A Multicenter, Two Part (Open-Label Single-Ascending Dose Followed by Double-Blind, Placebo-Controlled Repeat Dose) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of AXER-204 in Subjects with Chronic Spinal Cord Injury (the RESET* Study)

*RESET- Chronic SCI Study. **Re**NetX **S**afety **E**fficacy and **T**olerability of AXER-204 for Chronic SCI

PROTOCOL RNX-AX204-101
PHASE 1B/2A

AXER-204

IND #: 135648

NCT03989440

Sponsor:

ReNetX Bio, Inc.
157 Church St 19th Fl
New Haven, CT 06510
[redacted]
www.renetx.com

Date of Issue: FINAL V 4.0 October 1, 2020

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Email Address and Telephone Number
Study Medical Monitor	[redacted]	[redacted]
Study Director	George Maynard, PhD President and CSO	[redacted]
24-Hour emergency contact	**Primary:** [redacted] **Back-up:** [redacted]	[redacted]

PROTOCOL SPONSOR SIGNATURE PAGE

Title of Study

A Multicenter, Two Part (Open-Label Single-Ascending Dose followed by Double-Blind, Placebo-Controlled Repeat Dose) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of AXER-204 in Subjects with Chronic Spinal Cord Injury

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George Maynard, PhD
President and Chief Scientific Officer, ReNetX Bio, Inc.

[redacted] Digitally signed by George D. Maynard
Date: 2020.10.01 11:02:25 -04'00'

Signature Date

Gilbert Block, MD, PhD
Clinical Consultant to ReNetX Bio, Inc.

[redacted] 1 October 2020

Signature Date

[redacted]
Study Medical Monitor [redacted]

[redacted]

Signature Date

1. SYNOPSIS

Name of Sponsor/Company:
ReNetX Bio, Inc.

Name of Investigational Product:
AXER-204

Name of Active Ingredient:
hNgR(310)-Fc

Title of Study:
A Multicenter, Two Part (Open-Label Single-Ascending Dose followed by Double-Blind, Placebo-Controlled Repeat Dose) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of AXER-204 in Subjects with Chronic Spinal Cord Injury

Study center(s): Approximately 5 study centers in the United States (US)

Studied period (years):	**Phase of development:** 1b and 2a
Estimated date first subject enrolled: July 2019 (Part 1)	
Estimated date last subject completed: November 2020 (Part 1)	
Estimated date first subject enrolled: February 2021 (Part 2)	
Estimated date last subject completed: June 2022 (Part 2)	

Objectives:

Study RNX-AX204-101 is a two-part (Part- 1 and 2) study that will be run sequentially. Part 1 is considered a Phase 1b study, while Part 2 is considered a Phase 2a study. Each part has unique objectives.

Part 1 Single Ascending Dose

Primary Objectives

To evaluate the safety, tolerability, and pharmacokinetics (PK) of ascending, single intrathecal lumbar slow bolus infusions of AXER-204 in subjects with chronic spinal cord injury (CSCI).

Part 2 Repeat Dose

Primary Objectives

1. To evaluate the safety and tolerability of repeat intrathecal lumbar slow bolus infusions of AXER-204 compared to placebo in subjects with CSCI.
2. To evaluate the pharmacokinetics of repeat doses of AXER-204 in subjects with CSCI

Secondary Objectives (Part 2 only)

To assess the efficacy of repeat dose therapy of AXER-204 compared to placebo on function and activities of daily living (ADL) measures as assessed by:

- International Standards for Neurological Classification of SCI (ISNCSCI) Upper Extremity Motor Score (UEMS).
- Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP) prehension performance
- Version III of the Spinal Cord Independence Measure (SCIM III) self-care

Exploratory Objectives (Part 2 only)

To evaluate the efficacy of repeat dose therapy of AXER-204 compared to placebo as assessed by the following:

- ISNCSCI lower extremity motor and sensory scores
- GRASSP strength, sensation and prehension ability scores
- SCIM III mobility scores
- International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI)
- Patient Reported Outcomes
  - CUE-Questionnaire (CUE-Q). Assesses subject-reported upper limb function.
  - SF-36 v2. Provides a patient-reported Quality of Life (QoL) assessment. SF-36 will provide data on the subjects' perceived health and well-being over the course of the study.
  - Neuro-QOL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)
  - Patient's Global Impression of Change (PGIC) – Chronic SCI

Exploratory biomarkers of target engagement and axonal growth may be assessed

Methodology:

Study RNX-AX204-101 is a two-part study that will be run sequentially, with Part 2 planned to start after Part 1 has been completed. Each Part will be conducted at approximately 5 centers in the United States.

Eligible subjects will be ages 18 to 65 years inclusive, male or female, with a traumatic spinal cord injury that occurred at least 1 year prior to the screening date. Subjects must have significant neurological impairment of the hands and arms. Subjects who participated in Part 1 may be evaluated for enrollment in Part 2 provided at least 6 months will have elapsed between the dose received in Part 1 and the initiation of dosing in Part 2.

Part 1

Part 1 is a multicenter, open-label, single ascending dose study in subjects with chronic spinal cord injury. Four cohorts of 6 subjects each are planned, with subjects within each cohort expected to receive the same dose of study drug. Thus, up to 24 subjects will be enrolled in Part 1, and all will receive AXER-204.

Study drug will be administered sequentially, with at least 3 days between subjects being dosed within each cohort (following 72-hour safety assessment review by sponsor in conjunction with the investigators and medical monitor for each prior subject).

The study stages for Part 1 are:

- Screening (within 84 days prior to Day 1). Patients have 84 days from the time of signing informed consent to complete their screening assessments and, if needed, their washout period for prohibited concomitant medications. The screening laboratory tests must be completed within 28 days prior to Day 1.
- Treatment period: Check-in Day 1, administration of study drug, 3-night in-clinic stay, and discharge on Day 4 following the completion of all scheduled procedures.

- Follow-up: Subjects will have follow-up visits for up to 29 days post-dose as follows: subjects will receive a phone call on Study Days 5, 6, and 7 to inquire about their general health and will return to the clinic for visits on Study Day 8 (± 1 day), Study Day 15 (±3 days), and Study Day 29 or Early Termination (± 4 days). For each cohort in Part 1, the same general procedures will be applied, as follows.

Screening

All subjects must sign/e-sign an Informed Consent Form (ICF) prior to undergoing any screening procedures. Screening procedures will take place up to 84 days. Subjects will undergo an MRI to determine spinal cord structure and intrathecal space (Appendix 12); MRIs will be run locally and evaluated by a sponsor-arranged expert. Additional radiological assessments may be performed at the discretion of the Principal Investigator, including CT or MRI of the head and X-ray of the lumbar spine as additional evaluations to rule out potential contraindications for lumbar puncture. The subject's demographics, medical and surgical history, and prior and concomitant medications will be recorded. Screening/baseline assessments will be performed, and subjects will undergo blood draws where blood, serum collection, viral serology will be obtained, and urine samples will be collected. The screening laboratory tests must be completed within 28 days prior to Day 1.

Subjects will also be presented with a separate biobank ICF for review. If a subject agrees, samples of his/her CSF, blood, MRI scans and data collected in the study, will be stored for future research. A subject does not have to agree or sign the biobank ICF in order to be eligible to participate in this main study.

Prospective subjects must follow dosing restrictions as specified in the protocol for each medication listed in Exclusion Criteria.

Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene). Subjects using marijuana /THC-CBD preparations, opiates, sedative hypnotics, or tranquilizers may be permitted to participate in the trial provided the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.

In the event that a subject is rescreened, the original screening MRI and expert review of the images may be used for the rescreening provided the MRI was completed within 6 months of rescreening. Similarly, neurological examinations and questionnaires do not need to be repeated provided the rescreening occurs within 84 days of the time of data collection.

In-Clinic Treatment Period:

Eligible subjects will be admitted to the clinic on the evening prior to or on the day of dosing (Study Day 1) dependent on clinical site requirements. Following final pre-treatment assessments, subjects will undergo a lumbar puncture (LP) and receive their single dose of study drug administered via intrathecal lumbar slow bolus infusion by the Principal Investigator or a trained and licensed designee. Dosing will be according to Table 2.

Subjects will remain in-clinic until discharge on Study Day 4 and will undergo daily safety assessments and observation.

Blood and CSF samples will be obtained. The timing for serum and CSF sample collection may be adjusted for subsequent cohorts based on PK data from the preceding cohorts. In addition to undergoing PK analysis, serum samples obtained from blood collected at pre-dose and on Study Days 8 and 29 will be analyzed for the presence of anti-drug antibodies (ADA).

Table 2: Treatment by Cohort - Part 1 (Study RNX-AX204-101)

Cohort	Treatment	Number Subjects
1	3 mg AXER-204	6
2	30 mg AXER-204	6
3	90 mg AXER-204	6
4	200 mg AXER-204	6

Follow-up:

Sites will contact the subjects via telephone on Study Days 5, 6, and 7 to inquire as to their general health status.

Subjects will return to the Clinic on Study Days 8 (±1d), 15 (±3d), and 29 (±4d). On Study Days 8 (±1d) and 29 (±4d), CSF and serum PK samples will be collected. Blood will be collected for clinical laboratory testing and serum for PK on Day 15 (±3d). Vital signs, AEs, and general health status will be assessed at each follow-up visit and end of study assessments will be performed on Study Day 29 (±4d).

Dose Escalation in Part 1

Dose escalation decisions will be made jointly by the investigators, sponsor, and medical monitor. The investigators, sponsor, and medical monitor may also make adjustments to the dosing plan, as appropriate for reasons of safety and tolerability.

Data and Safety Monitoring Board (DSMB)

In order to ensure the utmost safety of subjects, the sponsor will also use an independent Data and Safety Monitoring Board (DSMB). Each time the DSMB is engaged, a recommendation to proceed from the DSMB will be required in order for the study to continue (i.e. to resume if stopped or ongoing study will be stopped if DSMB does not recommend proceeding). During Part 1, the DSMB will be consulted prior to resuming the study if any of the stopping criteria are met. The DSMB will also be asked to review the safety and tolerability data from Part 1 before starting Part 2. The DSMB will meet during Part 2 after the first subject has completed 3 months of dosing and approximately every 3 months thereafter while dosing continues in the study (allowing for potential scheduling logistics). In addition to the pre-determined DSMB data review meeting, the DSMB may be engaged at any time at the request of an investigator, the sponsor, or medical monitor. A charter will be written to describe the DSMB's objectives, schedule for data reviews, and general responsibilities in respect to the study. All DSMB decisions will be documented in writing, and where required, submitted to the institutional review board (IRB) for their review or information.

Dose Escalation Rules for Part 1

Dose escalation (for each sequential cohort) will not occur until 6 subjects in the prior cohort have completed the initial 3 day in-clinic period AND at least two subjects have completed their Day 29 post-dose follow-up visit. Determination of whether to escalate dose in the subsequent cohort will be made by the sponsor in conjunction with the investigators and medical monitor after review of all clinical and any available PK data. Review will include adverse events (AEs) and serious AEs (SAEs), and specifically the following potential stopping criteria will be evaluated prior to each dose escalation. If the dose is well tolerated in the completed dose group, the sponsor, in conjunction with the investigators and medical monitor, will recommend escalation to the next dose level.

Stopping Rules/Study Interruption/Discontinuation Notice

The investigators and medical monitor in conjunction with the sponsor may elect to stop dosing or stop the study based on any treatment emergent concerns. Dosing will be stopped due to the

occurrence of any individual adverse events which, in the judgment of the investigators and medical monitor in conjunction with the sponsor, need further characterization with respect to progression and reversibility before further dosing is conducted. Such adverse events may include non-serious unusual events. If dosing is stopped, review of the data by the investigators and medical monitor in conjunction with the sponsor and the DSMB must occur before dosing can be resumed. Dosing will only be resumed with DSMB approval.

Pharmacokinetic and anti-drug antibody test results will not be required for dose escalation unless it is determined to be advisable by the sponsor in conjunction with the investigators and medical monitor based on emergent data from the study. CSF and serum samples will be analyzed for each cohort immediately after all subjects have been dosed. The sponsor may direct earlier analysis of a partially completed cohort if completion of the cohort is delayed or partial cohort data is desired to aid in interpretation of any emergent clinical data.

Part 2

Part 2 is a multicenter, randomized, double-blind, placebo-controlled, repeat dose study in CSCI subjects. Approximately 32 subjects will be randomized (ratio 1:1) to receive AXER-204 or placebo (an isotonic phosphate buffered saline formulation). Subject to review of the safety, tolerability, and pharmacokinetic data from Part 1 and DSMB approval, the dose will be 200 mg given once every 3 weeks for 15 weeks as outlined in the schedule of events. Subject to DSMB approval, the dose may be reduced to 90 mg and the dose interval may be modified based on data from Part 1 but is not expected to be less than once every 14 days or more than 28 days. Subject to DSMB approval, the dose and dose frequency may also be adjusted during Part 2 based on emergent safety and tolerability data.

The study stages for Part 2 are:

- Screening (within 84 days prior to Day 1). Patients have 84 days from the time of signing informed consent to complete their screening assessments and, if needed, their washout period for prohibited concomitant medications. The screening laboratory tests must be completed within 28 days prior to Day 1.
- Treatment Period (15 weeks). Investigational product given approximately every 21 days for up to 104 days per subject. A telephone call to assess status regarding any adverse events will be conducted on Study Day 8 (±3 days).
- Follow-up (21 weeks). Following the last Treatment Period dose of investigational product or Early Termination of dosing, a telephone call to assess status regarding any adverse events will be conducted on Study Day 137 (± 7 days) and two follow-up visits will occur at Study Days 169 (± 7 days) and 253 (± 7 days).

Screening

All subjects must sign/e-sign an Informed Consent Form (ICF) prior to undergoing any screening procedures. Screening procedures will take place up to 84 days. Subjects will undergo an MRI to determine spinal cord structure and intrathecal space; MRIs will be run locally and evaluated by a sponsor-arranged expert. Additional radiological assessments may be performed at the discretion of the Principal Investigator, including CT or MRI of the head and X-ray of the lumbar spine as additional evaluations to rule out potential contraindications for lumbar puncture. The subject's demographics, medical and surgical history, and prior and concomitant medications will be recorded. Screening assessments will be performed, and subjects will undergo blood draws where blood, serum collection, viral serology will be obtained, and urine samples will be collected. The screening laboratory tests must be completed within 28 days prior to Day 1.

Subjects will also be presented with a separate biobank ICF for review. If a subject agrees samples of his/her CSF, blood, MRI scans and data collected in the study, will be stored for future research. A subject does not have to agree or sign the biobank ICF in order to be eligible to participate in the main study.

Prospective subjects must follow dosing restrictions as specified in the protocol for each medication listed in Exclusion Criteria.

Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene). Subjects using marijuana /THC-CBD preparations, opiates, sedative hypnotics, or tranquilizers may be permitted to participate in the trial provided the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.

In the event that a subject is rescreened, the original screening MRI and expert review of the images may be used for the rescreening provided the MRI was completed within 6 months of rescreening. Similarly, neurological examinations and questionnaires do not need to be repeated provided the rescreening occurs with 84 days of the time of data collection.

Treatment Period

Eligible subjects will be randomized to either AXER-204 or to placebo. The randomization will be stratified based on pre-treatment American Spinal Injury Association Impairment Scale (AIS) grade (AIS A,B vs. AIS C,D) and prior receipt of study drug in Part 1 (Received AXER-204 in Part 1 vs. Did not receive AXER-204 in Part 1).

Subjects will receive their baseline assessments and assigned (double-blind) treatment on Study Day 1. A telephone call to assess status regarding any adverse events will be conducted on Study Day 8 (± 3 days). Subjects will then return to the Clinic on Day 21 (± 5 days) for safety, efficacy, and PK assessments and their second dose of investigational product. Thereafter, subjects will return approximately every 21 days, at Study Days 42 (± 5 days) (third dose), 63 (± 5 days) (fourth dose), 84 (± 5 days) (fifth dose), 104 (± 5 days) (sixth dose), for safety, efficacy, and PK assessments (pre-dose) and investigational product administration.

Cerebrospinal fluid samples will be collected pre-dose at each treatment (dosing) visit, including Study Day 1, during a single LP procedure for collecting and dosing. Serum for PK and immunogenicity (ADA) testing will be collected pre-dose at the timepoints specified in the schedule of events within 4 hours prior to investigational product administration. Serum will also be collected for PK at 4 h post-dose at specified visits.

For dosing visits that include neurological exams and questionnaires (e.g. ISNCSCI, GRASSP, SCIM III self-care and mobility), these assessments should be performed prior to dosing. Depending on scheduling considerations, subjects may be asked to return the following day for dose administration. Under this circumstance, nearby overnight accommodations will be arranged for the subject upon request.

Following dosing, patients will remain under the observation of study personnel in the hospital setting (eg, may include infusion center, PACU, recovery suite, observation unit, short stay center) for 4 hours for safety monitoring. Thereafter, if deemed clinically stable by the Investigator, patients may leave the hospital setting. If further safety observation is directed by the investigator, the subject may be directed to remain at a nearby overnight accommodation or home (if within a reasonable distance) and report the next morning for examination or to remain in the hospital overnight. Note that, under these circumstances, there is no requirement for an overnight hospital stay; if a decision is made to

keep the patient overnight for convenience (e.g. travel issues), this hospitalization should not initiate a serious adverse event report (e.g. local alternate accommodations not readily available).

Follow-Up

Study personnel will conduct telephone call with subjects on Study Day 137 (± 7 days) to assess status regarding any adverse events. Depending on the results, the subject may be asked to come to the clinic for evaluation. Subjects will return at Study Days 169 (± 7 days) and 253 (± 7 days) for safety and efficacy assessments.

Stopping Rules/Study Interruption/Discontinuation Notice

The investigators and medical monitor in conjunction with the sponsor may elect to stop dosing or stop the study based on any treatment emergent concerns. Dosing will be stopped due to the occurrence of any individual adverse events which, in the judgment of the investigators and medical monitor in conjunction with the sponsor, need further characterization with respect to progression and reversibility before further dosing is conducted. Such adverse events may include non-serious unusual events. If dosing is stopped, review of the data by the sponsor in conjunction with the investigators and medical monitor in conjunction with the sponsor and the Data and Safety Monitoring Board (see below regarding DSMB composition and charter) must occur before dosing can be resumed. Dosing will only be resumed with DSMB approval.

Data and Safety Monitoring Board (DSMB)

In order to ensure the utmost safety of subjects, the Sponsor will also use a Data and Safety Monitoring Board (DSMB). Each time the DSMB is engaged, a recommendation to proceed from the DSMB will be required in order for the study to continue (i.e. to resume if stopped or ongoing study will be stopped if DSMB does not recommend proceeding). The DSMB will review the safety and tolerability data from Part 1 before recommending starting Part 2. In addition to the pre-determined DSMB data review meetings, the DSMB may be engaged at any time at the request of an investigator, the sponsor, or medical monitor. A charter will be written to describe the DSMB's objectives, its membership, schedule for data reviews, and general responsibilities with respect to the study. All DSMB decisions will be documented in writing, and where required, submitted to the institutional review board (IRB) for their review or information.

Number of Subjects (planned):

Part 1 will enroll up to 24 subjects in cohorts of 6 subjects each. Part 2 will enroll approximately 32 subjects, randomized in a 1:1 ratio (and thus approximately 16 subjects per arm) to repeated doses of AXER-204 or of matching placebo.

