Statistical Analysis Plan

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. ReNetX Safety Efficacy and Tolerability of AXER-204 for Chronic SCI

ReNetX Bio, Inc
PROTOCOL RNX-AX204-101
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Approvals

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

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Version History

Version #	Description of Changes	Version Date
V1.0	Initial	31Jan2020
V2.0	Updated Section 5 and 8.7 to include ADA analysis	09Jun2020
V3.0	Updated to include analysis for part 2 of the study	09Sep2021
V4.0	Updated to move random coefficients model as secondary efficacy analysis, to include intercurrent events strategy for primary and secondary efficacy endpoints, and Section 7.4 for handling of randomization error	08Mar2022
V5.0	Updated Section 10 for changes in the planned statistical analyses	05Aug2022

Glossary of Abbreviations

Abbreviation	Term
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AIS	American spinal injury association (ASIA) impairment scale
AR(1)	Autoregressive
ARH(1)	Autoregressive with heterogeneity
ASIA	American spinal injury association
ATC	Anatomical therapeutic chemical
BMI	Body mass index
bpm	Beats per minute
BP	Blood pressure
BPI	Brief pain inventory
CGIC	Clinical Global Impression of Change
CI	Confidence interval
CS	Compound symmetry
CSCI	Chronic spinal cord injury
CSF	Cerebrospinal fluid
CTCAE	Common terminology criteria for adverse events
CUE-Q	Capabilities of upper extremity questionnaire
CV	Coefficient of variation
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
FAS	Full analysis set population
FDA	Food and drug administration
GRASSP	Graded redefined assessment of strength sensation and prehension
HR	Heart rate
ICH	International Conference on Harmonization
ISAFSCI	International standards to document remaining autonomic function after spinal cord injury
ISNCSCI	International standards for neurological classification of SCI
LEMS	Lower extremity motor score
LS	Least squares
MAR	Missing at random
MAS	Modified Ashworth scale
MedDRA	Medical dictionary for regulatory activities
mITT	Modified Intent to Treat
MMRM	Mixed-effects model for repeated measures
MNAR	Missing not at random
msec	Millisecond
MTD	Maximum tolerated dose
NCA	Non-compartmental approach
Neuro-QOL	Quality of life in neurological disorders

Abbreviation	Term
NLI	Neurological level of injury
PA	Prehension ability
PCS	Potentially clinically significant
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PP	Prehension performance
PPS	Per Protocol Set
PT	Preferred term
QoL	Quality of life
QTcF	QT interval using Fridericia correction formula
ROM	Range of motion
SAE	Serious Adverse Event
SCI	Spinal cord injury
SCIM III	Version III of the spinal cord independence measure
SD	Standard deviation
SF-36	Short form - 36 v2 health survey
SF-6D	Short form six-dimension
SF-6D_R2	Short form six-dimension release 2
SOC	System organ class
TEAE	Treatment-emergent adverse event
TOEP	Toeplitz
TOEPH	Toeplitz with heterogeneity
TFLs	Tables, figures and listings
UEMS	Upper extremity motor score
WHO	World health organization
ZPP	Zone of Partial Preservation

1. Source Documents

The Statistical Analysis Plan was written based on the following documentation:

Document	Date	Version
Protocol	01Oct2020	V4.0
eCRF	21JAN2021	V3.0

2. Protocol Details

2.1 Study Objectives

Study RNX-AX204-101 is a two-part (Parts 1 and 2) study that will be run sequentially. Each part has unique objectives. The start of Part 2 will also be contingent on Data and Safety Monitoring Board (DSMB) review of data from Part 1.

2.1.1 Part 1 Single Ascending Dose

2.1.1.1 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).

2.1.2 Part 2 Placebo-Controlled Repeat Dose

2.1.2.1 Primary Objective

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

2.1.2.2 Secondary Objectives

- 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:
    - Primary Efficacy Objective:
        - International Standards for Neurological Classification of SCI (ISNCSCI) Upper Extremity Motor Score (UEMS)
    - Secondary Efficacy Objectives:
        - Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP) prehension performance
        - Version III of the Spinal Cord Independence Measure (SCIM III) self-care
        - Patient Global Impression of Change (PGIC) – Chronic SCI

2.1.2.3 Exploratory Objectives

- To evaluate the efficacy of repeat dose therapy of AXER-204 compared to placebo as assessed by the following:
    - ISNCSCI UEMS for the side with the higher baseline score and the side with the lower baseline score
    - ISNCSCI total 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)
        - Clinical Global Impression of Change (CGIC) from GRASSP Prehension Performance Video Recordings
    - Modified Ashworth Scale (MAS) for spasticity.
    - Brief Pain Inventory (BPI) mean Pain score and mean activity interference score
- Exploratory biomarkers of target engagement and axonal growth may be assessed.

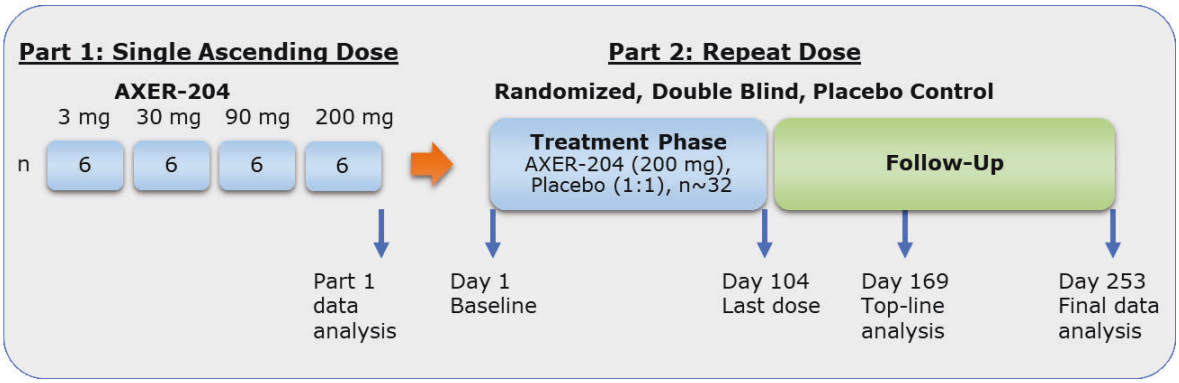
2.2 Overall Study Design

Study RNX-AX204-101 is a two-part study that will be run sequentially. Each Part will be conducted at approximately 5 centers in the United States.

For each Part, eligible subjects will be between the ages of 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, and with significant neurologic 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.

The study will be analyzed separately for Part 1 and Part 2 as illustrated in Figure 1. All Part 1 outputs will be created when Part 1 is finished and database for Part 1 is locked. For Part 2, when all enrolled patients have completed the 6-month visit, data will be cleaned and locked and then unblinded to be analyzed for the primary and secondary efficacy endpoints to compare treatment effects from baseline to Study Day 169. Although the data will be unblinded for [redacted] and ReNetX staff, the raters, patients and primary investigators will remain blinded until final database lock following Study Day 253. All safety summaries will also be created. When all patients have completed Study Day 253 visits, the database will be locked and all outputs including analysis for treatment effect on study day 253 will be created including all data points from start of the Part 2 to end of study for patients enrolled in Part 2.

Figure 1 Sequence of Data Analyses



2.2.1 Part 1

Part 1 is a multicenter, open-label, single ascending dose study in subjects with CSCI. Four cohorts of 6 subjects each are planned, with subjects within each cohort expected to receive the same dose of AXER-204. Up to 24 subjects will be enrolled in Part 1. 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.

The starting dose is 3 mg. Dose escalation will proceed to 30 mg, 90 mg, 200 mg contingent on safety and tolerability. 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

Study participation for each subject in Part 1 is expected to be up to 16 weeks in duration, with up to an 84-day screening period, a 3-day in-clinic treatment period, and a follow-up period through 29 days post-dose:

- Screening (up to 84 days prior to Study Day 1). Subjects 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. However, clinical laboratory tests required for screening must be completed within 28 days prior to Study 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 (ET) (± 4 days).

2.2.2 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.

Study participation for each subject in Part 2 is expected to be up to 337 days in duration, with up to an 84-day screening period, a 104-day treatment period, and then post treatment follow-ups at Study Days 137, 169, and 253:

- Screening (within 84 days prior to Day 1). Subjects 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 Study 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).
    - 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). The pre-treatment AIS grade is determined on Visit 2, Day 1.

- 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).

2.3 Sample Size

2.3.1 Part 1

The Part 1 sample size of 24 (6 subjects per dose) was derived empirically from experience with previous single ascending dose clinical studies in other disorders and is deemed appropriate to achieve the study objectives, with adequate exposure to assess safety for dose selection in Part 2.

2.3.2 Part 2

The Part 2 sample size of approximately 32 subjects was selected with the goal of ensuring adequate power for detecting meaningful treatment-related change in bilateral Upper Extremity Motor Score, UEMS (Score from 0 to 50). Little or no spontaneous improvement in motor score is expected in people with chronic SCI, more than one year from injury (i.e. **ΔUEMS = 0**) (Fawcett et al. 2007). As shown in Table 1, we have targeted detection of 5-point improvement in UEMS (and possibly less) as functionally relevant in the chronic cervical SCI patients recruited to this study. The potential impact of missing data and a correction for non-normal distribution of the data are not included in these estimates.

