SUPPLEMENTAL INFORMATION

Soluble Nogo-Receptor-Fc decoy (AXER-204) for neural repair in patients with chronic cervical spinal cord injury: a first-in-human and randomized clinical trial

George Maynard, PhD, Ramakrishnan Kannan, PhD, Jian Liu, MS, Weiwei Wang, PhD, Tu Kiet T. Lam, PhD, Xingxing Wang, MD, Crista Adamson, PhD, Craig Hackett, PhD, Prof Jan M. Schwab, MD, Prof Charles Liu, MD, Donald P. Leslie, MD, David Chen, MD, Prof Ralph Marino, MD, Prof Ross Zafonte, DO, Prof Adam Flanders, MD, Gilbert Block, MD, Erika Smith, MBA and Prof Stephen M. Strittmatter, MD

Contains Statistical Methods, Proteomic Methods, Supplemental Tables S1-S11, Supplemental Figures S1-S10, Clinical Protocol and Statistical Analysis Plan.

Statistical analysis of part 2 efficacy

An overview of the MMRM methods to assess the efficacy outcomes for part 2 is provided in the main text. An unstructured covariance structure was used to model the within-patient errors. If this analysis failed to converge, the following covariance structures were to be tested in order, and the first covariance structure that converged was to 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). A check on normality, homogeneity of variance of residuals, sphericity, and linearity for quantitative predictors was not performed as part of the statistical analysis plan. However, even if some of these assumptions were violated, it would not necessarily invalidate the method of mixed-effects model. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Significance tests was based on LS Means using Type III sum of squares.

In addition to the primary MMRM model for Day 169, a secondary random coefficients model was used to compare the rate of change per month (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, except patient and patient by visit were included as random effects. The unstructured covariance model was used. There was no statistically significant difference between the AXER 204 group and the placebo group for the efficacy outcomes.

Analyses of the key secondary outcome included planned sensitivity analyses. Multiple imputations assuming missing not at random and multiple imputations assuming missing at random were planned, but not performed, due to minimal missing data. The Per Protocol population consisted of patients who received at least 5 doses of the planned cumulative number of doses of study drug (AXER-204 or placebo) and had no important protocol deviations that might have impacted efficacy assessment. This population excluded one subject in each group. The MMRM results for the key secondary outcome UEMS in this population also showed no statistically significant difference in change from baseline to Study Day 169 between treatment groups.

Proteomic methods

From each sample, 100 µg protein was digested with trypsin, and peptides separated by reverse phase liquid chromatography and analyzed by mass spectrometry using a nanoACQUITY UPLC system (Waters Corporation, Milford, MA, USA) connected to a Thermo Orbitrap Fusion mass spectrometer (ThermoFisher Scientific, San Jose, CA, USA) by Data-Independent Analysis (DIA) mode. Collected DIA spectra were searched against a *Homo Sapiens* CSF proteome spectral library generated in-house using Scaffold DIA software v. 2.2.0 (Proteome Software, Portland, OR, USA). The collected raw DIA data files were individually searched against the spectral library with a peptide mass tolerance of 10 ppm and a fragment mass tolerance of 10 ppm. The data acquisition type was set to "Non-Overlapping DIA", and the maximum missed cleavages was set to 2. Fixed and dynamic modifications included carbamidomethylation of cysteine (+57.02) and oxidation of methionine (+15.99), respectively. Peptides were initially filtered by Percolator v. 3.01 at a threshold FDR of 0.01. Resulting peptides with charge states between 2 and 4 with peptide lengths of 6 - 30 amino acids residues were considered for quantitation. Peptide quantification was performed by EncyclopeDIA v. 0.9.6 and five of the highest quality retention time aligned fragment ions were selected for quantitation. Proteins containing redundant peptides were grouped to satisfy the principles of parsimony, and proteins were filtered at a threshold of two peptides per protein and a false discovery rate (FDR) of 1%. After protein identification, values for keratin and immunoglobulin were removed as likely contaminants from the skin or AXER-204, respectively. Immunoblots of human CSF samples (10 µg) from part 1 were performed with anti-APP primary antibody (1:500, rabbit anti- N-Terminal-APP, Cat# A8967, Sigma-Aldrich, Inc., St. Louis, MO, USA) or anti-APLP1 primary antibody (1:1000, # PA5-78795, Thermo Fisher Scientific (Invitrogen), Waltham, MA, USA), followed by infra-red fluorescent secondary antibody and LiCor imaging. ELISA assays for Aß40 and Aß42 levels were performed according to the manufacturer's kit instructions (Aß40 - #KHB3481, Aß42 - #KHB3544, Thermo Fisher Scientific (Invitrogen), Waltham, MA, USA).

Analysis of proteomic data

For each protein identified, the abundance from each individual in part 1 was normalized to that individual's Pre-Dose value (Day 0). In each of the four dose groups, the normalized protein abundance was averaged. Changes in relative abundance were compared for each dose and time. The 200 mg Day 1 (24 hour post-dose) normalized values were evaluated statistically by calculating a False Discovery Rate corrected by Benjamini-Hochberg step-down method with Q=12%, and uncorrected P value of 0.01. To select the group of proteins with substantial changes we utilized a cut-off of |log2(Fold Change)| >0.9 and False Discovery Rate P value <0.05. These values were determined empirically and by inspection of the data. To compare the effect of AXER-204 dosing on CSF proteins as a function of time, protein abundance normalized by Day 0 values from the same individual was analyzed by repeated measure ANOVA. Sphericity was not assumed, and the Geisser-Greenhouse correction was used in a mixed effects model. Multiple time points were compared to Day 0 with a Dunnett's correction for multiple comparisons. To compare the effect of AXER-204 dosing on CSF proteins as a function of dose, protein abundance normalized by Day 0 values from the same individual was analyzed by non-parametric Kruskal-Wallis test because multiple samples deviated significantly from a Gaussian distribution. Different doses were compared to the 3 mg dose with a Dunn's correction for multiple comparisons.

The CSF proteins regulated by AXER-204 were mapped to gene ontology (GO) pathways using ClueGO[44]. AXER-204-regulated proteins that mapped to particular gene ontology clusters were assessed for protein-protein interactions in the String database (<string-db.org>)[45].

Supplemental Table S1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Men or women between the ages of 18 and 65 years, inclusive 2. Traumatic spinal cord injury that occurred ≥ 1 year ago 3. Cervical spinal cord injury with serious neurological deficit as evidenced by 1) bilateral ISNCSCI UEMS between 4 and 36 points inclusive, and 2) bilateral GRASSP prehension ability score between 4 and 17 points inclusive 4. Confirmation by MRI of the following: a. Chronic SCI (persistent spinal cord lesion) b. For AIS grade of A without sensory or motor zone of partial preservation extending at least two levels caudal to the level of injury, no apparent transection of the cord c. CSF space spanning the lesion 5. Read, understood, and provided written informed consent after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.	1. Penetrating injury to the cord or spinal cord trauma caused by ballistic injury including gunshot that did not penetrate the spinal cord 2. Women who are pregnant or lactating, and women of childbearing potential except those using adequate birth control measures. All female participants must have a negative serum pregnancy test at Screening and women of childbearing potential must have a negative urine pregnancy run locally at the Randomization/Pre-Dose Visit on Study Day 1. All participants (male and female) as well as non-study female partners of male participants, must use adequate birth control measures during the course of the study and for at least 10 weeks after the participants' last dose of investigational product • Adequate or effective contraception is defined as double barrier contraception (eg, condom plus spermicide in combination with a female condom, diaphragm, cervical cap, contraceptive sponge, implants, injectables, combined oral contraceptives, sexual abstinence (total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable), or sexual intercourse with only a vasectomized partner. Participants and/or partners who are surgically sterile or women with confirmed postmenopausal status are exempt from this requirement. 3. History of stroke, cerebrovascular injury, or elevated intracranial pressure 4. Contraindications for lumbar puncture 5. Requiring mechanical ventilatory assistance of any type 6. Body mass index (BMI) ≥ 35 kg/m^2 or body weight <50 kg 7. Botulinum toxin injection, with the exception of bladder treatments, within 4 months prior to study 8. History of life threatening allergic or immune-mediated reaction to vaccines, or biologic drugs, at any time or any life threatening allergic or immune-mediated reaction within the past 12 months. 9. Systemic use of immunosuppressants within the past 2 months with the exception of mineralocorticoids 10. Significant deformities, contractures (with less than 50% of normal range of motion at affected joints), or any issues that limit completion of UEMS with the ISNCSCI exam 11. Recent changes in anti-spasmodic or anti-spasticity medications. Anti-spasmodic or anti-spasticity medication is permitted providing that the subject has been on a stable dose for at least 12 weeks before the Screening Visit (Visit 1) and agrees to remain on a stable dose throughout the course of the study 12. Any orthopedic injury, recent surgeries, or current diagnosis of any primary diseases affecting upper limb function outside of SCI (eg, infection, tumor, congenital malformations, Huntington's disease, Parkinson's disease) 13. Participants fitted with an implanted pump or port for delivery of therapeutics to the CSF 14. Uncontrolled medical condition including but not limited to cardiovascular disease, sleep apnea, obstructive lung disease, severe neuropathic or severe chronic pain, severe autonomic dysreflexia 15. Participation in any other investigational drug or device trial within 30 days or within 5 half-lives of the investigational drug or any past participation in a SCI cellular therapy trial. 16. Regular use of the following concomitant medications that might confound efficacy and/or safety assessments is prohibited, including, but not limited to, the following:

	a. Antipsychotic drugs **with the exception of use** of these mood stabilizers for the adjunctive treatment of depression provided the subject is on a stable dose for at least 12 weeks prior to Screening and the dose is not anticipated to change during participation in the trial. b. Anticoagulants, however, daily low dose aspirin (81mg) therapy is permitted. c. Opiates, sedative hypnotics, or tranquilizers **unless used to treat anxiety, pain, or sleep disorder** and the dosage and frequency of use are not considered likely to interfere with evaluation of safety and efficacy endpoints in the trial. Determination of exclusion due to use of a specific medication from these classes of medications will be made by the Principal Investigator in conjunction with the Medical Monitor and sponsor physician based on medical assessment of factors including the dosage, frequency of use, and medical condition being treated. d. Use of tumor necrosis factor [TNF] inhibitors e. Use of Class 1 antiarrhythmic. 17. Use of antidepressants (SSRI, SNRI, TCA, buspirone) is PERMITTED but limited to subject being on a stable dose for at least 12 weeks 18. History of severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with trial participation or investigational product administration or could interfere with the interpretation of trial results and including but not limited to the following: • human immunodeficiency virus (HIV) infection • active chronic hepatitis B or hepatitis C infection including hepatitis B surface antigen and hepatitis C antigen positive participants with or without abnormal liver enzymes • immunosuppressive disease • chronic renal disease/failure as evidenced by estimated glomerular filtration rate (eGFR) of <60 • concurrent neurodegenerative disease • cardiovascular: uncontrolled hypertension, unstable angina, myocardial infarction or symptomatic congestive heart failure within the past 12 months or serious uncontrolled and clinically significant cardiac arrhythmia as determined by the investigator • dementia or significantly altered mental status including brain injury with ongoing cognitive signs and symptoms that would prohibit the understanding or rendering of informed consent and compliance with the requirements of the protocol 19. Evidence or self-report of alcohol or drug abuse within the previous 12 months 20. Any conditions that in the judgement of the investigator would make the subject inappropriate for entry into the trial

Supplemental Table S2. Overall Summary of Treatment-Emergent Adverse Events in Part 1 and 2 (Safety Population)

	Part 1					Part 2		
	AXER-204					AXER-204 200 mg N = 14 n (%)	Placebo N = 13 n (%)	Total N = 27 n (%)
	3 mg N = 6 n (%)	30 mg N = 6 n (%)	90 mg N = 6 n (%)	200 mg N = 6 n (%)	Total N = 24 n (%)			
Patients with AEs	5 (83%)	4 (67%)	5 (83%)	6 (100%)	20 (83%)	14 (100%)	10 (77%)	24 (89%)
Number of AEs	14	9	15	34	72	138	82	220
Patients with AEs maximum severity								
Grade 1	4 (67%)	4 (67%)	3 (50%)	2 (33%)	13 (54%)	2 (14%)	3 (23%)	5 (19%)
Grade 2	1 (17%)	0	2 (33%)	4 (67%)	7 (29%)	8 (57%)	4 (31%)	12 (44%)
Grade 3	0	0	0	0	0	4 (29%)	3 (23%)	7 (26%)
Grade 4	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0
Patients with treatment-related AEs[a]	1 (17%)	3 (50%)	4 (67%)	4 (67%)	12 (50%)	10 (71%)	9 (69%)	19 (70%)
Patients with AEs leading to discontinuation from study	0	0	0	0	0	0	0	0
Patients with AESIs	3 (50%)	2 (33%)	5 (83%)	4 (67%)	14 (5%)	14 (100%)	10 (77%)	24 (89%)
Patients with SAEs	0	0	0	0	0	4 (29%)	2 (15%)	6 (22%)
Patients with treatment-related SAEs[a]	0	0	0	0	0	0	1 (8%)	1 (4%)
Patients with SAEs leading to discontinuation from study	0	0	0	0	0	0	0	0
Patients with SAEs leading to death	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in Safety Population in each treatment group; n = number of patients with valid observations; SAE = serious adverse event

a = Included AEs considered by the investigator as definitely, possibly, or probably related to study treatment or with unknown/missing relationship to study treatment.