Diagnosis and main criteria for eligibility:

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Men or women between the ages of 18 and 65 years, inclusive
2. Traumatic spinal cord injury that occurred ≥ 1 year ago
3. Cervical spinal cord injury with serious neurological deficit as evidenced by 1) bilateral ISNCSCI UEMS between 4 and 36 points inclusive, and 2) bilateral GRASSP prehension ability score between 4 and 17 points inclusive
4. Confirmation by MRI of the following:
    a. Chronic SCI (persistent spinal cord lesion)
    b. For AIS grade of A without sensory or motor zone of partial preservation extending at least two levels caudal to the level of injury, no apparent transection of the cord

c. CSF space spanning the lesion

5. Read, understood, and provided written informed consent after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Penetrating injury to the cord or spinal cord trauma caused by ballistic injury including gunshot that did not penetrate the spinal cord
2. Women who are pregnant or lactating, and women of childbearing potential except those using adequate birth control measures. All female subjects must have a negative serum pregnancy test at Screening and women of childbearing potential must have a negative urine pregnancy run locally at the Randomization/Pre-Dose Visit on Study Day 1. All subjects (male and female) as well as non-study female partners of male subjects, must use adequate birth control measures during the course of the study and for at least 10 weeks after the subjects' last dose of investigational product
    - Adequate or effective contraception is defined as double barrier contraception (eg, condom plus spermicide in combination with a female condom, diaphragm, cervical cap, contraceptive sponge, implants, injectables, combined oral contraceptives, sexual abstinence (total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable), or sexual intercourse with only a vasectomized partner. Subjects and/or partners who are surgically sterile or women with confirmed postmenopausal status are exempt from this requirement.
3. History of stroke, cerebrovascular injury, or elevated intracranial pressure
4. Contraindications for lumbar puncture
5. Requiring mechanical ventilatory assistance of any type
6. Body mass index (BMI) $\geq$ 35 kg/m^2 or body weight <50 kg
7. Botulinum toxin injection, with the exception of bladder treatments, within 4 months prior to study
8. History of life threatening allergic or immune-mediated reaction to vaccines, or biologic drugs, at any time or any life threatening allergic or immune-mediated reaction within the past 12 months.
9. Systemic use of immunosuppressants within the past 2 months with the exception of mineralocorticoids
10. Significant deformities, contractures (with less than 50% of normal range of motion at affected joints), or any issues that limit completion of UEMS with the ISNCSCI exam
11. Recent changes in anti-spasmodic or anti-spasticity medications. Anti-spasmodic or anti-spasticity medication is permitted providing that the subject has been on a stable dose for at least 12 weeks before the Screening Visit (Visit 1) and agrees to remain on a stable dose throughout the course of the study
12. Any orthopedic injury, recent surgeries, or current diagnosis of any primary diseases affecting upper limb function outside of SCI (eg, infection, tumor, congenital malformations, Huntington's disease, Parkinson's disease)
13. Subjects fitted with an implanted pump or port for delivery of therapeutics to the CSF

14. Uncontrolled medical condition including but not limited to cardiovascular disease, sleep apnea, obstructive lung disease, severe neuropathic or severe chronic pain, severe autonomic dysreflexia
15. Participation in any other investigational drug or device trial within 30 days or within 5 half-lives of the investigational drug or any past participation in a SCI cellular therapy trial.
16. Regular use of the following concomitant medications that might confound efficacy and/or safety assessments is prohibited, including, but not limited to, the following:
    a. Antipsychotic drugs **with the exception of use** of these mood stabilizers for the adjunctive treatment of depression provided the subject is on a stable dose for at least 12 weeks prior to Screening and the dose is not anticipated to change during participation in the trial.
    b. Anticoagulants, however, daily low dose aspirin (81mg) therapy is permitted.
    c. Opiates, sedative hypnotics, or tranquilizers **unless used to treat anxiety, pain, or sleep disorder** and the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.
    d. Use of tumor necrosis factor [TNF] inhibitors
    e. Use of Class 1 antiarrhythmic.
17. Use of antidepressants (SSRI, SNRI, TCA, buspirone) is PERMITTED but limited to subject being on a stable dose for at least 12 weeks
18. History of severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with trial participation or investigational product administration or could interfere with the interpretation of trial results and including but not limited to the following:
    - human immunodeficiency virus (HIV) infection
    - active chronic hepatitis B or hepatitis C infection including hepatitis B surface antigen and hepatitis C antigen positive subjects with or without abnormal liver enzymes
    - immunosuppressive disease
    - chronic renal disease/failure as evidenced by estimated glomerular filtration rate (eGFR) of <60
    - concurrent neurodegenerative disease
    - cardiovascular: uncontrolled hypertension, unstable angina, myocardial infarction or symptomatic congestive heart failure within the past 12 months or serious uncontrolled and clinically significant cardiac arrhythmia as determined by the investigator
    - dementia or significantly altered mental status including brain injury with ongoing cognitive signs and symptoms that would prohibit the understanding or rendering of informed consent and compliance with the requirements of the protocol
19. Evidence or self-report of alcohol or drug abuse within the previous 12 months

20. Any conditions that in the judgement of the investigator would make the subject inappropriate for entry into the trial

Investigational product, dosage and mode of administration:

AXER-204 is a human fusion protein to promote axon growth and recovery of neurological function. AXER-204 is administered by intrathecal lumbar slow bolus injection.

Part 1:

Dosage will be by cohort, with 4 sequentially-treated cohorts planned. Intrathecal doses of AXER-204 below 90 mg will be diluted and delivered as a solution in 10 mL of isotonic phosphate buffered saline. Both the 90 mg dose and 200 mg dose will be dosed with the current study drug concentration. All administration will be given following a removal of an equivalent volume of CSF. Intrathecal injections will be given at a rate of 100 mL/hr using a medically approved syringe pump (eg, 12 minutes to administer 20 mL) to avoid significant disruption of natural CSF flow and pressure and monitored by medical personnel.

The starting dose of 3 mg is estimated to be below the pharmacologically active dose. Dose escalation will proceed to 30 mg, 90 mg, 200 mg contingent on safety, tolerability, and available PK. Thus, dosing volumes will be given as follows:

- Cohort 1: 3 mg, 10 mL
- Cohort 2: 30 mg, 10 mL
- Cohort 3: 90 mg, 9 mL
- Cohort 4: 200 mg, 20 mL

Part 2

Subject to review of the safety, tolerability, and pharmacokinetic data from Part 1 and DSMB approval, the dose will be 200 mg given once every 3 weeks for 15 weeks as outlined in the schedule of events. Subject to DSMB approval, the dose may be reduced to 90 mg and the dose interval may be modified based on data from Part 1 but is not expected to be less than once every 14 days or more than 28 days. Subject to DSMB approval, the dose and dose frequency may also be adjusted during Part 2 based on emergent safety and tolerability data.

The maximum volume of injection by intrathecal lumbar slow bolus injection is limited to 20 mL in this study based on published tolerance data from studies with other agents employing the same route of administration. If an injection volume of 20 mL, corresponding to a 200 mg dose of AXER-204, is reached in Part 1 dose escalation portion of the study with acceptable safety and tolerance, the 200 mg dose will be designated as the dose for Part 2 at the discretion of the Sponsor in conjunction with the investigators, DSMB, and medical monitor.

Duration of treatment:

Part 1 is a single-dose treatment for each subject. Subjects will have up to an 84-day screening period, a 3-day in-clinic treatment period, and a follow-up period through 29 days post-dose. Thus, study participation for each subject in Part 1 is expected to be approximately up to 16 weeks in duration.

Part 2 Placebo-controlled Repeat Dose Portion. Subjects will have up to an 84-day screening period, a 104-day treatment period with injections given every 21 days through Day 104, and then post treatment follow-ups at Study Days 137, 169, and 253. The follow-up on Study Day 137 will consist of a telephone call conducted by study personnel to assess status regarding any adverse events. Thus, study participation for each subject in Part 2 is expected to be up to approximately 337 days in duration.

Reference therapy, dosage and mode of administration:

Part 1 does not include placebo.

Part 2 includes a matching placebo control, to be given at the same intervals and volume as the investigational product. Placebo consists of a phosphate buffered saline formulation.

At each study site, for each dose to be administered in Part 2, an unblinded pharmacist will prepare prefilled syringes for dose administration in order to maintain the blind for study personnel administering the investigational product and performing all other study procedures.

Criteria for evaluation:

Pharmacokinetics:

Both serum and cerebrospinal fluid samples will be collected for analyses, as shown in Table 3 and Table 4.

In Part 1, a window relative to the nominal timepoint is allowed for sample collection as follows:

- Blood serum pharmacokinetic samples will be collected at 0 hour (immediately pre-dose), and 1 h (±10 min), 6 h (±10 min), 12 h (±10 min), and 24 h (±10 min) post-dose, as well as at Study Day 4 (72h ± 10 min), 8 (±1d), 15 (±3d), and 29 (±4d).
- Cerebrospinal fluid samples (CSF) will be collected via lumbar puncture at 0 hour (immediately pre-dose), 24 h (±2h) Study Day 4 (72 h ±4h), and Study Days 8 (±1d), and 29 (±4d).

The timing for serum and CSF sample collection may be adjusted for subsequent cohorts based on pharmacokinetic data from the preceding cohorts. Serum PK samples collected at pre-dose and on Study Days 8 and 29 will be analyzed for the presence of anti-drug antibodies (ADA).

In Part 2, Visits 3-7 (Study Days 21, 42, 63, 84, 104) will have a window of ±5 days and Visits 8 and 9 (Study Days 169 and 253) will have a window of ±7 days. CSF samples will be collected for PK analysis pre-dose on Study Days 1, 21, 42, 63, 84, and 104. The CSF sample collected on Study Day 253 will also be analyzed for PK. Serum samples will be collected for PK analysis pre-dose and 4 h post-dose on Study Days 1, 21, 42, 63, 84, and 104. Serum will also be collected for PK analysis on Study Days 169 and 253. Pre-dose serum will be collected for ADA analysis on Study Days 1, 21, 42, 63, 84, and 104. Serum will also be collected for ADA analysis on Study Days 169 and 253. A subset of the CSF samples may also be analyzed for ADAs depending on development and presence of ADAs in the serum. Part 2 serum and CSF from subjects receiving placebo will be collected but will not be analyzed for PK and ADAs.

In Part 2 on Study Days 1, 21, 42, 63, 84, and 104 a window relative to the nominal timepoint is allowed for sample collection as follows:

- Blood serum pharmacokinetic samples will be collected at 0 hour (within 4 h pre-dose), and 4 h (±10 min) post-dose
- Cerebrospinal fluid samples (CSF) will be collected via lumbar puncture at 0 hour (immediately pre-dose)

Table 3: Part 1 Pharmacokinetic Sampling Schedule (Study RNX-AX204-101)

	Day 1 (Dosing day)	Day 2 (24 hours post-dose)	Day 4 (72 hours post-dose)	Day 8	Day 15	Day 29
Cerebrospinal Fluid	Pre-Dose	X	X	X		X

Serum	Pre-Dose, and post-dose at Hours 1, 6, 12	X	X	X	X	X
Serum aliquot for ADA	X (Pre-Dose)			X		X

Table 4: Part 2 Pharmacokinetic Sampling Schedule (Study RNX-AX204-101)

Study Phase	**Treatment Phase Window at Visits 3-7 ± 5 days**						**Follow-Up ± 7 days**	
Study Day Month (M)	**1**	**21**	**42**	**63**	**84**	**104**	**169 M6**	**253/ET M9**
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Cerebrospinal Fluid	X	X	X	X	X	X		X
Serum	X	X	X	X	X	X	X	X
Serum aliquot for ADA	X	X	X	X	X	X	X	X
Abbreviations: M = month, ET = Early Termination								

Efficacy

Part 1

Part 1 is focused on safety, tolerability, and pharmacokinetics. However, a subset of efficacy assessments are to be performed including:

- ISNCSCI. ISNCSCI is a comprehensive clinician-administered neurological exam for SCI. It is widely used for research and clinical (neurologic) description to fully assess sensory and motor functioning and level of injury in traumatic SCI. The UEMS will be calculated from the ISNCSCI.
- GRASSP. GRASSP is a clinician administered test that assesses strength in 10 key muscles in the upper extremity as well as dexterity and fine motor skills.
- SCIM III self-care and mobility scores. SCIM III measures functional outcomes in three sections: self-care, respiration and sphincter management, and mobility. The current study will employ the self-care and mobility subscores.

Part 2

The primary objective of Part 2 is to evaluate the safety, tolerability, and pharmacokinetics of repeat dosing. In addition, a number of efficacy assessments are included as secondary endpoints. The key secondary efficacy endpoint for Part 2 will be within-subject change from pre-treatment baseline and slope for UEMS as compared to placebo. The same trained raters should be used for a particular patient as much as possible. The assessments will be performed in the order outlined in Section 11.2.

Additional secondary efficacy endpoints will include within-subject changes from pre-treatment baseline and slope for:

- GRASSP prehension performance scores. GRASSP is a clinician-administered test with three subset scores that assesses strength in 10 key muscles in the upper extremity as well as dexterity and fine motor skills.
- SCIM III self-care scores. Although the SCIM III measures functional outcomes in three sections: self-care, respiration and sphincter management, and mobility, the current study will employ the self-care and mobility subscores. The evaluation will be administered by interview of the patient by a clinician.

Exploratory endpoints will include within-subject changes over time from pre-treatment in:

- ISNCSCI lower extremity motor and sensory scores. ISNCSCI is a comprehensive clinician-administered neurological exam for SCI. It is widely used for research and clinical (neurological) description to fully assess sensory and motor functioning and level of injury in traumatic SCI.
- GRASSP strength, sensation and prehension ability scores
- SCIM III mobility scores
- ISAFSCI. The ISAFSCI will be used to document autonomic control of the heart, blood pressure, sweating, and temperature regulation. Lower urinary tract function, bowel function, and sexual function will be scored.
- Patient Reported Outcomes
  - CUE-Questionnaire (CUE-Q). Assesses subject-reported upper limb function.
  - SF-36 v2. Provides a patient-reported Quality of Life (QoL) assessment. SF-36 will provide data on the subjects' perceived health and well-being over the course of the study.
  - Neuro-QOL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)
  - PGIC – Chronic SCI

Exploratory biomarkers of target engagement and axonal growth may be assessed.

Safety:

Safety will be evaluated similarly for both Parts, through the collection of data from:

- Physical examinations
- Vital signs
- 12-lead electrocardiograms
- Laboratory parameters (hematology, blood chemistry, and urinalysis). Analysis of CSF for protein, cell count, and glucose.
- Treatment-emergent adverse events (TEAEs).
  - TEAEs will be defined as any AE occurring during or after the injection of study drug or placebo.
  - TEAEs will be limited to those events occurring within 28 days after the last visit.

Condition-specific safety outcomes will include adverse changes in:

- ISNCSCI, GRASSP and all of the neurological measures evaluated for efficacy
- Spasticity (Modified Ashworth Scale). A clinician administered examination for spasticity which measures muscle tone. A score of 0-4 is assigned to each muscle group evaluated. Note: Testing will exclude fingers and thumb.
- Pain (BPI). A self-administered questionnaire used to assess the severity of a subject's pain and the impact of this pain on the subject's daily functioning.

Statistical Methods

A general description is included here for the investigator. A detailed Statistical Analysis Plan will be submitted to the IND prior to unblinding the database for Part 2.

Sample Size

The Part 1 sample size was derived empirically from experience with previous single ascending dose clinical studies in other disorders and is deemed appropriate to achieve the study objectives.

The Part 2 sample size was selected to ensure adequate power for detecting treatment-related change in bilateral UEMS (Score from 0 to 50).

A 5-point difference, between the treated and placebo groups, in the change from baseline to 6 months in bilateral UEMS is considered clinically meaningful. Analysis of historical data for cervical SCI patients for the period between ~6-12 months following acute SCI indicates a standard deviation of bilateral UEMS change over 6 months to be around 3 to 4 points.

With a sample size of 12 subjects per active and placebo group, Part 2 of the study has 80% power with Type I error of α=0.05 (two sided), assuming a 5-point difference as indicated above, and with a common standard deviation within each treatment group of approximately 4 in the change from baseline to 6 months in bilateral UEMS.

Accounting for uncertainties in the assumptions based upon historical data used to extrapolate for estimating the sample size in this study and the need for estimation of missing data a sample size of approximately 16 subjects per treatment arm (32 total) will be randomized.

Stages of Analysis

The analysis for this study will be performed in three stages, with the first analysis performed upon completion of the clinical portion of Part 1, the second analysis (including the core efficacy assessment) performed upon completion Day 169 of Part 2 (ie, after all subjects have completed through Study Day 169), and the final analysis performed upon completion of the post-treatment follow-up phase of Part 2 (Day 253). The methods applied to each analysis will be consistent with the objectives of the study.

The blind will be maintained for all blinded study personnel (including investigators and subjects) through the completion of Day 169 of Part 2. After completion of Day 169, designated sponsor staff and external consultants/contractors required to perform the analysis will be unblinded to the treatment allocations in order to complete data analysis though Day 169. The blind will be maintained for site investigators and subjects through completion of Day 253 unless the blind must be broken sooner for safety or regulatory reasons.

General Methods

Data will be tabulated using both descriptive and inferential statistics where specified.

- For Part 1, data will be tabulated by dose cohort as well as pooled (all subjects combined), and no inferential statistics are planned.
- For Part 2, data will be tabulated for each treatment group separately (placebo and AXER-204) to allow for visual inspection of outcomes between the arms. Inferential statistical comparison of the treatment groups is planned.

For both Parts, all data collected will be included in by-domain data listings, sorted by subject number and time point, or as appropriate.

No hypothesis testing will be performed for demographics, background, or safety data.

Continuous data will be summarized by presenting the number of subjects (n), means, mean changes from baseline, mean % changes from baseline (where appropriate), standard deviations, minimum, First quartile (Q1), median, third quartile (Q3), and maximum values. The number of subjects with missing data will be indicated.

Categorical data will be summarized by presenting the number of subjects (n), the number of subjects with missing data as well as counts and percentages in each of the categories. Percentages will be based upon the number of subjects with available data.

When inferential testing is applied to all efficacy assessments, dichotomous/binary categorical efficacy endpoints will be assessed via a 2-sided Fisher's Exact test or Chi-square test as appropriate. Continuous efficacy endpoints will also present least-squares means and p-values from hypothesis testing of efficacy endpoints using mixed-effects model for repeated measures (MMRM).

Additional details will be included in the statistical analysis plan (SAP) which will be finalized prior to unblinding Part 2 of the study and any amendments to it made prior to locking the database and unblinding the study.

Handling of Missing Data

Every attempt will be made to collect all protocol required data at each time point.

Imputations will only be performed for efficacy data and for missing or partial dates, missing severity or relationship to investigational product. Missing AE or CM dates and missing severity or relationship to study drug will always use a conservative approach. Details will be included in the SAP.

For subjects who discontinue treatment (for any reason), subjects will continue to be followed and key efficacy endpoints and safety data collected where possible.

Analysis Populations

Safety Population: Safety outcomes will be assessed for all subjects who are given at least one dose of investigational product.

Full Analysis Set (FAS) Population: Efficacy outcomes will be evaluated using the FAS, defined as all subjects randomized, treated with at least 1 dose of investigational product, and with at least one post-baseline assessment of efficacy.

Per Protocol Population: The per protocol population will be a subset of FAS and include subjects who received at least 80% of study drug and have no major protocol deviations that would impact efficacy assessment.

Alpha Level Considerations

All inferential testing will be performed using two-sided 5% Type I error (α), and therefore 2-sided p-values ≤ 0.05 will be considered statistically significant in this study.

The first hypothesis test will be the key secondary efficacy endpoint of change in bilateral UEMS from baseline to Study Day 169 using the MMRM model as detailed below. Additional secondary efficacy endpoints tested will be the change in GRASSP prehension performance from baseline and slope to Study Day 169 and of change in SCIM self-care from baseline to Study Day 169.

Efficacy Endpoints

Changes from pre-treatment to each on-treatment time point will be calculated, with the primary time point at Day 169. Shifts over time in ordinal endpoints will be presented, with comparisons between treatment groups assessed using a CMH row mean scores statistic at each time point. Slope of change will also be evaluated.

Safety Endpoints

Changes from pre-treatment will be calculated in a similar fashion as for the efficacy endpoints, but no inferential statistics will be provided for safety endpoints. Shifts from baseline in electrocardiogram (ECG) will be tabulated for heart rate and QTcF. Other endpoints will be assessed according to the scale of the variable.

Pharmacokinetic Endpoints

Concentration data in both blood serum and in CSF will be assessed descriptively over time. Correlation with efficacy and safety outcomes may be performed, as the data warrant.
Potential Open-Label Extension Study The sponsor may, pending data outcomes from this current study, initiate an open-label extension study at a later date. This study would provide subjects who participated in Study RNX-AX204-101, during either Part 1 only and those receiving placebo in Part 2, the potential opportunity to participate in a repeat-dose study with AXER-204. Initiation of the open-label extension study will be contingent on satisfactory results from the current clinical study (Part 1 and Part 2) supportive of continued development, funding, and the requisite regulatory and IRB approvals.

Table 5: Part 1 Schedule of Events (Study RNX-AX204-101)[1]

Study Phase	**Screening**	**In-Clinic Treatment**					**Post-Treatment Follow-Up**			
Study Day	**-84 through -1**	**1**		**2**	**3**	**4**	**5, 6, 7[2]**	**8 ± 1 days**	**15 ± 3 days**	**29/ET[3] ± 4 days**
		Pre-Dose	**Post**							
Visit Number	**1**	**2**					**Phone Call[4]**	**3**	**4**	**5**
Informed consents (Main & Biobank)	X									
Register Subject/Contact EDC/Assign Subject ID	X									
Inclusion & Exclusion Criteria	X	X								
Instructions for potential washout period for concomitant medications and for alcohol use	X									
Urine sample for drug screen[5]	X									
Medical/Disease History	X	X								
Full Physical Examination & Ht/Wt	X									X
Demographics	X									
Vital signs (BP, pulse, RR or pulse ox, oral temp)[6]	X	X	X	X	X	X		X	X	X
ECG[7]	X	X	X			X				
Serum pregnancy, chorionic gonadotropin	X									
MRI[8]	X									
ISNCSCI assessment, including AIS (Clinician Assessed)	X									X
SCIM III self-care and mobility subscores (Clinician Assessed)	X									X
GRASSP (Clinician Assessed)	X									X
Admission/Discharge to/from Clinic		Admit				Discharge				
Physical Examination (abbreviated)		X				X				
CSF collection (for PK assessment)[10]		X		X		X		X		X
Dosing of Investigational Product		Dosing								
Study Drug Accountability			X							
Serum (for PK and ADA assessment)[9]		X	Hr 1, 6, 12	X		X		X	X	X
Modified Ashworth Scale (Clinician Assessed)	X									X
SF-36 v2 Health Survey (Subject Reported)	X									X
Neuro-QOL v1.0 – Upper Extremity Function (Fine Motor, ADL) (Subject Reported)	X									X
Brief Pain Inventory (Subject Reported)	X									X
ISAFSCI (Clinician Assessed)	X									X
Clinical laboratory sample collection[10]	X	X		X	X	X			X	X
Viral Serology[11]	X									X
Urinalysis	X									X

Study Phase	**Screening**	**In-Clinic Treatment**					**Post-Treatment Follow-Up**			
Study Day	**-84 through -1**	**1**		**2**	**3**	**4**	**5, 6, 7[2]**	**8 ± 1 days**	**15 ± 3 days**	**29/ET[3] ± 4 days**
		Pre-Dose	**Post**							
Visit Number	**1**	**2**					**Phone Call[4]**	**3**	**4**	**5**
Urine pregnancy test[12]		X								X
Prior and Concomitant Medications	Prior		Concomitant (On-going)							
Adverse Events[13]			Treatment-Emergent (On-going)							
Serious Adverse Events	Pre-Treatment		Treatment-Emergent (On-going)							

[1] Abbreviations: AE = adverse events, ECG = electrocardiogram, EDC = electronic data capture. ET = early termination. ID = identification, PK = pharmacokinetic, SAE = serious adverse event

[2] Note: Day 7 phone call may be skipped if Day 8 visit actually occurs on Day 7.