Table 1 Estimated power as a function of enrollment, effect size, and normal variability of the outcome measure (Δ UEMS)

	Δ UEMS = 5		**Δ UEMS = 4**		**Δ UEMS = 3**	
Enrollment	**SD = 3**	**SD = 4**	**SD = 3**	**SD = 4**	**SD = 3**	**SD = 4**
32	99%	96%	95%	78%	78%	53%
26	98%	92%	90%	68%	68%	45%
20	94%	85%	80%	56%	56%	35%

SD = Standard deviation of the change in UEMS
Based on 2 sided α = 0.05 using NQuery (Version 4.0).

Δ UEMS: A smaller improvement in ΔUEMS (e.g. 2 points) could be clinically meaningful if it occurred in a muscle group essential for a particular activity of daily living such as grasping in the chronic SCI population. A 3-point improvement in

UEMS has been identified as the minimum clinically important difference in acute cervical SCI patients (Scivoletto et al. 2013). Although a minimum clinically important difference in UEMS has not been determined for chronic SCI patients, chronic SCI patients may have greater awareness of personal benefit resulting from changes due to their stable baseline function (Wu et al. 2015).

Standard Deviation (SD): Although we estimated SD of 3 and 4, the data from the 23 patients evaluated at screening and Day 29 in Part 1 of this trial yielded a SD for ΔUEMS of 2.0 which may be more representative of variability in our patient population and the rater consistency attained in the trial that may provide us with even higher power.

3. Efficacy and Safety Variables

3.1 Efficacy Variables

3.1.1 Part 1

3.1.1.1 Primary Efficacy Endpoints

Not applicable.

3.1.1.2 Secondary Efficacy Endpoints

Not applicable.

3.1.1.3 Other Efficacy Endpoints

In Part 1, the following efficacy assessments will be collected in eCRF and will be summarized descriptively:

- International Standards for Neurological Classification of SCI (ISNCSCI) motor and sensory scores. The ISNCSCI scale includes a motor and sensory examination for each side of the body (left/right). Higher values indicate better function with the maximum scores corresponding to normal function.
  The following 4 subscores will be summarized:
  - Upper Extremity Motor Score (UEMS) with scores ranging from 0-50;
  - Lower Extremity Motor Score (LEMS) with scores ranging from 0-50;
  - Pin Prick Sensory Score with scores ranging from 0-112;
  - Light Touch Sensory Score with scores ranging from 0-112.
- Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP) scores (Kalsi-Ryan et al. 2012a, Kalsi-Ryan et al. 2012b). The GRASSP is a clinical impairment measure for the upper limbs through three domains

(strength, sensation and prehension) that are important in describing arm and hand function. Higher scores indicate better function.
The following 4 subscores will be summarized:
  - Strength total scores (left and right) with scores ranging from 0-50 for each side;
  - Sensation total scores (left and right) with scores ranging from 0-12 for each side;
  - Prehension Ability total scores (left and right) with scores ranging from 0-12 for each side;
  - Prehension Performance total scores (left and right) with scores ranging from 0-20 for each side.
- Spinal Cord Independence Measure (SCIM III) self-care and mobility domain scores (Catz et al. 2007, Itzkovich et al. 2007). The SCIM III is a questionnaire evaluating activities of daily living (ADL) regarding self-care, mobility, and respiration and sphincter management. Higher scores correspond to better ability to carry out ADL. The current study will employ the self-care and mobility subscores.
  The following 2 subscores will be summarized:
  - Self-care with scores ranging from 0-20;
  - Mobility with scores ranging from 0-40.

The following efficacy assessments collected in eCRF will be listed:

- Additional items from the ISNCSCI: neurological level for sensory and motor for right and left, neurological level of injury, American Spinal Injury Association (ASIA) impairment scale, and zone of partial preservation for right and left;
- Data collected for the following additional measures: SF-36 Health Survey, Neuro-QOL Upper Extremity Function, International standards to document remaining autonomic function after spinal cord injury (ISAFSCI).

3.1.2 Part 2

The ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary and secondary efficacy objectives. Each estimand is defined according to the following five attributes:

- The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
- The **population** of subjects targeted by the clinical question.

- The **variable** (or endpoint) to be obtained for each subject that is required to address the clinical question.
- The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
- A **population-level summary** for the variable providing a basis for comparison between treatment conditions.

The primary efficacy and secondary efficacy endpoints were selected as the best available to provide assessments of changes in motor function, ability to carry out activities of daily living, and any important changes related to the patient's condition of chronic SCI. A brief description and rationale for each is as follows:

3.1.2.1 Estimand for the Primary Efficacy Endpoint: Bilateral Upper Extremity Motor Score (UEMS)

The primary estimand is the change from baseline in ISNCSCI Bilateral Upper Extremity Motor Score (UEMS) to Study Day 169 between AXER-204 and placebo in patients with chronic spinal cord injury (CSCI).

UEMS is the primary efficacy measure and represents the upper extremity component of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) motor exam. Although historically a total motor score of 100 for all extremities was calculated, for the last decade it has not been recommended to add the upper limb and lower limb scores together. Examination of the metric properties of the motor score indicates that it should be separated into two scales, one composed of the 5 upper limb muscle functions on left and right, and one of the 5 lower limb muscle functions left and right, with a maximum score of 50 each (Marino and Graves 2004, Graves et al. 2006).

Based on the expected mechanism of action of AXER-204 and the focus on subjects with cervical cord injury, the upper limb score has been selected as the primary endpoint measure. The overall motor score remains part of the exploratory analyses. Similarly, other recent SCI therapeutic intervention clinical trials have included change in UEMS as the primary efficacy endpoint (Fehlings et al. 2018, Levi et al. 2019).

The ISNCSCI is the most well-established and validated scale of motor and sensory function in spinal cord injury treatment and rehabilitation. ISNCSCI assessments are standardized by the governing body American Spinal Injury Association in conjunction with the International Spinal Cord Society. The UEMS portion of the ISNCSCI evaluates muscle strength controlled by five myotomes on each side of

the body. The muscles tested, the corresponding levels, and the expected functional relevance of each level are illustrated in Table 2.

Table 2 UEMS: Neurological Levels, Muscles, Functional Importance for Activities of Daily Living

Spinal Level	Muscle group	Personal Independence	Wheelchair Management	Transfers
C5	Elbow flexors	Type, feed	Manipulate brake, push on the flat	
C6	Wrist extensors	Drink, wash, shave, dress upper body	Remove armrests/ footplates	From chair to bed or car
C7	Elbow extensors	Turn in bed, dress lower body	Wheel over uneven ground	From chair to toilet or chair or bath
C8	Finger flexors	Bladder and bowel care	Negotiate curbs	From chair to bath
T1	Small finger abductors		Balance on rear wheels	From chair to floor

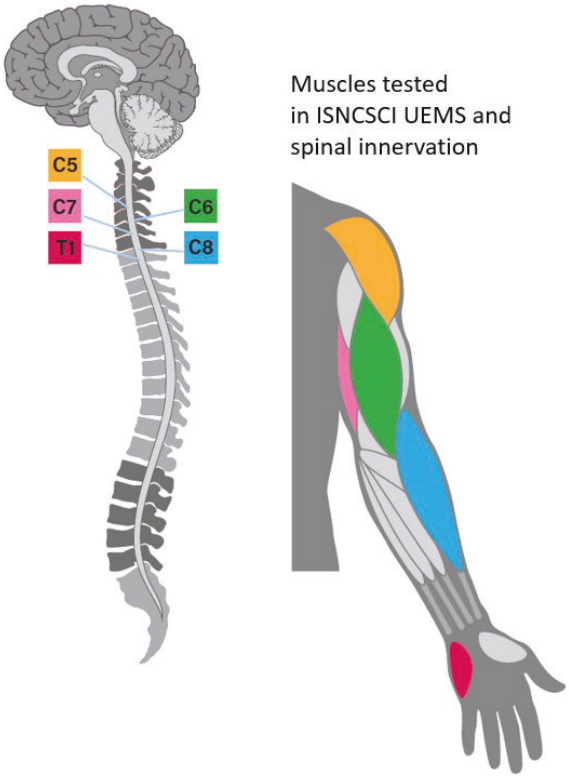
Adapted from van Hedel and Curt (van Hedel and Curt 2006).

Scoring: Each muscle is given a score between 0 and 5 as follows (Rupp et al. 2021):

0 = Total paralysis
1 = Palpable or visible contraction
2 = Active movement, full range of motion (ROM) with gravity eliminated
3 = Active movement, full ROM against gravity
4 = Active movement, full ROM against moderate resistance in a muscle specific position
5 = (Normal) active movement, full ROM against full resistance in a muscle-specific position expected from an otherwise unimpaired person

Figure 2 is provided to visually show the impact of each neurological level and the muscle groups impacted. The inclusion criteria for the trial selects a functionally homogenous group of patients in terms of impaired arm and hand function controlled by spinal cord nerves at the C5-T1 levels (UEMS =4-36, GRASSP PP = 4-17). Of note, this means that the trial enrolls subjects with cervical level injury with neurologically complete and incomplete injuries and spanning all ASIA impairment scale grades (A, B, C, D) for patients with SCI.

Figure 2 Illustration of Muscles Tested in UEMS and Controlling Spinal Neurologic Levels



The minimum clinically important change for bilateral UEMS has been estimated to be 3-points for **acute and subacute** SCI patients with a mean time from injury of 52 days (Scivoletto et al. 2013). In general, cervical SCI patients with a clinically important change in UEMS also improved functionally. This correlation between change in UEMS and function may be anticipated given the muscle groups evaluated in the test and their utility for carrying out activities of daily living. UEMS typically remains stable for chronic SCI patients, it is anticipated that even small changes may be considered significant from the perspective of patients (Wu et al. 2015).