Notes: All AEs included in the table are treatment-emergent AEs. Treatment-emergent AEs were events with a 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 worsened on or after the date of first dose of study treatment. Treatment-emergent AEs were limited to those events that occurred within 28 days after the last visit. Patients with more than 1 TEAE in a particular category were counted only once in that category. For maximum severity, patients with multiple AEs were counted under the category of their most severe AE. Adverse events were coded using the MedDRA dictionary (Version 22.0). Severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

Supplemental Table S3. Most Frequent Treatment-Emergent Adverse Events in Part 1 Safety Population

System Organ Class Preferred Term	AXER-204				Total
	3 mg (N = 6) n (%)	30 mg (N = 6) n (%)	90 mg (N = 6) n (%)	200 mg (N = 6) n (%)	(N = 24) n (%)
Patients with any AEs	5 (83%)	4 (67%)	5 (83%)	6 (100%)	20 (83%)
Nervous system disorders	4 (67%)	2 (33%)	4 (67%)	5 (83%)	15 (63%)
Headache	*3 (50%)*	*1 (17%)*	*3 (50%)*	*5 (83%)*	*12 (50%)*
Paresthesia	*0*	*0*	*2 (33%)*	*2 (33%)*	*4 (17%)*
Muscle spasticity	*0*	*1 (17%)*	*0*	*1 (17%)*	*2 (8%)*
General disorders and administration site conditions	1 (17%)	3 (50%)	1 (17%)	3 (50%)	8 (33%)
Pyrexia	*0*	*2 (33%)*	*1 (17%)*	*2 (33%)*	*5 (21%)*
Injury, poisoning and procedural complications	1 (17%)	1 (17%)	1 (17%)	2 (33%)	5 (21%)
Procedural headache	*1 (17%)*	*0*	*1 (17%)*	*1 (17%)*	*3 (13%)*
Musculoskeletal and connective tissue disorders	1 (17%)	0	2 (33%)	2 (33%)	5 (21%)
Back pain	*1 (17%)*	*0*	*1 (17%)*	*1 (17%)*	*3 (13%)*
Investigations	1 (17%)	1 (17%)	0	1 (17%)	3 (13%)
Blood pressure increased	*0*	*1 (17%)*	*0*	*1 (17%)*	*2 (8%)*
Gastrointestinal disorders	0	0	0	2 (33%)	2 (8%)
Skin and subcutaneous tissue disorders	2 (33%)	0	0	0	2 (8%)

Frequency >5% of the Total Patients

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in Safety Population in each treatment group; n = number of patients with valid observations

Notes: Percentages were calculated based on N. All AEs included in the table are treatment-emergent AEs. Patients with more than 1 AE within a particular SOC were only counted once in that SOC. Patients with more than 1 AE within a particular PT were only counted once in that PT. The table is displayed in descending overall frequency by SOC and in descending overall frequency by PT within SOC, and then alphabetically. Adverse events were coded using the MedDRA Dictionary (Version 22.0).

Supplemental Table S4. Most Frequent Treatment-Emergent Adverse Events in Part 2 Safety Population

System Organ Class Preferred Term	AXER-204 200 mg (N = 14) n (%)	Placebo (N = 13) n (%)	Total (N = 27) n (%)
Patients with any AEs	14 (100%)	10 (77%)	24 (89%)
Nervous system disorders	13 (93%)	8 (62%)	21 (78%)
Headache	*13 (93%)*	*6 (46%)*	*19 (70%)*
Paresthesia	*3 (21%)*	*5 (39%)*	*8 (30%)*
Pleocytosis	*6 (43%)*	*0*	*6 (22%)*
Muscle spasticity	*4 (29%)*	*1 (8%)*	*5 (19%)*
Infections and infestations	8 (57%)	4 (31%)	12 (44%)
Urinary tract infection	*6 (43%)*	*4 (31%)*	*10 (37%)*
Cellulitis	*1 (7%)*	*1 (8%)*	*2 (7%)*
Gastrointestinal disorders	5 (36%)	6 (46%)	11 (41%)
Constipation	*1 (7%)*	*2 (15%)*	*3 (11%)*
Nausea	*1 (7%)*	*2 (15%)*	*3 (11%)*
Musculoskeletal and connective tissue disorders	6 (43%)	5 (39%)	11 (41%)
Back pain	*3 (21%)*	*4 (31%)*	*7 (26%)*
Muscle tightness	*2 (14%)*	*1 (8%)*	*3 (11%)*
Neck pain	*2 (14%)*	*0*	*2 (7%)*
Pain in extremity	*1 (7%)*	*1 (8%)*	*2 (7%)*
Injury, poisoning and procedural complications	5 (36%)	5 (39%)	10 (37%)
Autonomic dysreflexia	*0*	*3 (23%)*	*3 (11%)*
Post lumbar puncture syndrome	*1 (7%)*	*1 (8%)*	*2 (7%)*
Thermal burn	*1 (7%)*	*1 (8%)*	*2 (7%)*
Investigations	6 (43%)	1 (8%)	7 (26%)
Blood pressure increased	*1 (7%)*	*1 (8%)*	*2 (7%)*
CSF protein increased	*2 (14%)*	*0*	*2 (7%)*
Skin and subcutaneous tissue disorders	4 (29%)	3 (23%)	7 (26%)
Hyperhidrosis	*1 (7%)*	*1 (8%)*	*2 (7%)*
General disorders and administration site conditions	3 (21%)	1 (8%)	4 (15%)
Chills	*2 (14%)*	*0*	*2 (7%)*
Fatigue	*1 (7%)*	*1 (8%)*	*2 (7%)*
Renal and urinary disorders	2 (14%)	2 (15%)	4 (15%)
Urinary incontinence	*2 (14%)*	*1 (8%)*	*3 (11%)*
Psychiatric disorders	3 (21%)	0	3 (11%)
Mental fatigue	*2 (14%)*	*0*	*2 (7%)*

Frequency >5% of the Total Patients

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in Safety Population in each treatment group; n = number of patients with valid observations

Notes: Percentages were calculated based on N. All AEs included in the table are treatment-emergent AEs. Treatment-emergent AEs were events with a 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 worsened on or after the date of first dose of study treatment. Treatment-emergent AEs were limited to those events that occurred within 28 days after the last visit. Patients with more than 1 AE within a particular SOC were only counted once in that SOC. Patients with more than 1 AE within a particular PT were only counted once in that PT. The table is displayed in descending overall frequency by SOC and in descending overall frequency by PT within SOC, and then alphabetically. Adverse events were coded using the MedDRA Dictionary (Version 22.0).

Supplemental Table S5. Most Frequent Treatment-Related Treatment-Emergent Adverse Events in Part 1 Safety Population

System Organ Class Preferred Term	AXER-204 3 mg (N = 6) n (%)	AXER-204 30 mg (N = 6) n (%)	AXER-204 90 mg (N = 6) n (%)	AXER-204 200 mg (N = 6) n (%)	Total (N = 24) n (%)
Patients with any AEs	1 (17%)	3 (50%)	4 (67%)	4 (67%)	12 (50%)
Nervous system disorders	0	1 (17%)	3 (50%)	4 (67%)	8 (33%)
Headache	*0*	*1 (17%)*	*1 (17%)*	*3 (50%)*	*5 (21%)*
Paresthesia	*0*	*0*	*2 (33%)*	*2 (33%)*	*4 (17 %)*
Hypertonia	*0*	*0*	*0*	*1 (17%)*	*1 (4%)*
Muscle spasticity	*0*	*0*	*0*	*1 (17%)*	*1 (4%)*
Neurological symptom	*0*	*0*	*0*	*1 (17%)*	*1 (4%)*
General disorders and administration site conditions	1 (17%)	2 (33%)	1 (17%)	2 (33%)	6 (25%)
Pyrexia	*0*	*2 (33%)*	*1 (17%)*	*1 (17%)*	*4 (17%)*
Chills	*0*	*0*	*0*	*1 (17%)*	*1 (4%)*
Feeling hot	*1 (17%)*	*0*	*0*	*0*	*1 (4%)*
Swelling	*0*	*0*	*1 (17%)*	*0*	*1 (4%)*
Injury, poisoning and procedural complications	0	1 (17%)	1 (17%)	0	2 (8%)
Infusion related reaction	*0*	*1 (17%)*	*0*	*0*	*1 (4%)*
Procedural headache	*0*	*0*	*1 (17%)*	*0*	*1 (4%)*
Musculoskeletal and connective tissue disorders	0	0	1 (17%)	0	1 (4%)
Back pain	*0*	*0*	*1 (17%)*	*0*	*1 (4%)*
Renal and urinary disorders	0	1 (17%)	0	0	1 (4%)
Urinary incontinence	*0*	*1 (17%)*	*0*	*0*	*1 (4%)*

Frequency >5% of the Total Patients

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in Safety Population in each treatment group; n = number of patients with valid observations

Notes: Percentages were calculated based on N. All AEs included in the table are treatment-related treatment-emergent AEs. Patients with more than 1 AE within a particular SOC were only counted once in that SOC. Patients with more than 1 AE within a particular PT were only counted once in that PT. The table is displayed in descending overall frequency by SOC and in descending overall frequency by PT within SOC, and then alphabetically. Adverse events were coded using the MedDRA Dictionary (Version 22.0).

Supplemental Table S6. Most Frequent Lumbar Puncture-Related Treatment-Emergent Adverse Events in Part 2 Safety Population

System Organ Class Preferred Term	AXER-204 200 mg (N = 14) n (%)	Placebo (N = 13) n (%)	Total (N = 27) n (%)
Patients with any AEs	13 (93%)	8 (62%)	21 (78%)
Nervous system disorders	13 (93%)	6 (46%)	19 (70%)
Headache	*13 (93%)*	*5 (39%)*	*18 (67%)*
Pleocytosis	*6 (43%)*	*0*	*6 (22%)*
Paresthesia	*3 (21%)*	*2 (15%)*	*5 (19%)*
Muscle spasticity	*2 (14%)*	*1 (8%)*	*3 (11%)*
Cerebrospinal fluid leakage	*0*	*1 (8%)*	*1 (4%)*
Neuropathy peripheral	*1 (7%)*	*0*	*1 (4%)*
Musculoskeletal and connective tissue disorders	5 (36%)	4 (31%)	9 (33%)
Back pain	*3 (21%)*	*3 (23%)*	*6 (22%)*
Muscle tightness	*2 (14%)*	*1 (8%)*	*3 (11%)*
Neck pain	*2 (14%)*	*0*	*2 (7%)*
Musculoskeletal stiffness	*1 (7%)*	*0*	*1 (4%)*
Myalgia	*1 (7%)*	*0*	*1 (4%)*
Gastrointestinal disorders	2 (14%)	2 (15%)	4 (15%)
Anal incontinence	*0*	*1 (8%)*	*1 (4%)*
Nausea	*1 (7%)*	*0*	*1 (4%)*
Odynophagia	*1 (7%)*	*0*	*1 (4%)*
Vomiting	*0*	*1 (8%)*	*1 (4%)*
Injury, poisoning and procedural complications	1 (7%)	3 (23%)	4 (15%)
Autonomic dysreflexia	*0*	*2 (15%)*	*2 (7%)*
Post lumbar puncture syndrome	*1 (7%)*	*1 (8%)*	*2 (7%)*
Investigations	3 (21%)	1 (8%)	4 (15%)
CSF protein increased	*2 (14%)*	*0*	*2 (7%)*
Blood pressure increased	*0*	*1 (8%)*	*1 (4%)*
Body temperature decreased	*1 (7%)*	*0*	*1 (4%)*
General disorders and administration site conditions	2 (14%)	0	2 (7%)
Chills	*1 (7%)*	*0*	*1 (4%)*
Fatigue	*1 (7%)*	*0*	*1 (4%)*
Skin and subcutaneous tissue disorders	1 (7%)	1 (8%)	2 (7%)
Blister	*0*	*1 (8%)*	*1 (4%)*
Hyperhidrosis	*1 (7%)*	*0*	*1 (4%)*

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in Safety Population in each treatment group; n = number of patients with valid observations

Notes: Percentages were calculated based on N. All AEs included in the table are lumbar puncture procedure-related treatment-emergent AEs. Treatment-emergent AEs were events with a 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 worsened on or after the date of first dose of study treatment. Treatment-emergent AEs were limited to those events that occurred within 28 days after the last visit. Lumbar puncture procedure-related AEs included AEs considered by the investigator as definitely, probably, or possibly related to lumbar puncture or with unknown/missing relationship to lumbar puncture. Patients with more than 1 AE within a particular SOC were only counted once in that SOC. Patients with more than 1 AE within a particular PT were only counted once in that PT. The table is displayed in descending overall frequency by SOC and in descending overall frequency by PT within SOC, and then alphabetically. Adverse events were coded using the MedDRA Dictionary (Version 22.0).

Supplemental Table S7. Anti-Drug Antibody (ADA) Responses

Serum Antidrug Antibody Titers in Four Positive Participants							
Day 1	**Day 21**	**Day 42**	**Day 63**	**Day 84**	**Day 104**	**Day 169**	**Day 253**
	5		10				
			5				
			5		160	40	5
			<5				

Notes: Of the 14 patients exposed to AXER-204 in part 2, four patients had confirmed ADA responses in pre-dose serum samples collected at the indicated study days. Each row reports the serum titer for ADA responses from one of the four positive individuals as detected using a sensitive validated method. Briefly, a bridging assay employed the Meso Scale Discovery (MSD) electrochemiluminescence (ECL) platform and used AXER-204 to capture ADA and ruthenylated AXER-204 to detect antibodies which bind to the biotherapeutic, AXER-204. An acid dissociation step was included to increase drug tolerance. Ruthenylated drug was detected using an MSD S600 plate reader. The presence of antidrug antibody was determined by comparing the signal in the sample or control to a statistically derived threshold, the assay cut point. This assay employed three confirmatory assays targeting the whole molecule, the human Nogo Receptor 1 (NgR1) portion of the molecule, and the human IgG Fc portion of the AXER-204 molecule. The titer is calculated as the MRD x dilution factor at which normalized signal falls below the established titer cutpoint. The MRD for the assay is 5.

Supplemental Table S8. Protein Identification and Quantification by CSF LC/MS/MS.

Separate Excel file listing protein name, accession, detailed description, number of peptides identified, and quantification for each sample analysis.

Supplemental Table S9. Proteins Significantly Up- or Down-Regulated by 200 mg AXER-204 at Day 1.

