Safety and efficacy of intrathecal antibodies to Nogo-A in patients with acute cervical spinal cord injury: a randomised, double-blind, multicentre, placebo-controlled, phase 2b trial

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Lancet Neurol 2025; 24: 42–53

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Summary

Background Spinal cord injury results in permanent neurological impairment and disability due to the absence of spontaneous regeneration. NG101, a recombinant human antibody, neutralises the neurite growth-inhibiting protein Nogo-A, promoting neural repair and motor recovery in animal models of spinal cord injury. We aimed to evaluate the efficacy of intrathecal NG101 on recovery in patients with acute cervical traumatic spinal cord injury.

Methods This randomised, double-blind, placebo-controlled phase 2b clinical trial was done at 13 hospitals in the Czech Republic, Germany, Spain, and Switzerland. Patients aged 18–70 years with acute, complete or incomplete cervical spinal cord injury (neurological level of injury C1–C8) within 4–28 days of injury were eligible for inclusion. Participants were initially randomly assigned 1:1 to intrathecal treatment with 45 mg NG101 or placebo (phosphate-buffered saline); 18 months into the study, the ratio was adjusted to 3:1 to achieve a final distribution of 2:1 to improve enrolment and drug exposure. Randomisation was done using a centralised, computer-based randomisation system and was stratified according to nine distinct outcome categories with a validated upper extremity motor score (UEMS) prediction model based on clinical parameters at screening. Six intrathecal injections were administered every 5 days over 4 weeks, starting within 28 days of injury. Investigators, study personnel, and study participants were masked to treatment allocation. The primary outcome was change in UEMS at 6 months, analysed alongside safety in the full analysis set. The completed trial was registered at ClinicalTrials.gov, NCT03935321.

Findings From May 20, 2019, to July 20, 2022, 463 patients with acute traumatic cervical spinal cord injury were screened, 334 were deemed ineligible and excluded, and 129 were randomly assigned to an intervention (80 patients in the NG101 group and 49 in the placebo group). The full analysis set comprised 78 patients from the NG101 group and 48 patients from the placebo group. 107 (85%) patients were male and 19 (15%) patients were female, with a median age of 51·5 years (IQR 30·0–60·0). Across all patients, the primary endpoint showed no significant difference between groups (with UEMS change at 6 months 1·37 [95% CI –1·44 to 4·18]; placebo group mean 19·20 [SD 11·78] at baseline and 30·91 [SD 15·49] at day 168; NG101 group mean 18·23 [SD 15·14] at baseline and 31·31 [19·54] at day 168). Treatment-related adverse events were similar between groups (nine in the NG101 group and six in the placebo group). 25 severe adverse events were reported: 18 in 11 (14%) patients in the NG101 group and seven in six (13%) patients in the placebo group. Although no treatment-related fatalities were reported in the NG101 group, one fatality not related to treatment occurred in the placebo group. Infections were the most common adverse event affecting 44 (92%) patients in the placebo group and 65 (83%) patients in the NG101 group.

Interpretation NG101 did not improve UEMS in patients with acute spinal cord injury. Post-hoc subgroup analyses assessing UEMS and Spinal Cord Independence Measure of self-care in patients with motor-incomplete injury indicated potential beneficial effects that require investigation in future studies.

Funding EU program Horizon2020; Swiss State Secretariat for Education, Research and Innovation; Wings for Life; the Swiss Paraplegic Foundation; and the CeNeReg project of Wyss Zurich (University of Zurich and Eidgenössische Technische Hochschule Zurich).

Introduction

Traumatic spinal cord injury leads to lifelong sensorimotor and autonomic dysfunction, with neurological deficits stemming from disruption of spinal cord axons. In combination with the many secondary disease states that can ensue, spinal cord injury can severely decrease quality

Research in context

Evidence before this study

A systematic PubMed search for articles published in English up to Aug 22, 2024, for "traumatic spinal cord injury" and "clinical trial" and "Nogo-A" yielded two publications (one describes results of the anti-Nogo phase 1 study; one is a meta-analysis focusing on mesenchymal stem cells). Traumatic spinal cord injury causes acute irreversible damage to neural tissue. Although standard acute care (including timely spinal surgery and advanced medical care), improves outcomes, and intensive rehabilitation helps maximise residual function, no therapy has proven effective in promoting neuroregeneration and neurological recovery. Previous trials have often relied on the American Spinal Injury Association Impairment Scale for the selection and stratification of participants which, with its five categories (A–E), might not adequately balance patients with varying injury severities across treatment groups. A crucial need remains for biomarkers that can accurately predict clinical efficacy.