Thus, change in ISNCSCI UEMS provides a robust and well-established measure of muscle function with relevance to functional changes for patients.

3.1.2.1.1 Treatment Condition of Interest

The treatment condition of interest is AXER-204 administered every 21 days, and is compared against the alternative treatment condition of placebo administered every 21 days.

3.1.2.1.2 Population

The population is subjects with chronic spinal cord injury (CSCI) defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 4.0.

3.1.2.1.3 Endpoint

The endpoint is the change from baseline in ISNCSCI Bilateral Upper Extremity Motor Score (UEMS) to Study Day 169.

3.1.2.1.4 Handling of Intercurrent Events

The following intercurrent events are anticipated during the study. Table 3 describes how intercurrent events will be collected and handled within the analysis.

Table 3 Handling of Intercurrent Events for the Primary Estimand

Intercurrent event	Data collection and analysis
Important protocol deviation, including use of prohibited medication, prior to assessment scheduled on Study Day 169	Patients will be followed and data collected after the intercurrent event will be used in analysis in line with the treatment policy strategy, i.e. regardless of the intercurrent event.
Did not receive at least 5 doses (~80%) of the planned cumulative number of doses of treatment	
Did not perform at least one post-baseline assessment	Patients who experienced the intercurrent event will be excluded from analysis in line with a principal stratum strategy.
Discontinuation from the study prior to assessment scheduled on Study Day 169	Patient's measurements up until the time of the intercurrent event will be used in analysis in line with the while on treatment policy, i.e. the endpoint is only evaluable in patients who complete the assessment scheduled on Study Day 169.

3.1.2.1.5 Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be the difference between AXER-204 and placebo in estimated least squares means of change from baseline in ISNCSCI Bilateral UEMS at Study Day 169 as estimated through a mixed-effects model for repeated measures (MMRM) as defined in section 8.5.2.1.

3.1.2.1.6 Sensitivity Estimand for the Primary Efficacy Objective

The robustness of the assumptions of the primary estimand will be evaluated through the use of a sensitivity estimand through the following alternative approach to intercurrent events (Table 4).

Table 4 Handling of Intercurrent Events for the Sensitivity Estimand for the Primary Efficacy Objective

Intercurrent event	Data collection and analysis
Important protocol deviation, including use of prohibited medication, prior to assessment scheduled on Study Day 169	Patients who experienced the intercurrent event will be excluded from analysis in line with a principal stratum strategy.
Did not receive at least 5 doses (~80%) of the planned cumulative number of doses of treatment	
Did not perform at least one post-baseline assessment	
Discontinuation from the study prior to assessment scheduled on Study Day 169	Patient's measurements up until the time of the intercurrent event will be used in analysis in line with the while on treatment policy, i.e. the endpoint is only evaluable in patients who complete the assessment scheduled on Study Day 169.

3.1.2.2 Estimand for 1st Secondary Efficacy Endpoint: Bilateral Prehension Performance (PP)

One of the secondary estimands is change from baseline in GRASSP Bilateral prehension performance (PP) total score to Study Day 169 between AXER-204 and placebo in patients with chronic spinal cord injury (CSCI).

The Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP V2) prehension performance sub-scale assesses performance of four tasks that mimic everyday activities of daily living. Patients are asked to 1) pour water from a bottle into a cup, 2) pull 9 pegs one-by-one out of holes on one side of a board and insert them into holes on the opposite side, 3) pick up a key, insert it into a lock and turn the key, and 4) pick up 4 nuts, one-by-one, and screw them onto matching screws. The required grasping pattern for each of the four tasks is illustrated in Figure 3.

Figure 3 GRASSP Prehension Performance Illustration

Scores are assigned as follows:

0: The task cannot be conducted at all
1: The task cannot be completed, (less than 50% of the task)
2: The task is not completed, (50% or more of the task)
3: The task is conducted (completed) using tenodesis or an alternative grasp other than the expected grasp.
4: The task is conducted using the expected grasp with difficulty (lack of smooth movement or difficult slow movement)
5: The task is conducted without difficulties using the expected grasping pattern and unaffected hand function

Each task must be completed within 75 seconds and the number of drops is recorded. Each side is tested and the scores combined to obtain the bilateral score.

There is a substantial concurrence between GRASSP prehension performance and activities of daily living from a patient perspective (Kalsi-Ryan et al. 2019).

Accordingly, GRASSP prehension performance provides an objective, clinician-evaluated measure of function in performing activities of daily living.

3.1.2.2.1 Treatment Condition of Interest

The treatment condition of interest is the same as section 3.1.2.1.1.

3.1.2.2.2 Population

The population is the same as section 3.1.2.1.2.

3.1.2.2.3 Endpoint

The endpoint is the change from baseline in GRASSP Bilateral prehension performance (PP) score to Study Day 169.

3.1.2.2.4 Handling of Intercurrent Events

The intercurrent events strategy is the same as section 3.1.2.1.4.

3.1.2.2.5 Population-level Summary for Comparison between Treatment Conditions

The treatment effect is the same as section 3.1.2.1.5, except the endpoint is as described in section 3.1.2.2.3.

3.1.2.2.6 Sensitivity Estimand for the 1st Secondary Efficacy Objective

The sensitivity estimand is the same as section 3.1.2.1.6.

3.1.2.3 Estimand for 2nd Secondary Efficacy Endpoint: SCIM III Self Care

One of the secondary estimands is change from baseline in SCIM III Self Care score to Study Day 169 between AXER-204 and placebo in patients with chronic spinal cord injury (CSCI).

The Spinal Cord Independence Measure, Version III (SCIM III) questionnaire has been widely used to assess performance of activities of daily living. It relies on patient responses to 17 questions across three domains: self-care, respiration and sphincter management, and mobility. This study is collecting data for self-care and mobility and self-care has been selected as a secondary efficacy measure based on the expectation that the change in this domain will be most reflective of changes in arm and hand function being measured with the primary efficacy measure of change in ISNCSCI UEMS.

The self-care sub-scale is comprised of four questions to determine the level of independence in feeding, bathing (upper body, lower body), dressing (upper body, lower body), and grooming with a possible score of 0-20 points.

The SCIM III minimal clinically important difference has not been determined for patients with chronic SCI.

3.1.2.3.1 Treatment Condition of Interest

The treatment condition of interest is the same as section 3.1.2.1.1.

3.1.2.3.2 Population

The population is the same as section 3.1.2.1.2.

3.1.2.3.3 Endpoint for the Secondary Estimand

The endpoint is the change from baseline in SCIM III Self Care score to Study Day 169.

3.1.2.3.4 Handling of Intercurrent Events

The intercurrent events strategy is the same as section 3.1.2.1.4.

3.1.2.3.5 Population-level Summary for Comparison between Treatment Conditions

The treatment effect is the same as section 3.1.2.1.5, except the endpoint is as described in section 3.1.2.3.3.

3.1.2.3.6 Sensitivity Estimand for the 2nd Secondary Efficacy Objective

The sensitivity estimand is the same as section 3.1.2.1.6.

3.1.2.4 Estimand for 3rd Secondary Efficacy Endpoint: Patient Global Impression of Change (PGIC)

One of the secondary estimands is Patient Global Impression of Change (PGIC) responder rate at Study Day 169 between AXER-204 and placebo in patients with chronic spinal cord injury (CSCI).

The PGIC instrument captures the patient's overall evaluation of response to treatment. Specifically, the PGIC asks: "Since beginning this clinical trial, how would you describe the overall change (if any) related to your chronic spinal cord injury?" The patient is asked to report the degree to which they have changed since entering the treatment period using a 7-point Likert scale (1= 'Much worse', 2='Worse', 3=' A little worse', 4='No change', 5='A little better', 6='Better, 7=''Much better') and "If better or worse, what has changed?". Patients that have evaluation results including "Much better", "Better", or "A little better" at Study Day 169 are considered Responders. This provides a global assessment from the patient's perspective and may capture anticipated and unanticipated changes that occur during the study.

Overall, these scales administered by trained raters in this double blinded, placebo-controlled study will provide a reliable assessment of treatment-related changes from baseline in upper extremity motor function, including performance of activities of daily living, and capture any changes related to the patient's own assessment of their chronic SCI.

Rater Training: Given the importance of these measures to assess functional changes, activities of daily living and clinical relevance, ReNetX established a comprehensive training for raters across all measures including certification directly from the groups that developed and standardized these measures.

3.1.2.4.1 Treatment Condition of Interest

The treatment condition of interest is the same as section 3.1.2.1.1.

3.1.2.4.2 Population

The population is the same as section 3.1.2.1.2.

3.1.2.4.3 Endpoint

The endpoint is the Patient Global Impression of Change (PGIC) responder rate at Study Day 169. Patients that have evaluation results including "Much better", "Better", or "A little better" are considered Responders, whereas patients that have evaluation results including "Much worse", "Worse", "A little worse", or "No change" are considered Non-Responders.

3.1.2.4.4 Handling of Intercurrent Events

The intercurrent events strategy is the same as section 3.1.2.1.4.

3.1.2.4.5 Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be the difference between AXER-204 and placebo in percentages of PGIC responder rate at Study Day 169 as estimated through a Fisher's Exact Test as defined in section 8.5.2.2.