Name	Accession	log2(FC)	-log10(P)
RTN4R	Q9BZR6	12.39	2.40
KCRB	P12277	4.07	2.34
FSTL5	Q8N475	3.99	2.41
CH3L2	Q15782	3.97	2.41
APOB	P04114	3.64	2.71
FMOD	Q06828	3.33	2.56
CD5L	O43866	2.95	2.45
APOC1	P02654	2.77	3.58
CBPN	P15169	2.41	2.83
LBP	P18428	2.39	2.76
HPTR	P00739	2.37	2.49
CATC	P53634	2.28	2.99
HGFA	Q04756	2.06	2.47
CPN2	P22792	2.04	2.22
GAS6	Q14393	2.04	2.10
FIBA	P02671	2.03	2.38
FIBB	P02675	2.00	2.25
APOC2	P02655	2.00	2.13
FIBG	P02679	1.98	2.27
GUAD	Q9Y2T3	1.91	2.78
TIMP1	P01033	1.84	4.25
ITIH1	P19827	1.84	2.81
COMP	P49747	1.76	2.40
APOC3	P02656	1.75	2.73
EF1A1	P68104	1.72	2.40
CNTP2	Q9UHC6	1.68	3.00
ACTB	P60709	1.66	4.53
ALS	P35858	1.64	2.55
KVD13	A0A0C4	1.60	2.22
CD14	P08571	1.57	3.26

ITIH2	P19823	1.56	2.71
ITIH4	Q14624	1.55	3.98
LICH	P38571	1.50	2.80
FA9	P00740	1.47	2.97
CO8B	P07358	1.46	3.32
APOM	O95445	1.45	3.12
FA12	P00748	1.43	4.46
VCAM1	P19320	1.42	2.33
PON1	P27169	1.42	2.35
CO8G	P07360	1.40	3.79
HV353	P01767	1.37	2.47
THBG	P05543	1.37	4.12
CO5	P01031	1.37	3.23
KAIN	P29622	1.33	4.42
PGRP2	Q96PD5	1.19	3.29
HABP2	Q14520	1.18	2.01
APOA1	P02647	1.10	4.50
C1RL	Q9NZP8	1.07	3.29
CATB	P07858	1.06	2.05
IPSP	P05154	1.05	3.64
CATL1	P07711	1.03	2.27
PROF1	P07737	0.96	2.04
APOA2	P02652	0.92	3.28
IGSF8	Q969P0	-0.90	2.98
CNTN2	Q02246	-0.90	3.68
UFO	P30530	-0.92	3.74
SEZ6	Q53EL9	-0.93	2.61
GOLM1	Q8NBJ4	-0.94	2.16
NTRK2	Q16620	-0.94	3.96
FBLN7	Q53RD9	-0.95	2.07
CD166	Q13740	-0.95	2.66
TETN	P05452	-0.97	3.43
OMGP	P23515	-0.98	3.14
NOV	P48745	-0.98	3.10
PGCB	Q96GW7	-0.98	3.64
WFKN2	Q8TEU8	-0.99	3.72
T132A	Q24JP5	-1.00	2.56
PSAP	P07602	-1.00	5.20
HYOU1	Q9Y4L1	-1.01	3.51
COCH	O43405	-1.02	2.55
LYNX1	P0DP58	-1.02	2.98
GDIA	P31150	-1.02	3.00
ADGRL1	O94910	-1.03	5.49
ALDOC	P09972	-1.03	2.50
AMD	P19021	-1.04	3.01
CRTAC1	Q9NQ79	-1.04	3.06
CAB45	Q9BRK5	-1.04	2.29
CA2D1	P54289	-1.04	2.46
NRCAM	Q92823	-1.06	3.47
IBP5	P24593	-1.06	2.82
IBP7	Q16270	-1.06	2.05
PENK	P01210	-1.06	2.48
NEGR1	Q7Z3B1	-1.07	3.64
SHSA5	Q8N114	-1.07	3.28
TPIS	P60174	-1.07	3.56
ICAM5	Q9UMF0	-1.08	2.49
MA1A1	P33908	-1.08	3.74
ACBP	P07108	-1.08	3.74
THY1	P04216	-1.08	2.86
CADM1	Q9BY67	-1.08	4.32
PRIO	P04156	-1.09	2.28
PCSK1	Q9UHG2	-1.09	2.87
NPTXR	O95502	-1.10	3.66
PRRT3	Q5FWE3	-1.10	2.69

NTRI	Q9P121	-1.10	3.53
PEBP1	P30086	-1.11	3.72
SCRG1	O75711	-1.11	4.41
AGRL3	Q9HAR2	-1.13	2.93
SPON1	Q9HCB6	-1.15	2.84
MUC18	P43121	-1.15	4.53
C99L2	Q8TCZ2	-1.16	2.93
NCHL1	O00533	-1.17	3.38
PTPRS	Q13332	-1.19	4.47
MANS1	Q9H8J5	-1.19	3.86
SPRC	P09486	-1.20	3.27
NCAN	O14594	-1.21	4.41
ENDD1	O94919	-1.21	3.10
EPHA4	P54764	-1.21	2.61
NEUM	P17677	-1.21	2.01
NEC1	P29120	-1.21	2.97
SE6L1	Q9BYH1	-1.22	2.00
AJAP1	Q9UKB5	-1.23	2.18
FAM3C	Q92520	-1.24	3.74
DAF	P08174	-1.24	2.53
CADM2	Q8N3J6	-1.24	2.75
GLU2B	P14314	-1.25	3.00
GFRA2	O00451	-1.26	2.39
PCDH1	Q08174	-1.26	3.56
NELL2	Q99435	-1.26	3.35
OPCM	Q14982	-1.27	2.90
RARR2	Q99969	-1.27	2.01
CGRE1	Q99674	-1.27	2.18
NLGN2	Q8NFZ4	-1.27	2.81
CSTN1	O94985	-1.28	2.87
LSAMP	Q13449	-1.28	3.66
CADH4	P55283	-1.28	3.18
LY6H	O94772	-1.30	3.48
C1S	P09871	-1.31	3.98
APLP1	P51693	-1.31	4.57
CADH2	P19022	-1.31	2.77
CAD13	P55290	-1.31	2.80
CD048	Q5BLP8	-1.32	3.19
SORC3	Q9UPU3	-1.32	2.29
TICN1	Q08629	-1.32	4.15
APP	P05067	-1.33	3.94
SLIK1	Q96PX8	-1.33	2.93
GRN	P28799	-1.33	2.46
C1QC	P02747	-1.33	3.56
NBL1	P41271	-1.33	4.47
SPRL1	Q14515	-1.34	3.01
SMS	P61278	-1.36	2.67
DKK3	Q9UBP4	-1.36	3.97
TICN3	Q9BQ16	-1.36	3.02
WFDC2	Q14508	-1.37	3.26
RNAS1	P07998	-1.37	3.26
TTHY	P02766	-1.37	2.28
NCAM1	P13591	-1.38	4.31
YIPF3	Q9GZM5	-1.38	4.50
TGON2	O43493	-1.39	2.92
GDF11	O95390	-1.39	3.21
KLK6	Q92876	-1.39	3.44
SUSD5	O60279	-1.40	3.02
TIMP2	P16035	-1.41	2.81
CALR	P27797	-1.41	2.60
INAM1	C9JVW0	-1.42	2.54
NEUS	Q99574	-1.43	2.90
SHPS1	P78324	-1.43	2.93
MT3	P25713	-1.43	2.67

CMGA	P10645	-1.44	2.23
RNAS6	Q93091	-1.44	2.45
SCG2	P13521	-1.46	2.91
UBB	P0CG47	-1.47	3.25
GLT13	Q8IUC8	-1.50	2.76
TNR21	O75509	-1.53	2.89
CYTC	P01034	-1.56	4.09
VTM2A	Q8TAG5	-1.56	2.56
VGF	O15240	-1.57	2.40
VTM2B	A6NLU5	-1.57	3.09
IGS21	Q96ID5	-1.57	2.86
SODC	P00441	-1.62	3.09
ANFC	P23582	-1.63	2.07
CD59	P13987	-1.64	3.93
P3IP1	Q96FE7	-1.65	3.80
TICN2	Q92563	-1.66	2.12
C1QA	P02745	-1.68	2.74
CD44	P16070	-1.68	2.50
ETBR2	O60883	-1.70	3.03
PTPR2	Q92932	-1.70	2.59
ABCA2	Q9BZC7	-1.71	2.70
NSG1	P42857	-1.76	2.69
NPY	P01303	-1.79	3.41
LAMP1	P11279	-1.79	3.63
SCG1	P05060	-1.81	3.02
PTGDS	P41222	-1.88	3.13
SCG5	P05408	-1.98	3.31
PDXL2	Q9NZ53	-2.00	2.67
FGFR2	P21802	-2.05	3.11
DNER	Q8NFT8	-2.09	5.22
PNOC	Q13519	-2.16	2.87
SPIT2	O43291	-2.64	4.45

Supplemental Table S10. Enriched Gene Ontology Groups in Down-Regulated CSF Proteome After 200 mg AXER-204

	Group	Group P Value Corrected with Bonferroni step down	GO	Term	Term P Value Corrected with Bonferroni step down	Genes
Biological Function	synapse organization and axon development	1.78E-23	**GO:0050808**	**synapse organization**	**3.17E-14**	**[ADGRL1, ADGRL3, APP, BCAN, C1QA, C1QC, CDH2, CLSTN1, CNTN2, DNER, EPHA4, GAP43, IGSF21, NEGR1, NELL2, NLGN2, NRCAM, NTRK2, PRNP, PTPRS, SDF4, SEZ6, SEZ6L, SLITRK1, SPARCL1, SPOCK2]**
			GO:0061564	**axon development**	**4.40E-11**	**[ALCAM, APLP1, APP, CDH2, CDH4, CHL1, CNTN2, CRTAC1, EPHA4, FGFR2, GAP43, GDI1, GRN, MT3, NCAM1, NELL2, NPPC, NRCAM, NTRK2, PTPRS, RNASE1, SLITRK1, THY1, TNFRSF21]**
			GO:0007409	axonogenesis	2.40E-09	[ALCAM, APLP1, APP, CDH2, CDH4, CHL1, CNTN2, EPHA4, FGFR2, GAP43, GDI1, MT3, NCAM1, NELL2, NPPC, NRCAM, NTRK2, PTPRS, RNASE1, SLITRK1, THY1]
			GO:0008038	neuron recognition	1.04E-08	[APP, CNTN2, CRTAC1, EPHA4, GAP43, NRCAM, NTM, OPCML, TNFRSF21]
			GO:0007416	Synaps3 e assembly	1.35E-07	[ADGRL3, APP, CDH2, CLSTN1, DNER, GAP43, NEGR1, NLGN2, NRCAM, NTRK2, PTPRS, SLITRK1, SPOCK2]
			GO:0050807	regulation of synapse organization	6.79E-07	[ADGRL1, APP, CDH2, CLSTN1, EPHA4, NEGR1, NELL2, NLGN2, NRCAM, NTRK2, PRNP, PTPRS, SLITRK1]
			GO:0048708	astrocyte differentiation	2.36E-05	[APP, C1QA, CNTN2, EPHA4, GAP43, GPR37L1, GRN, MT3]
			GO:0050770	regulation of axonogenesis	3.21E-05	[CDH2, CDH4, CNTN2, EPHA4, GDI1, MT3, NTRK2, PTPRS, SLITRK1, THY1]
			GO:0007411	axon guidance	1.97E-04	[ALCAM, APP, CDH4, CHL1, CNTN2, EPHA4, GAP43, NCAM1, NELL2, NRCAM, RNASE1]
			GO:0031102	neuron projection regeneration	6.19E-04	[EPHA4, GAP43, GRN, OMG, PTPRS, THY1]
			GO:0051963	regulation of synapse assembly	9.44E-04	[APP, CLSTN1, NEGR1, NLGN2, NTRK2, PTPRS, SLITRK1]
			GO:1901888	regulation of cell junction assembly	2.13E-03	[APP, CLSTN1, NEGR1, NLGN2, NTRK2, PTPRS, RNASE1, SLITRK1, THY1]
			GO:0048675	axon extension	3.28E-03	[ALCAM, CDH4, GDI1, MT3, NELL2, NRCAM, PTPRS]
			GO:2000809	positive regulation of synaptic vesicle clustering	3.69E-03	[CDH2, NLGN2]
			GO:0099173	postsynapse organization	3.95E-03	[CDH2, EPHA4, GAP43, NELL2, NLGN2, NRCAM, PRNP, PTPRS]
			GO:0099068	postsynapse assembly	4.17E-03	[CDH2, GAP43, NLGN2, PTPRS]
			GO:0099175	regulation of postsynapse organization	4.30E-03	[CDH2, EPHA4, NELL2, NRCAM, PRNP, PTPRS]

			GO:0070570	regulation of neuron projection regeneration	7.41E-03	[EPHA4, GRN, PTPRS, THY1]
			GO:0010977	negative regulation of neuron projection development	8.11E-03	[EPHA4, GDI1, MT3, PRKCSH, PTPRS, SPOCK1, THY1]
			GO:1901890	positive regulation of cell junction assembly	9.93E-03	[CLSTN1, NLGN2, NTRK2, RNASE1, SLITRK1, THY1]
			GO:0099084	postsynaptic specialization organization	9.96E-03	[CDH2, GAP43, NLGN2, PTPRS]
	gliogenesis and axon guidance	5.83E-16	GO:0008038	neuron recognition	1.04E-08	[APP, CNTN2, CRTAC1, EPHA4, GAP43, NRCAM, NTM, OPCML, TNFRSF21]
			GO:0042063	**gliogenesis**	**1.79E-07**	**[ABCA2, APP, C1QA, CDH2, CNTN2, DNER, EPHA4, GAP43, GPR37L1, GRN, MT3, NPPC, NTRK2, PENK, SOD1, TNFRSF21]**
			GO:0048708	astrocyte differentiation	2.36E-05	[APP, C1QA, CNTN2, EPHA4, GAP43, GPR37L1, GRN, MT3]
			GO:0007411	**axon guidance**	**1.97E-04**	**[ALCAM, APP, CDH4, CHL1, CNTN2, EPHA4, GAP43, NCAM1, NELL2, NRCAM, RNASE1]**
			GO:0021782	glial cell development	2.83E-04	[ABCA2, APP, C1QA, CNTN2, GRN, MT3, NTRK2, SOD1]
			GO:0031102	neuron projection regeneration	6.19E-04	[EPHA4, GAP43, GRN, OMG, PTPRS, THY1]
			GO:0098883	synapse pruning	4.02E-03	[C1QA, C1QC, EPHA4]
	neuron recognition	5.92E-11	**GO:0008038**	**neuron recognition**	**1.04E-08**	**[APP, CNTN2, CRTAC1, EPHA4, GAP43, NRCAM, NTM, OPCML, TNFRSF21]**
			GO:0048708	astrocyte differentiation	2.36E-05	[APP, C1QA, CNTN2, EPHA4, GAP43, GPR37L1, GRN, MT3]
			GO:0007413	axonal fasciculation	7.06E-05	[CNTN2, CRTAC1, EPHA4, NRCAM, TNFRSF21]
			GO:0007411	axon guidance	1.97E-04	[ALCAM, APP, CDH4, CHL1, CNTN2, EPHA4, GAP43, NCAM1, NELL2, NRCAM, RNASE1]
	gliogenesis	1.16E-09	**GO:0042063**	**gliogenesis**	**1.79E-07**	**[ABCA2, APP, C1QA, CDH2, CNTN2, DNER, EPHA4, GAP43, GPR37L1, GRN, MT3, NPPC, NTRK2, PENK, SOD1, TNFRSF21]**
			GO:0048708	astrocyte differentiation	2.36E-05	[APP, C1QA, CNTN2, EPHA4, GAP43, GPR37L1, GRN, MT3]
			GO:0021782	glial cell development	2.83E-04	[ABCA2, APP, C1QA, CNTN2, GRN, MT3, NTRK2, SOD1]
			GO:0046688	response to copper ion	1.17E-03	[APP, MT3, PAM, PRNP, SOD1]
	endopeptidase regulator activity	1.19E-08	**GO:0061135**	**endopeptidase regulator activity**	**2.49E-09**	**[ABCA2, APP, CST3, MT3, PCSK1N, PEBP1, PRNP, SERPINI1, SPINT2, SPOCK1, SPOCK2, SPOCK3, TIMP2, WFDC2, WFIKKN2]**