[3] ET: early termination. Subjects who terminate the treatment prematurely (including those withdrawn from the study) should have all assessments performed according to the protocol. However, subjects who discontinue from the study may only have assessments performed per the ET visit.

[4] Phone calls from the site to the subject will be made each day (Study Days 5, 6, and 7) after discharge from the clinic. Subjects will be queried for general health.

[5] Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene). Patients must abstain from drinking alcohol and using recreational marijuana in US states where marijuana is legal, for at least 3 days prior to laboratory screening assessments on nominal Day-28.

[6] Vital signs (blood pressure, pulse rate, respiratory rate or pulse oximetry, and oral body temperature) will be measured after the patient has been in a sitting or recumbent position for 5 minutes. Frequency noted below:
Screening visit - Once
Day 1 - Pre-dose, post-dose, then every 3 hours for 1st 24 h following dosing
Day 2-Day 4 (until discharge from the clinical unit) - Starting at 24 h post-dose, take vitals every 6 hours
Day 8, 29 - Pre-LP, post-LP, then every 3 hours until subject leaves the unit
Day 15 - Pre-blood draw

[7] ECGs will be taken in triplicate, 5 minutes apart, will be obtained after the patient has been in a supine (resting) position for at least 5 minutes. At Visit 2, triplicate ECGs will be taken twice, pre-and post-dose. All ECGs will be read locally.

[8] MRIs will be read by a sponsor-arranged expert prior to subject enrollment into the study

[9] Serum samples collected and analyzed for ADA pre-dose and on Study Days 8 and 29

[10] Clinical Laboratory Sample Collection: Sample collected on Study Days 1-4 are to be processed locally. INR/PTT is required prior to the Day 1 lumbar puncture procedure with repeat INR/PTT tests on subsequent Study Days at the direction of the Principal Investigator.

[11] Infectious disease testing at Screening and Visit 5 (Study Day 29/ET) will include: HIV-1/HIV-2 antibody, hepatitis B surface antigen, hepatitis C antibody.

[12] Urine Pregnancy Test will be performed locally on site for women of childbearing potential.

[13] Adverse Events are only collected upon the start of study drug. Events occurring prior to this are to be reported as part of the subject medical history. However, SAEs are to be collected from the time of informed consent.

Table 6: Part 2 Schedule of Events (Study RNX-AX204-101)[1]

Study Phase	**Screening**	**Treatment Phase Window at Visits 3-7 ± 5 days**							**Follow-Up ± 7 days**		
Study Day	**-84 through -1**	**1**	**8 (±3 days)**	**21**	**42**	**63**	**84**	**104**	**137 Month 5**	**169 Month 6**	**253/ET[2] Month 9**
Visit Number	**1**	**2**		**3**	**4**	**5**	**6**	**7**		**8**	**9**
Informed consents (Main & Biobank)	X										
Register Subject/Contact EDC/Assign Subject ID	X										
Inclusion/Exclusion Criteria	X	X									
Instructions for potential washout period for concomitant medications and for alcohol use	X										
Demographics	X										
Medical/Disease History	X	X									
Randomization		X									
MRI[2]	X										
Telephone call[3]			X						X		
Full Physical Examination & Ht/Wt	X										X
Physical Examination (abbreviated)		X		X	X	X	X	X		X	
Vital Signs (BP, pulse, RR or Pulse Ox, oral temp)[4]	X	X		X	X	X	X	X		X	X
ECG[5]	X	X		X	X	X	X	X		X	X
ISNCSCI assessment including AIS	X	X		X		X		X		X	X
GRASSP[6]	X	X				X		X		X	X
SCIM III self-care and mobility subscores		X				X		X		X	X
Modified Ashworth Scale		X								X	X
Brief Pain Inventory		X								X	X
Neuro-QOL v1.0 – Upper Extremity Function (Fine Motor, ADL)		X								X	X
SF-36 v2 Health Survey		X								X	X
CUE-Q		X								X	X
PGIC Chronic SCI		X								X	X
ISAFSCI		X								X	X
CSF collection (pre-dose if dosing visit)[7]		X		X	X	X	X	X			X
Clinical laboratory sample collection (CSF)		X		X	X	X	X	X			X
Dosing of Investigational Product		X		X	X	X	X	X			
Investigational Product Accountability		X		X	X	X	X	X			
Serum collection for PK (pre-dose & 4 h post-dose if dosing visit)		X		X	X	X	X	X		X	X
Serum collection for ADA (pre-dose if dosing visit)		X		X	X	X	X	X		X	X
Clinical laboratory sample collection[8]	X	X		X		X		X		X	X
Viral Serology[9]	X									X	X
Serum pregnancy, chorionic gonadotropin	X										
Urine Pregnancy Test[10]		X		X	X	X	X	X		X	X

Study Phase	**Screening**	**Treatment Phase Window at Visits 3-7 ± 5 days**							**Follow-Up ± 7 days**		
Study Day	**-84 through -1**	**1**	**8 (±3 days)**	**21**	**42**	**63**	**84**	**104**	**137 Month 5**	**169 Month 6**	**253/ET[2] Month 9**
Visit Number	**1**	**2**		**3**	**4**	**5**	**6**	**7**		**8**	**9**
Urine sample for drug screen[11]	X										
Urinalysis	X	X		X		X		X		X	X
Prior and Concomitant Medications	Prior	Concomitant (On-going)							Post-Trt		
Adverse Events[12]		Treatment-Emergent (On-going)							Post-Trt		
Serious Adverse Events	Pre-Trt	Treatment-Emergent (On-going)							Post-Trt		

[1] Abbreviations: ADA = anti-drug antibody, AE = adverse events, ECG = electrocardiogram, EDC = electronic data capture. ET = early termination. ID = identification, PK = pharmacokinetic, SAE = serious adverse event

[2] MRIs will be run locally and findings read by a sponsor-arranged expert prior to subject enrollment into the study.

[3] Telephone call to inquire about any AEs and determine if subject should come to clinic for evaluation.

[4] Vital signs (blood pressure, pulse rate, respiratory rate or pulse oximetry, and oral body temperature) will be measured after the patient has been in a sitting or recumbent position for 5 minutes. Vitals will be taken pre-dose, post dose, then every 2 hours until subject leaves the unit

[5] ECGs will be taken in triplicate, 5 minutes apart, and will be obtained after the patient has been in a supine (resting) position for at least 5 minutes. ECGs are taken pre-dose at visits where study drug is administered. ECGs will be read locally.

[6] GRASSP prehension ability and prehension performance testing will be video recorded.

[7] Remove aliquot for CSF labs before processing CSF for pharmacokinetics/biomarkers and biobank samples.

[8] Clinical Laboratory Sample Collection: INR/PTT is required prior to the Day 1 lumbar puncture procedure with repeat INR/PTT tests on subsequent Study Days only if directed by the Principal Investigator. Screening labs must be completed within 28 days of enrollment.

[9] Infectious disease testing at Screening, Visit 8 (Month 6) and Visit 9 (Month 9) will include: HIV-1/HIV-2 antibody, hepatitis B surface antigen, hepatitis C antibody.

[10] Urine Pregnancy Test will be performed locally on site for women of childbearing potential.

[11] Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene).

[12] Adverse Events are only collected upon the start of study drug. Events occurring prior to this are to be reported as part of the subject medical history. However, SAEs are to be collected from the time of informed consent.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 7: Abbreviations and Specialist Terms (Study RNX-AX204-101)

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
AIS	American Spinal Injury Association Impairment Scale
ANCOVA	Analysis of Covariance
BMI	Body mass index
BPI	Brief Pain Inventory
BUN	Blood urea nitrogen
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CRO	Contract research organization
CSCI	Chronic Spinal Cord Injury
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CUE-Q	Capabilities of Upper Extremity – Questionnaire
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated Glomerular Filtration Rate
ER	Emergency room
ET	Early termination
FAS	Full analysis set population
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRASSP	Graded Redefined Assessment of Strength, Sensation and Prehension
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
DSMB	Data and Safety Monitoring Board

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Integrated response technology
ISAFSCI	International Standards to document remaining Autonomic Function after Spinal Cord Injury
ISNCSCI	International Standards for Neurological Classification of SCI
LP	Lumbar Puncture
LSMean	Least Square Means
MEP	Motor Invoked Potentials
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OAE	Other significant adverse event
PACU	Post-Anesthesia Care Unit
PGIC	Patient's Global Impression of Change
PI	Principal Investigator
PK	Pharmacokinetics
PRN	Pro re nata (as needed)
QoL	Quality of Life
QTcF	QT interval using Fridericia Correction Formula
SAE	Serious adverse event
SCIM III	Version III of the Spinal Cord Independence Measure
SF-36	Short Form - 36 v2 Health Survey
SNRI	serotonin norepinephrine reuptake inhibitor
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UEMS	upper extremity motor score
UMC	Uppsala Monitoring Centre
US	United States
WHO	World Health Organization

4. INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the Sponsorship of ReNetX Bio, Inc. (the sponsor) at approximately 5 investigational centers in the United States.

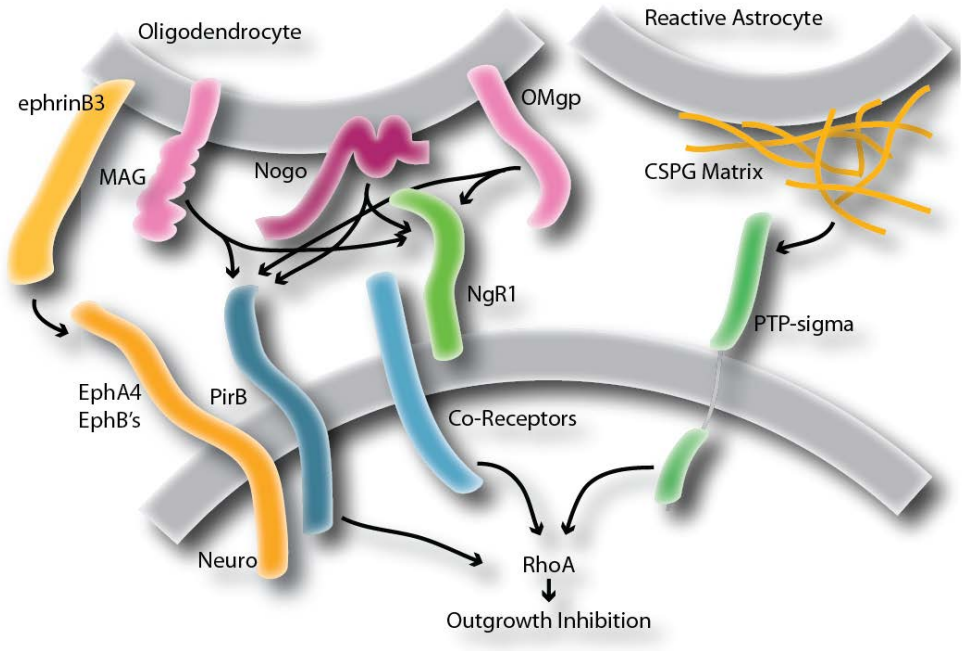
The contact information for the Medical Monitor along with the telephone numbers of the other contact persons for the sponsor are listed in Table 1. Contact information for [redacted], the designated Contract Research Organization, (CRO), and other vendors are listed in the Investigator Site File provided to each site.

5. INTRODUCTION

5.1. AXER-204, a Human NoGo Trap Fusion Protein

Mammalian brain and spinal cord networks stabilize during development, such that axonal growth in the adult CNS is either non-existent or extremely limited. After adult CNS injury, the extracellular factors that maintain axonal stability restrict axonal growth and permit only severely limited recovery of function. Adult extracellular axonal growth inhibitors include a group of proteins from the oligodendrocyte, Nogo-A, MAG, OMgp, and ephrin-B3, which interact with axonal receptors, including NgR1, NgR2, PirB, and EphA4 [Liu 2006, Schwab 2014]. Extracellular proteoglycans, containing chondroitin sulfates, also inhibit axonal sprouting in the adult CNS, particularly near sites of astrogliosis and scar formation [Ohtake 2015, Sharma 2012]. There is substantial molecular cross talk between ligands and receptors. The key inhibitory ligands Nogo, MAG, and OMgp all bind and activate NgR1 on axons to inhibit axonal extension. Likewise, PirB (LILRB2) has been found to bind Nogo, MAG, and OMgp and to mediate axonal growth inhibition. Consistent with partially overlapping roles in axonal inhibition, simultaneous genetic deletion of Nogo, MAG, and OMgp has greater impact on axonal growth and functional recovery following CNS injury than deletion of a single inhibitor [Cafferty 2010]. A representation of the role of Nogo, MAG, and OMgp and other key regulators of axonal growth in the adult CNS is presented in Figure 1.

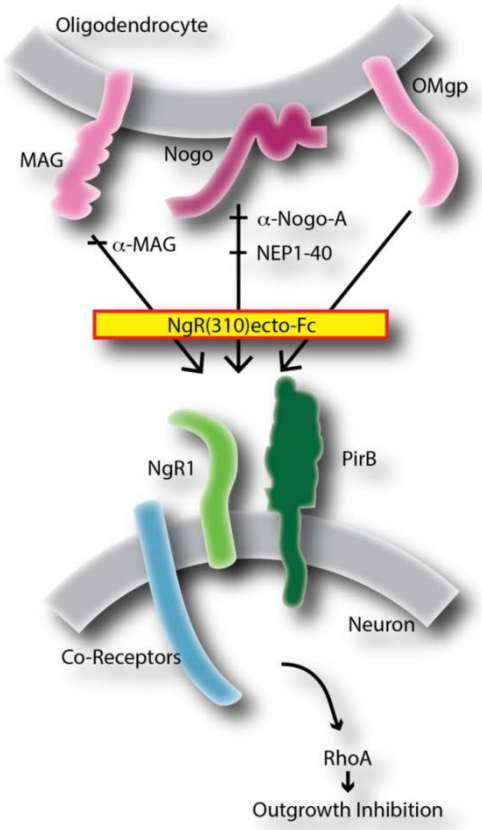
Figure 1: Key Components Regulating Axonal Growth in the Adult Mammalian Central Nervous System



Targeting one ligand or one receptor in the inhibitory adult CNS pathways has been shown to yield some benefit in certain specific pre-clinical spinal cord injury (SCI) models. Based on these observations, anti-Nogo antibodies are entering clinical trials for new (subacute) SCI. In distinction, NoGo Trap (AXER-204, Nogo Receptor decoy, hNgR1(310)ecto-Fc Ala Ala)

represents a mechanistically superior approach to promoting axonal growth following injury as it binds three key inhibitors, Nogo, MAG, and OMgp, and blocks their interaction with endogenous NgR1 and other receptors (Figure 2). Consistent with this mechanism, NoGo Trap has been shown in multiple laboratories to promote axonal growth and recovery of function in a variety of pre-clinical models of CNS injury including stroke [Lee 2004], dorsal root crush injury [Harvey 2009], acute transection SCI [Li 2004], and acute/sub-acute contusion SCI [Ji 2006, Wang 2006, Wang 2014]. Most critically, NoGo Trap supports axonal growth and functional recovery in chronic contusion SCI [Wang 2011], while no other blocker of extrinsic signals has reported efficacy in this setting. Recent pre-clinical studies have shown that intrathecal lumbar administration results in broad CNS distribution in rat and non-human primate and that intermittent intrathecal bolus injection of the protein provides equivalent restoration of function in rat contusion SCI in comparison to previously obtained results employing continuous infusion [Wang 2014]. AXER-204 promotes corticospinal axon growth and the use of the impaired forelimb during spontaneous feeding and the impaired hindlimb during locomotion non-human primates with cervical hemisection SCI [Wang 2020].

Figure 2: Putative Mechanism of AXER-204



The present clinical evaluation of AXER-204 is being conducted in subjects with chronic SCI. This plan is based on the enhanced feasibility for detecting treatment-related functional improvements in subjects with otherwise stable deficits [Fawcett 2007, NSCISC 2018]. The

substantially larger chronic SCI patient population compared to acute SCI cases should facilitate enrollment of this study and has the potential to translate into benefit for many more individuals.

5.2. Nonclinical Summary

Nonclinical data are summarized for AXER-204. In addition, data from nonclinical studies with various surrogate proteins, primarily a rat form of the NoGo Trap protein, are included. AXER-204 binds to the myelin associated ligands Nogo (measured using Nogo-66 fragment), MAG, and OMgp in ELISA format in vitro. Likewise, binding to MAG and OMgp has been measured using a Fluorescence Resonance Energy Transfer (FRET) assay. Consistent with the binding profile, AXER-204 prevents Nogo-22 mediated inhibition of cultured axon growth. AXER-204 promotes functional recovery following contusion spinal cord injury in rat with either continuous infusion into the cerebrospinal fluid (CSF) via intracerebroventricular cannula or intermitted bolus intrathecal administration. Moreover, the intermittent intrathecal treatment increased the growth of raphespinal axons after injury.

A number of additional evaluations in spinal cord injury models were conducted using the rat form of the protein. Overall, the pharmacological effects include functional recovery and enhanced axon growth. Of particular importance, NoGo Trap was found to enhance functional recovery in chronic contusion injury in rat – supporting evaluation in chronic SCI. In pharmacokinetics studies, AXER-204 distributed broadly in the CSF, spinal cord tissue, and brain tissue following intrathecal administration. Tissue half-life was prolonged over the half-life in CSF. Daily intrathecal bolus infusions of AXER-204 in non-GLP 14-day range finder toxicology studies in rat and monkey did not identify adverse effects from test article (No observed adverse effect level [NOAEL] was maximum feasible dose volume for each study). CSF and serum exposure were confirmed in each study. Similarly, no test article-related toxicity was observed in GLP toxicology studies with administration of AXER-204 by intrathecal bolus infusions every other day in rat for two months and in monkey for up to 108 days. Accordingly, the no observed effect level (NOEL) for rat and monkey was equivalent to the maximum feasible dose. Toxicology studies employed frequent bolus infusions in order to maximize the cumulative dose evaluated.

Off-target effects such as toxicity due to systemic exposure are not anticipated with AXER-204 because the requisite ligands Nogo, MAG, and OMgp are mostly localized in the CNS and AXER-204 exposure is predominantly localized to the CNS following intrathecal administration in animal studies. Nonetheless, a one-month GLP rat toxicology study employing intravenous dosing was completed and the maximum dose tested was found to be equivalent to the NOAEL.

Please refer to the AXER-204 Investigator's Brochure for a more detailed description of toxicology investigations.

5.3. Clinical Experience with AXER-204 and Lumbar Puncture

The present study represents the first evaluation of AXER-204 in humans.

There is extensive published clinical experience with lumbar puncture (LP) procedures representative of those required for administration of AXER-204. The most common adverse events (AEs) associated with LP consist of post-LP back pain and post-LP headache. This protocol includes procedures designed to minimize the incidence and severity of AEs associated

with LP including optimal choice of spinal needle, removal of an equivalent volume of CSF relative to the volume of investigational product injected, and a controlled rate of slow bolus injection of investigational product.

5.4. Rationale for Dose Selection

In Part 1, the initial dose escalation sequence for the study is 3, 30, 90, and 200 mg. The starting dose 3 mg was selected to be 30-fold below the estimated human pharmacologically active dose of 90 mg. Adjusting for cross-species scaling by CSF volume, toxicology studies did not identify AXER-204 related toxicity when given at equivalent (monkey) or at three-fold higher (rat) doses vs. the maximum planned human dose when given every other day by slow bolus intrathecal administration for up to 57 days in rat and 108 days in monkey. Similarly, adjusting for cross-species scaling by CSF volume and accounting for the more frequent dosing in the GLP toxicology studies, the cumulative doses given in rat and monkey toxicology exceeded the maximum feasible human dose by at least 21-fold and 8-fold respectively. The maximum doses in toxicology were the maximum feasible doses based on the tolerable volumes for intrathecal administration. The 3 and 30 mg doses will be diluted from the formulation to provide a constant injection volume of 10 mL. The 90 mg and 200 mg doses will be given without dilution resulting in dosing volumes of 9 mL and 20 mL respectively. The dose volumes were selected based on published studies and drug label information for other therapeutics describing safety and drug distribution following intrathecal administration.