3.1.2.4.6 Sensitivity Estimands for the 3rd Secondary Efficacy Objective

The first sensitivity estimand is the same as section 3.1.2.1.6. Another sensitivity estimand will follow an alternative approach to intercurrent events (Table 5).

Table 5 Handling of Intercurrent Events for the Sensitivity Estimand for the 3rd Secondary Efficacy Objective

Intercurrent event	Data collection and analysis
Important protocol deviation, including use of prohibited medication, prior to assessment scheduled on Study Day 169	Patients will be followed and data collected after the intercurrent event will be used in analysis in line with the treatment policy strategy, i.e. regardless of the intercurrent event.
Did not receive at least 5 doses (~80%) of the planned cumulative number of doses of treatment	
Did not perform at least one post-baseline assessment	Patients who experienced the intercurrent event will be excluded from analysis in line with a principal stratum strategy.
Discontinuation from the study prior to assessment scheduled on Study Day 169	Among patients who experienced the intercurrent event, the intercurrent event will be integrated in the response variable in line with the composite variable strategy, i.e. considered to be Non-Responder (4='No change').

3.1.2.5 Exploratory Efficacy Endpoints

3.1.2.5.1 Change from baseline to Study Day 169

- ISNCSCI Unilateral UEMS of the side with higher baseline scores ranging from 0-25. For each patient, choose the side with higher baseline unilateral UEMS score and all post-baseline value and change from baseline values for the same side will be analyzed. If the baseline scores for each side are equal, then the right side will be grouped with the higher baseline UEMS scores for analysis.
- ISNCSCI Unilateral UEMS of the side with lower baseline scores ranging from 0-25. If the baseline scores for each side are equal, then the left side will be grouped with the lower baseline UEMS scores for analysis. The analysis will be similar to the one with higher baseline UEMS scores as described above.
- ISNCSCI Bilateral Motor score (including both upper and lower extremity for both left and right sides) with scores ranging from 0-100.
- ISNCSCI Bilateral Sensory score - light touch (sum of right total and left total) with scores ranging from 0-112.

- ISNCSCI Bilateral Sensory score – pin prick (sum of right total and left total) with scores ranging from 0-112.
- GRASSP Bilateral Strength score (sum of score from left and right) with scores ranging from 0-100.
- GRASSP Bilateral Sensation total score (sum of score from left and right) with scores ranging from 0-24.
- GRASSP Bilateral Prehension Ability (PA) total scores (sum of score from left and right) with scores ranging from 0-24.
- SCIM III mobility score (see section 3.1.1 for details) with scores ranging from 0-40.
- CUE – Questionnaire (CUE-Q) total score with scores ranging from 0-128. CUE-Q contain 17 questions each on a scale of 0 to 4 to assess subject reported upper limb function for both arms or hands including Ability to reach or lift, Ability to pull and push with arms, Moving and positioning arm and wrist, and Using hands and fingers.
- Neuro-QoL upper extremity function t-score, with overall raw score ranging from 20-100. Neuro-QoL upper extremity function questionnaire consist 20 questions to assess upper extremity function (fine motor or ADL). All questions are rated on a 1- to 5-point verbal rating scale with higher score associated with better function.
- SF-36 score. SF-36 V2 provides a patient-reported QoL assessment on subjects' perceived health and well-being over the course of the study. The following derived scales will be determined (Optum PRO CoRE):
    - Bodily Pain
    - General Health
    - Mental Health
    - Mental Component
    - Physical Component
    - Physical Functioning
    - Social Functioning
    - Role Emotional
    - Role Physical
    - Vitality
    - SF-6D (Utility Index)
    - SF-6D_R2 (Utility Index Release 2)

3.1.2.5.2 Other exploratory efficacy endpoints

- ISNCSCI ASIA impairment scale (AIS) with scales including A, B, C, D, E (protocol Appendix 3) at Study Day 169.
- ISNCSCI Neurological Motor level at Study Day 169.
- ISNCSCI Neurological Sensory level at Study Day 169.
- ISNCSCI Neurological Level of Injury (NLI) at Study Day 169.
- ISAFSCI assessments at Study Day 169. The ISAFSCI documents autonomic control of the heart, blood pressure, sweating and temperature regulation with findings equal to one of the following values: Normal, Abnormal, Unknown, or Unable to assess. Scores for lower urinary tract, bowel or sexual function will also be collected whereas score 0= complete loss of control; 1= Reduced or Altered Neurological Function; 2 = Normal function; NT=Unable to assess.
- Clinical Global Impression of Change (CGIC) from GRASSP Prehension Performance Video Recordings. Details are included below as this measure has been added beyond specific information included in the protocol. Conducted by a blinded rater who is trained on the scales and also has a C5/C6 injury to provide the perspective of the patient population we intend to treat with our therapy: Given the importance of this measure for functional, ADL as well as patient/clinically relevant changes, the GRASSP prehension performance assessment is video recorded at each time point to visually document changes reflected in the scoring as well as changes that may or may not be captured on the scale.

  CGIC Evaluation

  Compared to baseline, how would you describe the overall change (if any) related to performance of the GRASSP prehension performance tasks?

  Choose ONE.

  _____Much worse (1)

  _____Worse (2)

  _____A little worse (3)

  _____No change (4)

  _____A little better (5)

  _____Better (6)

  _____Much better (7)

  If better or worse, what has changed? _____

With the exception of the CGIC, all efficacy endpoints will also be analyzed for Study Day 253.

3.2 Safety Variables

The following safety variables will be included for both Part 1 and Part 2:

- Study treatment exposure;
- Treatment-emergent adverse events (TEAEs);
- Clinical laboratory tests including hematology, clinical chemistry, and urinalysis;
- Physical examinations;
- Vital signs;
- 12-lead electrocardiograms (ECGs);
- Condition-specific safety outcomes, including the following:
    - Spasticity. Modified Ashworth Scale (MAS) (Pandyan et al. 1999) is a clinician administered examination for spasticity which measures muscle tone around selected limb joints. The total MAS score will be calculated and summarized for both part 1 and part 2. In addition, for part 2, bilateral total scores for Elbow, Wrist, Hamstrings, Quadriceps, Gastrocnemius, and Soleus will be analyzed to compare between treatment group with control group.
    - Pain. Brief Pain Inventory (BPI) (Cleeland and Ryan 1994) is 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. The following scores will be calculated and summarized:
        - BPI pain severity for each of the four severity items ("worst," "least," "average," and "now"). For part 2, mean BPI pain score at Study Day 169 and change from baseline will be analyzed to compare treatment group with control group.
        - BPI pain interference. For part 2, mean BPI pain interference score at Study Day 169 and change from baseline will be analyzed to compare treatment group with control group.

4. Pharmacokinetic variables

- Serum and CSF samples will be collected and analyzed for concentrations of AXER-204 at planned time points following the schedules for Part 1 or Part 2, as described in the protocol.
- Pharmacokinetic (PK) parameters will also be determined (section 8.6.1) using a non-compartmental approach (NCA) for Part 1.

5. Immunogenicity variables

Pre-dose Anti-drug antibody (ADA) serum will be collected for ADA analysis for both Part 1 and Part 2 following the protocol defined schedule. The following immunogenicity variables will be analyzed:

- Anti-drug antibody (ADA) incidence

6. Analysis Population

6.1 All Randomized Set (Part 2)

The All Randomized Set will consist of all randomized Part 2 subjects. Subjects will be analyzed according to their randomized treatment.

6.2 Safety Population (Part 1 and Part 2)

The Safety Population will consist of all subjects treated with at least one dose of study treatment. Safety outcomes will be assessed using the Safety Population. For Part 2, safety outcomes, including the condition-specific safety outcomes as described in section 8.8.7, will be analyzed according to their actual treatment received.

6.3 Full Analysis Set (Part 1)

The Full Analysis Set (FAS) will consist of all subjects who had at least one dose of study treatment and at least one post-baseline ISNCSCI assessment in Part 1. Efficacy outcomes in Part 1 will be summarized using FAS.

6.4 Modified Intent to Treat Analysis set (Part 2)

The Modified Intent to Treat (mITT) Analysis Set consist of all Part 2 subjects who were randomized and had at least one dose of study treatment and at least one post-baseline ISNCSCI assessment. Efficacy outcomes for Part 2 will be evaluated using the mITT analysis set. Subjects will be analyzed according to their randomized treatment.

6.5 PK Analysis Set (Part 1 and Part 2)

The PK Analysis Set will include all subjects who received at least 1 dose of study drug and had evaluable PK data. All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to the PK analysis set. PK analysis will be conducted for PK analysis set. Subjects will be analyzed according to their randomized treatment.

6.6 Antidrug Antibody Analysis Set (Part 1 and Part 2)

The Antidrug Antibody (ADA) Analysis Set will include all subjects who received at least 1 dose of study treatment and had at least one post-baseline ADA. This analysis set will be used to summarize ADA results. Subjects will be analyzed according to their randomized treatment.

6.7 Per Protocol Set (Part 2 only)

The Per Protocol Set (PPS) will be a subset of mITT and consist of subjects who received at least 5 doses (~80%) of the planned cumulative number of doses of study drug and have no important protocol deviations that might impact efficacy assessment.

The important protocol deviations leading to exclusion from the PPS may include but not limited to the following: violation of key inclusion/exclusion criteria, use of prohibited medications as defined by the study protocol or in discussion with the Sponsor and/or medical monitor, errors in treatment allocation, etc. All important protocol deviations leading to exclusion from the PPS will be reviewed and approved by the Sponsor prior to database lock and unblinding. Subjects will be analyzed according to their randomized treatment.