			GO:0010951	negative regulation of endopeptidase activity	8.57E-08	[APP, CD44, CST3, MT3, PCSK1N, PEBP1, PRNP, SERPINI1, SPINT2, SPOCK1, SPOCK2, SPOCK3, TIMP2, WFDC2, WFIKKN2]
			GO:0045861	negative regulation of proteolysis	8.30E-07	[APP, CD44, CST3, EPHA4, MT3, PCSK1N, PEBP1, PRNP, SERPINI1, SPINT2, SPOCK1, SPOCK2, SPOCK3, TIMP2, WFDC2, WFIKKN2]
			GO:0008191	metalloendopeptidase inhibitor activity	6.41E-06	[SPOCK1, SPOCK2, SPOCK3, TIMP2, WFIKKN2]
			GO:0004867	serine-type endopeptidase inhibitor activity	7.05E-05	[APP, PCSK1N, PEBP1, SERPINI1, SPINT2, SPOCK1, WFDC2, WFIKKN2]
	synapse maturation	2.55E-07	**GO:0060074**	**synapse maturation**	**4.53E-06**	**[ADGRL1, BCAN, CLSTN1, IGSF21, SEZ6, SEZ6L]**
	hormone activity	4.13E-06	**GO:0005179**	**hormone activity**	**8.56E-05**	**[CHGA, CHGB, NPPC, NPY, PENK, PNOC, SST, TTR, VGF]**
	amyloid precursor protein metabolic process	4.37E-06	**GO:0042982**	**amyloid precursor protein metabolic process**	**1.20E-04**	**[ABCA2, EPHA4, KLK6, NSG1, NTRK2, PRNP, SPON1]**
			GO:1902003	regulation of amyloid-beta formation	9.40E-04	[ABCA2, EPHA4, NTRK2, PRNP, SPON1]
			GO:0034205	amyloid-beta formation	2.15E-03	[ABCA2, EPHA4, NTRK2, PRNP, SPON1]
	central nervous system neuron differentiation	7.51E-05	**GO:0021953**	**central nervous system neuron differentiation**	**5.03E-03**	**[CNTN2, EPHA4, FGFR2, NELL2, NPY, NTRK2, SPOCK1, UBB]**
	cellular response to norepinephrine stimulus	1.03E-04	**GO:0071874**	**cellular response to norepinephrine stimulus**	**3.69E-03**	**[APLP1, APP]**
Cellular Compartment	postsynaptic membrane	7.51E-06	GO:0098936	intrinsic component of postsynaptic membrane	8.35E-06	[CDH2, CNTN2, EPHA4, NELL2, NLGN2, NRCAM, PTPRS, SLITRK1, SORCS3]
			GO:0045211	**postsynaptic membrane**	**1.88E-05**	**[CDH2, CLSTN1, CNTN2, EPHA4, IGSF21, NELL2, NLGN2, NRCAM, NSG1, PTPRS, SLITRK1, SORCS3]**
			GO:0099060	integral component of postsynaptic specialization membrane	2.53E-04	[CDH2, NLGN2, NRCAM, PTPRS, SLITRK1, SORCS3]
			GO:0099634	postsynaptic specialization membrane	3.10E-04	[CDH2, EPHA4, NLGN2, NRCAM, PTPRS, SLITRK1, SORCS3]
			GO:0098839	postsynaptic density membrane	3.23E-03	[EPHA4, NRCAM, PTPRS, SLITRK1, SORCS3]

			GO:0099061	integral component of postsynaptic density membrane	3.53E-03	[NRCAM, PTPRS, SLITRK1, SORCS3]
	tertiary granule	4.32E-06	**GO:0070820**	**tertiary granule**	**9.88E-06**	**[ALDOC, CD55, CD59, CST3, LAMP1, PRKCSH, PTPRN2, RNASE1, SIRPA, TIMP2]**
			GO:0101003	ficolin-1-rich granule membrane	1.07E-03	[CD55, LAMP1, PTPRN2, RNASE1, SIRPA]
	dense core granule	1.04E-05	**GO:0031045**	**dense core granule**	**2.92E-05**	**[CHGA, NPY, PENK, SCG2, SOD1]**
	neuron projection terminus	3.94E-05	**GO:0044306**	**neuron projection terminus**	**1.28E-04**	**[EPHA4, NPY, NTRK2, PCSK1, PENK, PNOC, PRNP, SCRG1]**
	platelet dense granule lumen	1.50E-04	**GO:0031089**	**platelet dense granule lumen**	**1.05E-03**	**[CLEC3B, FAM3C, RARRES2]**
	main axon	2.82E-04	**GO:0044304**	**main axon**	**1.13E-03**	**[APP, CNTN2, NRCAM, SPOCK1, THY1]**
	anchored component of plasma membrane	3.44E-04	**GO:0046658**	**anchored component of plasma membrane**	**1.03E-03**	**[CD59, CNTN2, IGSF21, PRNP, THY1]**

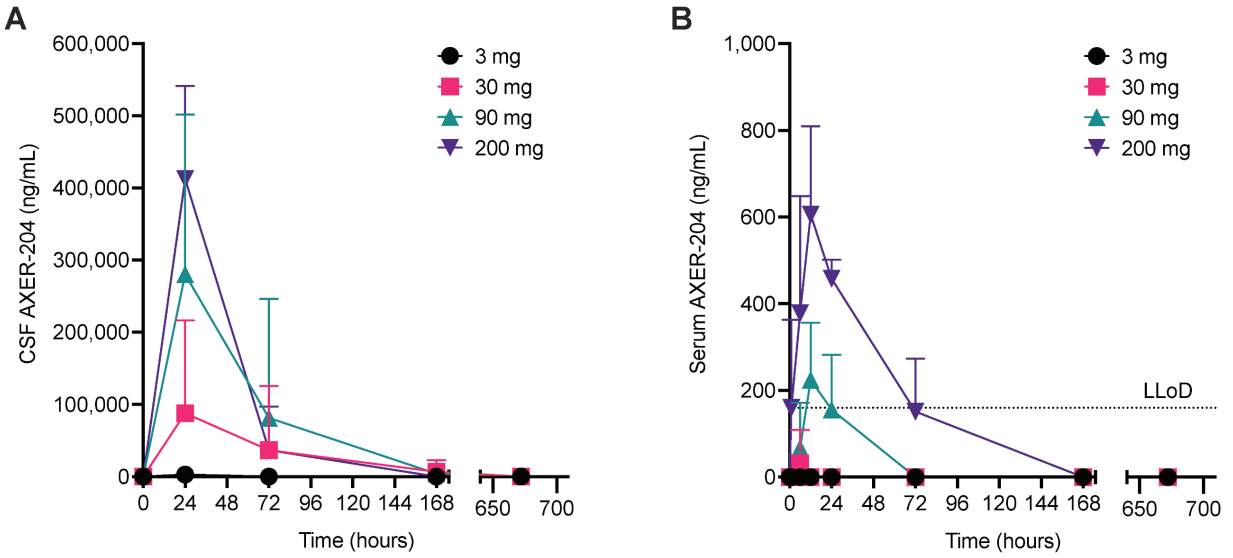
Supplemental Table S11. Enriched Gene Ontology Groups in Up-Regulated CSF Proteome After 200 mg AXER-204

	Group	Group P Value Corrected with Bonferroni step down	GO	Term	Term P Value Corrected with Bonferroni step down	Genes
Biological Function	**zymogen activation**	**6.87E-12**	**GO:0031638**	**zymogen activation**	**2.81E-13**	**[C1RL, CD5L, CTSL, F12, F9, FGA, FGB, FGG, HGFAC, HPR]**
			GO:0016485	protein processing	4.30E-10	[C1RL, CD5L, COMP, CPN1, CTSL, F12, F9, FGA, FGB, FGG, HGFAC, HPR]
			GO:0072378	blood coagulation, fibrin clot formation	5.05E-06	[F12, FGA, FGB, FGG]
			GO:1900047	negative regulation of hemostasis	1.58E-05	[COMP, F12, FGA, FGB, FGG]
			GO:0034114	regulation of heterotypic cell-cell adhesion	2.23E-05	[APOA1, FGA, FGB, FGG]
			GO:0031639	plasminogen activation	2.48E-05	[F12, FGA, FGB, FGG]
			GO:0042730	fibrinolysis	3.91E-05	[F12, FGA, FGB, FGG]
			GO:2000352	negative regulation of endothelial cell apoptotic process	4.21E-05	[FGA, FGB, FGG, GAS6]
			GO:0070527	platelet aggregation	4.34E-05	[ACTB, COMP, FGA, FGB, FGG]
			GO:1900026	positive regulation of substrate adhesion-dependent cell spreading	1.29E-04	[APOA1, FGA, FGB, FGG]
			GO:1903035	negative regulation of response to wounding	1.38E-04	[F12, FGA, FGB, FGG, RTN4R]
			GO:0045907	positive regulation of vasoconstriction	3.52E-04	[FGA, FGB, FGG]
			GO:1902042	negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	4.60E-04	[FGA, FGB, FGG]
	regulation of lipoprotein particles	**4.47E-11**	**GO:0097006**	**regulation of plasma lipoprotein particle levels**	**4.47E-11**	**[APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOM, LIPA, PON1]**

			GO:0034383	low-density lipoprotein particle clearance	4.66E-04	[APOB, APOC3, LIPA]
			GO:0034384	high-density lipoprotein particle clearance	5.16E-09	[APOA1, APOA2, APOC2, APOC3, APOM]
			GO:0034447	very-low-density lipoprotein particle clearance	1.16E-05	[APOC1, APOC2, APOC3]
			GO:0034377	plasma lipoprotein particle assembly	6.02E-09	[APOA1, APOA2, APOB, APOC1, APOC3, APOM]
			GO:0034382	chylomicron remnant clearance	1.16E-05	[APOC1, APOC2, APOC3]
			GO:0050994	regulation of lipid catabolic process	2.72E-05	[APOA1, APOA2, APOC1, APOC2, APOC3]
			GO:0060191	regulation of lipase activity	1.31E-04	[APOA1, APOA2, APOC1, APOC2, APOC3]
			GO:0010916	negative regulation of very-low-density lipoprotein particle clearance	2.69E-06	[APOC1, APOC2, APOC3]
			GO:0046503	glycerolipid catabolic process	2.08E-06	[APOA1, APOA2, APOB, APOC1, APOC2, APOC3]
			GO:0050995	negative regulation of lipid catabolic process	4.31E-04	[APOA2, APOC1, APOC3]
			GO:0050996	positive regulation of lipid catabolic process	4.31E-04	[APOA1, APOA2, APOC2]
			GO:0034375	high-density lipoprotein particle remodeling	3.70E-08	[APOA1, APOA2, APOC1, APOC3, APOM]
			GO:0034379	very-low-density lipoprotein particle assembly	5.82E-05	[APOB, APOC1, APOC3]
			GO:0034380	high-density lipoprotein particle assembly	1.22E-04	[APOA1, APOA2, APOM]
			GO:0010901	regulation of very-low-density lipoprotein particle remodeling	7.40E-08	[APOA1, APOA2, APOC2, APOC3]
			GO:0048261	negative regulation of receptor-	3.78E-04	[APOC1, APOC2, APOC3]

				mediated endocytosis		
			GO:0060192	negative regulation of lipase activity	1.89E-04	[APOA2, APOC1, APOC3]
			GO:0006641	triglyceride metabolic process	1.83E-05	[APOA1, APOA2, APOB, APOC1, APOC2, APOC3]
			GO:0033700	phospholipid efflux	1.24E-08	[APOA1, APOA2, APOC1, APOC2, APOC3]
			GO:0034372	very-low-density lipoprotein particle remodeling	1.91E-06	[APOA1, APOA2, APOC2, APOC3]
			GO:0010896	regulation of triglyceride catabolic process	1.20E-04	[APOA1, APOC2, APOC3]
			GO:0032374	regulation of cholesterol transport	1.45E-06	[APOA1, APOA2, APOC1, APOC2, APOC3, PON1]
			GO:0032375	negative regulation of cholesterol transport	1.91E-06	[APOA2, APOC1, APOC2, APOC3]
			GO:0042304	regulation of fatty acid biosynthetic process	1.29E-04	[APOA1, APOC1, APOC2, APOC3]
			GO:0042632	cholesterol homeostasis	8.10E-06	[APOA1, APOA2, APOB, APOC2, APOC3, APOM]
			GO:0070328	triglyceride homeostasis	2.92E-04	[APOA1, APOC2, APOC3]
			GO:0033344	cholesterol efflux	1.96E-10	[APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOM, PON1]
			GO:0043691	reverse cholesterol transport	6.55E-08	[APOA1, APOA2, APOC2, APOC3, APOM]
			GO:0070508	cholesterol import	5.82E-05	[APOA1, APOA2, APOC3]
			GO:0120020	cholesterol transfer activity	4.37E-04	[APOA1, APOA2, APOB]
	endo-peptidase regulation	**5.19E-09**	**GO:0061134**	**peptidase regulator activity**	**6.41E-08**	**[C5, CTSC, GAS6, ITIH1, ITIH2, ITIH4, SERPINA4, SERPINA5, SERPINA7, TIMP1]**
			GO:0004866	endopeptidase inhibitor activity	1.31E-07	[C5, GAS6, ITIH1, ITIH2, ITIH4, SERPINA4, SERPINA5, SERPINA7, TIMP1]
			GO:0004867	serine-type endopeptidase inhibitor activity	1.28E-05	[ITIH1, ITIH2, ITIH4, SERPINA4, SERPINA5, SERPINA7]
	acute inflammatory response	**2.60E-07**	**GO:0002526**	**acute inflammatory response**	**3.77E-06**	**[APOA2, F12, HPR, ITIH4, LBP, TIMP1, VCAM1]**

