and records relevant to this study.

Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed and dated consent form will be obtained from the subject.

Record Retention

Investigators must retain all study records required by the applicable regulations in a secure and safe facility. All records are to be retained by the Investigator for at least 2 years after the United States Food and Drug Administration/local health authority approves the New Drug Application (NDA); or a minimum period of 2 years following the termination or withdrawal of the health regulatory agency exemption (e.g., Investigational New Drug (IND) or clinical trial application) under which the study was conducted, or for a period consistent with the record retention policies of the country where the study is being conducted.

Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the Study Patient Number (SPN) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SPNs only. Identifiable clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the FDA, or other relevant health authority representative.

Study Modification/Discontinuation

The study may be modified or discontinued at any time by the PI, IRB, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

9.2 Publication Policy

Publications and oral presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the specific policy developed for the study.

10.0 CONCLUSION

In summary, this is a small and open-label study by design, therefore necessitating cautious interpretation. However, the study's findings may provide invaluable data on glyburide's safety and pharmacokinetic profile as well as preliminary data on its ability to improve neurologic outcomes following SCI. Taken together, this data will allow for a more rational subsequent phase II/III trial design.

11.0 REFERENCES

1. Simard, J.M., et al., Glibenclamide in Cerebral Ischemia and Stroke. Neurocrit Care, 2013.
2. Sheth, K.N., et al., Pilot study of intravenous glyburide in patients with a large ischemic stroke. Stroke, 2014. 45(1): p. 281-3.
3. Walters, B.C., et al., Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update. Neurosurgery, 2013. 60 Suppl 1: p. 82-91.
4. Grossman, R.G., et al., A prospective, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. J Neurotrauma, 2014. 31(3): p. 239-55.
5. Bilgen, M., et al., Spatial and temporal evolution of hemorrhage in the hyperacute phase of experimental spinal cord injury: in vivo magnetic resonance imaging. Magn Reson Med, 2000. 43(4): p. 594-600.
6. Simard, J.M., et al., Endothelial sulfonylurea receptor 1-regulated NC Ca-ATP channels mediate progressive hemorrhagic necrosis following spinal cord injury. J Clin Invest, 2007. 117(8): p. 2105-13.
7. Balentine, J.D., Pathology of experimental spinal cord trauma. I. The necrotic lesion as a function of vascular injury. Lab Invest, 1978. 39(3): p. 236-53.
8. Chen, M., Y. Dong, and J.M. Simard, Functional coupling between sulfonylurea receptor type 1 and a nonselective cation channel in reactive astrocytes from adult rat brain. J Neurosci, 2003. 23(24): p. 8568-77.
9. Chen, M. and J.M. Simard, Cell swelling and a nonselective cation channel regulated by internal Ca2+ and ATP in native reactive astrocytes from adult rat brain. J Neurosci, 2001. 21(17): p. 6512-21.
10. Simard, J.M., et al., Newly expressed SUR1-regulated NC(Ca-ATP) channel mediates cerebral edema after ischemic stroke. Nat Med, 2006. 12(4): p. 433-40.
11. Simard, J.M., et al., Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications. Lancet Neurol, 2007. 6(3): p. 258-68.
12. Simard, J.M., et al., Sulfonylurea receptor 1 in central nervous system injury: a focused review. J Cereb Blood Flow Metab, 2012. 32(9): p. 1699-717.
13. Simard, J.M., et al., MRI evidence that glibenclamide reduces acute lesion expansion in a rat model of spinal cord injury. Spinal Cord, 2013. 51(11): p. 823-7.