7. DATA Handling

7.1 Time points

Day 1 is defined as the day of the first study treatment administration. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

For Part 1, all data will be analyzed using nominal study visits as defined in the Study Schedule in the protocol and eCRF. Data collected at unscheduled visits will not be included in summary tables but will be listed only, unless specified otherwise.

7.2 Visit Window (Part 2)

For part 2, time windows will be defined for both safety and efficacy assessments for summaries and values by visit as well as efficacy analysis. All data for unscheduled and scheduled visits have the potential to be included in the summary and analysis based on the actual date. The window for the visits following baseline will be constructed according to the following convention: the upper limit of the interval falls half way between the 2 visits if odd number of days exists between two consecutive visits. If an even number of days exists between two consecutive

visits then the upper limit will be taken as the midpoint value minus 1 days. For example, the visit windows for ISNCSCI assessment are:

- Day 1, visit window NA
- Day 21, visit window 2 – 42
- Day 63, visit window 43 – 83
- Day 104, visit window 84 – 136
- Day 169, visit window 137 – 211
- Day 253, visit window 212 – end of study

If there is more than one value within a visit window then the closest value to the scheduled visit date will be included in the summary and analysis. If 2 events are equal distance from the scheduled visit date then the event with earlier date will be selected for analysis. For listings, all visits including unscheduled visits will be displayed by collected visit name.

7.3 Handling of Dropouts and Missing Data

Except for the data specified below, missing data will not be imputed.

7.3.1 Handling of Missing or Incomplete Dates

Incomplete dates (partial or missing dates) for adverse event (AE) and prior/concomitant medications will be imputed. The imputed dates will be used to determine treatment-emergent AEs or prior/concomitant medications. The subject data listings will present the observed data without imputation.

- For partial start dates:
  - If day is missing, then if the month and year of the event are the same as the month and year of treatment start date, the treatment start date will be imputed as the date; otherwise the first day of the month will be imputed;
  - If month and day are missing, then if the year of the event is the same as the year of treatment start date, the treatment start month and day will be imputed as the date; otherwise, 01JAN will be imputed.
- For partial stop dates,
  - if day is missing, then if the month and year of the event are the same as the month and year of treatment end date, the treatment end date will be imputed as the date; otherwise the last day of the month is imputed.
  - If month and day are missing, then if the year of the event is the same as the year of treatment end date, the treatment end month and day will be imputed for the date; otherwise, 31DEC will be imputed.
- For dates completely missing, no imputation will be done.

7.3.2 Handling of Missing Efficacy Endpoints

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

In situations where the efficacy endpoints are missing, all available data will be analyzed with a mixed-effects model for repeated measures (MMRM) as described in section 8.5.2.1. To evaluate robustness of results, sensitivity analyses will be performed with imputation methods for missing data as described in section 8.5.2.1.2.

7.4 Handling of Randomization Error (Part 2)

Eligible Part 2 patients 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).

For patients who were classified differently based on AIS grade or prior receipt of study drug in Part 1 at pre-treatment compared to their stratified randomization assignment, any such inconsistencies will be documented as randomization errors and protocol deviations. In any such cases, pre-treatment value will be used in preference to the stratified randomization value for TFL reporting.

8. Statistical Methods

8.1 General Principles

- All data processing, summarization and analyses will be performed using [redacted] SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.
- The following principles will be applied to all TFLs unless otherwise stated:

Table 6 Statistical Analysis General Principles

Principle	Value
Significant tests	Two sided and use a 5% significance level
Treatment group labels and order presented	Part 1: AXER-204 xx mg Part 2: AXER-204 200 mg; Placebo
Tables	Data in summary tables presented by dose cohort/treatment group, assessment (where applicable), and visit (where applicable).

Principle	Value
Listings	All data collected presented by dose cohort/treatment group, subject, and visit (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of subjects (N), mean, standard deviation (SD), median, minimum, maximum.
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator for percentages	Number of subjects in the analysis population, unless otherwise specified.
Include "Missing" as category	Yes, when the number missing is greater than zero for at least one dose cohort/treatment group.
Display for percentage	One decimal place, except for 100%
Display for 0 percentages	0
Display to one more decimal place than collected value	Mean, Median, Mean Difference
Display to two more decimal places than collected value	Standard Deviation
Limit of precision for displays	3 decimal places
Date Format	DDMMMYYYY
TFL orientation	Landscape
TFL output	For all tables and listings, 2.54 cm for the top/bottom/left/right margins and 8-point Courier New font

- For both safety and efficacy analysis, the baseline value will be defined as the last non-missing value before the first dose of study treatment.

8.2 Subject Disposition and Data Sets Analyzed

For Part 1, subject disposition will be listed and summarized by dose cohort and overall for the Safety population and will include the number and percentage of subjects that are included in each study population (Safety Population, FAS, PK analysis set, and ADA analysis set). For Part 2, subject will be listed and summarized by treatment group and overall for the All Randomized Set and will include the number and percentage of subjects included in each study population (Safety Population, mITT, PK analysis set, ADA analysis set, and PPS).

In addition, the number and percentage of subjects who complete the study and who discontinue early, including a breakdown of the primary reasons for discontinuation, will be presented.

8.3 Protocol Deviations

All protocol deviations for Part 1 will be listed.

For Part 2, Protocol deviation will be identified prior to database lock and unblinding. All protocol deviations will be listed. All important protocol deviations that impact the interpretation of efficacy outcome measures, leading to exclusion from the PPS, will be summarized by treatment group and overall for the mITT. Number and percentage of subjects with at least one important protocol deviations including a breakdown of type of protocol deviations will be summarized.

8.4 Demographics and Other Baseline Characteristics

8.4.1 Demographic and baseline characteristics

Demographic and baseline characteristics will be listed and summarized by dose cohort and overall for the Safety population. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years);
- Weight (kg);
- Height (cm);
- Body mass index (BMI) (kg/m^2);
- Time from injury (months), calculated as (date of the first dose of study treatment – date of injury)/30.4375, date of injury will be obtained from the demographics eCRF page.

BMI recorded in pounds and inches will be re-calculated as the following: BMI(kg/m^2) = BMI(lb/in^2) * 703.

The total counts and percentages of subjects will be presented for the categorical variables of:

- Gender (Female, Male);
- Race (American Indian Or Alaska Native, Asian, African American, Native Hawaiian Or Other Pacific Islander, White, Other);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown);
- Reproductive status (Fertile, Menopause, Sterilized, Unknown, Other);

- Injury ASIA Impairment Scale (A, B, C, D obtained from the ISNCSCI eCRF at screening;
- Neurological level of injury (C2, C3, C4, C5, C6, C7, C8, T1, T2), obtained from the ISNCSCI eCRF at screening;
- Cause of Spinal Cord Injury (Part 2 only) using the categories adopted by the National Spinal Cord Statistical Center.

Other baseline measurements, such as vital signs, will be summarized with the post-baseline measurements.

For Part 2, Demographic and baseline characteristics will be listed and summarized by treatment group and overall for the Safety population. The same list of demographic and baseline characteristics as those specified for Part 1 will be summarized by treatment group and overall. In addition, number and percentage of subjects who received study drug in Part 1 will be also summarized.

8.4.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 22.0 (or a later version if updated during the study)].

All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for the Safety population by system organ class (SOC) and preferred term (PT) for each dose cohort for Part 1 (or for each treatment group for Part 2) and overall. Subjects with more than one medical history within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one medical history within a particular PT are counted only once for that PT. Tables will be sorted in descending overall frequency by SOC, and then in descending overall frequency by PT within SOC, and then alphabetically.

8.4.3 Previous and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by [redacted] using the World Health Organization (WHO) Drug Dictionary [Version: Global B3-March 2019 (or a later version if updated during the study)] Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those with a start date and a stop date prior to the first dose date of study treatment;
- Concomitant medications are those with a start date on or after the first dose date of study treatment, or those with a start date before the first dose date of study treatment and a stop date on or after the first dose date of study treatment or ongoing at the end of study;

- New-onset medications are concomitant medications with a start date after the first dose of study treatment. New-onset medications are a subset of the full set of concomitant medications.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed together and summarized separately for the Safety population by dose cohort for Part 1 (or by treatment group for Part 2) and overall.

The number and percentage of subjects using any medication will be displayed together with the number and percentage of subjects using at least one medication within each therapeutic class (ATC-Level 2) and generic term. Tables will be sorted in descending overall frequency by the ATC level and in descending overall frequency by generic term, and then alphabetically.

8.5 Efficacy

8.5.1 Part 1

All efficacy data will be listed. The following efficacy endpoints will be summarized by dose cohort and overall, and by visit using standard descriptive statistics for the FAS, changes from baseline will be also summarized:

- ISNCSCI upper extremity motor total score, obtained from eCRF;
- ISNCSCI lower extremity motor total score, obtained from eCRF;
- ISNCSCI pin prick sensory total score, obtained from eCRF;
- ISNCSCI light touch sensory total score, obtained from eCRF;
- GRASSP strength total score, calculated as the sum of the total strength score for the right side and the total strength score for the left side;
- GRASSP sensation total score, calculated as the sum of the total sensation score for the right side and the total sensation score for the left side;
- GRASSP prehension ability total score, calculated as the sum of the total prehension ability score for the right side and the total prehension ability score for the left side;
- GRASSP prehension performance total score, calculated as the sum of the total prehension performance score for the right side and the total prehension performance score for the left side;
- SCIM III self-care total score, obtained from eCRF;
- SCIM III mobility total score, obtained from eCRF.