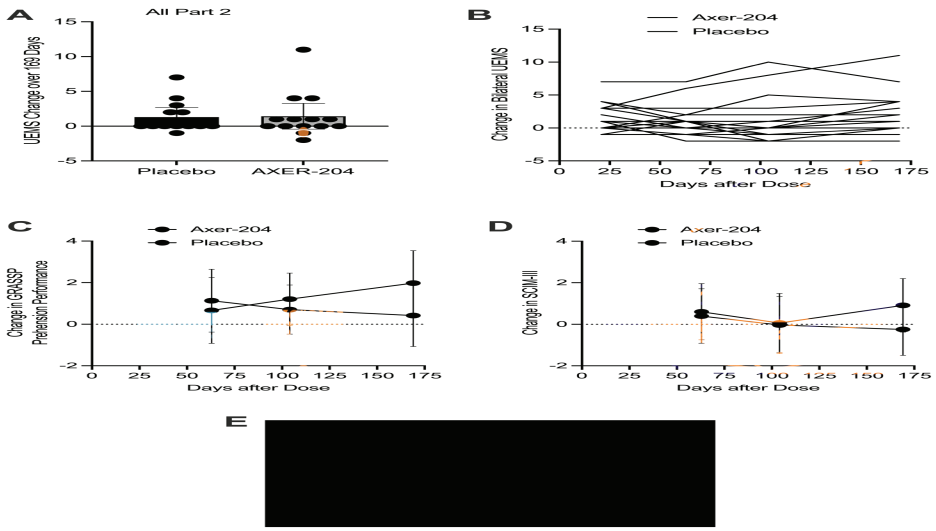
Cellular Compartment	**high-density lipoprotein particle**	**2.34E-15**	GO:0034366	spherical high-density lipoprotein particle	2.07E-16	[APOA1, APOA2, APOC2, APOC3, APOM, HPR, PON1]
			GO:0034364	**high-density lipoprotein particle**	**3.76E-16**	**[APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOM, HPR, PON1]**
			GO:0034361	very-low-density lipoprotein particle	1.03E-12	[APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOM]
			GO:0042627	chylomicron	1.18E-11	[APOA1, APOA2, APOB, APOC1, APOC2, APOC3]
			GO:0034363	intermediate-density lipoprotein particle	3.03E-07	[APOB, APOC2, APOC3]
			GO:0034362	low-density lipoprotein particle	6.76E-06	[APOB, APOC2, APOM]
	platelet alpha granule	**5.23E-07**	**GO:0031091**	**platelet alpha granule**	**7.84E-07**	**[FGA, FGB, FGG, GAS6, SERPINA5, TIMP1]**
	membrane attack complex	**3.08E-06**	**GO:0005579**	**membrane attack complex**	**6.16E-06**	**[C5, C8B, C8G]**



C

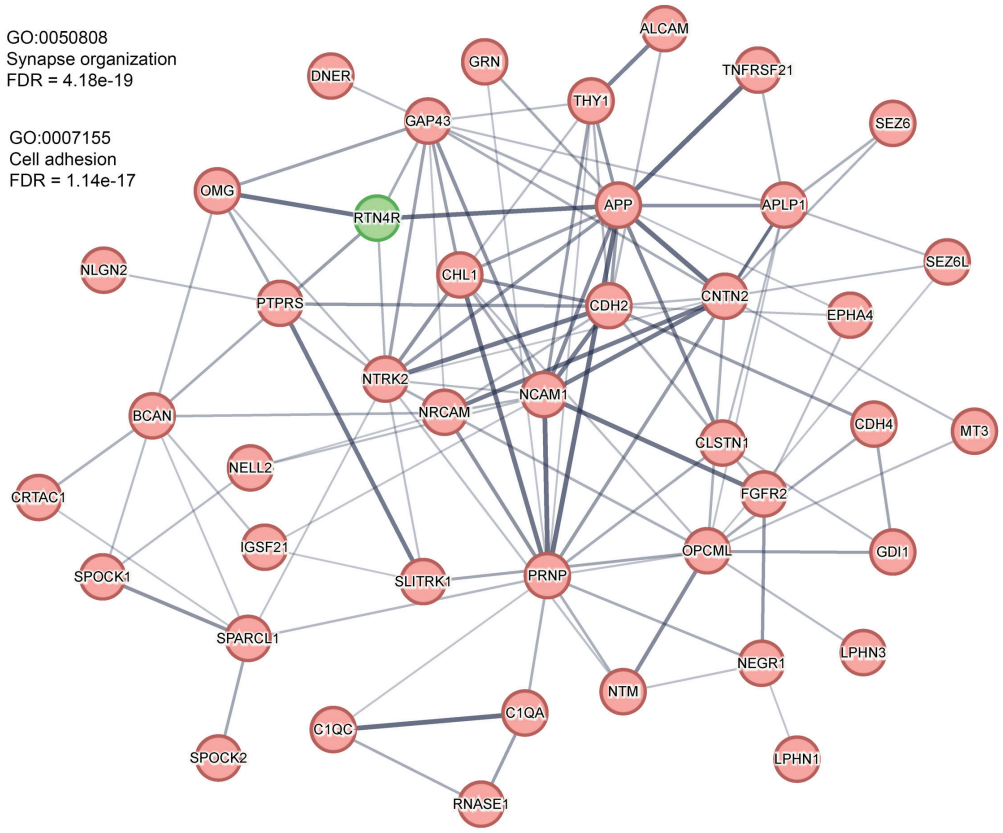
Fluid	Parameter	Statistic	AXER-204 3 mg (N = 6)	AXER-204 30 mg (N = 6)	AXER-204 90 mg (N = 6)	AXER-204 200 mg (N = 6)
CSF	$AUC_{0-\infty}$ (h*ng/mL)	Mean	ND	6,980,000	14,800,000	12,300,000
		SD	ND	13,400,000	19,600,000	8,180,000
		Median	ND	1,410,000	3,170,000	12,100,000
		Min	159,000	193,000	2,880,000	4,440,000
		Max	159,000	31,000,000	48,200,000	25,700,000
	C_{max} (ng/mL)	Mean	3,340	87,900	280,000	412,000
		SD	2,890	128,000	221,000	129,000
		Median	1,980	48,400	149,000	405,000
		Min	854	3,900	134,000	221,000
		Max	7,320	343,000	651,000	555,000
	t1/2 (h)	Mean	ND	23.1	13.5	12.5
		SD	ND	32.2	10.8	7.08
		Median	ND	7.57	7.14	11.8
		Min	11.8	5.71	6.32	6.04
		Max	11.8	80.4	31.6	23.8
Serum	$AUC_{0-\infty}$ (h*ng/mL)	Mean	ND	ND	ND	44,000
		SD	ND	ND	ND	12,900
		Median	ND	ND	ND	42,800
		Min	ND	ND	ND	30,300
		Max	ND	ND	ND	60,300
	C_{max} (ng/mL)	Mean	ND	ND	277	641
		SD	ND	ND	79.1	173
		Median	ND	ND	282	549
		Min	ND	190	166	514
		Max	ND	190	384	908
	t1/2 (h)	Mean	ND	ND	ND	53.9
		SD	ND	ND	ND	24.8
		Median	ND	ND	ND	47.7
		Min	ND	ND	ND	32.9
		Max	ND	ND	ND	87.1

Supplemental Figure S1. Pharmacokinetics of AXER-204.
(A) The level of AXER-204 protein in CSF is presented as a function of dose and time in Part 1. Data are mean + SD for n=6 per dose group.
(B) AXER-204 levels in serum from part 1. Mean + SD for n=6. The Lower Limit of Detection (LLoD) is indicated.
(C) Calculated C_{max}, AUC(0-inf) and t(1/2) values from A and B are listed. Mean, SD, median, maximum and minimum are listed.

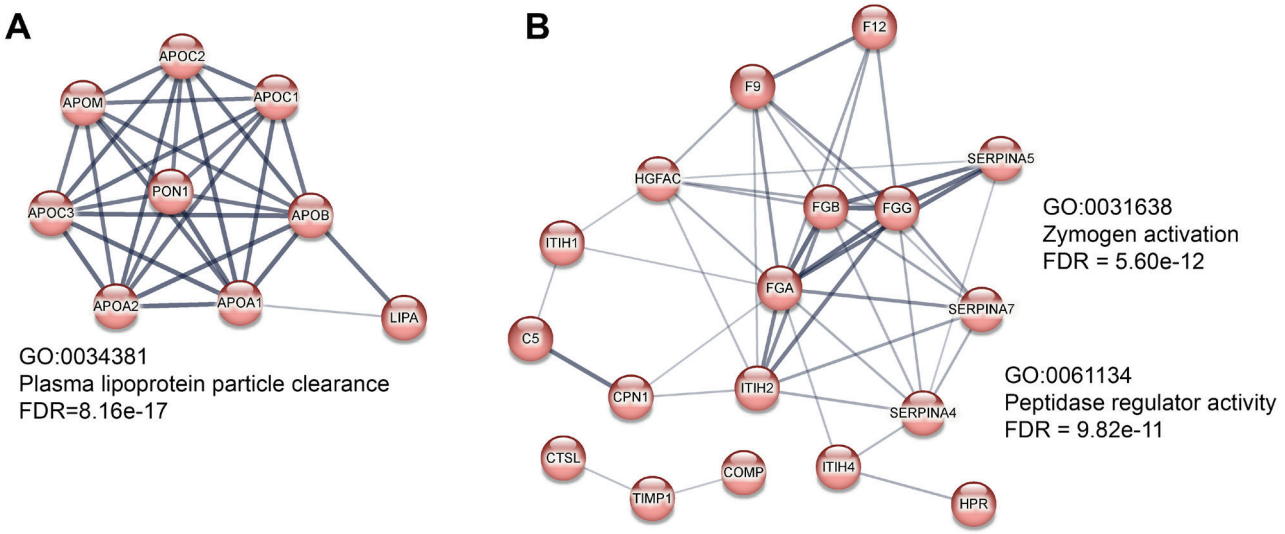


Supplemental Figure S2. Individual Participant Efficacy Outcome from Part 2.
(A) Change from baseline in bilateral UEMS of the ISNCSCI examination at day 169 is plotted for part 2 cohorts. Bars reflect mean with ± 95% CI for indicated individual participants.
(B) Change from baseline in bilateral UEMS of the ISNCSCI examination is plotted for individual patients as a function of time for n =14 for AXER-204 and n=13 for placebo.

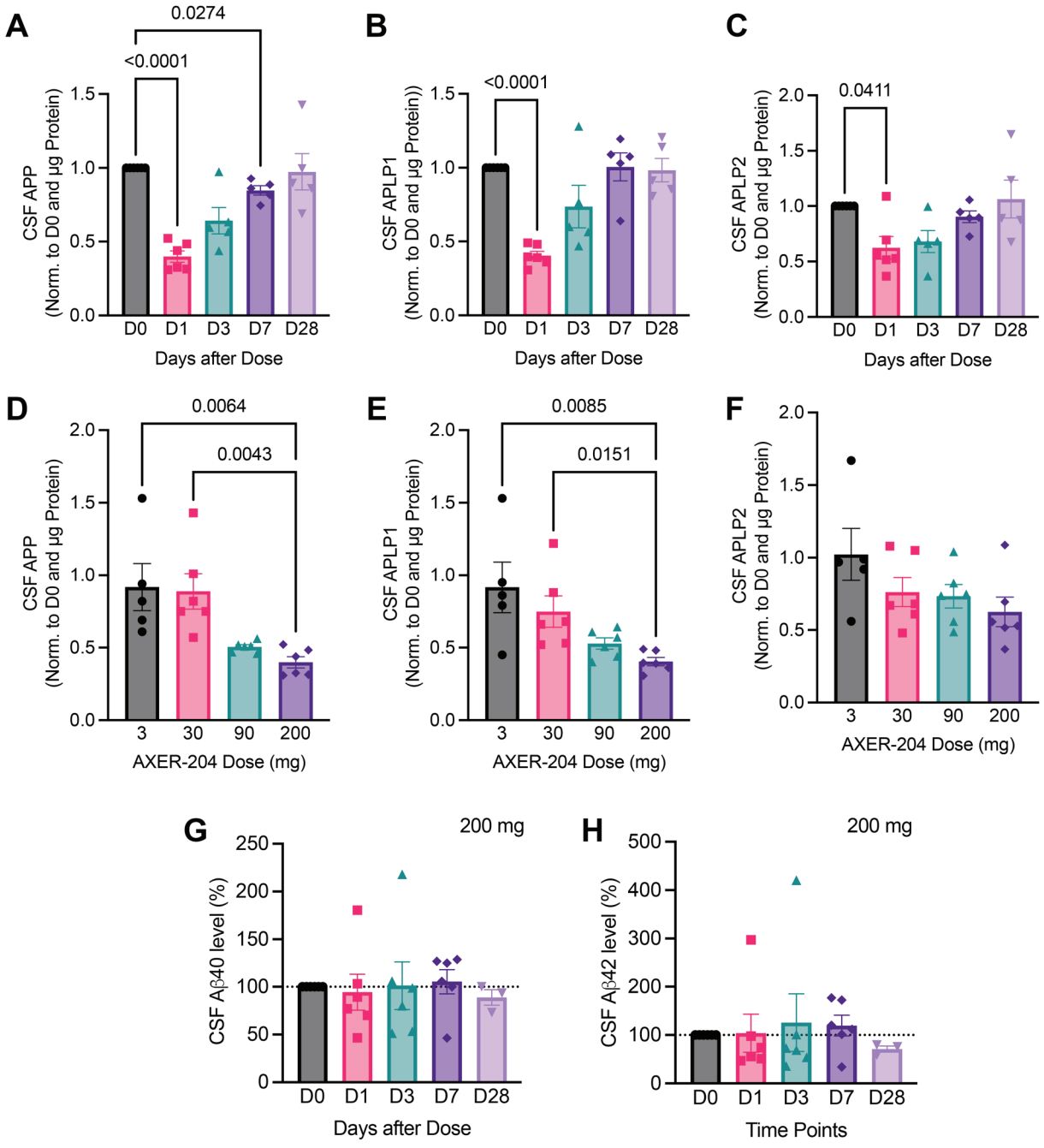
Supplemental Figure S3. Heat map of All CSF Proteome Changes after AXER-204 Dosing. Levels of all 685 proteins across dose and time illustrated with blue linear intensity for magnitude of log2(FC) decrease relative to corresponding Day 0 values, and orange intensity for increase relative to Day 0. Each box represents the average from 6 individual CSF samples each with two technical replicates.