Added value of this study

This phase 2b trial evaluated NG101, a recombinant human antibody targeting the neurite growth inhibitor Nogo-A, employing a novel stratification method using unbiased recursive partitioning (URP). It also incorporated exploratory MRI analysis of spinal tissue bridges and neurofilament light chain (NfL) concentrations in CSF. Although the primary outcome of upper extremity motor score (UEMS) did not show a significant difference overall, we found evidence of improvement in a secondary outcome, Spinal Cord Independence Measure (SCIM) of self-care, in the NG101-treated group. In post-hoc analyses, participants with incomplete motor spinal cord injury showed gains in UEMS and SCIM self-care, albeit not reaching the proposed minimal clinically important difference. NG101 was well tolerated with no safety concerns. MRI-based and soluble CSF-derived biomarkers validated clinically defined injury characteristics (motor completeness), confirming balanced treatment groups with respect to injury severity.

Implications of all the available evidence

These results support further investigation of antibodies to Nogo in people with motor-incomplete spinal cord injury. Advanced stratification methods that integrate structural integrity measures, such as tissue bridges and NfL, might refine treatment cohorts and improve the sensitivity and specificity of outcomes in future spinal cord injury trials. Additionally, our findings regarding the short half-life of NG101 in CSF suggest that higher dosing or adjusted dosing regimens should be explored to optimise therapeutic efficacy in subsequent studies.

of life and place substantial socioeconomic burdens on individuals and society.[1] Current therapeutic strategies are primarily mitigatory, focusing on spinal cord decompression or stabilisation surgery and comprehensive rehabilitation.[1]

A clear unmet need exists for effective interventions to improve clinical outcomes for people with spinal cord injury. Neuroregenerative therapies aim to promote axonal regrowth or neutralise endogenous molecules that inhibit such regrowth.[2] Nogo-A, a membrane protein prevalent in CNS myelin, is a potent inhibitor of neurite growth through its multiple inhibitory domains that activate independent receptors.[3] Monoclonal antibodies targeting Nogo-A neutralise the inhibitory activity of Nogo-A both in vitro[4,5] and in vivo, and these antibodies have been shown to mediate motor recovery in rodent and non-human primate models of spinal cord injury.[6] In a first-in-human clinical trial including 52 participants with acute traumatic spinal cord injury, repeated intrathecal bolus injections of the ATI355 antibody to Nogo-A over 28 days were feasible and well tolerated.[7]

Clinical assessments and trials in spinal cord injury typically use the American Spinal Injury Association Impairment Scale (AIS) for patient stratification and neurological outcome assessment. However, the AIS often does not capture clinically meaningful differences in severity and recovery, particularly in people with cervical spinal cord injury, and each AIS grade includes people with heterogeneous neurological impairments.[8,9] The unbiased recursive partitioning with conditional inference tree (URP-CTREE) technique allows for data-driven identification of more homogeneous outcome groups based on detailed clinical assessments according to the International Standards for Neurological Classification for Spinal Cord Injury (ISNCSCI); however, this technique has not been applied in an interventional clinical study.[10] This URP-CTREE approach should also permit the identification and prospective exclusion of individuals from spinal cord injury clinical trials who are likely to encounter ceiling effects with respect to primary endpoints such as upper or lower extremity motor score.

The aim of this randomised, placebo-controlled, multicentre phase 2b clinical trial (Nogo-A Inhibition in Spinal Cord Injury [NISCI]) was to investigate the effects of intrathecal treatment with an antibody directed against Nogo-A (NG101) on upper extremity motor score (UEMS) change at 6 months after acute traumatic cervical spinal cord injury.

Methods

Study design

This investigator-initiated, multicentre, multinational phase 2b clinical trial (NISCI) was done at eight specialised spinal cord injury centres in Germany, three in Switzerland, and one each in Spain and the Czech Republic, which were all part of the established European Multicenter Study about Spinal Cord Injury trial network (EMSCI) and in accordance with Good Clinical Practice guidelines. The clinical trial protocol received ethical

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approval from the ethics committee at Heidelberg University Hospital for all German sites (Afmu-815/2018), the Kantonale Ethikkommission Zurich for all Swiss sites (2016-01042), the Comité Ético de Investigación de la Fundació Unió Catalana Hospitals for the Spanish site (2016-001227-31), and the ethics committee for Multi-Centric Clinical Trials of the University Hospital Motol for the Czech site (EK-1367/19). An independent data and safety monitoring board (DSMB) composed of clinical trial and spinal cord injury experts periodically reviewed and evaluated the study data to ensure participant safety and monitor study conduct and progress. The study was registered at ClinicalTrials.gov, NCT03935321.