A conservative approach was applied in deriving the starting dose in Part 1 in order to enhance safety. For drugs delivered intrathecally, published FDA guidance suggests scaling based on compartment volumes and concentrations of the therapeutic [Guidance for Industry, FDA]. Using compartment volumes, the pharmacologic human equivalent dose (HED) is calculated by dividing the rat effective dose by rat CSF volume and multiplying by the CSF volume for human. This yields an estimated pharmacologic HED of 90 mg. The starting dose of 3 mg is anticipated to be free of detectable pharmacological effects using the method outlined in the Draft Guidance for Industry and Reviewers of November 2005 entitled "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult healthy Volunteers" and incorporates a safety factor of 30 compared to the estimated human Pharmacologically Active Dose of 90 mg. The maximum dose volume of 20 mL represents approximately 10-15% of total average CSF volume for adults and roughly 30% of spinal CSF volume [Kroin 1992, Thorne 2001, Sakka 2011]. The dose will be introduced immediately following collection of an equivalent volume of CSF and at a controlled constant rate of 100 mL/h (12 min for 20 mL). The bolus injection rate selected is five times the average time required to regenerate the CSF collected (20 mL/h) [Hladky 2014]. The time required to regenerate CSF collected by lumbar puncture has been found to approximately equal the time needed to normalize CSF pressure [Brinker 2014, Masserman 1934]. Thus, the sequence of CSF collection followed by controlled bolus infusion of an equivalent volume of investigational product is designed to reduce the impact on CSF pressure and flow. The controlled bolus injection rate selected is slower than the rate of injection specified for several marketed products administered intrathecally including: Omnipaque 10-17 mL injected over 1-2 min, a small amount of CSF may be removed prior to injection [OMNIPLAQUE Package Insert]; Methotrexate, usually 2-6 mL (up to 10 mL) injected over 1-3 min following removal of an equivalent volume of CSF; Spinraza 5 mL injected in children over 1-3 min after removal of 5

mL CSF [SPINRAZA Package Insert]. Published results indicate that volumes ranging from 10-30 mL of CSF can be administered in humans without adverse effects beyond occasional mild headache provided an equivalent volume of CSF is first removed [Papisov 2013, Rieselbach 1962a, Rieselbach 1962b, Rieselbach 1963]. The conservative controlled injection rate of AXER-204 following collection of an equivalent volume of CSF is designed to reduce the potential for adverse effects arising from disruption of CSF pressure and flow.

Distribution following bolus intrathecal administration is reported to depend strongly on injection volume, with smaller volumes favoring less rapid distribution. Rapid broad distribution to the cisterna magna is reported following bolus intrathecal lumbar administration provided a volume over 10% of total CSF is given [Papisov 2013, Rieselbach 1962a]. Estimates of total subarachnoid CSF volume in adults generally range between 90-170 mL and 150 mL is commonly taken as the volume for dose modeling [Brinker 2014, Kuttler 2010]. Thus, the range of AXER-204 dose volumes of 9-20 mL are selected to facilitate rapid and broad distribution over the length of the cord.

To ensure subject safety, dose selection for Part 2 of the study will be based on safety, tolerability, and pharmacokinetics data generated in Part 1 and the DSMB will review and approve dosing frequency and level before recommending starting Part 2. The maximum safe dose identified in Part 1 will be selected for repeated administration in Part 2. The frequency of dosing in Part 2 will be determined based on analysis of pharmacokinetic data. In addition, biomarkers of target engagement and mechanism engagement are under development with the objective of implementing these assays to aid in guiding dose frequency in Part 2. The dosing will be no more frequent than once every two weeks or as long as once every 4 weeks for Part 2. As described for Part 1, repeat-dose toxicology studies with much more frequent administration in rat and cynomolgus monkey did not identify AXER-204 toxicity.

6. TRIAL OBJECTIVES AND PURPOSE

Study RNX-AX204-101 is a two-part (Parts 1 and 2) study that will be run sequentially. Part 1 is considered a Phase 1b study, while Part 2 is considered a Phase 2a study. Each part has unique objectives.

6.1. Part 1 Single Ascending Dose

6.1.1. Primary Objective

To evaluate the safety, tolerability, and pharmacokinetics (PK) of ascending, single intrathecal lumbar slow bolus infusions of AXER-204 in subjects with chronic spinal cord injury (CSCI).

6.2. Part 2 Placebo-Controlled Repeat Dose

6.2.1. Primary Objectives

1. To evaluate the safety and tolerability of repeat intrathecal lumbar slow bolus infusions of AXER-204 compared to placebo in subjects with CSCI.
2. To evaluate the pharmacokinetics of repeat doses of AXER-204 in subjects with CSCI

6.2.2. Secondary Objectives

To assess the efficacy of repeat dose therapy of AXER-204 compared to placebo on functional and activities of daily living (ADL) measures as assessed by:

- International Standards for Neurological Classification of SCI (ISNCSCI) Upper Extremity Motor Score (UEMS)
- Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP) prehension performance
- Version III of the Spinal Cord Independence Measure (SCIM III) self-care

6.2.3. Exploratory Objectives

In Part 2, the efficacy of repeat dose therapy of AXER-204 compared to placebo as assessed by the following:

- ISNCSCI lower extremity motor and sensory scores
- GRASSP strength, sensation and prehension ability scores
- SCIM III mobility scores
- International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI)
- Patient Reported Outcomes
  - CUE-Questionnaire (CUE-Q). Assesses subject-reported upper limb function.

- SF-36 v2. Provides a patient-reported Quality of Life (QoL) assessment. SF-36 will provide data on the subjects' perceived health and well-being over the course of the study.
- Neuro-QOL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)
- PGIC – Chronic SCI

Exploratory biomarkers of target engagement and axonal growth may be assessed.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

Study RNX-AX204-101 is a two-part study that will be run sequentially, with Part 2 planned to start after Part 1 has completed. Each Part will be conducted at approximately 5 centers in the United States.

For each Part, eligible subjects will be ages 18 to 65 years inclusive, male or female, with a traumatic spinal cord injury that occurred at least 1 year prior to the screening date. Subjects must have significant neurological impairment of the hands and arms. Subjects who participated in Part 1 may be evaluated for enrollment in Part 2 provided at least 6 months will have elapsed between the dose received in Part 1 and the initiation of dosing in Part 2.

7.1.1. Part 1

Part 1 is a multicenter, open-label, single ascending dose study in subjects with chronic spinal cord injury. Four cohorts of 6 subjects each are planned, with subjects within each cohort expected to receive the same dose of study drug. Thus, up to 24 subjects will be enrolled in Part 1, and all will receive AXER-204.

If the Maximum Tolerated Dose (MTD) is reached prior to the fourth cohort, the sponsor may enroll the remaining subjects (up to a total enrollment of 24 for the study) to obtain further data at the tolerated dose levels. The sponsor in conjunction with the investigators and medical monitor will determine dose escalation according to the methods described in Section 7.3.3.

Study drug will be administered sequentially, with at least 3 days between subjects being dosed within each cohort (following 72-hour safety assessment review by the sponsor in conjunction with the investigators and medical monitor for each prior subject).

The study stages for Part 1 are:

- Screening (within 84 days prior to Day 1). Patients have 84 days from the time of signing informed consent to complete their screening assessments and, if needed, their washout period for prohibited concomitant medications. The screening laboratory tests must be completed within 28 days prior to Day 1.
- Treatment period: Check-in Day 1, administration of study drug, 3-night in-clinic stay, and discharge on Day 4 following the completion of all scheduled procedures.
- Follow-up: Subjects will have follow-up visits for up to 29 days post-dose as follows: subjects will receive a phone call on Study Days 5, 6, and 7 to inquire about their general health and will return to the clinic for visits on Study Day 8 (± 1 day), Study Day 15 (±3 days) and Study Day 29 or Early Termination (± 4 days). See Table 5 for the Schedule of Events for Part 1.

7.1.1.1. Screening

All subjects must sign/e-sign an Informed Consent Form (ICF) prior to undergoing any screening procedures. Screening procedures will take place up to 84 days. Subjects will undergo an MRI to determine spinal cord structure and intrathecal space (Appendix 12); MRIs will be run locally and evaluated by a sponsor-arranged expert. Additional radiological assessments may be

performed at the discretion of the Principal Investigator, including CT or MRI of the head and X-ray of the lumbar spine as additional evaluations to rule out potential contraindications for lumbar puncture. The subject's demographics, medical and surgical history, and prior and concomitant medications will be recorded. Screening/baseline assessments will be performed, and subjects will undergo blood draws where blood, serum collection, viral serology will be obtained, and urine samples will be collected.

Subjects will also be presented with a separate biobank ICF for review. If a subject agrees, samples of his/her CSF, blood, MRI scans and data collected in the study, will be stored for future research. A subject does not have to agree or sign the biobank ICF in order to be eligible to participate in this main study.

Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene). Subjects using marijuana /THC-CBD preparations, opiates, sedative hypnotics, or tranquilizers may be permitted to participate in the trial provided the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.

In the event that a subject is rescreened, the original screening MRI and expert review of the images may be used for the rescreening provided the MRI was completed within 6 months of rescreening. Similarly, neurological examinations and questionnaires do not need to be repeated provided the rescreening occurs within 84 days of the time of data collection.

7.1.1.2. In-Clinic Treatment Period

Eligible subjects will be admitted to the clinic on the evening prior to or on the day of dosing (Study Day 1) dependent on clinical site requirements. Following final pre-treatment assessments, subjects will undergo a lumbar puncture (LP) and receive their single dose of study drug administered via intrathecal lumbar slow bolus infusion by the Principal Investigator or a trained and licensed designee. Dosing will be according to Table 8.

Subjects will remain in-clinic until discharge on Study Day 4 and will undergo daily safety assessments and observation.

Blood and CSF samples will be obtained. The timing for serum and CSF sample collection may be adjusted for subsequent cohorts based on PK data from the preceding cohorts. In addition to undergoing PK analysis, serum samples obtained from blood collected at pre-dose and on Study Days 8 and 29 will be analyzed for the presence of anti-drug antibodies (ADA).

Table 8: Treatment by Cohort (Part 1, Study RNX-AX204-101)

Cohort	Treatment	Number of Subjects
1	3 mg AXER-204	6
2	30 mg AXER-204	6

3	90 mg AXER-204	6
4	200 mg AXER204	6

7.1.1.3. Follow-Up

Sites will contact the subjects via telephone on Study Days 5, 6, and 7 to inquire as to their general health status.

Subjects will return to the Clinic on Study Day 8 (±1d), for CSF and serum PK assessments, on Day 15 (±3d) for blood collection (serum PK analysis), and again on Study Day 29 (±4d) (for end of study assessments). Vital signs, concomitant medications, AEs, and general health status will be assessed at each visit.

7.1.2. Part 2

Part 2 is a multicenter, randomized, double-blind, placebo-controlled, repeat dose study in CSCI subjects. Approximately 32 subjects will be randomized (ratio 1:1) to receive AXER-204 or placebo (an isotonic phosphate buffered saline formulation). Subject to review of the safety, tolerability, and pharmacokinetic data from Part 1 and DSMB approval, the dose will be 200 mg given once every 3 weeks for 15 weeks as outlined in the schedule of events. Subject to DSMB approval, the dose may be reduced to 90 mg and the dose interval may be modified based on data from Part 1 but is not expected to be less than once every 14 days or more than 28 days. Subject to DSMB approval, the dose and dose frequency may also be adjusted during Part 2 based on emergent safety and tolerability data.

The study stages for Part 2 are:

- Screening (within 84 days prior to Day 1). Patients have 84 days from the time of signing informed consent to complete their screening assessment and, if needed, their washout period for prohibited concomitant medications. The screening laboratory tests must be completed within 28 days prior to Day 1.
- Treatment Period (15 weeks). Study treatment given every 2-4 weeks for 15 weeks in total per subject.
- Follow-up (21 weeks). Following the last Treatment Period dose of investigational product or Early Termination of dosing, a telephone call to assess status regarding any adverse events will be conducted on Study Day 137 (± 7 days) and follow-up visits will occur at Study Days 169 (± 7 days) and 253 (± 7 days).

See Table 6 for the Schedule of Events for Part 2.

7.1.2.1. Screening

All subjects must sign/e-sign an Informed Consent Form (ICF) prior to undergoing any screening procedures. Screening procedures will take place up to 84 days. Subjects will undergo an MRI to determine spinal cord structure and intrathecal space; MRIs will be run locally and evaluated by a sponsor-arranged expert. Additional radiological assessments may be performed at the discretion of the Principal Investigator, including CT or MRI of the head and X-ray of the lumbar spine as additional evaluations to rule out potential contraindications for lumbar

puncture. The subject's demographics, medical and surgical history, and prior and concomitant medications will be recorded. Screening assessments will be performed, and subjects will undergo blood draws where blood, serum collection, viral serology will be obtained, and urine samples will be collected.

Subjects will also be presented with a separate biobank ICF for review. If a subject agrees, samples of his/her CSF, blood, MRI scans and data collected in the study, will be stored for future research. A subject does not have to agree or sign the biobank ICF in order to be eligible to participate in this main study.

Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene). Subjects using marijuana /THC-CBD preparations, opiates, sedative hypnotics, or tranquilizers may be permitted to participate in the trial provided the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.

In the event that a subject is rescreened, the original screening MRI and expert review of the images may be used for the rescreening provided the MRI was completed within 6 months of rescreening. Similarly, the ISNCSCI and GRASSP do not need to be repeated provided the rescreening occurs with 84 days of the time of data collection.

7.1.2.2. Treatment Phase

Eligible subjects will be randomized to either AXER-204 or to placebo. The randomization will be stratified based on pre-treatment AIS grade (AIS A,B vs. AIS C,D) and prior receipt of study drug in Part 1 (Received AXER-204 in Part 1 vs. Did not receive AXER-204 in Part 1).

Subjects will undergo baseline assessments and receive their assigned (double-blind) treatment on Study Day 1. Study personnel will conduct telephone call with subjects on Study Day 8 (± 3 days) to assess status regarding any adverse events. Subjects will then return to the Clinic on Day 21 (± 5 days) for safety, efficacy, and PK assessments and their second dose of study investigational product. Thereafter, subjects will return approximately every 21 days, at Study Days 42 (± 5 days) (third dose), 63 (± 5 days) (fourth dose), 84 (± 5 days) (fifth dose), 104 (± 5 days) (sixth dose), for safety, efficacy, and PK assessments (pre-dose) and investigational product administration.

Cerebrospinal fluid samples will be collected pre-dose at each treatment (dosing) visit, including Study Day 1, during a single LP procedure for collecting and dosing. Serum for PK and immunogenicity (ADA) testing will be collected pre-dose at specified visits (See Table 11), within 4 hours prior to investigational product administration. Serum will also be collected for PK at 4 h post-dose at specified visits.

7.1.2.3. Follow-Up

Study personnel will conduct telephone call with subjects on Study Day 137 (± 7 days) to assess status regarding any adverse events. Depending on the results, the subject may be asked to come

to the clinic for evaluation. Subjects will return at Study Days 169 (± 7 days), and 253 (± 7 days) for safety and efficacy assessments.

7.2. Number of Subjects

Part 1 will enroll up to 24 subjects in cohorts of 6 subjects each.

Part 2 will enroll approximately 32 subjects, randomized in a 1:1 ratio (and thus approximately 16 subjects per arm) to repeated doses of AXER-204 or of matching placebo.

If the dropout rate is such that the power of the study could be compromised, or that the study objectives cannot reliably be achieved, the Sponsor may elect to replace those subjects who discontinue prematurely, provided discontinuation is not due to adverse events related to investigational product administration.

7.3. Treatment Assignment

7.3.1. Part 1

Dosage will be by cohort, with 4 sequentially-treated cohorts planned. Intrathecal doses of AXER-204 below 90 mg will be diluted and delivered as a solution in 10 mL of isotonic phosphate buffered saline. Both the 90 mg dose and 200 mg dose will be dosed with the current study drug concentration. All administration will be given following a removal of an equivalent volume of CSF. Intrathecal injections will be given at a rate of 100 mL/hr using a medically approved syringe pump (eg, 12 minutes to administer 20 mL) to avoid significant disruption of natural CSF flow and pressure.

The starting dose of 3 mg is estimated to be below the pharmacologically active dose. Dose escalation will proceed to 30 mg, 90 mg, 200 mg contingent on safety, tolerability, and available PK. Thus, dosing volumes will be given as follows:

- Cohort 1: 3 mg, 10 mL
- Cohort 2: 30 mg, 10 mL
- Cohort 3: 90 mg, 9 mL
- Cohort 4: 200 mg, 20 mL

7.3.2. Part 2

Subject to review of the safety, tolerability, and pharmacokinetic data from Part 1 and DSMB approval, the dose will be 200 mg given once every 3 weeks for 15 weeks as outlined in the schedule of events. Subject to DSMB approval, the dose may be reduced to 90 mg and the dose interval may be modified based on data from Part 1 but is not expected to be less than once every 14 days or more than 28 days. Subject to DSMB approval, the dose and dose frequency may also be adjusted during Part 2 based on emergent safety and tolerability data.

The maximum volume of injection by intrathecal lumbar slow bolus injection is limited in this study to approximately 20 mL based on published tolerance data from studies with other agents employing the same route of administration. If an injection volume of 20 mL, corresponding to a 200 mg dose of AXER-204, is reached in Part 1 dose escalation portion of the study with

acceptable safety and tolerance, the 200 mg dose will be designated as the dose for Part 2 at the discretion of the Sponsor in conjunction with the investigators, DSMB, and medical monitor.

7.3.3. Dose Escalation Decisions and Data and Safety Monitoring Board (DSMB) Dose Escalation in Part 1

Dose escalation decisions will be made jointly by the investigator, sponsor, and medical monitor. The investigator, sponsor, and medical monitor may also make adjustments to the dosing plan, as appropriate for reasons of safety and tolerability. Dose escalation (for each sequential cohort) will not occur until 6 subjects in the prior cohort have completed the initial 3 day in-clinic period AND at least two subjects have completed their Day 29 post-dose follow-up visit. Determination of whether to escalate dose in the subsequent cohort will be made jointly by the investigators, sponsor, and medical monitor after review of all clinical and available PK data. Review will include AEs and serious AEs (SAEs), and specifically the following potential stopping criteria will be evaluated prior to each dose escalation.

7.3.3.1. Stopping Rules/Study Interruption/Discontinuation Notice (Part 1)

The investigators and medical monitor in conjunction with the sponsor may elect to stop dosing or stop the study based on any treatment emergent concerns. Dosing will be stopped due to the occurrence of any individual adverse events which, in the judgment of the investigators and medical monitor in conjunction with the sponsor, need further characterization with respect to progression and reversibility before further dosing is conducted. Such adverse events may include non-serious unusual events. If dosing is stopped, review of the data by the investigators and medical monitor in conjunction with the sponsor and the DSMB must occur before dosing can be resumed. Dosing will only be resumed with DSMB approval.

Pharmacokinetic and anti-drug antibody test results will not be required for dose escalation unless it is determined advisable by the sponsor in conjunction with the investigators and medical monitor based on emergent data from the study. CSF and serum samples will be analyzed for each cohort immediately after all subjects have been dosed. The sponsor may direct earlier analysis of a partially completed cohort if completion of the cohort is delayed or partial cohort data is desired to aid in interpretation of any emergent clinical data.

If the investigators and medical monitor in conjunction with the sponsor determine that the dose is well tolerated in the completed dose group, dosing will proceed to the next dose level.

7.3.3.2. Stopping Rules/Study Interruption/Discontinuation Notice (Part 2)

The investigators and medical monitor in conjunction with the sponsor may elect to stop dosing or stop the study based on any treatment emergent concerns. Dosing will be stopped due to the occurrence of any individual adverse events which, in the judgment of the investigators and medical monitor in conjunction with the sponsor, need further characterization with respect to progression and reversibility before further dosing is conducted. Such adverse events may include non-serious unusual events. If dosing is stopped, review of the data by the sponsor in conjunction with the investigators and medical monitor in conjunction with the sponsor and the Data and Safety Monitoring Board (see below regarding DSMB composition and charter) must occur before dosing can be resumed. Dosing will only be resumed with DSMB approval.

7.3.4. Data and Safety Monitoring Board

In order to ensure the utmost safety of subjects, the sponsor will also use a Data and Safety Monitoring Board (DSMB). Each time the DSMB is engaged, a recommendation to proceed from the DSMB will be required in order for the study to continue (i.e. to resume if stopped or ongoing study will be stopped if DSMB does not recommend proceeding). The DSMB will review the safety and tolerability data from Part 1 before recommending starting Part 2 and during Part 2 after the first subject has completed 3 months of dosing and approximately every 3 months thereafter while dosing continues in the study (allowing for potential scheduling logistics). In addition to the pre-determined DSMB data review meetings, the DSMB may be engaged at any time at the request of an investigator, the sponsor, or medical monitor, or if stopping rules are triggered. A charter will be written to describe the DSMB's objectives, its membership, schedule for data reviews, and general responsibilities in respect to the study. All DSMB decisions will be documented in writing, and where required, submitted to the institutional review board (IRB) for their review or information.