8.5.2 Part 2

8.5.2.1 Primary Efficacy Endpoint and Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in bilateral UEMS to Study Day 169.

The null and alternative hypothesis for this endpoint 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, 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.

Primary analysis to compare the change from baseline in bilateral UEMS to Study Day 169 will be based upon a mixed-effects model for repeated measures (MMRM) using the mITT.

The MMRM model will include treatment (AXER-204 vs. Placebo), all post-baseline visits up until Study Day 169 (Study day 21, 63, 104, and 169), treatment-by-visit interaction, AIS grade (A, B vs C, D), and prior receipt of study drug in Part 1 (yes vs. no) as the fixed categorical effects, the baseline bilateral UEMS measurement as a covariate, and treatment-by-baseline UEMS interaction.

An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, the following covariance structures will be tested in order, and the first covariance structure that converges will be used:

- toeplitz with heterogeneity (TOEPH)
- autoregressive with heterogeneity (ARH(1))
- compound symmetry with heterogeneous variances (CSH)
- toeplitz (TOEP)
- autoregressive (AR(1))
- compound symmetry without heterogeneous variances (CS)

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on LS Means using Type III sum of squares.

Based on the MMRM, analysis of comparisons between treatment groups at each post-randomization visit will be performed. The primary analysis will be to compare

treatment effect at Study Day 169. The adjusted means for each treatment group and the estimated treatment differences for the treatment comparisons will be presented for each post-randomization visit together with 95% confidence intervals for the differences and p-values for the treatment comparisons. The adjusted means and estimated treatment differences for the treatment comparisons will also be plotted, with corresponding 95% confidence intervals.

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum) will be provided for baseline, post treatment and change from baseline by treatment group and visit.

8.5.2.1.1 Primary Efficacy Endpoint and Secondary Efficacy Analysis

A random coefficients model will be used to compare the rate of change (slope) in bilateral UEMS from start of study treatment until Study Day 169 between treatment group and control group. The model is similar to the MMRM model (section 8.5.2.1), except subject and subject by visit will be included as random effects. The unstructured covariance model will be used. If the computational algorithm fails to converge, the following covariance structures will be analyzed: TOEPH, ARH(1), CSH, TOEP, AR(1), CS. Reporting of model results will include the model estimate for the overall rate of change in bilateral UEMS and 95% CI, estimated treatment or control group rates and 95% CIs, and mean difference between treatment and control group along with the p-values. The adjusted means and estimated treatment differences for the treatment comparisons will also be plotted with corresponding 95% confidence intervals.

8.5.2.1.2 Sensitivity Analysis

Three sensitivity analyses will be performed for the primary efficacy endpoint.

- **Multiple imputations assuming missing not at random (MNAR)**

Sensitivity analysis will be performed using multiple imputations with unobserved data imputed prior to fitting the linear regression. An assumption of MNAR will be made based upon an approach using multiple imputations with missing data for all subjects imputed from a regression model estimated from patients in the placebo group who stay on until Study Day 169. The imputation model will include the randomization strata and the corresponding baseline value as predictor. The method of multiple imputations (MI) (Ratitch et al. 2013) using Pattern Mixture Model (Little and Wang 1996) will be used. The amount of non-monotone missing data is expected to be minimal and hence any non-monotone missing bilateral UEMS will be imputed using the Markov Chain Monte-Carlo method. SAS PROC MI

and MIANALYZE will be used to generate 100 complete datasets and combine the results from each complete dataset analyzed using the same MMRM model as described above in section 8.5.2.1.

- **Multiple imputations assuming missing at random (MAR)**

An assumption of Missing at Random (MAR) will be made and subject's missing bilateral UEMS data will be imputed using those with available data within the treatment group they were assigned to using an approach similar to above as described in section 8.5.2.1.

- **Excluding patients with important protocol deviations and who did not receive 80% of the planned treatment**

An analysis excluding patients with deviations that may affect the efficacy of the study treatment will be conducted in per protocol set. The same MMRM method as the primary analysis as described in section 8.5.2.1 will be used. This analysis will use the principal stratum strategy, to assess the sensitivity of the results to the occurrence of the intercurrent events like important protocol deviations prior to assessment scheduled on Study Day 169 and not receiving at least 5 doses (~80%) of the planned cumulative number of doses of treatment as described in section 3.1.2.1.6.

8.5.2.1.3 Subgroup Analysis

Subgroup analyses using the same methods as the primary and secondary analyses as described in sections 8.5.2.1 and 8.5.2.1.1 will be conducted comparing the primary efficacy endpoint between the treatment group and control group to assess consistency of treatment effects across potential prognostic factors.

The following subgroup of mITT will be analyzed for the primary efficacy endpoint.

- AIS grade (A, B vs C, D)
- Received study drug in Part 1 vs. Did not receive study drug in Part 1
- AIS grade (A vs. B, C, D)
- Time since injury ≤5 years vs >5 years

No adjustment to the significance level for testing will be made for subgroup analysis since all these subgroup analyses will be considered exploratory.

8.5.2.2 Secondary Efficacy Endpoints

- For Change from baseline in GRASSP Bilateral PP total score to Study Day 169, analysis will be conducted using the same methodology as that used for the primary efficacy endpoint (sections 8.5.2.1 and 8.5.2.1.1).
- For Change from baseline in SCIM III Self Care score to Study Day 169, analysis will be conducted using the same methodology as that used for the primary efficacy endpoint (sections 8.5.2.1 and 8.5.2.1.1).
- Fisher's exact test at two-sided significance level 0.05 will be used to test if there is a difference of PGIC responses (1='Much worse', 2='Worse', 3=' A little worse', 4='No change', 5='A little better', 6='Better, 7=''Much better') at Study Day 169 between patients in treatment group and control group. In addition, Fisher's exact test to compare responder rate (proportion of patient in mITT Analysis set with responses of 'A little better', 'Better', or 'Much better') at Study Day 169 between the two treatment groups will conducted. A descriptive table summarizing number and percentage of patients for each of the seven above responses by visit and treatment group will be created.

8.5.2.2.1 Sensitivity Analysis

- For Change from baseline in GRASSP Bilateral PP total score to Study Day 169 and Change from baseline in SCIM III Self Care score to Study Day 169, sensitivity analyses will be conducted using the same methodology and model as that used for the primary efficacy endpoint (section 8.5.2.1.2).
- For PGIC responder rate, the analysis described above will be conducted for the per protocol set to evaluate if deviations from protocol affect treatment effect assessed by PGIC.
- For PGIC responder rate, the analysis described above will be repeated, except subjects who discontinued the study prior to the assessment scheduled for Study Day 169 will be assigned a response of 4='No change'. This analysis will use the composite variable strategy, to assess the sensitivity of the results to the occurrence of the intercurrent events like discontinuation from the study prior to assessment scheduled on Study Day 169 as described in section 3.1.2.4.6.

8.5.2.3 Exploratory Efficacy Endpoints

For exploratory efficacy endpoints of changes from baseline in assessment results (as listed in section 3.1.2.5.1), analysis will be conducted using the same methodology as that used for the primary efficacy endpoint (sections 8.5.2.1 and 8.5.2.1.1).

For other exploratory efficacy endpoints at Study Day 169:

- ISNCSCI ASIA impairment scale (A, B, C, D, E) will be summarized descriptively as the number and percent of subjects with each response at each visit by treatment group.
- ISNCSCI Neurological Motor level will be summarized descriptively as the number and percent of subjects by body part by treatment group.
- ISNCSCI Neurological Sensory level will be summarized descriptively as the number and percent of subjects by body part by treatment group.
- ISNCSCI Neurological Level of Injury (NLI) will be summarized descriptively as the number and percent of subjects by body part by treatment group.
- ISAFSCI assessments: for each system/organ, shift table of baseline evaluation to Study Day 169 evaluation will be created.
- Clinical Global Impression of Change (CGIC) from GRASSP Prehension Performance Video Recordings. Assessments of Baseline compared to Day 169 will be completed and scores will be assigned using the 7-point Likert scale questions shown below and the Fisher's exact test at two-sided significance level 0.05 will be used to test if there is a difference in ratings (1= 'Much worse', 2='Worse', 3=' A little worse', 4='No change', 5='A little better', 6='Better, 7=''Much better') at Study Day 169 between patients in treatment group and control group. In addition, the Fisher's exact test will be used to compare responder rate (proportion of patient in mITT Analysis set with responses of 'A little better', 'Better', or 'Much better') at Study Day 169 between the two treatment groups. A descriptive table summarizing number and percentage of patients for each of the seven above responses by visit and treatment group will be created.

All efficacy endpoints will also be analyzed for Study Day 253 similar to the analysis conducted for Study Day 169 for each corresponding endpoint. All post treatment values up until Study Day 253 will be included in the analysis of treatment effect for Study Day 253.

8.6 Pharmacokinetic Assessment

8.6.1 Pharmacokinetic Analysis

In Parts 1 and 2, individual serum and CSF concentrations at each sampling time-point for AXER-204 will be presented by listings and descriptive summary statistics. Individual and mean serum and CSF concentration versus time data will be plotted

on linear and semi-logarithmic scales. In Part 1, all PK parameters will be presented by individual listings and summary statistics.