14. Simard, J.M., et al., Spinal cord injury with unilateral versus bilateral primary hemorrhage--effects of glibenclamide. Exp Neurol, 2012. 233(2): p. 829-35.
15. Popovich, P.G., et al., Independent evaluation of the effects of glibenclamide on reducing progressive hemorrhagic necrosis after cervical spinal cord injury. Exp Neurol, 2012. 233(2): p. 615-22.
16. Simard, J.M., et al., Brief suppression of Abcc8 prevents autodestruction of spinal cord after trauma. Sci Transl Med, 2010. 2(28): p. 28ra29.
17. Woo, S.K., et al., The sulfonylurea receptor 1 (Sur1)-transient receptor potential melastatin 4 (Trpm4) channel. J Biol Chem, 2013. 288(5): p. 3655-67.
18. Gerzanich, V., et al., De novo expression of Trpm4 initiates secondary hemorrhage in spinal cord injury. Nat Med, 2009. 15(2): p. 185-91.
19. Simard, J.M., et al., Comparative effects of glibenclamide and riluzole in a rat model of severe cervical spinal cord injury. Exp Neurol, 2012. 233(1): p. 566-74.
20. Grossman, R.G., et al., Incidence and severity of acute complications after spinal cord injury. J Neurosurg Spine, 2012. 17(1 Suppl): p. 119-28.
21. Grossman, R.G., et al., North American Clinical Trials Network for the Treatment of Spinal Cord Injury: goals and progress. J Neurosurg Spine, 2012. 17(1 Suppl): p. 6-10.
22. Catz, A. and M. Itzkovich, Spinal Cord Independence Measure: comprehensive ability rating scale for the spinal cord lesion patient. J Rehabil Res Dev, 2007. 44(1): p. 65-8.
23. Popovich, P.G. and J.M. Simard, Improving the efficiency and efficacy of glibenclamide in limiting progressive hemorrhagic necrosis following traumatic spinal cord injury, in 2012-2015, DOD.
24. Kuhle, J., et al., Serum neurofilament light chain is a biomarker of human spinal cord injury severity and outcome. J Neurol Neurosurg Psychiatry, 2014.
25. Yokobori, S., et al., Acute Diagnostic Biomarkers for Spinal Cord Injury: Review of the Literature and Preliminary Research Report. World Neurosurg, 2013.
26. Kwon, B.K., et al., Inflammatory and structural biomarkers in acute traumatic spinal cord injury. Clin Chem Lab Med, 2011. 49(3): p. 425-33.
27. Aarabi, B., et al., Intramedullary lesion expansion on magnetic resonance imaging in patients with motor complete cervical spinal cord injury. J Neurosurg Spine, 2012. 17(3): p. 243-50.

28. Hurlbert, R.J., Strategies of medical intervention in the management of acute spinal cord injury. Spine (Phila Pa 1976), 2006. 31(11 Suppl): p. S16-21; discussion S36.
29. Wilson, J.R., et al., The impact of facet dislocation on clinical outcomes after cervical spinal cord injury: results of a multicenter North American prospective cohort study. Spine (Phila Pa 1976), 2013. 38(2): p. 97-103.
30. Fehlings, M.G., et al., Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One, 2012. 7(2): p. e32037.
31. Juneja, R., et al., Computerized intensive insulin dosing can mitigate hypoglycemia and achieve tight glycemic control when glucose measurement is performed frequently and on time. Crit Care, 2009. 13(5): p. R163.
32. Hadley, M.N. and B.C. Walters, Introduction to the Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries. Neurosurgery, 2013. 72 Suppl 2: p. 5-16.
33. Ahuja CS, Fehlings M. Concise Review: Bridging the Gap: Novel Neuroregenerative and Neuroprotective Strategies in Spinal Cord Injury. Stem Cells Translational Medicine. 2016;5(7):914-924. doi:10.5966/sctm.2015-0381.
34. DiaBeta [Package Insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2009.
35. Kobayakawa K, Kumamaru H, Saiwai H, et al. Acute hyperglycemia impairs functional improvement after spinal cord injury in mice and humans. Science Translational Medicine. 2014; 6(256). doi:10.1126/scitranslmed.3009430.
36. Remedy Pharmaceuticals' Drug CIRARA™ Cut Death Rates From Severe Stroke by More Than Half. [Press Release]. Scottsdale, AZ: Neurocritical Care Society Annual Meeting. October 9, 2015.

APPENDIX 1: Modified NACTN Chart
See attached document

APPENDIX 2: SAE Case Report Form
See attached document