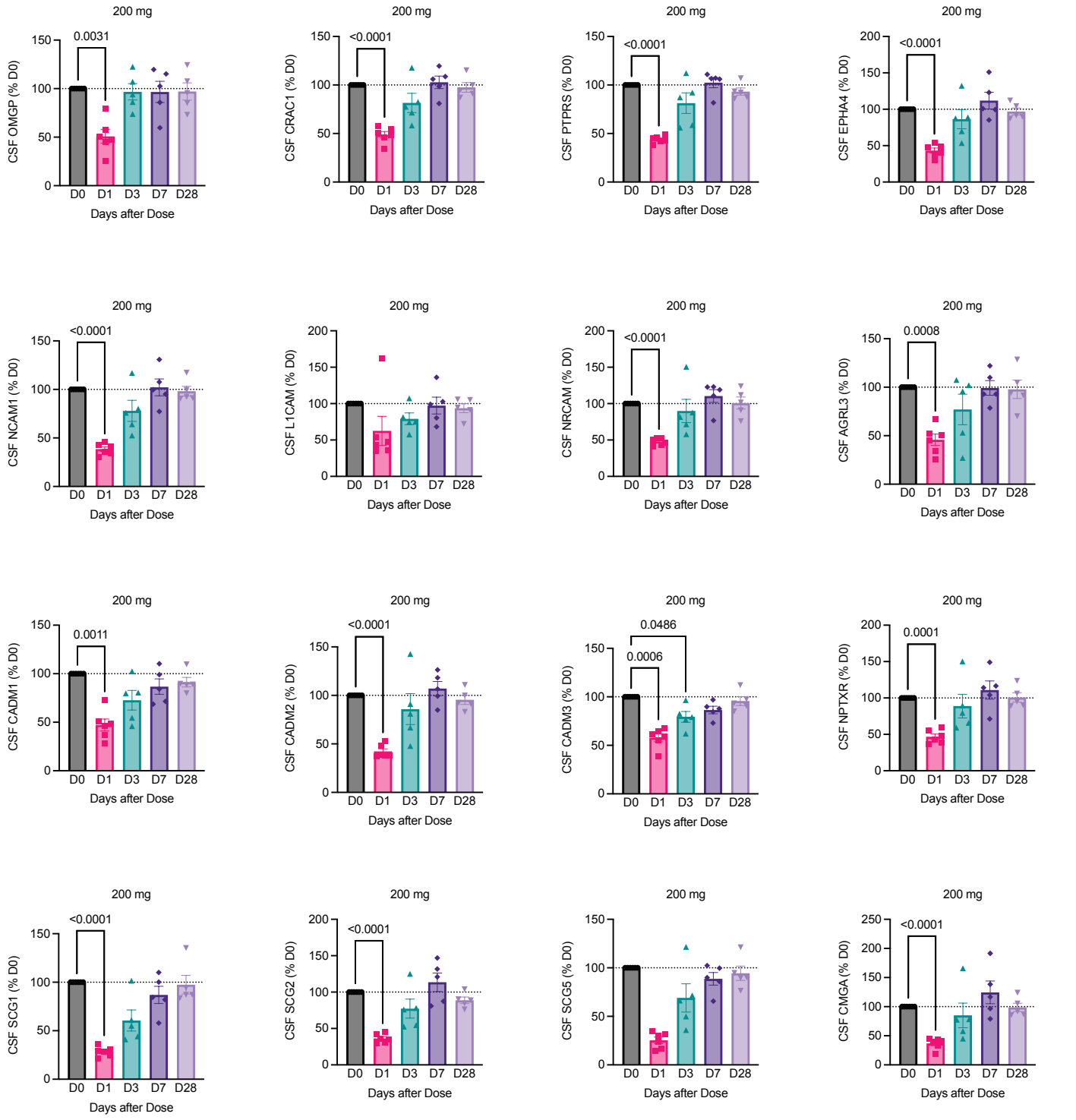
Supplemental Figure S4. CSF Protein Interaction Networks Down-Regulated after AXER-204 dosing. Protein-protein interaction network of amongst proteins significantly down-regulated by AXER-204 in the Synaptic Organization and Axon Development cluster of GO terms from C using <string-db.org> analysis. RTN4R is added in green to the GO cluster proteins. The width of the connecting lines reflects the strength of evidence supporting functional interaction from <string-db.org>[45].



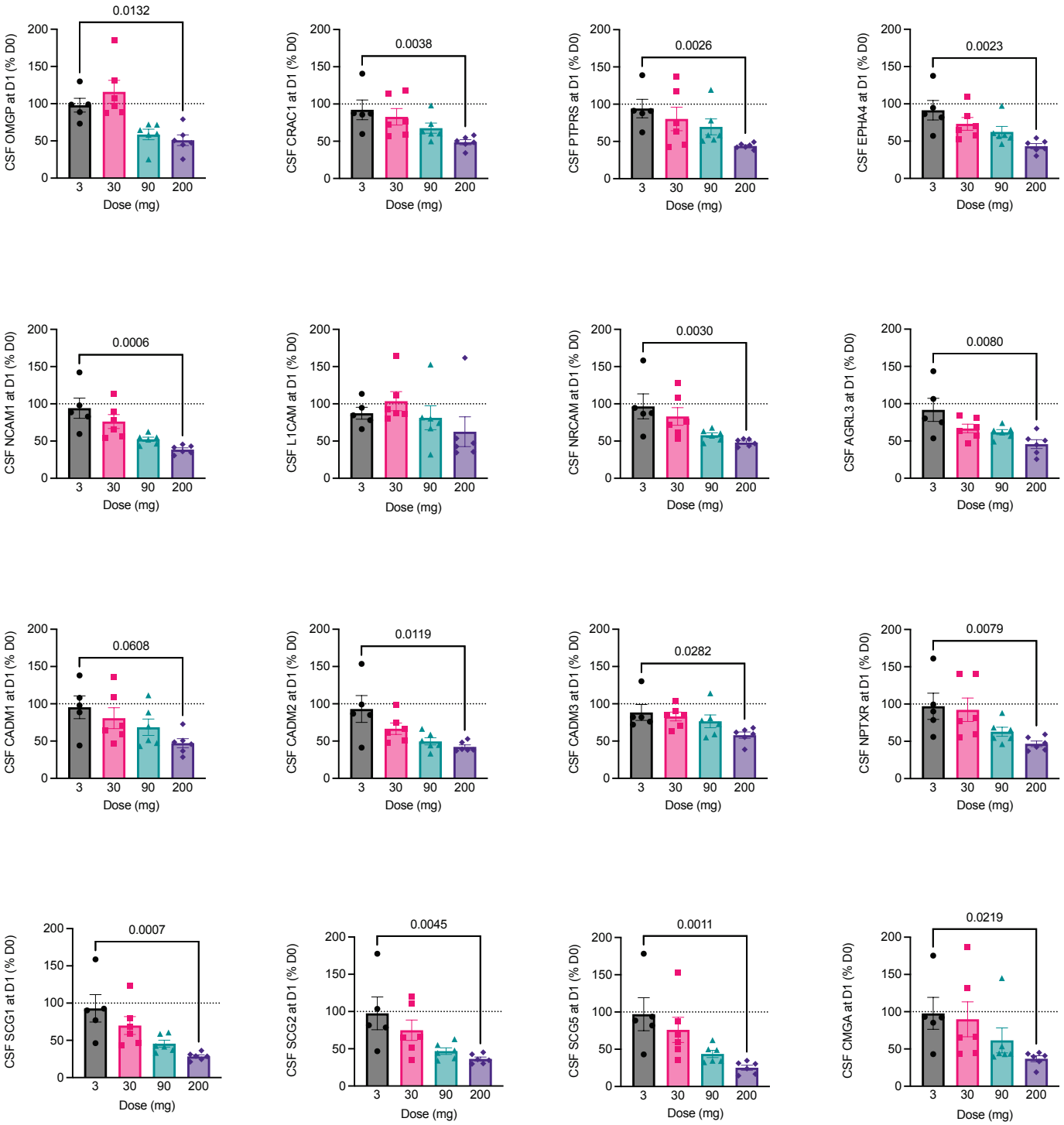
Supplemental Figure S5. CSF Protein Interaction Networks Up-Regulated after AXER-204 dosing. Protein-protein interaction network of amongst proteins significantly up-regulated by AXER-204 in the Regulation of Lipoprotein Particles pathway cluster (A) and the Zymogen Activation pathway cluster (B) of GO terms using <string-db.org> analysis. The width of the connecting lines reflects the strength of evidence supporting functional interaction from <string-db.org>.



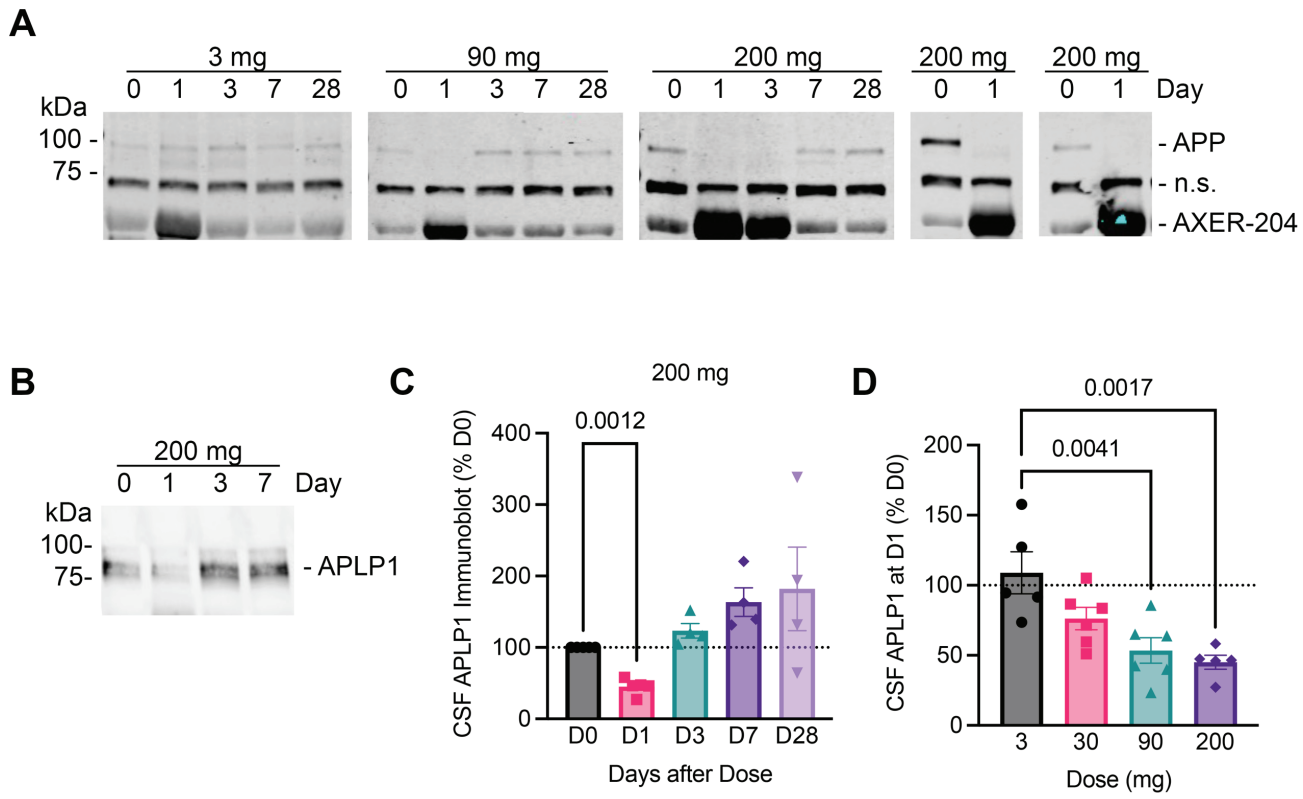
Supplemental Figure S6. CSF Proteomic Changes of APP Family Proteins after AXER-204.
(A-F) Quantitation of APP, APLP1 and APLP2 levels in CSF from LC/MS/MS as a function of time after 200 mg or of dose at Day 1. Data are normalized by Day 0 values from the same individual, graphed as mean ± SEM. To compare the effect of AXER-204 as a function of time, data were analyzed by repeated measure ANOVA with a mixed effects model versus Day 0. To assess AXER-204 as a function of dose, a Kruskal-Wallis test versus the 3 mg values was used. P values <0.05 are shown. Each dot represents a different CSF sample.
(G-H) Quantitation of Aß40 or Aß42 levels in CSF from ELISA as a function of time after 200 mg AXER-204. Data are normalized by Day 0 values from the same individual, graphed as mean ± SEM. To compare the effect of AXER-204 as a function of time, data were analyzed by repeated measure ANOVA with a mixed effects model versus Day 0. P values <0.05 are shown. Each dot represents a different CSF sample.