Summary statistics for concentration and PK parameter data will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, number of observations, geometric mean and geometric coefficient of variation (CV%).

In Part 1, the following pharmacokinetic parameters will be determined where possible from the serum and CSF concentrations of AXER-204 using non-compartmental methods performed using Phoenix WinNonlin (Certara, Inc., Version 8.1 or higher):

Parameter	Definition
$AUC_{0\text{-}tlast}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time zero to infinity
$\%AUC_{extrap}$	Area under the concentration-time curve extrapolated from last quantifiable concentration to infinity as a percentage of total AUC
C_{max}	Maximum observed concentration
t_{max}	Time of the maximum observed concentration
$t_{1/2}$	Apparent terminal elimination half-life
CL/F	Apparent total serum clearance
V_z/F	Apparent volume of distribution during the terminal elimination phase (serum only)

In addition, dose normalised values (suffixed DN) for $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max} will be determined by dividing the original PK parameter by mg.

Additional pharmacokinetic parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual post-dose times recorded in the raw data. If actual sampling times are missing, nominal times may be used.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest T_{max} will be reported.

AUC will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up/log down rule).

The parameters based on observed C_{last} will be reported.

The following regression related pharmacokinetic parameters will be determined and presented in the listings:

Parameter	Definition
λz	Elimination rate constant
λz upper	End of exponential fit
λz lower	Start of exponential fit
λz N	Number of data points included in the log-linear regression
t1/2_interval ratio	Ratio of $t_{1/2}$ relative to the λz interval (λz upper - λz lower)
Rsq_adj	Adjusted coefficient for determination of exponential fit

8.6.1.1 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

- Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows;
    - Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
    - If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
    - If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

8.6.1.2 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

- **Number of Data Points**
    - At least three data points will be included in the regression analysis and preferably should not include C_{max}.
- **Goodness of Fit**
    - When assessing terminal elimination phases, the R^2 adjusted (Rsq_adj) value will be used as a measure of the goodness of fit of the data points to the determined line.
    - An elimination half-life will generally only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7. Exceptions can be made (e.g. CSF) for exploratory purposes.
- **Period of Estimation**
    - Time period used for the estimation of apparent terminal elimination half-lives, where possible, will be over at least two half-lives ($t_{1/2}$_interval ratio).
    - Where $t_{1/2}$_interval ratio < 2 the robustness of the value(s) may be discussed in the study report.

8.6.1.3 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.
- For any partial AUC determination (i.e. AUC over a dosing interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.
- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 20% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 20% may be excluded from descriptive statistics at the discretion of pharmacokineticist.

8.6.1.4 Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected pharmacokinetic profile, it may be appropriate to exclude this

point from the pharmacokinetic analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

8.6.2 Presentation of Pharmacokinetic Data

8.6.2.1 Presentation Pharmacokinetic Concentration Data

- The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a concentration data series to be summarised.
    - For the calculation of summary statistics, BLQ values will be set to zero.
    - If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
    - Where there is NR, these will be set to missing.
    - If there are less than three values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
    - If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
    - If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

8.7 Immunogenicity Analysis

All anti-drug antibody (ADA) data collected in eCRF will be listed for the ADA analysis set. Positive ADA status for a sample is defined as having the screen assay reported as detected and the confirmatory assay reported as confirmed. Negative ADA status for a sample is defined as either having an assay reported as negative or having the screen assay reported as detected and the confirmatory assays reported as not confirmed.

The number and percentage of subjects with positive or negative ADA status will be summarized by dose cohort for Part 1 or by treatment group for Part 2 and time point.

8.8 Safety

All safety analyses will be conducted for the Safety population.

8.8.1 Extent of Exposure

Exposure data for the study treatment will be listed for both Part 1 and Part 2.

For Part 2, the following variables will be summarized for each treatment group:

- Treatment duration: Treatment duration (days) is defined as the date of last infusion – the date of first infusion +1.
- Number of infusions
- Cumulative dose: cumulative dose is defined as the sum of all doses taken during treatment period.
- Type of modification including drug interrupted, withdrawn, reduced, delayed/not given, or rate changed.

8.8.2 Adverse Events

All adverse events (AEs) recorded on the eCRF will be coded using the MedDRA dictionary [Version 22.0 (or a later version if updated during the study)] and classified as pre-treat AEs, or treatment-emergent AEs as follows:

- Pre-treat AEs are events that start prior to the date of first dose of study treatment;
- TEAEs are events with start date on or after the date of first dose of study treatment, or with a start date prior to the date of first dose of study treatment whose severity worsens on or after the date of first dose of study treatment. TEAEs will be limited to those events occurring within 28 days after the last injection of study treatment, with AEs occurring after that being defined as post-treatment. AEs with missing start date after applying imputation rules will be considered as TEAEs.

Assessment of AE severity will be based on the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). Missing severity will not be imputed.

The relationship between an AE and study treatment is assessed as definitely, probably, possibly, unlikely, or not related. A treatment-related AE is an AE considered by the investigator as definitely, possibly, or probably related to study treatment or with unknown/missing relationship to study treatment.

All AE data will be listed. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of serious AEs (SAEs), AEs leading to discontinuation from study, AEs of special interest, and AEs resulting in death will be produced.

Summary tables of TEAEs by dose cohort for Part 1 or by treatment group for Part 2 and overall will be produced.

An overview table will summarize the number and percentage of subjects with at least one of the following TEAEs, where subjects with more than one TEAE in a particular category are counted only once in that category:

- Any TEAE;
- TEAE by maximum severity;
- Treatment-related TEAE;
- TEAE leading to discontinuation from study;
- TEAE of Special Interest;
- Serious TEAE;
- Treatment-related serious TEAE;
- Serious TEAE leading to discontinuation from study;
- Serious TEAE leading to death.

The number of total TEAEs will be also included in the overview table.

The number and percentage of subjects reporting each TEAE will be summarized by SOC and PT, or PT. Tables will be sorted in descending overall frequency by SOC, and then in descending overall frequency by PT within SOC, and then alphabetically. The following summaries will be produced:

- TEAEs, by SOC and PT;
- TEAEs, by PT;
- TEAEs, by SOC and PT and maximum severity;
- Treatment-related TEAEs, by SOC and PT;
- Lumbar Puncture procedure related TEAEs, by SOC and PT (Part 2 only);
- TEAEs leading to discontinuation from study, by SOC and PT;
- TEAEs of Special Interest, by SOC and PT;
- Serious TEAEs, by SOC and PT;
- Treatment-related serious TEAEs, by SOC and PT;
- Lumbar Puncture procedure related serious TEAEs, by SOC and PT (Part 2 only);
- Serious TEAEs leading to discontinuation from study, by SOC and PT;
- Serious TEAEs leading to death, by SOC and PT.

In the above summaries, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT.

8.8.3 Laboratory Evaluations

All clinical laboratory data will be listed. Data for the following hematology, clinical chemistry, urinalysis and CSF laboratory (part 2 only) analytes (Table 7) will be summarized by dose cohort for Part 1 or treatment group for Part 2 and overall, and by visit. If data for any additional analytes are also recorded, then these will be listed only.

Table 7 Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis	CSF Analysis (Part 2)
Hematocrit Hemoglobin Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Platelet count Red blood cell (RBC) count Red cell distribution width (RDW) White Blood Cell (WBC) Count including differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Alanine transaminase (ALT) Albumin Alkaline phosphatase Aspartate transaminase (AST) Bicarbonate Blood urea nitrogen Calcium Chloride Cholesterol Creatine kinase Creatinine Direct bilirubin Gamma-Glutamyl transferase (GGT) Glucose Lactate dehydrogenase Phosphorus Potassium Sodium Total bilirubin Total protein Triglycerides Uric acid	Blood Glucose Ketones pH Protein Specific gravity Urine bilirubin	Total protein Glucose Red blood cells count White blood cells count Lymphocytes count Neutrophils count

All laboratory data will be reported in Conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Hematology and clinical chemistry data will be summarized for each dose cohort using standard descriptive statistics. Changes from baseline will also be summarized. Shift

tables presenting movement in and out of reference range from baseline to each scheduled post-baseline visit will also be provided.

Number and percentage of subjects having any clinically significant laboratory value during post-baseline will be summarized for hematology, clinical chemistry, and urinalysis analytes. In addition, number and percentage of subjects having new-onset potentially clinically significant (PCS) laboratory values will be summarized. A PCS value is defined as a value that is out-of-reference-range. New-onset value for an analyte 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. The denominator for calculating the percentage is the number of subjects without any PCS values at baseline and with at least one post-baseline assessment.

For each laboratory analyte, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the study treatment administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

8.8.4 Vital Signs

The following vital signs will be listed and summarized by dose cohort and overall, and by visit for Part 1:

- systolic and diastolic blood pressure (mmHg);
- pulse rate (bpm);
- Pulse Oximetry (%);
- respiration rate (breaths/min);
- body temperature (°C);
- weight (kg);
- BMI (kg/m^2).

Temperature will be displayed in degrees Celsius (°C); temperatures recorded in degrees Fahrenheit (°F) will be converted as: [temperature (°C) = (temperature (°F) – 32)×5/9]. Height will be displayed in centimeters (cm); height recorded as inches (in) will be converted as: [height (cm) = height (in)*2.54]. Weight will be displayed in kilograms (kg); weight recorded as pounds (lb) will be converted as: [weight (kg) = weight (lb)*0.45359237]. BMI recorded in pounds and inches will be re-calculated as the following: BMI(kg/m^2) = BMI(lb/in^2) * 703.