7.4. Criteria for Study Termination

If the dosing is stopped during the study due to safety and tolerability concerns, a recommendation from the DSMB that it is safe to resume dosing will be required in order to continue dosing.

All decisions will be documented in writing, and where required, submitted to the institutional review board/independent ethics committee (IRB/IEC) for their review or information.

8. STUDY ENTRY CRITERIA

8.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Men or women between the ages of 18 and 65 years, inclusive
2. Traumatic spinal cord injury that occurred ≥ 1 year ago
3. Cervical spinal cord injury with serious neurological deficit as evidenced by 1) bilateral ISNCSCI UEMS between 4 and 36 points inclusive, and 2) bilateral GRASSP prehension ability score between 4 and 17 points inclusive
4. Confirmation by MRI of the following:
    a. Chronic SCI (persistent spinal cord lesion)
    b. For AIS grade of A without sensory or motor zone of partial preservation extending at least two levels caudal to the level of injury, no apparent transection of the cord
    c. CSF space spanning the lesion
5. Read, understood, and provided written informed consent after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.

8.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Penetrating injury to the cord or spinal cord trauma caused by ballistic injury including gunshot that did not penetrate the spinal cord
2. Women who are pregnant or lactating, and women of childbearing potential except those using adequate birth control measures. All female subjects must have a negative serum pregnancy test at Screening and women of childbearing potential must have a negative urine pregnancy at the Randomization/Pre-Dose Visit on Study Day 1. All subjects (male and female) as well as non-study female partners of male subjects, must use adequate birth control measures during the course of the study and for at least 10 weeks after the subjects' last dose of investigational product
    - Adequate or effective contraception is defined as double barrier contraception (eg, condom plus spermicide in combination with a female condom, diaphragm, cervical cap, contraceptive sponge, implants, injectables, combined oral contraceptives, sexual abstinence (total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable), or sexual intercourse with only a vasectomized partner. Subjects and/or partners who are surgically sterile or women with confirmed postmenopausal status are exempt from this requirement.
3. Contraindications for lumbar puncture
4. History of stroke, cerebrovascular injury, or elevated intracranial pressure

5. Requiring mechanical ventilatory assistance of any type
6. Body mass index (BMI) ≥ 35 kg/m^2 or body weight <50 kg
7. Botulinum toxin injection, with the exception of bladder treatments, within 4 months prior to study
8. History of life threatening allergic or immune-mediated reaction to vaccines, or biologic drugs, at any time or any life threatening allergic or immune-mediated reaction within the past 12 months.
9. Systemic use of immunosuppressants within the past 2 months with the exception of mineralocorticoids
10. Significant deformities, contractures (with less than 50% of normal range of motion at affected joints), or any issues that limit completion of UEMS with the ISNCSCI exam
11. Recent changes in anti-spasmodic or anti-spasticity medications. Anti-spasmodic or anti-spasticity medication is permitted providing that the subject has been on a stable dose for at least 12 weeks before the Screening Visit (Visit 1) and agrees to remain on a stable dose throughout the course of the study
12. Any orthopedic injury, recent surgeries, or current diagnosis of any primary diseases affecting upper limb function outside of SCI (eg, infection, tumor, congenital malformations, Huntington's disease, Parkinson's disease)
13. Subjects fitted with an implanted pump or port for delivery of therapeutics to the CSF
14. Presence of a self-reported uncontrolled medical condition including but not limited to cardiovascular disease, sleep apnea, obstructive lung disease, severe neuropathic or severe chronic pain, severe autonomic dysreflexia
15. Participation in any other investigational drug or device trial within 30 days or within 5 half-lives of the investigational drug or any past participation in a SCI cellular therapy trial
16. Regular use of the following concomitant medications that might confound efficacy and/or safety assessments is prohibited, including, but not limited to, the following:
    a. Antipsychotic drugs **with the exception of use** of these mood stabilizers for the adjunctive treatment of depression at least 12 weeks prior to Screening and the dose is not anticipated to change during participation in the trial.
    b. Anticoagulants, however, daily low dose aspirin (81 mg) therapy is permitted.
    c. Opiates, sedative hypnotics, or tranquilizers **unless used to treat anxiety, pain, or sleep disorder** and the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.
    d. Tumor necrosis factor (TNF) inhibitors
    e. Use of Class 1 antiarrhythmic.

17. Use of antidepressants (SSRI, SNRI, TCA, buspirone) is PERMITTED but limited to subject being on a stable dose for at least 12 weeks
18. History of severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with trial participation or investigational product administration or could interfere with the interpretation of trial results and including but not limited to the following:
    - human immunodeficiency virus (HIV) infection
    - active chronic hepatitis B or hepatitis C infection including hepatitis B surface antigen and hepatitis C antigen positive subjects with or without abnormal liver enzymes
    - immunosuppressive disease
    - chronic renal disease/failure as evidenced by estimated glomerular filtration rate (eGFR) of <60
    - concurrent neurodegenerative disease
    - cardiovascular: uncontrolled hypertension, unstable angina, myocardial infarction or symptomatic congestive heart failure within the past 12 months or serious uncontrolled and clinically significant cardiac arrhythmia as determined by the investigator
    - dementia or significantly altered mental status including brain injury with ongoing cognitive signs and symptoms that would prohibit the understanding or rendering of informed consent and compliance with the requirements of the protocol
19. Evidence or self-report of alcohol or drug abuse within the previous 12 months
20. Any conditions that in the judgement of the investigator would make the subject inappropriate for entry into the trial

Note: GFR will be estimated using the Cockcroft-Gault equation [Cockcroft and Gault 1976].

9. WITHDRAWAL OF SUBJECTS

9.1. Subject Withdrawal Criteria

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. The reason for a subject discontinuing from the study will be recorded in the source documents and electronic case report form (eCRF). A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. A subject will be considered lost-to-follow-up after 3 failed attempts to contact subject are made. Efforts should be documented on the subject's record. In any circumstance, every effort should be made to document subject outcome, if possible. The Site Principal Investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted earlier. A discontinuation must be reported immediately to the sponsor if it is due to a serious adverse event. The final evaluation required by the protocol will be performed (as per the early termination assessments). The Site Principal Investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

If the dropout rate is such that the power of the study could be compromised, or that the study objectives cannot reliably be achieved, the sponsor may elect to replace those subjects who discontinue prematurely.

10. TREATMENT OF SUBJECTS

Part 1 is a single-dose treatment for each subject. Subjects will have an approximate 84-day screening period, a 3-day in-clinic treatment period, and a follow-up through 28 days post-dose. Thus, study participation for each subject in Part 1 is expected to be approximately 16 weeks in duration.

Part 2 includes a repeat dose injection regimen. Subjects will have an approximate 84-day screening period, a 104-day treatment period (with injections given approximately every 21 days through Day 104) and then post treatment follow-ups at Study Days 137, 169, and 253. Thus, study participation for each subject in Part 2 is expected to be up to approximately 337 days in duration.

10.1. Description of Study Drug & Placebo

Investigational product will be packaged in single use identical vials containing 5 mL. Each vial contains placebo or 50 mg of AXER-204. Vials will be packaged appropriately for shipment.

Study drug and placebo will be distributed to the clinical site from a designated distribution center. The sponsor will provide the investigator with adequate quantities of study drug, placebo, and supplies to dose each subject. Specific details regarding study drug, placebo, dose preparation, and accountability will be described in a pharmacy manual at the clinic.

Table 9: Study Drug and Placebo (Study RNX-AX204-101)

	Study Drug & Placebo	
Product Name:	Placebo (Part 2 and used in preparing low doses in Part 1)	AXER-204
Route of Administration	Intrathecal injection	Intrathecal injection
Physical Description	Colorless solution	Colorless solution, may contain white or translucent particles *
Manufacturer	[redacted]	[redacted]

* AXER-204 drug product may contain inherent proteinaceous particles. These are removed by filtration during dose preparation. Studies have been completed confirming the potency, purity, and safety of AXER-204 after filtration.

10.2. Concomitant Medications

All concomitant medications, whether prescription, over-the-counter, herbal treatments, or other therapy, taken or used by the patient within 28 days of screening through end of study assessments will be recorded in the subject's medical record and in the Concomitant Medications eCRF.

Regular use of medications which, in the assessment of the Principal Investigator, may confound efficacy and/or safety assessments is prohibited. Such medications may include but are not limited to:

- Anticoagulants
- antipsychotic drugs
- marijuana
- opiates
- sedative hypnotics
- tranquilizers.

Daily low dose aspirin (81 mg) therapy is permitted.

Antipsychotic drugs used as mood stabilizers for the adjunctive treatment of depression as well as antidepressants (SSRI, SNRI, TCA, buspirone) are permitted provided the subject is on a stable dose for at least 12 weeks prior to Screening and the dose is not anticipated to change during participation in the trial.

Marijuana /THC-CBD preparations, opiates, sedative hypnotics, or tranquilizers are permitted only if the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. As needed (PRN) use of nonsteroidal anti-inflammatories and acetaminophen is permitted.

Prospective subjects who at the time of screening are taking medications that the Principal Investigator judges may confound efficacy and/or safety assessments (listed in Exclusion Criteria, Section 8.2) must stop them, after signing Informed Consent and receiving instructions on the discontinuation of these medications, two weeks or five half-lives –whichever is longer- prior to investigational product administration. The prospective subject must be willing to discontinue treatment and the Investigator must deem this feasible. The prospective subject taking prohibited medication at the time of screening will be considered eligible at the time of investigational product administration (Visit 2, Study Day 1) provided no reintroduction of the prohibited medication is being considered, the appropriate time window since last administration has elapsed, and the subject continues to meet other eligibility criteria. Subjects must remain off prohibited medications until all assessments are completed in the study. Determination of exclusion due to use of a specific medication from these classes of prohibited medications will be made by the Principal Investigator in conjunction with the Medical Monitor based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.

Concomitant medications will be coded using the World Health Organization (WHO Drug) Dictionary.

10.3. Treatment Compliance

Treatment compliance with investigational product during the treatment periods is expected to be high, as subjects will be dosed directly in the clinic under well-controlled conditions. The date, start and stop time of investigational product administration, dose and quantity of investigational

product administered will be recorded on the source documents and eCRF. Non-compliance with other aspects of the study protocol (eg, use of prohibited medications, missed study visits) will be documented on the subject's source document and on the eCRF.

10.4. Randomization and Blinding

10.4.1. Part 1

Part 1 does not include placebo, is open-label, and there is no randomization. Subjects will be enrolled and treated sequentially, with at least 3 days (72 hours) between dosing of consecutive patients. This wait-period will allow for a review of safety data collected during the in-clinic treatment phase prior to each new subjects' dosing.

10.4.2. Part 2

Central randomization will be implemented in the study. At the pre-dose visit (Visit 2) Study Day 1, eligible subjects will be randomly assigned in a 1:1 ratio to one of two treatment groups based on a randomization schedule prepared prior to study start by a statistician. To enroll the patient on Study Day 1, the investigator or designee will enter the subject identification number that was assigned at Screening Visit on the enrollment page in the electronic data capture (EDC) system. The EDC will assign a unique treatment code, which will be linked to the appropriate treatment group as assigned by the randomization schema.

Eligible subjects will be randomized to either AXER-204 or to placebo. The randomization will be stratified based on pre-treatment AIS grade (AIS A,B vs. AIS C,D) and prior receipt of study drug in Part 1 (Received AXER-204 in Part 1 vs. Did not receive AXER-204 in Part 1).

The blind will be maintained for all blinded study personnel (including investigators and subjects) through the completion of Day 169 of Part 2, and thus only designated Sponsor staff, members of the DSMB, and other designated unblinded personnel will have access to unblinded information prior to database lock for the Day 169 analysis. At each study site, an unblinded pharmacist will prepare prefilled syringes for dose administration in order to maintain the blind for study personnel administering the investigational product and performing all other study procedures. After completion of Day 169, designated sponsor staff and external consultants/contractors required to perform the analysis will be unblinded to the treatment allocations in order to complete data analysis though Day 169. The blind will be maintained for site investigators and subjects through completion of Day 253 unless the blind must be broken sooner for safety or regulatory reasons.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. A formal unblinding process will be used to ensure security and maintenance of the blind. However, the investigator should contact the sponsor before breaking the blind. When the blind has been broken for a subject, the reason must be fully documented and entered on the source document and eCRF for that subject.

Data that may potentially unblind the treatment assignment (eg, PK samples) will be handled such that the integrity of the blind is maintained and the potential for bias minimized. This may include making special provisions such as segregating the data in question from view by the investigator and site study staff, sponsor clinical team, and others as appropriate.

The bioanalytical laboratory personnel will be open to the randomization codes in order to facilitate PK analytical work and ADA testing. Personnel are not to communicate or imply in any manner, information associated with this to others at the clinical site, the sponsor, its consultants, designated CRO, or other vendors.

A formal analysis of the data will be performed once all subjects have completed their treatment period and follow-up assessments through Day 169. This efficacy analysis will be performed as the primary assessment of efficacy in the study; the study will continue through the follow-up period to Study Day 253. A second efficacy analysis will be conducted at Study Day 253.

11. STUDY PROCEDURES

11.1. Part 1

Each investigator will be assigned a unique site code. This site code will be concatenated with the screening number to assure that each subject will be uniquely identified in the clinical database. Site numbering will begin with 01 preceded by the number 1, and screening numbers will begin with 001. As subjects are screened, the next subject qualified chronologically at a site will be assigned the next number in ascending numerical order. Thus, the subject identification number for the first subject enrolled in Cohort 1 at the first site activated will be 101-001. The first subject enrolled in Cohort 1 at the second site activated will be 102-001 and so on.

Subjects will participate in the study for a total duration of up to 16 weeks. Visits will be scheduled at:

- Screening Visit 1 (Study Days -84 to -1)
- In-Clinic Treatment Visit 2 (Study Days 1 through 4)
- Post Treatment Follow-up
  - Phone calls on Study Days 5, 6, and 7
  - Visits 3 and 5 (Study Days 8 and 29/early termination [ET])
  - Visit 4 (Study Day 15)
  - Refer to the Schedule of Events (Table 5) for all the procedures and assessments to be performed during Part 1. The following sections provide important details of the procedures to be completed for each period.

11.1.1. Screening Period, Visit 1 (Study Days -84 through -1)

Subjects will sign an ICF before any screening-related procedures are performed. The Screening Visit (Visit 1) should occur between Study Days -84 to -1 and screening procedures completed during this time period.

Subjects will also be presented with a separate biobank ICF for review. If a subject agrees, samples of his/her CSF, blood, MRI scans and data collected in the study, will be stored for future research. A subject does not have to agree or sign the biobank ICF in order to be eligible participate in the main study.

Once the subject has consented to participate in the study (including having blood samples drawn and CSF and serum collection for PK assessment), the subject should be registered in the EDC system and a 6-digit subject identification number assigned by the designated study site personnel. This number will be used to identify each subject throughout the study and will be entered on all study-related documentation and subject medical chart.

- Note: At either Screening (Visit 1) or Pre-Dose (Visit 2), if a subject is a screen failure, not eligible to receive study drug, or if the subject withdraws or is discontinued from the study, his/her subject identification number cannot be reissued or assigned to another subject.

The inclusion and exclusion criteria should be carefully assessed. The subject's demographics, medical and surgical history, and prior and concomitant medications will be recorded.

Each subject will undergo a full physical examination including height and weight. The physical examination may be performed by the investigator, a sub-investigator who is a medical doctor, or a qualified nurse practitioner or physician's assistant in accordance with the site's current practice and in accordance with local requirements as applicable.

Blood samples will be obtained for biochemistry, hematology laboratory tests, and viral serology. A urine sample for urinalysis will be collected.

A serum pregnancy test will be obtained on all female subjects.

Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene). Subjects using marijuana /THC-CBD preparations, opiates, sedative hypnotics, or tranquilizers may be permitted to participate in the trial provided the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.

Vital signs (blood pressure, pulse rate, respiratory rate or pulse oximetry, and oral body temperature) will be obtained after the subject has been in a sitting (or recumbent) position for 5 minutes. A 12-lead ECG will be taken in triplicate, 5 minutes apart, after the patient has been in a supine (resting) position for at least 5 minutes.

Subjects will have several scales administered by a clinician who is trained to administer these. Where possible, the order for evaluating these scales should be followed as defined in Section 11.2. These include the full ISNCSCI scale, SCIM III self-care and mobility scale, GRASSP, Modified Ashworth Scale, and autonomic evaluations as per ISAFSCI. Subjects will also be administered several questionnaires at this visit, including:

- BPI (Appendix 9)
- SF-36 v2 (Appendix 6)
- Neuro-QOL (Appendix 7).

A magnetic resonance imaging scan will be obtained as described (Appendix 12). The MRI must be completed and results known and made available to the principal investigator prior to the subject's admittance to the clinic on Visit 2 (Pre-Dose). Results from the MRI will be read by a sponsor-arranged expert.

Subjects who fail to meet any entry criterion that can be assessed at that time are considered to be screen failures and are not required to return for additional visits (although a subject can be seen at any time for safety reasons). Subjects who are screen failed due to lab values can be re-screened as determined by the principal investigator in consultation with the study medical monitor. Subjects who rescreen will be assigned a new screening number.

Serious AEs will be recorded and monitored starting at the time of subject signing the ICF.

Upon completion of the Screening Visit (Visit 1), subjects will be given an appointment reminder card that contains the date and time for their next visit.

See the schedule of events (Table 5) for details on the assessments on each Study Day.

11.1.2. In-Clinic Treatment, Visit 2 (Study Days 1 to 4 [Pre-Dose and Post-Dose])

Eligible subjects will be admitted to the clinical site on the evening prior to or morning of the scheduled dosing depending on site's requirements. If during this visit and prior to dosing a subject is determined to no longer be eligible to continue in the study, the appropriate Screening eCRFs will be completed and the subject deemed a Screen Failure and will not be required to return for additional visits (although a subject can be seen at any time for safety reasons.)

All inclusion and exclusion criteria, medical and surgical history, and prior medications will be reviewed for a second time to confirm eligibility. New SAEs and concomitant medications reported by the subject since the Screening Visit (Visit 1) will be recorded on the eCRF. A urine pregnancy test will be performed on all women of childbearing potential.

Results obtained during the Screening Visit (Visit 1) including the results of the MRI scan must be reviewed by the investigator prior to subject treatment with study drug to ensure subject remains eligible for the study.

Vital signs (blood pressure, pulse rate, respiratory rate or pulse oximetry, and oral body temperature) will be obtained after the patient has been in a sitting position for 5 minutes. 12-lead pre- and post-dose ECG will be taken in triplicate, 5 minutes apart, after the patient has been in a supine (resting) position for at least 5 minutes. An abbreviated physical exam should be performed.

If the subject remains eligible for study participation, the EDC will be accessed to enroll the subject, visit information will be entered, and the required eCRFs completed. The research pharmacist will be contacted regarding the subject's enrollment and for specifics about the timing of the scheduled lumbar puncture as well as preparation and availability of study drug necessary for the intrathecal administration of AXER-204.

During the lumbar puncture, an amount of CSF approximately equivalent to the amount of study drug to be injected into the intrathecal space (~9-20 mL) will be obtained pre-dose for CSF/PK assessment, spinal cord injury biobanking, and potentially biomarker analysis. For the 20 mL maximum dose, at least 15 mL of CSF should be collected immediately prior to administration. If at least 15 mL cannot be collected, the principal investigator may elect to discontinue the subject from the trial or to ask the subject to return on the following day for a second attempt after additional hydration. In this situation, the subject may be directed to remain at a nearby overnight accommodation or home (if within a reasonable distance) and report the next morning for examination or to remain in the hospital overnight. Note that, under these circumstances, there is no requirement for an overnight hospital stay; if a decision is made to keep the patient overnight for convenience (e.g. travel issues), this hospitalization should not initiate a serious adverse event report (e.g. local alternate accommodations not readily available). Study Drug AXER-204 will be administered via slow bolus infusion intrathecal administration. Details including dose and quantity administered, physician administering the study drug, and date and time of administration will be recorded on the eCRF and in the subject's record. Post lumbar puncture and post-dose subjects are to be monitored for any adverse events.

If a lumbar puncture fails to return CSF after two attempts, it is recommended that fluoroscopy be scheduled to assist in achieving successful LP. Likewise, it is recommended that the lumbar puncture procedure be suspended if the CSF sample is bloody or turbid. Decisions regarding the lumbar puncture procedure are at the discretion of the site principal investigator.

The subject is to be confined to the clinic on Study Days 2, and 3, and discharged on Study Day 4 after all required assessments have been completed. See the schedule of events (Table 5) for details on the assessments on each Study Day.