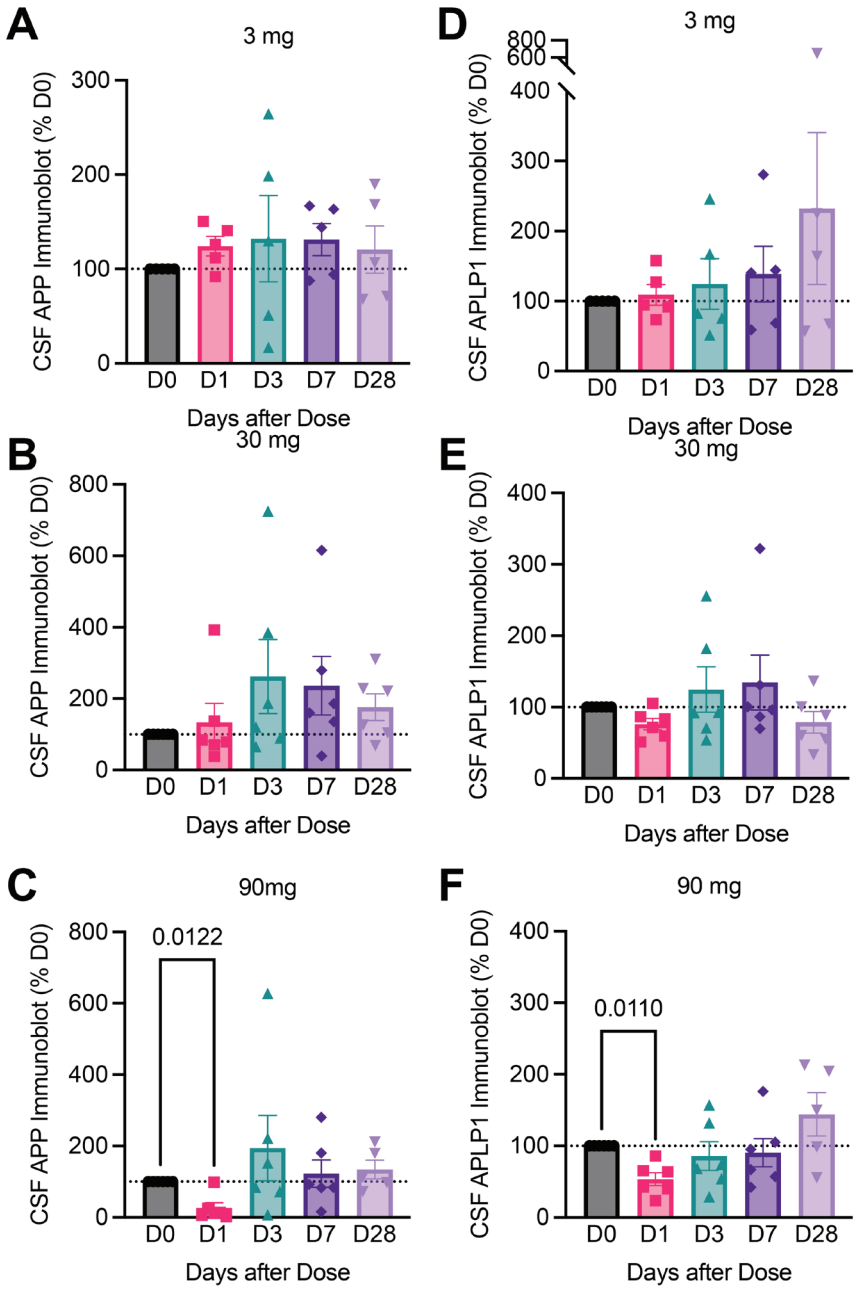
Supplemental Figure S7. Time Dependence of CSF Proteomic Changes of Multiple Synaptic Adhesion Proteins after 200 mg AXER-204. Quantitation of multiple protein levels in CSF from LC/MS/MS as a function of a function of time after 200 mg dose. Data are normalized by Day 0 values from the same individual, graphed as mean ± SEM. To compare the effect of AXER-204 as a function of time, data were analyzed by repeated measure ANOVA with a mixed effects model versus Day 0. P values <0.05 are shown. Each dot represents a different CSF sample.



Supplemental Figure S8. Dose Dependence of CSF Proteomic Changes of Multiple Synaptic Adhesion Proteins after AXER-204. Quantitation of multiple protein levels in CSF from LC/MS/MS as a function of dose at Day 1. The Day 1 data are normalized by Day 0 values from the same individual, graphed as mean ± SEM. To assess AXER-204 as a function of dose, a Kruskal-Wallis test versus the 3 mg values was used. P values <0.05 are shown. Each dot represents a different CSF sample.



Supplemental Figure S9. Immunoblot of APP Family Proteins after AXER-204 Dosing.
(A) Immunoblot of APP immunoreactivity in CSF after AXER-204 part 1 dosing. The AXER-204 dose and time after intrathecal administration are indicated. Results from one 3 mg case, one 90 mg case and three 200 mg cases shown. Mol wt marker migration is shown at left (kDa). The mobility of APP, a non-specific band and AXER-204 cross-reactive with secondary antibody are indicated at right.
(B) Immunoblot of APLP1 immunoreactivity in CSF after 200 mg AXER-204 dosing. The AXER-204 dose and time after intrathecal administration are indicated. Mol wt marker migration is shown at left (kDa). The mobility of APLP1 is indicated at right.
(C, D) APLP1 level in CSF quantitated from immunoblots as in H as a function of time after 200 mg (I) or of dose at Day 1 (J). Data are normalized by Day 0 values from the same individual, graphed as mean ± SEM. To compare the effect of AXER-204 as a function of time, data were analyzed by repeated measure ANOVA with a mixed effects model versus Day 0. To assess AXER-204 as a function of dose, a Kruskal-Wallis test versus the 3 mg values was used. P values <0.05 are shown. Each dot represents a different CSF sample.



Supplemental Figure S10. Changes in CSF Immunoblot of APP Family Proteins at Low Dose AXER-204. Quantitation of APP (A-C) or APLP1 (D-F) level in CSF from densitometry of immunoblots as in main Figure 5 as a function of time after 3 mg (A, D), 30 mg (B, E) or 90 mg (C, F) of AXER-204. Data are normalized by Day 0 values from the same individual, graphed as mean ± SEM. To compare the effect of AXER-204 as a function of time, data were analyzed by repeated measure ANOVA with a mixed effects model versus Day 0. P values <0.05 are shown. Each dot represents a different CSF sample.

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

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

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

AXER-204

IND #: 135648

Sponsor:

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

Date of Issue: FINAL V 4.0 October 1, 2020

This document is confidential and is the sole property of ReNetX Bio, Inc. It is to be distributed for review only to investigators, potential investigators, consultants, trial staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from ReNetX Bio, Inc., unless it is necessary to obtain informed consent from potential trial subjects.

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

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

PROTOCOL SPONSOR SIGNATURE PAGE

Title of Study

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

Sponsor

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

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

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

Signature Date

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

[redacted] 1 October 2020

Signature Date

[redacted]
Study Medical Monitor [redacted]

[redacted]

Signature Date

1. SYNOPSIS

Name of Sponsor/Company:
ReNetX Bio, Inc.

Name of Investigational Product:
AXER-204

Name of Active Ingredient:
hNgR(310)-Fc

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

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

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

Objectives:

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

Part 1 Single Ascending Dose

Primary Objectives

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

Part 2 Repeat Dose

Primary Objectives

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

Secondary Objectives (Part 2 only)

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

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

Exploratory Objectives (Part 2 only)

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

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

Exploratory biomarkers of target engagement and axonal growth may be assessed

Methodology:

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

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

Part 1

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

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

The study stages for Part 1 are:

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

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

Screening

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

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

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

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

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

In-Clinic Treatment Period:

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

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

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

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

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

Follow-up:

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

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

Dose Escalation in Part 1

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

Data and Safety Monitoring Board (DSMB)

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

Dose Escalation Rules for Part 1

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

Stopping Rules/Study Interruption/Discontinuation Notice

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

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

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

Part 2

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

The study stages for Part 2 are:

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

Screening

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

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

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

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

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

Treatment Period

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

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

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

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

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

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

Follow-Up

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

Stopping Rules/Study Interruption/Discontinuation Notice

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

Data and Safety Monitoring Board (DSMB)

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

Number of Subjects (planned):

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

Diagnosis and main criteria for eligibility:

Inclusion Criteria

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

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

c. CSF space spanning the lesion

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

Exclusion Criteria

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

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

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

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

Investigational product, dosage and mode of administration:

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

Part 1:

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

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

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

Part 2

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

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

Duration of treatment:

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

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

Reference therapy, dosage and mode of administration:

Part 1 does not include placebo.

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

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

Criteria for evaluation:

Pharmacokinetics:

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

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

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

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

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

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

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

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

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

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

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

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

Efficacy

Part 1

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

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

Part 2

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

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

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

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

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

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

Safety:

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

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

Condition-specific safety outcomes will include adverse changes in:

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

Statistical Methods

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

Sample Size

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

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

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

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

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

Stages of Analysis

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

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

General Methods

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

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

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

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

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

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

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

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

Handling of Missing Data

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

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

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

Analysis Populations

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

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

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

Alpha Level Considerations

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

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

Efficacy Endpoints

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

Safety Endpoints

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

Pharmacokinetic Endpoints

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

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

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

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

[1] Abbreviations: AE = adverse events, ECG = electrocardiogram, EDC = electronic data capture. ET = early termination. ID = identification, PK = pharmacokinetic, SAE = serious adverse event
[2] Note: Day 7 phone call may be skipped if Day 8 visit actually occurs on Day 7.
[3] ET: early termination. Subjects who terminate the treatment prematurely (including those withdrawn from the study) should have all assessments performed according to the protocol. However, subjects who discontinue from the study may only have assessments performed per the ET visit.
[4] Phone calls from the site to the subject will be made each day (Study Days 5, 6, and 7) after discharge from the clinic. Subjects will be queried for general health.
[5] Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene). Patients must abstain from drinking alcohol and using recreational marijuana in US states where marijuana is legal, for at least 3 days prior to laboratory screening assessments on nominal Day-28.
[6] Vital signs (blood pressure, pulse rate, respiratory rate or pulse oximetry, and oral body temperature) will be measured after the patient has been in a sitting or recumbent position for 5 minutes. Frequency noted below:
Screening visit - Once
Day 1 - Pre-dose, post-dose, then every 3 hours for 1st 24 h following dosing
Day 2-Day 4 (until discharge from the clinical unit) - Starting at 24 h post-dose, take vitals every 6 hours
Day 8, 29 - Pre-LP, post-LP, then every 3 hours until subject leaves the unit
Day 15 - Pre-blood draw
[7] ECGs will be taken in triplicate, 5 minutes apart, will be obtained after the patient has been in a supine (resting) position for at least 5 minutes. At Visit 2, triplicate ECGs will be taken twice, pre-and post-dose. All ECGs will be read locally.
[8] MRIs will be read by a sponsor-arranged expert prior to subject enrollment into the study
[9] Serum samples collected and analyzed for ADA pre-dose and on Study Days 8 and 29
[10] Clinical Laboratory Sample Collection: Sample collected on Study Days 1-4 are to be processed locally. INR/PTT is required prior to the Day 1 lumbar puncture procedure with repeat INR/PTT tests on subsequent Study Days at the direction of the Principal Investigator.
[11] Infectious disease testing at Screening and Visit 5 (Study Day 29/ET) will include: HIV-1/HIV-2 antibody, hepatitis B surface antigen, hepatitis C antibody.
[12] Urine Pregnancy Test will be performed locally on site for women of childbearing potential.
[13] Adverse Events are only collected upon the start of study drug. Events occurring prior to this are to be reported as part of the subject medical history. However, SAEs are to be collected from the time of informed consent.

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

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

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

[1] Abbreviations: ADA = anti-drug antibody, AE = adverse events, ECG = electrocardiogram, EDC = electronic data capture. ET = early termination. ID = identification, PK = pharmacokinetic, SAE = serious adverse event
[2] MRIs will be run locally and findings read by a sponsor-arranged expert prior to subject enrollment into the study.
[3] Telephone call to inquire about any AEs and determine if subject should come to clinic for evaluation.
[4] Vital signs (blood pressure, pulse rate, respiratory rate or pulse oximetry, and oral body temperature) will be measured after the patient has been in a sitting or recumbent position for 5 minutes. Vitals will be taken pre-dose, post dose, then every 2 hours until subject leaves the unit
[5] ECGs will be taken in triplicate, 5 minutes apart, and will be obtained after the patient has been in a supine (resting) position for at least 5 minutes. ECGs are taken pre-dose at visits where study drug is administered. ECGs will be read locally.
[6] GRASSP prehension ability and prehension performance testing will be video recorded.
[7] Remove aliquot for CSF labs before processing CSF for pharmacokinetics/biomarkers and biobank samples.
[8] Clinical Laboratory Sample Collection: INR/PTT is required prior to the Day 1 lumbar puncture procedure with repeat INR/PTT tests on subsequent Study Days only if directed by the Principal Investigator. Screening labs must be completed within 28 days of enrollment.
[9] Infectious disease testing at Screening, Visit 8 (Month 6) and Visit 9 (Month 9) will include: HIV-1/HIV-2 antibody, hepatitis B surface antigen, hepatitis C antibody.
[10] Urine Pregnancy Test will be performed locally on site for women of childbearing potential.
[11] Urine testing for drugs of abuse will include the standard 9-drug panel (amphetamines, cocaine, marijuana, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and propoxyphene).
[12] Adverse Events are only collected upon the start of study drug. Events occurring prior to this are to be reported as part of the subject medical history. However, SAEs are to be collected from the time of informed consent.