All vital signs data will be listed. For Part 1, vital signs data including blood pressure, pulse rate, pulse oximetry, respiration rate, and temperature and changes from baseline for the following time points will be summarized by dose cohort and visit using standard descriptive statistics:

- Day 1 Pre-Dose;

- Day 1 Post-Dose first measurement;
- First Measurement for Days 2, 3, 4, 8, 15, and 29.

For Part 2, same set of vital sign variables and change from baseline will be summarized by treatment group and the time points below.

- Day 1 Pre-Dose;
- Day 1 Post-Dose first measurement;
- First Measurement for Days 21, 42, 63, 84, 104, 169, and 253.

For both Part 1 and Part 2, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the study treatment administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

8.8.5 Electrocardiograms

The following quantitative ECG measurements will be listed and summarized by dose cohort for Part 1 or by treatment group for Part 2 and overall, and by visit:

- heart rate (bpm);
- RR interval (msec), calculated as (60/HR)*1000;
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia corrected QT (QTcF) interval (msec), calculated as QT/$\sqrt[3]{RR/1000}$.

Triplicate ECG will be taken in the study. Average values will be computed from available assessments from the triplicate ECGs to be used for data summaries.

The ECG measurements and changes from baseline in ECG will be listed and summarized using standard descriptive statistics.

An overall Investigator assessment of ECG will be listed and summarized as number and percentage of subjects with each assessment category by visit (categories: "normal", "abnormal, not clinically significant" and "abnormal, clinically significant").

Shifts from baseline (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) to the worst post-baseline interpretation will be presented.

The baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the study treatment administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

8.8.6 Physical Examination

Physical examination results (normal/abnormal) and details of abnormalities will be listed.

8.8.7 Condition-specific Safety Variables (Part 1 and Part 2)

The following condition-specific safety variables will be summarized by dose cohort for part 1 or by treatment group for part 2 and overall, and by visit using standard descriptive statistics, changes from baseline will be also summarized:

- Total MAS score, calculated as the sum of scores of all items. The MAS score for each item will be re-assigned as the following:

MAS score	Score used in analysis
0	0
1	1
1+	2
2	3
3	4
4	5

- BPI pain severity measured at "worst", "least", "average", and "now", obtained from eCRF;
- Mean BPI pain interference, calculated as the mean of all completed interference items if at least four of all seven items have been completed on a given administration.

For part 2, change from baseline in Bilateral MAS total scores for Elbow, Wrist, Hamstrings, Quadriceps, Gastrocnemius, and Soleus; mean BPI pain score; or mean BPI pain interference score, to Study Day 169 will be analyzed using the same methodology as that used for the primary efficacy endpoint (sections 8.5.2.1 and 8.5.2.1.1). Same statistical analysis will also be conducted for Study Day 253.

8.9 Interim Analysis

No interim analysis will be performed for this study.

9. Changes from the Protocol Specified Statistical Analyses

The following changes from protocol specified statistical analyses are made in this SAP.

9.1 Secondary efficacy endpoint

Patient Global Impression of Change (PGIC) responder rate will be considered secondary efficacy endpoint.

9.2 Exploratory efficacy endpoint

- In SAP, ISNCSCI UEMS for the side with the higher baseline score and the side with the lower baseline score will be analyzed as exploratory efficacy endpoint. If the baseline scores for each side are equal, then the right side will be grouped with the higher baseline UEMS scores for analysis.
- ISNCSCI total motor scores instead of lower extremity motor score are included in SAP as exploratory efficacy endpoints.
- Clinical Global Impression of Change (CGIC) from GRASSP Prehension Performance Video Recordings

9.3 Analysis population

PK Analysis set and ADA analysis set were added in the SAP for analysis for PK and ADA, respectively. In addition, mITT analysis set was added for Part 2 and all Part 2 efficacy analysis will be conducted using mITT analysis set.

10. Changes in the Planned Statistical Analyses

The following changes in the planned statistical analyses indicated below are being made after all enrolled Part 2 patients have completed the 6-month visit, cleaning and unblinding of data, and completion of the 6-month top-line analysis for the primary, secondary and exploratory efficacy endpoints to compare treatment effects from baseline to Study Day 169 and prior to final database lock following 9-month visit or Study Day 253 (as described in section 2.2). The availability of results of this analysis was limited to the unblinded ReNetX staff and [redacted] Biostatistics and Programming team. The changes were requested by the unblinded ReNetX staff after review of results and approved by [redacted] Biostatistics and Programming team.

10.1 Post Hoc Exploratory Analysis for Efficacy Endpoints to Study Day 169

Results from the primary efficacy analysis, based upon a mixed-effects model for repeated measures (MMRM) as described in section 8.5.2.1, showed that there was no statistically significant difference at the two-sided 5% significance level between AXER-204 and Placebo groups in the primary efficacy endpoint. Additionally, the MMRM subgroup exploratory analyses (as described in section 8.5.2.1.3) did not show statistical significant difference between treatment and control groups in the primary endpoint at the unadjusted two-sided 5% significance level, but there is visually a potential trend toward treatment effect in the subgroups AIS grade (B, C, D) and no prior receipt of study drug in Part 1.

Therefore, ReNetX performed exploratory analyses on several endpoints in these subgroups, which suggested that three endpoints had visually a higher change from baseline in AXER-204 group compared to Placebo group, and proposed additional post hoc analyses that may reveal treatment effect for the following efficacy endpoints. Similar to the subgroup analyses (section 8.5.2.1.3), the alpha from the primary efficacy analysis has been used, so no adjustment to the significance level for testing will be made because all these analyses will be considered exploratory. For this reason, no formal conclusions can be drawn from any differences, and p-values will be provided for descriptive purposes only.

- **Primary efficacy endpoint:** Change from baseline in bilateral UEMS to Study Day 169 ranging from 0-50.
- **Secondary efficacy endpoint:** Change from baseline in GRASSP bilateral PP to Study Day 169 ranging from 0-40.
- **Exploratory efficacy endpoint:** Change from baseline in ISNCSCI bilateral motor score (including both upper and lower extremity for both left and right sides) to Study Day 169 ranging from 0-100.

- **Including patients with AIS grade (B, C, D)**

An analysis including patients with AIS grade (B, C, D) will be conducted in the mITT Analysis set. The same MMRM method as the primary analysis as described in section 8.5.2.1 will be used. Since subgroup analysis of AIS grade (A vs. B, C, D) on the primary efficacy endpoint have already been performed as part of the planned analysis, analysis will only be done on the secondary and exploratory efficacy endpoints.

- **Including patients with no prior recent of study drug in Part 1**

An analysis including patients with no prior receipt of study drug in Part 1 will be conducted in the mITT Analysis set. The same MMRM method as the primary analysis as described in section 8.5.2.1 will be used. Since subgroup analysis of prior receipt of study drug in Part 1 (yes vs. no) on the primary efficacy endpoint have already been performed as part of the planned analysis, analysis will only be done on the secondary and exploratory efficacy endpoints.

- **Including patients with AIS grade (B, C, D) and no prior receipt of study drug in Part 1**

An analysis including patients with AIS grade (B, C, D) and no prior receipt of study drug in Part 1 will be conducted in the mITT Analysis set. The same MMRM method as the primary analysis as described in section 8.5.2.1 will be used.

10.2 Post Hoc Exploratory Analysis for Efficacy Endpoints to Study Day 253

All efficacy endpoints as described in section 10.1 will also be analyzed for Study Day 253 similar to the analysis conducted for Study Day 169 for each corresponding endpoint. All post treatment values up until Study Day 253 will be included in the analysis of treatment effect for Study Day 253. Since no subgroup analyses were performed for Study Day 253 as part of the planned analyses, all three exploratory analyses will be performed on the primary efficacy endpoint as well as the secondary and exploratory efficacy endpoints.

10.3 Clarifications to Pre Hoc Slope Analysis

Clarifications to the secondary efficacy analysis, based upon a random coefficients model that compared the rate of change (slope) in the primary efficacy endpoint as described in section 8.5.2.1.1, was implemented prior to treatment unblinding for the 6-month top-line analysis (as described in section 2.2). The slope will measure rate of change of bilateral UEMS per month instead of per day in the interest of readability. Conversions from day to month will be baseline as Study month 0, Study day 21 as Study month 1, Study day 63 as Study month 2, Study day 104 as Study month 4, Study day 169 as Study month 6, and Study day 253 as Study month 9.

The slope analysis is similar to the MMRM model in the primary efficacy analysis as described in section 8.5.2.1, but will include bilateral UEMS as the dependent variable; treatment, AIS grade (A,B vs C,D) and prior receipt of study drug in Part

1 (yes vs. no) as the fixed categorical effects; as well as visit (Study month 0, 1, 2, 4, and 6) and treatment-by-visit interaction as the fixed continuous effects; and subject and subject by visit as the random effects. The unstructured covariance model will be used. In contrast to the primary efficacy analysis in section 8.5.2.1, if the computational algorithm fails to converge, the following will be tested in order, and the first that converges will be used: variance components covariance structure, removing random effect subject by visit and unstructured covariance structure, and removing random effect subject by visit and variance components covariance structure. Reporting and plotting of the model results will follow as described in section 8.5.2.1.1, but excluding overall rate of change in bilateral UEMS and 95% CI.

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