Prior to discharge from the clinical unit on Study Day 4, subjects will be given an appointment reminder card that contains the date and time of their next visit.

11.1.3. Post-Treatment Follow-up Phone Calls, Study Days 5, 6, and 7

Subjects do not have to visit the clinic for Post-treatment follow-up on Days 5, 6, and 7 unless necessary to follow-up on adverse events. Subjects will receive a telephone call from study site personnel inquiring as to their general health. Any reported adverse events experienced by a subject will be documented in the subject's records and on the eCRF. Subjects will also be reminded about their next visit to the study site.

11.1.4. Post Treatment Follow-up Visits 3 & 4 (Study Days 8 and 15)

At Visit 3, Study Day 8, subjects' vital signs (BP, pulse, respiratory rate or pulse oximetry, and oral body temperature) will be obtained. Subjects will undergo a lumbar puncture and will have CSF collected for PK assessments. Blood samples will be collected and serum samples for PK assessments and presence of ADA will be obtained. Information on changes or newly administered concomitant medications as well as any new or ongoing AEs will be collected.

Subjects will be given instructions to return to the study site for the next visit and provided an appointment reminder card.

During Visit 4, Study Day 15, blood samples will be collected for clinical laboratory testing and serum samples obtained for PK analysis. Information on changes to ongoing and any new concomitant medication as well as any new or ongoing AEs will be recorded on the eCRF and in the patient's record.

At the completion of the visit, subjects will be given an appointment reminder card that contains the date and time of their next visit to the study site.

11.1.5. Post Treatment Follow-up Visit 5 (Study Day 29/ET)

Visit 5 (Study Day 29/ET) is to be conducted on subjects who will be completing the study as well as those who terminate early or are withdrawn from the study.

At this visit, a full physical exam will be performed. The subject will be weighed and weight recorded on the eCRF. Vital signs (BP, pulse, respiratory rate or pulse oximetry, and oral body temperature) will be obtained. A urine pregnancy test will be obtained on all females of childbearing potential.

Subjects will undergo lumbar puncture for CSF collection for PK assessments. Blood sampling for laboratory testing including viral serology will also be obtained. Serum for PK and the presence of ADA will be analyzed. Urine sample will be obtained for urinalysis.

Information on changes or newly administered concomitant medications as well as any new or ongoing AEs will be recorded on the eCRF.

All scales should, if possible, be administered by the same clinician who administered the scales during the Screening period. These shall be completed in the order as noted in 11.2 and include the full ISNCSCI scale, SCIM III self-care and mobility scale, GRASSP, Modified Ashworth Scale, and autonomic evaluations as per ISAFSCI. Subjects will also be administered several questionnaires at this visit, including:

- BPI (Appendix 9)
- SF-36 v2 (Appendix 6)
- Neuro-QOL (Appendix 7)

Subjects' completion or termination from the study (in the case of subjects who terminate early from the study or who are withdrawn) will be recorded on the eCRF and in the subjects' record.

11.2. Part 2

Each investigator will be assigned a unique site code. This site code will be concatenated with the screening number to assure that each subject will be uniquely identified in the clinical database. Site numbering will begin with 01 preceded by the number 2, and screening numbers will begin with 001. As subjects are screened, the next subject qualified chronologically at a site will be assigned the next number in ascending numerical order. Thus, the subject identification number for the first subject screened at the first site will be 201-001. The first subject enrolled at the second site will be 202-001 and so on.

Subjects will participate in the study for a total duration of up to approximately 337 days. Visits will be scheduled at Screening Visit 1 (Study Days -84 to -1), Treatment Phase with Visit 2 occurring on Study Day 1 and subsequent dosing visits occurring approximately every 21 days encompassing Visits 3-7 (Study Days 21 through 104). There will be telephone calls to assess status regarding any adverse events on Study Day 8 and Study Day 137. Post-treatment follow-up visits will occur at Visits 8 and 9 (Study Days 169 and 253).

Refer to the Schedule of Events (Table 6) for all the procedures and assessments performed during the study. The following sections provide important details of the procedures. Where possible, the order that the key measures are to be performed is as follows.

- ISNCSCI
- Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP) Note: GRASSP prehension ability and prehension performance testing will be video recorded.
- Modified Ashworth Scale, fingers and thumb excluded
- SCIM III Self-Care & Mobility subscores
- Brief Pain Inventory
- Neuro-QOL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)
- SF-36 v2

- CUE-Q
- PGIC – Chronic SCI
- International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI)

11.2.1. Screening Period, Visit 1 (Study Days -84 through -1)

Subjects will sign an ICF before any screening-related procedures are performed. The Screening Visit (Visit 1) should occur between Study Days -84 to -1.

Subjects will also be presented with a separate biobank ICF for review. If a subject agrees, samples of his/her CSF, blood, MRI scans and data collected in the study, will be stored for future research. A subject does not have to agree or sign the biobank ICF in order to be eligible participate in this main study.

Once the subject has consented to participate in the study (including PK and CSF sampling) and has signed the ICF, the subject should be registered in the EDC system and a 6-digit subject identification number will be assigned. This number will be used to identify each subject throughout the study and will be entered on all documentation for a subject and into the EDC.

- Note: At any time during Visit 1 or Visit 2, if a subject is not eligible to receive investigational product, or if the subject withdraws or is discontinued from the study, their subject identification number cannot be reissued or assigned to another subject.

The inclusion and exclusion criteria should be carefully assessed. The subject's demographics, medical and disease history, and prior and concomitant medications will be recorded.

Each subject will undergo a full physical examination including height and weight. The physical examination may be performed by the investigator, a sub-investigator who is a medical doctor, or a qualified nurse practitioner or physician's assistant in accordance with the site's current practice and in accordance with local requirements as applicable.

Blood samples will be obtained for biochemistry, hematology laboratory tests, and viral serology. A urine sample for urinalysis will be collected. A serum pregnancy test will be obtained on all female subjects. (Section 8). Note: The screening laboratory assessments must be completed within 28 days of enrollment.

Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene). Subjects using marijuana /THC-CBD preparations, opiates, sedative hypnotics, or tranquilizers may be permitted to participate in the trial provided the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated.

Vital signs (blood pressure, pulse rate, pulse oximetry, and oral body temperature) will be obtained after the patient has been in a sitting position for 5 minutes. A 12-lead pre-dose ECG

will be taken in triplicate, 5 minutes apart, after the patient has been in a supine (resting) position for at least 5 minutes.

Subjects will be assessed by ISNCSCI and GRASSP and their UEMS and GRASSP prehension ability scores will be used to assess eligibility.

An MRI scan will be scheduled and must be completed and results known and made available to the Principal Investigator prior to the subject check in to the clinic on Visit 2 (Pre-Dose). Results from the MRI scan will be run locally and findings read by sponsor arranged expert.

Subjects who fail to meet any entry criterion that can be assessed at that time are considered to be screen failures and are not required to return for additional visits (although a subject can be seen at any time for safety reasons). Subjects may be re-screened as determined by the Principal Investigator in consultation with the Study Medical Monitor.

Serious AEs will be recorded and monitored starting at the time of subject signing the ICF.

Upon completion of the Screening Visit (Visit 1), subjects will be given an appointment reminder card that contains the date and time for their next visit.

11.2.2. Treatment Phase, Visits 2 through 7 (Study Days 1 through 104)

At Visit 2, Study Day 1, eligible subjects will visit the clinical site to undergo the scheduled lumbar puncture. Subject will be randomized in the EDC at this visit.

If prior to randomization during this visit a subject is determined to no longer be eligible to continue in the study, the appropriate Screening eCRFs will be completed and the subject deemed a Screen Failure.

All inclusion and exclusion criteria, medical and surgical history, and prior medications will be reviewed for a second time. New SAEs and concomitant medications reported by the subject since the Screening Visit (Visit 1) will be recorded on the eCRF. A urine pregnancy test will be performed on all women of childbearing potential.

Results obtained during the Screening Visit (Visit 1) including the results of the MRI scan must be reviewed by the investigator prior to subject treatment with investigational product to ensure subject remains eligible for the study. Subjects who do not continue to be eligible to participate in the study are screen failures and are not required to return for additional visits (although a subject can be seen at any time for safety reasons).

At Visit 2, Study Day 1 the following baseline assessments will be performed in the following order prior to dosing:

- ISNCSCI
- Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP). Note: GRASSP prehension ability and prehension performance testing will be video recorded.
- Modified Ashworth Scale, fingers and thumb excluded
- SCIM III Self-Care & Mobility subscores
- Brief Pain Inventory

- Neuro-QOL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)
- SF-36 v2 Health Survey
- CUE-Q
- PGIC – Chronic SCI
- International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI)

Note: Baseline ISNCSCI UEMS and GRASSP prehension ability scores may fall outside of the lower and upper bounds of the inclusion criteria for these measures by up to 3 points without impacting eligibility (i.e. bilateral UEMS must be 1-39 and bilateral GRASSP prehension ability may be 1-20 at baseline). Subjects with scores at baseline (Visit 2, Study Day 1) that fall outside of the UEMS and GRASSP prehension ability inclusion criteria by more than 3 points will not be eligible to continue in the study.

Vitals will be taken pre-dose, post dose, then every 2 hours until subject leaves the unit. Vital signs (blood pressure, pulse rate, respiratory rate or pulse oximetry, and oral body temperature) will be obtained after the patient has been in a sitting position for 5 minutes. A 12-lead pre-dose ECG will be taken in triplicate, 5 minutes apart, after the patient has been in a supine (resting) position for at least 5 minutes. The ECG will be read locally. An abbreviated physical exam will be performed.

The randomization page in the EDC will be accessed to randomize the subject, visit information will be entered, and the required eCRFs completed. The research pharmacist will be contacted regarding the subject's randomization and for specifics about the timing of the scheduled lumbar puncture and preparation and availability of study drug or placebo necessary for the intrathecal administration of investigational product.

Serum will be collected for PK and ADA analysis as detailed in Section 13.2.

If a lumbar puncture fails to return CSF after two attempts, it is recommended that fluoroscopy be scheduled to assist in achieving successful LP. Likewise, it is recommended that the lumbar puncture procedure be suspended if the CSF sample is bloody or turbid. Decisions regarding the lumbar puncture procedure are at the discretion of the site principal investigator. Additionally, investigators may make an assessment based on a given patient that all LPs will be conducted under fluoroscopy.

During the lumbar puncture, an amount of CSF approximately equivalent to the amount of investigational product to be injected into the intrathecal space (~9-20 mL) will be obtained pre-dose for CSF/PK assessment, spinal cord injury biobanking, and potentially biomarker analysis. For the 20 mL maximum dose, at least 15 mL of CSF should be collected immediately prior to administration. If at least 15 mL cannot be collected, the principal investigator may elect to skip dosing for the visit or to ask the subject to return on the following day for a second attempt after additional hydration. In this situation, the subject may be directed to remain at a nearby overnight accommodation or home (if within a reasonable distance) and report the next morning for examination or to remain in the hospital overnight. Note that, under these circumstances, there is no requirement for an overnight hospital stay; if a decision is made to keep the patient overnight for convenience (e.g. travel issues), this hospitalization should not initiate a serious

adverse event report (e.g. local alternate accommodations not readily available). Investigational product will be administered via slow bolus infusion intrathecal administration. Details including dose and quantity administered, physician administering the investigational product, and date and time of administration will be recorded on the eCRF and in the subject's record. Post lumbar puncture and post-dose subjects are to be monitored for any adverse events.

The Site Principal Investigator may discontinue a subject from the study due to unsuccessful collection of CSF to allow for isovolumetric dose administration if the subject has not received any doses and they consider it unlikely that further dosing attempts will be successful. Subjects who received at least one dose of investigational product should complete the remaining visits to monitor for safety and efficacy as per the schedule of events. Under this circumstance, further per-protocol LP attempts should not be made. Conducting all LPs under fluoroscopy should be considered if difficulties in obtaining adequate CSF collection is encountered.

For dosing visits that include neurological exams and questionnaires (e.g. ISNCSCI, GRASSP, SCIM III self-care and mobility), these assessments should be performed prior to dosing. Depending on scheduling considerations, subjects may be asked to return the following day for dose administration. Under this circumstance, nearby overnight accommodations will be arranged for the subject upon request.

Following dosing, patients will remain under the observation of study personnel in the hospital setting (eg, may include infusion center, PACU, recovery suite, observation unit, short stay center) for 4 hours for safety monitoring. Thereafter, if deemed clinically stable by the Investigator, patients may leave the hospital setting. If further safety observation is directed by the investigator, the subject may be directed to remain at a nearby overnight accommodation or home (if within a reasonable distance) and report the next morning for examination or to remain in the hospital overnight. Note that, under these circumstances, there is no requirement for an overnight hospital stay; if a decision is made to keep the patient overnight for convenience (e.g. travel issues), this hospitalization should not initiate a serious adverse event report (e.g. local alternate accommodations not readily available). Upon completion of the visit, subjects will be given an appointment reminder card that contains the date and time of the follow-up telephone call and for their next visit.

A telephone call to assess status regarding any adverse events will be conducted on Study Day 8.

At Study Visits 3 through 7 (Study Days 21 through 104), subjects will receive either AXER-204 or placebo via slow bolus infusion intrathecal administration.

At Study Visits 3 through 7, (Study Days 21 through 104), 12-Lead ECGs, abbreviated physical examinations vitals will be obtained. Vitals will be taken pre-dose, post dose, then every 2 hours until subject leaves the unit. Serum collection for PK will be obtained pre-dose and 4 hours post-dose, CSF will be collected pre-dose (as part of the dosing procedure), urine pregnancy tests will be administered on all women of childbearing potential. Changes to concomitant medication will be assessed and recorded as well as adverse events and serious adverse events.

At Visit 3 (Study Day 21) the following efficacy assessments will be performed prior to dosing:

- ISNCSCI

At Visits 5 and 7 (Study Days 63 and 104), the following efficacy assessments will be performed prior to dosing in the order listed:

- ISNCSCI
- GRASSP. Note: GRASSP prehension ability and prehension performance testing will be video recorded.
- SCIM III self-care and mobility subscores

Upon completion of the visit, subjects will be given an appointment reminder card that contains the date and time when they will receive a telephone call and the date and time of their next visit.

11.2.3. Follow-up on Study Day 137

Study Day 137 will consist of a telephone Study personnel will conduct telephone call to assess status regarding any adverse events. Depending on the results, the subject may be asked to come to the clinic for evaluation.

11.2.4. Follow-up Visits 8 and 9 (Study Days 169 and 253)

At Visits 8 and 9 (Study Days 169 and 253), 12-Lead ECGs, physical examinations (abbreviated at Visit 8; full exam at Visit 9, with height/weight), vitals will be performed. Serum samples will be collected for PK and ADA analysis as detailed in Section 13.2. Blood will be collected for laboratory testing and viral serology, and urine collected for urinalysis. Urine pregnancy tests will be conducted for women of childbearing potential. Changes to concomitant medication will be assessed and recorded as well as AEs and SAEs. CSF will be collected at Visit 9 (Study Day 253).

In Study Visits 8 and 9, subjects will have all efficacy and QoL assessments performed (see the Schedule of Events for specifics, Table 6), in the following order:

- ISNCSCI
- GRASSP. Note: GRASSP prehension ability and prehension performance testing will be video recorded.
- Modified Ashworth Scale, fingers and thumb excluded
- SCIM III Self-Care & Mobility subscores
- Brief Pain Inventory
- Neuro-QOL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)
- SF-36 v2 Health Survey
- CUE-Q
- PGIC – Chronic SCI
- International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI)

GRASSP prehension ability and prehension performance testing will be video recorded.

12. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

Investigational product will be provided to the clinical sites.

12.1. Study Drug

Single-use vials with labels and an outer fiberboard carton with a single panel label will have the following information:

- LEI - hNgR(310)-Fc Drug Product
- Concentration: 10 mg/mL
- Volume: 5 mL
- Storage: ≤ - 65° C
- Caution: Filter Before Use - New Drug-Limited by United States Law to Investigation Use Only
- Manufactured by [redacted]

The clinical trial supply label will be in accordance with ICH GCP and local requirements for investigational product labelling.

12.2. Investigational Product Packaging and Labeling

Investigational products are for investigational use only and the products supplied for this study are intended for use only within the context of this study. The investigational product supplied for this study should be stored in a secure, temperature controlled, locked place with restricted access, maintained under adequate security until dispensed for subject use or returned to the sponsor.

For all shipments of study drug, site study personnel shall note a 6-month use limit date based on the date of thaw of the vials. A label will be supplied to record the thaw date and storage use limit date on the box containing the vials. Placebo expiry shall be defined in a memo included with the shipment and will be extended as warranted via memo when new stability data becomes available. A label will be supplied to record the expiry date on the box containing the vials. The label shall be updated if the expiry is extended before the placebo in the box is fully depleted.

12.3. Investigational Product Storage

AXER-204 is formulated as an isotonic solution in Phosphate Buffered Saline and is provided in 5 mL vials. It will be shipped to sites frozen at -80 °C (on dry ice). Upon receipt it shall be placed in the refrigerator at 2-8 °C in a secure location and allowed to thaw for a minimum of 16 hours prior to use in dose preparation. Once thawed, AXER-204 shall be kept stored in the refrigerator at 2-8 °C for up to 6 months prior to use. After thawing, the vials containing AXER-204 should NOT be shaken or vigorously agitated as this may result in generation of foam and particles. Contact the sponsor for instructions in the event there is a deviation from the required storage conditions.

Placebo consists of Phosphate Buffered Saline and is provided in 5 mL vials. It will be shipped to sites at a temperature of 2-8 °C. Upon receipt it shall be placed in the refrigerator at 2-8 °C.

12.4. Investigational Product Preparation

Refer to the dose preparation appendix in the Pharmacy Manual describing the details regarding dose preparation.

12.5. Investigational Product Management

The pharmacist or their designee will verify that investigational product supplies are received intact and in the correct amounts by signing and dating the investigational product receipt section at the bottom of the packing list. The person receiving the supplies must verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable investigational product in a given shipment will be documented in the study files. The pharmacist must notify the sponsor or designee of any damaged or unusable investigational product supplied to the site.

The site will maintain a Study Drug and Placebo Inventory Log (includes, but not limited to, the following: lot number, number of units received, expiry date, and number of vials and syringes dispensed. The site will also maintain patient-specific investigational product dispensing logs.

An overall accountability of investigational product will be performed and verified throughout the study and at the site closeout visit. Upon completion of the study, copies of the investigational product accountability records will be returned to the sponsor. All used and unused study investigational product supplies will be inventoried and accounted, and any used or unused supplies which have not been destroyed locally shall be returned to the sponsor or designee at the end of the study. By signing the Investigator Agreement page of this protocol, the investigator agrees not to supply investigational product to any person(s) not enrolled in the study.

12.6. Investigational Product Accountability

Subjects will be treated at the clinical site, in-patient clinical unit, or other approved location and therefore the Pharmacist or other investigational staff via documentation of receipt of the investigational product and dosing/treatment given will perform/maintain accountability.

12.7. Investigational Product Handling and Disposal

Records of receipt, dispensing records and inventory forms, as applicable, will be examined and reconciled during and at the end of the study. Both the investigational product that is used during the study, as well as any remaining unused investigational product, must be accounted for on study drug and placebo accountability records provided to the PI by the sponsor or their designee or documented per site SOPs.

At the end of the study or when instructed by the sponsor or designee, all used and unused investigational product vials, accompanied by a packing slip, must be returned to the designated clinical supplies vendor for disposal or destroyed per site SOPs. If used investigational product vials and/or unused but expired investigational product vials were destroyed locally per site policies or procedures, destruction should be documented on the accountability log.

In addition, a copy of all completed investigational product accountability records must be retained in the Investigators' Study Files, with a copy sent to the sponsor or their designee.

The product is to be stored in a safe place (locked facility) at the appropriate temperature.

13. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

13.1. Efficacy

Site personnel will be trained and certified to perform the efficacy assessments. The same raters will be used for evaluation of a given subject insofar as possible. Raters will be blinded to treatment for Part 2 of the trial.

13.1.1. Part 1

Part 1 is focused on safety, tolerability, and pharmacokinetics. However, a subset of efficacy assessments are included, as follows:

- ISNCSCI. ISNCSCI is a comprehensive clinician-administered neurological exam for SCI. It is widely used for research and clinical (neurologic) description to fully assess sensory and motor functioning and level of injury in traumatic SCI. The UEMS will be calculated from the full ISNCSCI and evaluated separately.
- GRASSP [Kalsi-Ryan 2012a, Kalsi-Ryan 2012b]. GRASSP is a clinician administered test with three subset scores that assesses strength in 10 key muscles in the upper extremity as well as dexterity and fine motor skills.
- SCIM III self-care and mobility scores [Catz 2007, Itzkovich 2007]. SCIM III measures functional outcomes in three sections: self-care, respiration and sphincter management, and mobility. The current study will employ the self-care and mobility subscores.

13.1.2. Part 2

The primary objective of Part 2 is to evaluate the safety, tolerability, and pharmacokinetics of repeat dosing. In addition, a number of efficacy assessments are included as secondary endpoints. The key secondary efficacy endpoint for Part 2 will be within-subject change from pre-treatment baseline and slope for UEMS as compared to placebo. The UEMS is collected as part of the ISNCSCI (Appendix 3).