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

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

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

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

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

4. INVESTIGATORS AND STUDY PERSONNEL

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

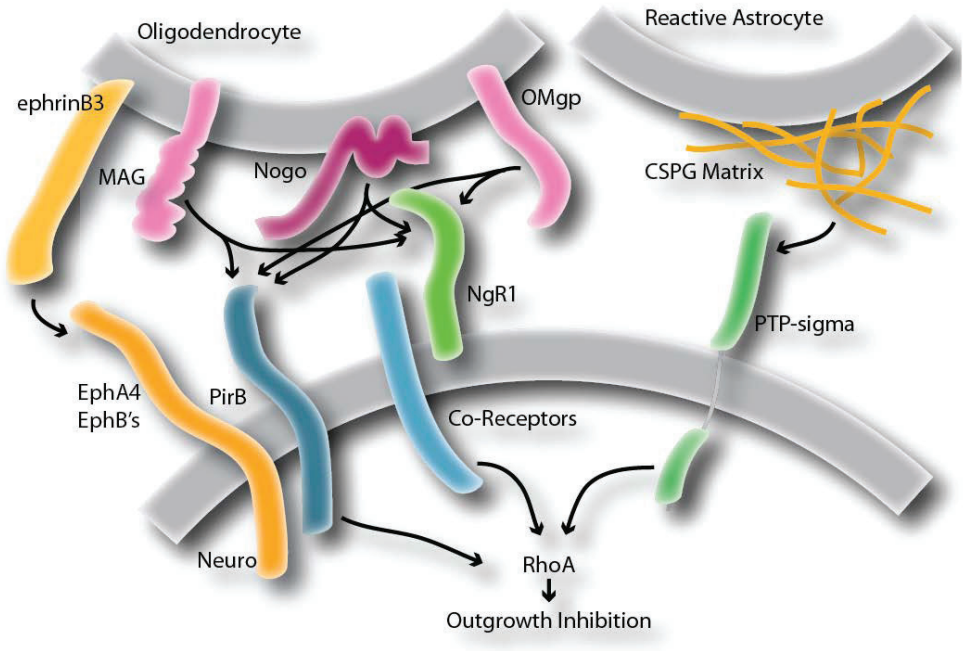
The contact information for the Medical Monitor along with the telephone numbers of the other contact persons for the sponsor are listed in Table 1. Contact information for [redacted], the designated Contract Research Organization, (CRO), and other vendors are listed in the Investigator Site File provided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

5. INTRODUCTION

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

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

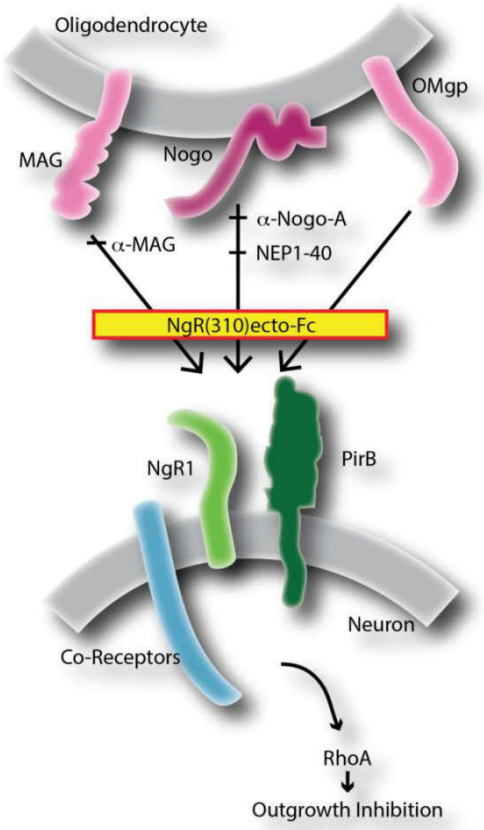
Figure 1: Key Components Regulating Axonal Growth in the Adult Mammalian Central Nervous System



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

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

Figure 2: Putative Mechanism of AXER-204



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

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

5.2. Nonclinical Summary

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

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

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

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

5.3. Clinical Experience with AXER-204 and Lumbar Puncture

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

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

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

5.4. Rationale for Dose Selection

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

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

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

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

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

6. TRIAL OBJECTIVES AND PURPOSE

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

6.1. Part 1 Single Ascending Dose

6.1.1. Primary Objective

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

6.2. Part 2 Placebo-Controlled Repeat Dose

6.2.1. Primary Objectives

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

6.2.2. Secondary Objectives

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

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

6.2.3. Exploratory Objectives

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

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

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

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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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

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

7.1.1. Part 1

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

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

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

The study stages for Part 1 are:

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

7.1.1.1. Screening

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

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

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

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

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

7.1.1.2. In-Clinic Treatment Period

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

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

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

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

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

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

7.1.1.3. Follow-Up

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

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

7.1.2. Part 2

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

The study stages for Part 2 are:

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

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

7.1.2.1. Screening

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

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

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

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

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

7.1.2.2. Treatment Phase

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

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

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

7.1.2.3. Follow-Up

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

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

7.2. Number of Subjects

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

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

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

7.3. Treatment Assignment

7.3.1. Part 1

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

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

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

7.3.2. Part 2

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

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

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

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

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

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

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

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

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

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

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

7.3.4. Data and Safety Monitoring Board

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

7.4. Criteria for Study Termination

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

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

8. STUDY ENTRY CRITERIA

8.1. Subject Inclusion Criteria

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

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

8.2. Subject Exclusion Criteria

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

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

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

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

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

9. WITHDRAWAL OF SUBJECTS

9.1. Subject Withdrawal Criteria

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

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

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

10. TREATMENT OF SUBJECTS

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

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

10.1. Description of Study Drug & Placebo

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

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

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

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

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

10.2. Concomitant Medications

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

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

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

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

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

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

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

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

10.3. Treatment Compliance

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

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

10.4. Randomization and Blinding

10.4.1. Part 1

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

10.4.2. Part 2

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

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

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

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

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

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

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

11. STUDY PROCEDURES

11.1. Part 1

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11.2. Part 2

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- ISNCSCI

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

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

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

11.2.3. Follow-up on Study Day 137

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

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

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

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

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

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

12. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

Investigational product will be provided to the clinical sites.

12.1. Study Drug

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

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

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

12.2. Investigational Product Packaging and Labeling

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

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

12.3. Investigational Product Storage

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

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

12.4. Investigational Product Preparation

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

12.5. Investigational Product Management

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

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

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

12.6. Investigational Product Accountability

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

12.7. Investigational Product Handling and Disposal

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

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

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

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

13. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

13.1. Efficacy

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

13.1.1. Part 1

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

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

13.1.2. Part 2

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

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

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

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

- ISNCSCI lower extremity motor and sensory scores

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

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

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

13.2. Pharmacokinetics

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

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

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

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

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

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

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

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

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

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

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

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

Abbreviations: M = month, ET = Early Termination.

13.2.1. Serum

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

13.2.2. Cerebrospinal Fluid

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

13.2.3. Shipment of Pharmacokinetic Samples

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

14. ASSESSMENT OF SAFETY

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

14.1. Safety Parameters

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

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

Condition-specific safety outcomes will include:

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

14.1.1. Demographic/Medical History

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

14.1.2. Vital Signs

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

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

14.1.3. Physical Examination

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

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

14.1.4. Electrocardiogram (ECG)

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

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

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

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

14.1.5. Laboratory Assessments

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

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

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

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

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

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

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

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

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

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

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

14.1.5.1. Other Laboratory Tests

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

14.1.5.2. Virus Serology

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

14.1.5.3. Drug Screen

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

14.2. Adverse and Serious Adverse Events

14.2.1. Definition of Adverse Events

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

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

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

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

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

14.2.2. Abnormal Test Findings

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

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

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

14.2.3. Adverse Events of Special Interest (AESI)

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

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

14.2.4. Serious Adverse Event (SAE)

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

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

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

14.2.4.1. Hospitalization

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

Hospitalization does not include the following:

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

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

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

14.2.5. Adverse Event Reporting

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

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

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

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

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

14.2.5.1. Severity Assessment

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

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

14.2.5.2. Causality Assessment

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

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

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

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

14.2.5.3. Exposure *in Utero*

An exposure in-utero occurs if:

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

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

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

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

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

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

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

14.2.5.4. Reporting Requirements

14.2.5.4.1. Serious Adverse Reporting Requirements

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

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

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

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

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

14.2.5.5. Non-Serious Adverse Event Reporting Requirements

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

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

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

14.2.5.6. Sponsor Reporting Requirements to Regulatory Authorities

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

15. STATISTICS

15.1. Sample Size

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

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

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

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

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

15.2. Stages of Analysis

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

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

15.3. General Methods

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

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

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

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

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

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

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

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

15.4. Handling of Missing Data

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

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

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

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

15.5. Subgroups

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

15.6. Analysis Populations

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

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

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

15.7. Alpha Level Considerations

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

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

15.8. Subject Disposition and Exposure

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

15.9. Demographics and Baseline Characteristics Analyses

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

15.10. Efficacy Endpoints

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

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

15.10.1. Part 2 Efficacy Endpoints

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

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

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

H_0: $\mu_A = \mu_P$

H_A: $\mu_A \neq \mu_P$

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

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

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

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

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

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

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

15.11. Safety Endpoints

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

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

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

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

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

Other safety outcomes will include:

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

Condition-specific safety outcomes will include:

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

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

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

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

15.12. Pharmacokinetic Endpoints

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

16. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

17. ETHICS

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

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

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

17.2. Ethical Conduct of the Study

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

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

17.3. Subject Information and Consent

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

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

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

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

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

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

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

18. DATA HANDLING AND RECORDKEEPING

18.1. Case Report Forms

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

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

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

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

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

18.2. Record Retention

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

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

19. PUBLICATION POLICY

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

19.1. Publications by Investigators

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

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

20. LIST OF REFERENCES (ALPHABETICAL)

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21. INVESTIGATORS AGREEMENT

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

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Medical Institution

_____

Date

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

[redacted] Study ID: 000000169744
Document Version: Version 5.0 Final
Document Date: 05AUG2022

[redacted]

Table of Contents

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.

Approved by

[redacted] ***Lead Statistician Approval***

[redacted] [redacted]
Biostatistician 2
I authored this document
05 Aug 2022 10:37 AM -05:00

Signature Date

[redacted] Biostatistician 2
Printed Name/Title

[redacted] ***Pharmacokineticist Approval***

[redacted] [redacted]
Director, Pharmacokinetics
I approved this document
11 Aug 2022 2:59 PM +01:00

Signature Date

[redacted] Director, Pharmacokinetics
Printed Name/Title

ReNetX Approval:

[redacted] Digitally signed by George D. Maynard
Date: 2022.08.05 12:00:19 -04'00'

Signature Date

George D. Maynard, President and Chief Scientific Officer, ReNetX Bio, Inc.
Printed Name/Title

Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted], Associate Director, Biostatistics	Peer Review Statistician	Version 4/5	[redacted]
[redacted], Director, Biostatistics	Peer Review Statistician	Version 1/2	[redacted]
[redacted], Principal Statistical Programmer	Lead Programmer	Version 1/2/4/5	[redacted]
[redacted]	Director, Pharmacokinetics	Version 1/4	[redacted]
[redacted]	Senior Medical Director	Version 2/4	[redacted]
George Maynard	Study Director	Version 1/2/4/5	ReNetX
Gilbert Block	Chief Medical Officer	Version 2/4/5	ReNetX
Stephen Strittmatter	Medical Consultant	Version 1	ReNetX

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.

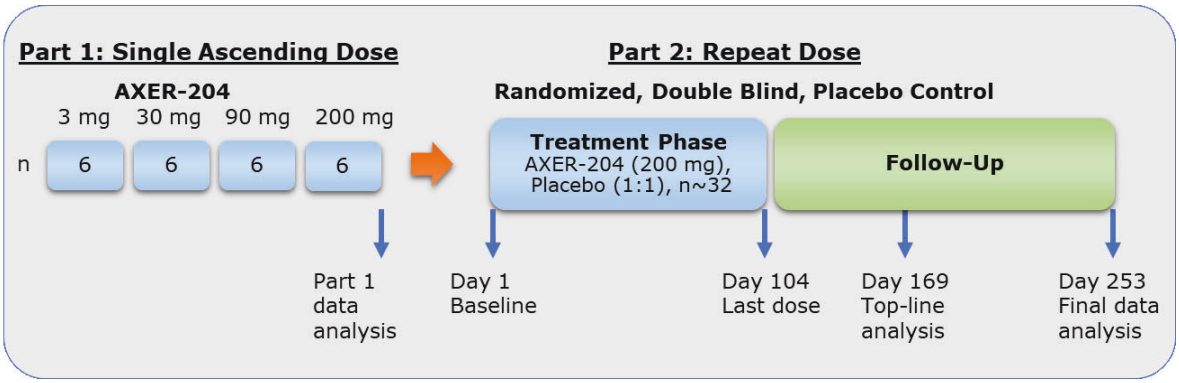
2.2 Overall Study Design

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

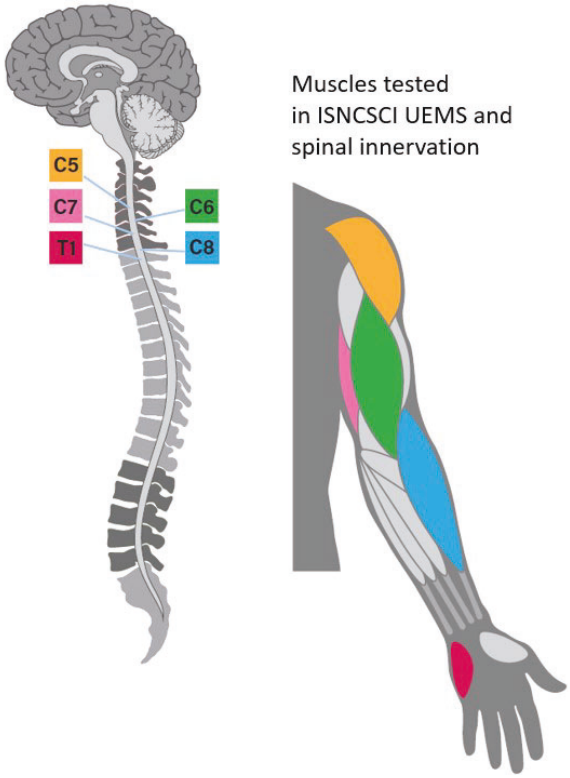
Adapted from van Hedel and Curt (van Hedel and Curt 2006).

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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