Additional secondary efficacy endpoints will include changes from pre-treatment baseline and slope for:

- Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP) prehension performance scores. GRASSP is a clinician administered test with three subset scores that assesses strength in 10 key muscles in the upper extremity as well as dexterity and fine motor skills (Appendix 4).
- Version III of the Spinal Cord Independence Measure (SCIM III) self-care. SCIM III measures functional outcomes in three sections: self-care, respiration and sphincter management, and mobility. The current study will employ the self-care and mobility subscores. The evaluation will be administered by a clinician (Appendix 8).

Exploratory functional endpoints will include within-subject changes from pre-treatment baseline and slope for:

- ISNCSCI lower extremity motor and sensory scores

- GRASSP strength, sensation and prehension ability scores
- SCIM III mobility scores
- Patient Reported Outcomes
  - CUE-Questionnaire (CUE-Q) [Marino 2012, Marino 2015]. Assesses subject-reported upper limb function (Appendix 2).
  - SF-36 v2 - Provides an investigator-evaluated Quality of Life (QoL) assessment for subjects. SF-36 will provide data on the subjects' perceived health and well-being over the course of the study (Appendix 6).
  - Neuro-QOL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL) - (Appendix 7).
  - PGIC – Chronic SCI (Appendix 10) – Provides a patient-reported global impression of change in the symptoms, activity limitations, emotions and overall quality of life with chronic spinal cord injury since beginning the trial.
- ISAFSCI [Krassioukov 2012]. The ISAFSCI will be used to document autonomic control of the heart, blood pressure, sweating and temperature regulation. Lower urinary tract function, bowel function, and sexual function will be scored (Appendix 1).

Exploratory biomarkers of target engagement and axonal growth may be assessed.

Since the mechanism of action entails enhanced axonal growth and plasticity, changes attained through Study Day 169 are anticipated to be most relevant to assessing on-target effects of therapy.

13.2. Pharmacokinetics

Both serum and cerebrospinal fluid samples will be collected for analysis, as shown in Table 10 and Table 11.

In Part 1, a window relative to the nominal timepoint is allowed for sample collection as follows:

- Blood serum pharmacokinetic samples will be collected at 0 hour (immediately pre-dose), and 1 h (±10 min), 6 h (±10 min), 12 h (±10 min), and 24 h (±10 min) post-dose, as well as at Study Day 4 (72h ± 10 min), 8 (±1d), 15 (±3d), and 29 (±4d).
- Cerebrospinal fluid samples (CSF) will be collected via lumbar puncture at 0 hour (immediately pre-dose), 24 h (±2h) Study Day 4 (72 h ±4h), and Study Days 8 (±1d), and 29 (±4d).

The timing for serum and CSF sample collection may be adjusted for subsequent cohorts based on pharmacokinetic data from the preceding cohorts. Serum PK samples collected at pre-dose and on Study Days 8 and 29 will be analyzed for the presence of anti-drug antibodies (ADA).

In Part 2 , Visits 3-7 (Study Days 21, 42, 63, 84, 104) will have a window of ±5 days and Visits 8 and 9 (Study Days 169 and 253) will have a window of ±7 days. CSF samples will be collected for PK analysis pre-dose on Study Days 1, 21, 42, 63, 84, and 104. The CSF sample collected on Study Day 253 will also be analyzed for PK. Serum samples will be collected for

PK analysis pre-dose and 4 h post-dose on Study Days 1, 21, 42, 63, 84, and 104. Serum will also be collected for PK analysis on Study Days 169 and 253. Pre-dose serum will be collected for ADA analysis on Study Days 1, 21, 42, 63, 84, and 104. Serum will also be collected for ADA analysis on Study Days 169 and 253. A subset of the CSF samples may also be analyzed for ADAs depending on development and presence of ADAs in the serum. Part 2 serum and CSF from subjects receiving placebo will be collected but will not be analyzed for PK and ADAs.

In Part 2 on Study Days 1, 21, 42, 63, 84, and 104 a window relative to the nominal timepoint is allowed for sample collection as follows:

- Serum pharmacokinetic samples will be collected at 0 hour (within 4 h pre-dose), and 4 h (±10 min) post-dose
- Cerebrospinal fluid samples (CSF) will be collected via lumbar puncture at 0 hour (immediately pre-dose)

Table 10: Part 1 Pharmacokinetic Sampling Schedule (Study RNX-AX204-101)

	Day 1 (Dosing day)	**Day 2 (24 hours post-dose)**	**Day 4 (72 hours post-dose)**	**Day 8**	**Day 15**	**Day 29**
Cerebrospinal Fluid	Pre-Dose	X	X	X		X
Serum	Pre-Dose, and post-dose at Hours 1, 6, 12	X	X	X	X	X
Serum aliquot for ADA testing	X (Pre-dose)			X		X

Table 11: Part 2 Pharmacokinetic Sampling Schedule (Study RNX-AX204-101)

Study Phase	**Treatment Phase Window at Visits 3-7 ± 5 days**						**Follow-Up ± 7 days**	
Study Day Month	**1**	**21**	**42**	**63**	**84**	**104**	**169 Month 6**	**253/ET Month 9**
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Cerebrospinal Fluid	X	X	X	X	X	X		X
Serum	X	X	X	X	X	X	X	X
Serum aliquot for ADA testing	X	X	X	X	X	X	X	X

Abbreviations: M = month, ET = Early Termination.

13.2.1. Serum

Serum samples will be prepared for shipment according to the detailed procedure supplied. For research subjects that provided consent, the required quantity will be removed and processed into aliquots for inclusion in the spinal cord injury biobank. Study personnel are required to verify that a subject provided the required separate biobank informed consent permitting sample inclusion in the biobank before a portion of the serum is removed and processed for this purpose.

13.2.2. Cerebrospinal Fluid

Cerebrospinal fluid samples will be prepared for shipment according to the detailed procedure supplied. For research subjects that provided consent, from 9 to 20 mL will be removed and processed into aliquots for inclusion in the spinal cord injury biobank. Study personnel are required to verify that a subject provided the required biobank separate informed consent permitting sample inclusion in the biobank before a portion of the serum is removed and processed for this purpose.

13.2.3. Shipment of Pharmacokinetic Samples

Serum and CSF samples will be packed on dry ice and shipped to the designated lab for processing at pre-determined intervals. Specific instructions will be given to the site personnel.

14. ASSESSMENT OF SAFETY

The Schedule of Events for Part 1 given in Table 5, and for Part 2 in Table 6 provide the timing for assessments starting with the Screening Visits.

14.1. Safety Parameters

Safety will be evaluated similarly for both Parts, through the collection of data from:

- Physical examinations
- Vital signs
- 12-lead electrocardiograms
- Laboratory parameters (hematology, blood chemistry, and urinalysis)
- Treatment-emergent adverse events (TEAEs).
  - TEAEs will be defined as any AE occurring during or after the injection of investigational product.
  - TEAEs will be limited to those events occurring within 28 days after the last visit.

Condition-specific safety outcomes will include:

- ISNCSCI, GRASSP and all of the neurological measures evaluated for efficacy
- Spasticity (Modified Ashworth Scale) [Pandyan 1999]. A clinician administered examination for spasticity which measures muscle tone changes. A score of 0-4 is assigned to each muscle group evaluated (Appendix 5). Notes: Testing will exclude fingers and thumb. Scores are to be recorded for left and right sides for each muscle group tested.
- Pain (BPI) [Cleeland 1994]. A self-administered questionnaire used to assess the severity of a subject's pain and the impact of this pain on the subject's daily functioning.

14.1.1. Demographic/Medical History

Demographic information and medical history will be collected at Screening for determination of eligibility.

14.1.2. Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate or pulse oximetry, and oral body temperature, will be measured after the patient has been in a sitting/recumbent position for 5 minutes.

Height and weight will be captured as per the Schedule of Events. BMI will be derived.

14.1.3. Physical Examination

Physical examinations will be conducted and abnormalities will be described. At certain visits, as indicated in the Schedule of Events, only symptom-driven examinations (abbreviated physical examinations) will be performed.

Clinically significant changes, in the judgment of the investigator, in physical examination findings (abnormalities) will be recorded as adverse events.

14.1.4. Electrocardiogram (ECG)

A 12-lead ECG will be obtained on all subjects. The electrocardiogram will precede other evaluations in the sequence of operations at each timepoint as scheduled.

The screening ECG will be evaluated by a physician for the presence of abnormalities. Subjects with clinically significant abnormalities may not enter the study. The timing of these evaluations may be adjusted and additional evaluation times may be added, if indicated.

The 12-lead ECGs will be taken in triplicate. To minimize variability, patients should be in a supine (resting) position for at least 5 minutes prior to each ECG recording, 5 minutes between each ECG. If findings from the ECG performed at the Screening Visit (Visit 1) are clinically significant and would potentially prevent the subject from safely participating in the study (taking into account the patient's overall status, as well as the medication profile), the patient should not be enrolled (or randomized) and should be withdrawn from the study.

Triplicate ECGs will be performed twice during the Treatment/In-Clinic Visit (Visit 2) just prior to the lumbar puncture and within 60 minutes following administration of investigational product (and, for Part 2, at each subsequent dosing time point). Clinically significant abnormalities noted after investigational product administration are to be recorded as AEs. All ECGs will be read locally by appropriately trained staff.

14.1.5. Laboratory Assessments

The results of all laboratory tests required by the protocol will be recorded in the subject's eCRF. All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the Site Principal Investigator and the sponsor, or until a diagnosis that explains them is made. Abnormal laboratory test results that result in a change in study drug dosage or in discontinuation of the drug, or require intervention or diagnostic evaluation to assess the risk to the patient/subject, should be recorded as adverse events in the case report form. Investigators should review the CTCAE toxicity criteria that can be found at the following URL: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

All laboratory assessments will be collected as per the schedule of events (Table 5, Table 6).

The clinical laboratory tests analyzed in this study are provided in Table 12. The INRPTT, urine pregnancy testing and in-clinic safety laboratory tests requiring stat analysis will be processed locally. In addition, laboratory samples taken during Study Days 1-4 will be processed locally. All other laboratory tests will be analyzed by a central laboratory, [redacted]. All CSF, blood, and urine samples will be collected and sent to the central laboratory on the day of

collection unless otherwise instructed. INR/PTT is required prior to the Day 1 lumbar puncture procedure with repeat INR/PTT tests on subsequent Study Days only if directed by the Principal Investigator. Clinical laboratory results will be reviewed by the study investigator when results are known prior to enrollment/randomization, and results available for each collection during the study including prior to discharge from the in-patient clinic in Part 1 of the study. During the course of the study, abnormal laboratory values should be repeated and subjects interviewed for evidence of clinical signs and symptoms consistent with the laboratory abnormality. Subjects with abnormal laboratories at screening can be rescreened (ie, lab repeated) for inclusion into the study within the 28-day screening window specified for labs. A Laboratory Manual will be provided separately for processing and shipping procedures.

Table 12: Laboratory Parameters to be Assessed (Study RNX-AX204-101)

Hematology	**Serum Chemistry**	
Hemoglobin	Glucose	Albumin
Hematocrit	Blood urea nitrogen	
Platelet count (or estimate)	Creatinine	Creatine kinase
White blood cell count including differential (absolute values only)	Total bilirubin	Calcium
	Alkaline phosphatase	Total Cholesterol
	Alanine transaminase (ALT)	
Red blood cell (RBC) count	Aspartate transaminase (AST)	Direct bilirubin
Mean corpuscular volume (MCV) RBC morphology MCH MCHC RDW	Sodium	Total protein
	Phosphorous	Triglycerides
Urinalysis	Potassium	Uric acid
pH	Chloride	
Specific gravity	Bicarbonate	
Blood	Lactate dehydrogenase	
Glucose		
Protein	**Coagulation**	
Ketones	Prothrombin time (PT)	
Urine Bilirubin	Activated partial thromboplastin time (PTT)	
	International normalized ratio (INR)	
CSF Analysis		
Cell counts	**Pregnancy tests**	
Total protein	Serum pregnancy	
Glucose	Urine pregnancy	

Table 13: Moderate and Marked Liver Function Abnormality Thresholds (Study RNX-AX204-101)

	AST/ALT	**Alkaline Phosphatase**	**Total Bilirubin**

Moderate	≥1.5 x ULN	≥1.2 x ULN	≥1.5 x ULN
Marked	≥3 x ULN	≥3 x ULN	≥2 x ULN
ULN is defined as the upper limit of normal if the pretreatment Baseline was normal, or the pretreatment baseline if it was abnormal.			

Moderate abnormal liver function tests should be repeated within 1 to 2 days. If they are confirmed, they should be repeated at intervals determined in consultation with the sponsor and medical monitor until they resolve.

Subjects with an AST/ALT elevation between >3x and 5x ULN must have this test repeated upon receipt of this value and the sponsor notified. If repeat analysis cannot be performed within 24 hours or if an AST/ALT value >3x ULN is confirmed, the subject must discontinue treatment immediately and the sponsor must be notified. The abnormal tests should be repeated within 48 hours of receipt of this value and then at 3 to 7-day interval until they resolve. In consultation with the sponsor, additional evaluation of the subject may be arranged. The additional evaluation may include GI consultation and additional laboratory tests (eg, HBV, HAV, and CMV serology, CPK, reticulocyte count).

14.1.5.1. Other Laboratory Tests

A serum pregnancy test will be performed at scheduled time points (see the Schedules of Events) on all women in both Parts 1 and 2. Serum tests are required at the Screening Visit (Visit 1) for Part 1 and Part 2. Urine pregnancy tests are required at the Dose Visits for Part 1 and Part 2 for women of childbearing potential and for Visits 8 and 9 for Part 2.

14.1.5.2. Virus Serology

Infectious disease testing will include: HIV-1/HIV-2 antibody, hepatitis B surface antigen, hepatitis C antibody.

14.1.5.3. Drug Screen

A urine sample for drug screening will minimally include amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene.

14.2. Adverse and Serious Adverse Events

14.2.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- clinically significant symptoms and signs
- abnormal test findings
- changes in physical examination findings
- hypersensitivity
- progression/worsening of underlying disease

Additionally, AEs may include the signs or symptoms resulting from:

- drug overdose
- drug misuse
- drug interactions
- exposure in utero

Diagnostic and therapeutic non-invasive and invasive procedures should not be reported as AEs. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

14.2.2. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- test result is associated with accompanying symptoms, and/or
- test result requires additional diagnostic testing or medical/surgical intervention, and/or
- test result leads to a discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

14.2.3. Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) for this study include possible allergic/immune reactions to administration of a protein therapeutic, AEs generally associated with lumbar puncture, and theoretical AEs arising from axon growth. No AESI have been identified from non-clinical toxicology studies with AXER-204. The following are considered AEs of Special Interest for this study:

- Immune/Allergic reactions: fever, rash, arthralgia, myalgia, hematuria, proteinuria, serositis, central nervous system complications, and hemolytic anemia. Injection site reactions may occur
- Events relating to the lumbar puncture procedure: infection, postdural puncture headache, bleeding, brainstem herniation, meningitis, back pain, excessive CSF leakage requiring blood patch
- Complicating infections: discitis and vertebral osteomyelitis
- Neurological symptoms or injuries: low back pain, radicular injury, abducens palsy
- Other: late onset of epidermoid tumors of the thecal sac, increased pain, increased spasticity

14.2.4. Serious Adverse Event (SAE)

An SAE or serious adverse drug reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization, except overnight hospital stays as outlined in Section 11.2.2 Treatment Phase, Visits 2 through 7 (Study Days 1 through 104) whereby a decision is made to keep the patient overnight for convenience (e.g. travel issues, local alternate accommodations not readily available).
- results in persistent or significant disability/incapacity, or
- results in congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

14.2.4.1. Hospitalization

Adverse events associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). Exception: overnight hospital stays as outlined in Section 11.2.2 Treatment Phase, Visits 2 through 7 (Study Days 1 through 104) whereby a decision is made to keep the patient overnight for convenience (e.g. travel issues, local alternate accommodations not readily available).

Hospitalization does not include the following:

- rehabilitation facilities
- hospice facilities
- respite care (eg, caregiver relief)
- skilled nursing facilities
- nursing homes
- routine emergency room admissions
- same day surgeries (as out-subject/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality)
- social admission (eg, subject has no place to sleep)
- administrative admission (eg, for yearly physical exam)
- protocol-specified admission during a study (eg, for a procedure required by the study protocol)
- optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery)
- preplanned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

14.2.5. Adverse Event Reporting

The investigator is to record all directly observed AEs and all AEs spontaneously reported by the subject in the source documents and eCRFs.

All observed or volunteered AEs regardless of treatment arm or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. For AEs with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the sponsor concurs with that assessment.

In order to ascertain if headaches are secondary to the lumbar puncture per se, the clinical characteristics of the headache, including positional exacerbations will be assessed and reported. For Part 1, adverse events should be recorded and monitored from the time of first dose through subject completion of the study up to 28 days post-dose, or until the investigator deems the AE as resolved or stable (unchanging). Serious AEs should be recorded and monitored from the time of signing of the informed consent form (ICF) through subject completion of the study up to 28 days after completion of the study, or until investigator deems the SAE as resolved or stable (unchanging).

For Part 2, adverse events should be recorded and monitored from the time of first dose up to 28 days after completion of the study (28 days after Month 9 visit or ET), or until the investigator deems the AE as resolved or stable (unchanging). Serious AEs should be recorded and monitored from the time of signing of the informed consent form (ICF) through subject completion of the study (28 days after Month 9 visit or ET), or until investigator deems the SAE as resolved or stable (unchanging).

14.2.5.1. Severity Assessment

The investigator will use the Common Terminology Criteria for Adverse Events (CTCAE) to determine the toxicity grade of AEs, found at the following URL: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

14.2.5.2. Causality Assessment

For all collected AEs, the investigator will determine each AE's causality based on temporal relationship and his/her clinical judgement. For each AE, relatedness will be assessed with respect to 1) investigational product and 2) the LP procedure. The degree of certainty about causality will be graded using the categories below and the investigator must record the causal relationship on the eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

Table 14: Relatedness Definitions (Study RNX-AX204-101)

Definitely related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study product intake and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study product (dechallenge) should be clinically plausible.
Probably related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after intake of the study product, is unlikely to be attributed to concurrent disease or other drugs or chemicals and follows a clinically reasonable response on withdrawal (dechallenge).
Possibly related	There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after intake of the study product). However, other factors may have contributed to the event (eg, the subject's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
Unlikely to be related	A clinical event, including an abnormal laboratory test result, whose temporal relationship to study product makes a causal relationship improbable (eg, the event did not occur within a reasonable time after intake of the study product) and in which other drugs, or chemicals, or underlying diseases provide

	plausible explanations (eg, the subject's clinical condition, other concomitant treatments).
Not Related	The AE is completely independent of study product intake, and/or evidence exists that the event is definitely related to another etiology.

14.2.5.3. Exposure *in Utero*

An exposure in-utero occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after being directly exposed to the investigational product (maternal exposure).
2. A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any subject becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the sponsor on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to the sponsor's product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to the investigational product by contact or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify the sponsor of the outcome. The investigator will provide this information as a follow-up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An Exposure in Utero report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a SAE case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting SAEs.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information regarding the exposure in utero may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the

investigator must obtain permission from the subject's partner in order to conduct any follow-up or collect any information.

14.2.5.4. Reporting Requirements

14.2.5.4.1. Serious Adverse Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

If an SAE occurs, the sponsor is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, notification to the sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of Exposure in Utero cases (Section 14.2.5.3).

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

To report the SAE, complete the SAE form electronically in the eCRF for the study. When the form is completed, [redacted] will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible for you to access the internet, fax a paper copy to [redacted]. As soon as internet service has been restored, send an email to [redacted] at [redacted]. [redacted] Safety personnel are available for SAE reporting on a 24-hour basis. Incoming reports are reviewed during normal business hours."

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE page of the eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

14.2.5.5. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the Adverse Event page(s) of the eCRF. It should be noted that the form for collection of SAE information is not the same as the Adverse Event eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. Adverse events should be reported using concise medical terminology on the eCRFs as well as on the form for collection of SAE information.

A non-serious AESI will be promptly entered in the eCRF and reported on expedited basis (within 24 hours) to the sponsor (or designee) to facilitate real-time review of patterns of toxicity. Investigators are to report AESIs in accordance with the SAE reporting process noted in

Section 14.2.5.4.1 within 24 hours of becoming aware of all AEs of Special Interest. All AESIs must be promptly assessed by the Medical Monitor within 24 hours of receipt.

14.2.5.6. Sponsor Reporting Requirements to Regulatory Authorities

Adverse events reporting, including serious unexpected serious adverse reactions (SUSAR), will be carried out in accordance with applicable local regulations.

15. STATISTICS

15.1. Sample Size

The Part 1 sample size was derived empirically from experience with previous single ascending dose clinical studies in other disorders and is deemed appropriate to achieve the study objectives.

The Part 2 sample size was selected to ensure adequate power for detecting treatment-related change in bilateral UEMS (Score from 0 to 50).

A 5-point difference, between the treated and placebo groups, in the change from baseline to 6 months in bilateral UEMS is considered clinically meaningful. Analysis of historical data for cervical SCI patients for the period between ~6-12 months following acute SCI indicates a standard deviation of bilateral UEMS change over 6 months to be around 3 to 4 points.

With a sample size of 12 subjects per active and placebo group, Part 2 of the study has 80% power with Type I error of α=0.05 (two sided), assuming a 5-point difference as indicated above, and with a common standard deviation within each treatment group of approximately 4 in the change from baseline to 6 months in bilateral UEMS.

Accounting for uncertainties in the assumptions based upon historical data used to extrapolate for estimating the sample size in this study and the need for estimation of missing data a sample size of approximately 16 subjects per treatment arm (32 total) will be randomized.

15.2. Stages of Analysis

The analysis for this study will be performed in three stages, with the first analysis performed upon completion of the clinical portion of Part 1, the second analysis (including the core efficacy assessment) performed upon completion Day 169 of Part 2 (ie, after all subjects have completed through Study Day 169), and the final analysis performed upon completion of the post-treatment follow-up phase of Part 2 (Day 253). The methods applied to each analysis will be consistent with the objectives of the study.

The blind will be maintained for all blinded study personnel (including investigators and subjects) through the completion of Day 169 of Part 2. After completion of Day 169, designated sponsor staff and external consultants/contractors required to perform the analysis will be unblinded to the treatment allocations in order to complete data analysis though Day 169. The blind will be maintained for site investigators and subjects through completion of Day 253 unless the blind must be broken sooner for safety or regulatory reasons.

15.3. General Methods

Data will be tabulated using both descriptive and inferential statistics where specified.

- For Part 1, data will be tabulated by dosing cohort as well as pooled (all subjects combined), and no inferential statistics are planned.
- For Part 2, data will be tabulated for each treatment group separately (placebo and AXER-204) to allow for visual inspection of outcomes between the arms. Inferential comparison of the treatment groups is planned.

For both Parts, all data collected will be included in by-domain data listings, sorted by subject number and time point, or as appropriate.

No hypothesis testing will be performed for demographics, background, or safety data.

Continuous data will be summarized by presenting the number of subjects (n), means, mean changes from baseline, mean % changes from baseline (where appropriate), standard deviations, minimum, First quartile (Q1), median, third quartile (Q3), and maximum values. The number of subjects with missing data will be indicated.

Categorical data will be summarized by presenting the number of subjects (n), the number of subjects with missing data as well as counts and percentages in each of the categories. Percentages will be based upon the number of subjects with available data.

When inferential testing is applied to all efficacy assessments, dichotomous/binary categorical efficacy endpoints will be assessed via a 2-sided Fisher's Exact test or Chi-square test as appropriate. Continuous efficacy endpoints will also present least-squares means and p-values from hypothesis testing of efficacy endpoints using mixed-effects model for repeated measures (MMRM).

Additional details will be included in the statistical analysis plan (SAP) which will be finalized prior to unblinding Part 2 of the study and any amendments to it made prior to locking the database and unblinding the study.

15.4. Handling of Missing Data

Every attempt will be made to collect all protocol required data at each time point.

Imputations will only be performed for efficacy data and for missing or partial dates, missing severity or relationship to investigational product. Missing AE or CM dates and missing severity or relationship to investigational product will always use a conservative approach. Details will be included in the SAP.

For subjects who discontinue treatment (for any reason), subjects will continue to be followed and key efficacy endpoints and safety data collected where possible.

The primary analyses for change in bilateral UEMS will use a mixed model repeated measures which automatically accounts for the missing data based upon the covariate structure assumed. To evaluate robustness of results, sensitivity analyses will be performed with imputation methods for missing data.

15.5. Subgroups

The sample size precludes analysis by-subgroup. However, exploratory assessment of any trends among subgroups (eg, by pre-treatment AIS grade) may be performed, after initial review if the data warrant.

15.6. Analysis Populations

Safety Population: Safety outcomes will be assessed for all subjects who are given at least one dose of investigational product.

Full Analysis Set (FAS) Population: Efficacy outcomes will be evaluated using the FAS, defined as all subjects randomized, treated with at least 1 dose of investigational product, and with at least one post-baseline assessment of efficacy.

Per Protocol Population: The per protocol population will be a subset of FAS and include subjects who received at least 80% of study drug and have no major protocol deviations that would impact efficacy assessment.

15.7. Alpha Level Considerations

All inferential testing will be performed using two-sided 5% Type I error (α), and therefore 2-sided p-values ≤ 0.05 will be considered statistically significant in this study.

The first hypothesis test will be the key secondary efficacy endpoint of change in bilateral UEMS from baseline to Study Day 169 using the MMRM model as detailed below. Additional secondary efficacy endpoints tested will be the change in GRASSP prehension performance from baseline to Study Day 169 and of change in SCIM self-care from baseline to Study Day 169.

15.8. Subject Disposition and Exposure

The numbers of subjects randomized (Part 2 only), completing or withdrawing, along with reasons for withdrawal, will be summarized by dose (Part 1) and treatment group (Part 2). Tabulation of the number of doses of investigational product, duration of treatment as well as total dose given will be provided.

15.9. Demographics and Baseline Characteristics Analyses

Demographic variables (age, sex, race, and ethnicity) as well as height (cm), weight (kg), Body Mass Index (BMI), temperature, heart rate, blood pressure and respiratory rate or pulse oximetry (from the vital signs) at baseline will be summarized using descriptive statistics. All demographic data will be provided in a data listing.

15.10. Efficacy Endpoints

For Part 1 efficacy, outcomes will be presented by each dosing cohort, with no inferential assessments among cohorts planned. Thus, for Part 1, efficacy will be presented only descriptively.

For Part 2, changes from pre-treatment to each on-treatment time point will be calculated, with the primary time point at Day 169. Shifts over time in ordinal endpoints will be presented, with comparisons between treatment groups assessed using a CMH row mean scores statistic at each time point. Slope of change will also be evaluated. Part 2 efficacy analysis is described in the following sections.

15.10.1. Part 2 Efficacy Endpoints

Change in bilateral UEMS from baseline to Day 169 will be evaluated as a key secondary endpoint for the trial.

Baseline bilateral UEMS is defined as the last non-missing bilateral UEMS prior to first treatment in Part 2.

The null and alternative hypothesis for this study are as follows:

H_0: $\mu_A = \mu_P$

H_A: $\mu_A \neq \mu_P$

Where H_0 and H_A refer to the Null and alternative hypothesis to be tested in this study, μ_A and μ_P refers to the mean change in bilateral UEMS from baseline to Study Day 169 for subjects randomized to AXER-204 and Placebo groups respectively.

Analysis to compare the change in bilateral UEMS from baseline to each post baseline visit will be based upon a mixed-effects model for repeated measures (MMRM) for the double-blind period using the FAS population.

Additional secondary efficacy endpoints will include change from baseline to Day 169 in the total GRASSP prehension performance score and change from baseline to Day 169 in SCIM III self-care score. The analyses for these scores will be handled the same way as the key secondary endpoint.

Exploratory efficacy endpoints will include changes from baseline to each post baseline value in each of the following endpoints.

- Change from baseline to each post baseline value for bilateral UEMS, GRASSP prehension performance, and SCIM III self-care scores.
- Bilateral ISNCSCI sensory and lower extremity motor scores
- Bilateral GRASSP strength, sensation and prehension ability scores
- Patient Reported Outcomes
  - CUE-Questionnaire (CUE-Q)
  - PGIC – Chronic SCI
  - SF-36 v2 Health Survey
  - Neuro-QOL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)
- ISAFSCI. The ISAFSCI will be used to document autonomic control of the heart, blood pressure, sweating and temperature regulation. Lower urinary tract function, bowel function, and sexual function will be scored.

Responder analyses may be performed to compare the proportion of responders in each treatment group. Details of responder analyses with thresholds used to define clinically meaningful improvements will be defined in the SAP.

Sensitivity analyses of the secondary and exploratory endpoints may be performed if the outcomes warrant further analysis.

15.11. Safety Endpoints

The safety analysis will be descriptive in nature. All safety data will be listed, and data will be tabulated by dose (Part 1) and treatment group (Part 2) where the data warrant. Safety data include:

- AEs, including assessment of lumbar infusion site
  - Events occurring prior to the first dose of investigational product or placebo will be defined as pre-treatment events.

  - For Part 1, TEAEs will be defined as any AE occurring during or after the injection of study drug. This will therefore include all events occurring through Day 29/ET.
  - For Part 2, TEAEs will be limited to those events occurring within 28 days after the last visit.

Incidence of AEs will be summarized for each treatment group/cohort by MedDRA system organ class (SOC) and preferred term, sorted in descending frequency by SOC, and then by preferred term within SOC. These summaries will be given by treatment in separate tables for each of the following TEAE event sets:

- All events
- Treatment related events (defined by a relationship to study drug of possible, probable, or definite).
- Serious adverse events
- Events leading to premature discontinuation from study
- Events by maximum severity
- AEs of Special Interest, ie, events relating to the lumbar puncture procedure (eg, infection, headache, back pain, excessive CSF leakage requiring blood patch).

Other safety outcomes will include:

- Clinical laboratory tests, including hematology, chemistry, metabolic, and urinalysis. Changes over time will be presented. Potentially clinically significant (PCS) ranges will be defined and used to determine the incidence of subjects experiencing new-onset PCS laboratory values, where new-onset is defined as a PCS value for a subject following initiation of study treatment for which the subject did NOT have a PCS value for that analyte PRIOR to initiation of study treatment.
- Vital signs including: respiratory rate or pulse oximetry, heart rate, temperature, and blood pressure, as per the schedule of events. BMI will be assessed, with height collected only at screening.
- Physical examination
- 12-lead ECG. ECG parameters will be analyzed in a fashion similar to that of clinical laboratory parameters.

Condition-specific safety outcomes will include:

- ISNCSCI, GRASSP and all of the neurological measures evaluated for efficacy
- Spasticity (Modified Ashworth Scale). A clinician administered examination for spasticity which measures muscle tone. A score of 0-4 is assigned to each muscle group evaluated. Note: Testing will exclude fingers and thumb.
- Pain (BPI). A self-administered questionnaire used to assess the severity of a subject's pain and the impact of this pain on the subject's daily functioning.

Concomitant treatments will be assessed according to the timing of their start/stop dates as they relate to the study drug treatment, as follows:

- Prior. Medications with start AND stop date before date of first dose of study drug or placebo.
- Concomitant. Medications with subject exposure that includes at least one dose of study drug or placebo.
- New-onset medications. Concomitant medications with a start date AFTER the first dose of study drug or placebo. New-onset medications are a subset of the full set of concomitant medications.
- Post-treatment medications. Medications with a start date at least 28 days AFTER the last dose of study drug or placebo.

Changes from pre-treatment will be calculated in a similar fashion as for the efficacy endpoints, but no inferential statistics will be provided for safety endpoints. Shifts from baseline in ECG will be tabulated for heart rate and QTcF. Other endpoints will be assessed according to the scale of the variable.

15.12. Pharmacokinetic Endpoints

Concentration data in both blood serum and in cerebrospinal fluid will be assessed descriptively over time. Correlation with efficacy and safety outcomes may be performed, as the data warrant.

16. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, the sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and good clinical practices (GCPs) are being followed. The monitors will review source documents to confirm that the data recorded on eCRFs are accurate. The investigator and institution will allow the sponsor monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by IRB/IEC, and/or to quality assurance audits performed by the sponsor, or companies working with or on behalf of the sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

17. ETHICS

17.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICFs, and other relevant documents, eg, subject instructions, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator Site File. Copies of IRB/IEC approvals should be forwarded to the sponsor.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and the sponsor in writing immediately after the implementation.

17.2. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation (ICH) guideline on Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

17.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of subject personal data.

The ICF must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The ICF used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and the sponsor before use.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed ICF and a copy provided to each subject.

17.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, the sponsor should be informed immediately.

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

18. DATA HANDLING AND RECORDKEEPING

18.1. Case Report Forms

As used in this protocol, the term eCRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

An eCRF is required and should be completed for each included subject. The completed original eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of the sponsor or appropriate regulatory authorities, without written permission from the sponsor.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the eCRFs and any other data collection forms. The eCRFs must be signed by the investigator to attest that the data contained on the eCRFs is true. Any corrections to entries made on the eCRFs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the eCRFs must match the data in those charts.

In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at the sponsor and clearly identify those data that will be recorded on the eCRF, and for which the eCRF will stand as the source document.

18.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another investigator, another institution, or to the sponsor. The investigator must obtain the sponsor's written permission before disposing of any records, even if retention requirements have been met.

19. PUBLICATION POLICY

Publication of study results is discussed in the Clinical Study Agreement.

19.1. Publications by Investigators

All information concerning the product, as well as any matter concerning the operation of the sponsor or its delegate, such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by the sponsor or its delegate and are unpublished, are confidential and must remain the sole property of the sponsor or its delegate. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the sponsor or its delegate is obtained. The sponsor has full ownership of the eCRFs completed as part of the study.

All publications and presentations of the results of the Study are governed by the applicable provisions of the Clinical Trial Agreement between the sponsor (or its delegate) and the institution. By signing the study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the sponsor or its delegate. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The Investigator may not publish or present any information on this study without the express written approval of the sponsor or its delegate. Additionally, the sponsor or its delegate may, for any reason, withhold approval for publication or presentation. Such manuscript or materials should be provided for sponsor/delegate review only after the final database, is available.

20. LIST OF REFERENCES (ALPHABETICAL)

AXER-204 [Investigator's Brochure] Version #2.0. New Haven, CT: ReNetX Bio, Inc. 2020

Brinker T, Stopa E, Morrison J, Klinge P. A new look at cerebrospinal fluid circulation. *Fluids Barriers CNS*. 2014;11:10.

Cafferty WB, Duffy P, Huebner E, Strittmatter SM. MAG and OMgp synergize with Nogo-A to restrict axonal growth and neurological recovery after spinal cord trauma. *J Neurosci*. 2010;30(20):6825–6837.

Catz A, Itzkovich M, Tesio L, et al. A multicenter international study on the Spinal Cord Independence Measure, version III: Rasch psychometric validation. *Spinal Cord*. 2007;45(4):275–291.

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23(2):129–38.

Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16(1): 31-41.

Fawcett JW, Curt A, Steeves JD, et al. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord.* 2007;45(3):190–205.

Guidance for industry on estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research Web site. https://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf%23search=%27guidekines+for+industry+sfe+starting%27 Updated July 2005. Accessed Aug 10, 2018.

Harvey PA, Lee DHS, Qian F, Weinreb PH, Frank E. Blockade of Nogo receptor ligands promotes functional regeneration of sensory axons after dorsal root crush. *J Neurosci*. 2009;29(19):6285–6295.

Hladky SB, Barrand MA. Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence. *Fluids Barriers CNS*. 2014;11(1):26.

Itzkovich M, Gelernter I, Biering-Sorensen F, et al., The Spinal Cord Independence Measure (SCIM) version III: reliability and validity in a multi-center international study. *Disabil Rehabil*. 2007;29(24):1926–1933.

Ji B, Li M, Budel S, et al. Effect of combined treatment with methylprednisolone and soluble Nogo-66 receptor after rat spinal cord injury. *Eur J Neurosci*. 2005;22(3):587–594.

Kalsi-Ryan S, Beaton D, Curt A, et al. The Graded Redefined Assessment of Strength Sensibility and Prehension: reliability and validity. *J Neurotrauma.* 2012;29(5):905–1014.

Kalsi-Ryan S, Curt A, Verrier MC, Fehlings MG. Development of the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): reviewing measurement specific to the upper limb in tetraplegia. *J Neurosurg Spine*. 2012;17(1 Suppl):65–76.

Krassioukov A, Biering-Sørensen F, Donovan W, et al., International standards to document remaining autonomic function after spinal cord injury. *J Spinal Cord Med.* 2012;35(4):201–310.

Kroin JS. Intrathecal drug administration. Present use and future trends. *Clin Pharmacokinet*. 1992;22(5):319–326.

Kuttler A, Dimke T, Kern S, Helmlinger G, Stanski D, Finelli LA. Understanding pharmacokinetics using realistic computational models of fluid dynamics: biosimulation of drug distribution within the CSF space for intrathecal drugs. *J Pharmacokinet Pharmacodyn*. 2010;37(6):629–644.

Lee JK, Kim JE, Sivula M, Strittmatter SM. Nogo receptor antagonism promotes stroke recovery by enhancing axonal plasticity. *J Neurosci*. 2004;24(27):6209–6217.

Li S, Liu BP, Budel S, et al. Blockade of Nogo-66, myelin-associated glycoprotein, and oligodendrocyte myelin glycoprotein by soluble Nogo-66 receptor promotes axonal sprouting and recovery after spinal injury. *J Neurosci.* 2004;24(46):10511–10520.

Liu BP, Cafferty WBJ, Budel SO, Strittmatter SM. Extracellular regulators of axonal growth in the adult central nervous system. *Philos Trans R Soc Lond B Biol Sci*. 2006;361(1473):1593-1610.

Marino RJ, Kern SB, Leiby B, Schmidt-Read M, Mulcahey MJ. Reliability and validity of the capabilities of upper extremity test (CUE-T) in subjects with chronic spinal cord injury. *J Spinal Cord Med*. 2015;38(4):498–504.

Marino RJ, Patrick M, Albright W, et al., Development of an objective test of upper-limb function in tetraplegia: the capabilities of upper extremity test. *Am J Phys Med Rehabil*. 2012;91(6):478–486.

Masserman JH. Cerebrospinal hydrodynamics: IV. clinical experimental studies. *Arch Neur Psych*. 1934;32(3):523–553.

NSCISC Spinal Cord Injury, Facts and Figures at a Glance. National Spinal Cord Injury Statistical Center Web site. https://www.nscisc.uab.edu/Public/Facts%20and%20Figures%20-%202018.pdf Accessed Aug 10, 2018.

Ohtake Y, Li S. Molecular mechanisms of scar-sourced axon growth inhibitors. *Brain Res*. 2015:1619:22–35.

OMNIPAQUE™ (iohexol) Injection Drug Approval Package. US Department of Health and Human Services, Food and Drug Administration Web site. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018956s095,020608s031lbl.pdf. Updated July 1993. Accessed Aug 10, 2018.

Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil.* 1999;13(5):373–383.

Papisov MI, Belov VV, Gannon KS. Physiology of the intrathecal bolus: the leptomeningeal route for macromolecule and particle delivery to CNS. *Mol Pharm*. 2013;10(5):1522–1532.

https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html Updated 2018. Accessed Aug 10, 2018.

Rieselbach RE, Di Chiro G, Freireich EJ, Rall DP. Subarachnoid distribution of drugs after lumbar injection. *N Engl J Med*. 1962;267:1273–1278. PubMed PMID: 13973811

Rieselbach RE, Morse EE, Rall DP, Frei E 3rd, Freireich EJ. Treatment of Meningeal leukemia with intrathecal aminopterin. Cancer Chemother Rep. 1962 Feb;16:191-6. PubMed PMID: 14492194.

Rieselbach RE, Morse EE, Rall DP, Frei E 3rd, Freireich EJ. Intrathecal aminopterin therapy of meningeal leukemia. Arch Intern Med. 1963 May;111:620-30. PubMed PMID: 13973810.

Sakka L, Coll G, Chazal J. Anatomy and physiology of cerebrospinal fluid. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2011;128(6):309–316.

Schwab ME, Strittmatter SM. Nogo limits neural plasticity and recovery from injury. *Curr Opin Neurobiol.* 2014;27:53–60.

Sharma K, Selzer ME, Li S. Scar-mediated inhibition and CSPG receptors in the CNS. *Exp Neurol*. 2012;237(2):370–378.

SPINRAZA™ (nusinersen) injection, for intrathecal use. US Department of Health and Human Services, Food and Drug Administration Web site. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf, Updated 2016. Accessed Aug 10, 2018.

Thorne RG, Frey WH 2nd. Delivery of neurotrophic factors to the central nervous system: pharmacokinetic considerations. *Clin Pharmacokinet*. 2001;40(12):907–946.

Wang X, Baughman KW, Basso DM, Strittmatter SM. Delayed Nogo receptor therapy improves recovery from spinal cord contusion. *Ann Neurol*. 2006;60(5):540–549.

Wang X, Duffy P, McGee AW, et al., Recovery from chronic spinal cord contusion after Nogo receptor intervention. *Ann Neurol*. 2011;70(5):805–821.

Wang X, Yigitkanli K, Kim CY, et al. Human NgR-Fc decoy protein via lumbar intrathecal bolus administration enhances recovery from rat spinal cord contusion. *J Neurotrauma.* 2014;31(24):1955–1966.

Wang X, Zhou T, Maynard GD, et al. Nogo receptor decoy promotes recovery and corticospinal growth in non-human primate spinal cord injury. *Brain.* 2020 Jun 1;143(6):1697-1713.

21. INVESTIGATORS AGREEMENT

I have read the protocol, RNX-AX204-101 and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Printed Name of Investigator

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Signature of Investigator

_____

Medical Institution

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Date