Participants

Adult patients aged 18–70 years within 4–28 days of traumatic cervical spinal cord injury (neurological level of injury C1–C8) were eligible for screening. Enrolment was based on individual predictions for UEMS outcome at 168 days post-baseline using URP (appendix p 5).[10] This approach, validated in an independent study,[11] allowed for the exclusion of patients predicted to reach a ceiling of UEMS recovery at 6 months, as they would be unlikely to benefit from the intervention (appendix pp 5–9, 17). Full eligibility criteria are available in the appendix (pp 6–9). The predicted outcome cohorts (URP nodes; appendix pp 9, 17) comprised participants with distinct motor and sensory score patterns and varying injury severities (AIS grades) at the screening visit. Written informed consent was obtained from all participants before screening. Gender (male or female) information was self-reported. Race and ethnicity information was not recorded due to restrictions in all participating countries.

Randomisation and masking

Patients were randomly allocated to treatment stratified by URP nodes at screening using the Big Stick Design method.[12] Initially, patients were randomised to either the antibody against Nogo-A (NG101) or placebo (1:1) allowing for a maximum imbalance of three patients per URP node using a centralised, computerised randomisation system (appendix p 9). 18 months into the study, the allocation was adjusted to 3:1 to achieve a final distribution of 2:1 to improve enrolment and drug exposure compared with the initial 1:1 allocation. Randomisation resulted in a number corresponding to that of an available treatment package at the site. All participants and study site staff (excluding staff preparing the injections) remained masked to the treatment assignment until day 168. The staff responsible for injection preparation were instructed to maintain treatment concealment in the event of their accidental unmasking. After the last patient had their final study visit the database was locked and the primary analysis was defined in the statistical analysis plan. Thereafter, designated sponsor staff were unmasked.

For more on the **computerised randomisation system** see https://randomizer.at

Procedures

At each site, qualified site staff prepared and dispensed the study medication in individual patient-specific vials. Participants received intrathecal 3 mL bolus injections at the L3 or L4 level, administered by the treating investigator using bevelled needles (diameter 0·5–0·9 mm; Spinocan Quincke, B Braun, Melsungen, Germany). Patients assigned to NG101 received 45 mg of this, a fully human recombinant antibody blocking Nogo-A activity (appendix p 5); the drug product was generated (by the Wyss Zurich Translational Medicine Platform) from the drug substance ATI355 antibody (donated by Novartis Pharma, Basel, Switzerland[7]) and dissolved in 3 mL phosphate-buffered saline. The placebo group received 3 mL phosphate-buffered saline only. Respective solutions were aspirated into 5 mL syringes, which appeared identical for NG101 and placebo. Treatment began within 4–28 days after injury and consisted of six 3 mL injections given every 5 days over 25 days (appendix p 18). Each clinical site followed its standard in-patient rehabilitation programme for up to 6 months post-injury. UEMS was measured at screening (2–28 days after spinal cord injury); baseline (day before treatment initiation); and on days 30, 84, and 168. Measures for secondary endpoints were collected at baseline and on days 30, 84, and 168 and were the total motor score, lower extremity motor score, and total light touch and pinprick scores (all according to ISNCSCI), and functional assessments that included Spinal Cord Independence Measure III (SCIM), the Graded and Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) test, the Walking Index for Spinal Cord Injury (WISCI), the 10 m walk test (10MWT), and the 6-min walking test (6MWT). Neurophysiological endpoints (analysed only in participants with available data) were ulnar nerve conducting velocity and tibial, C6, and C8 dermatomal somatosensory evoked potentials, and these endpoints were measured at screening and on days 30, 84, and 168. Bladder assessments (Qualiveen questionnaire, bladder function assessment, and bladder diary) were obtained at screening and on days 84 and 168.

Participants underwent MRI at screening and at days 30 and 168 using a standardised clinical MRI protocol across all sites.[13] The protocol included sagittal T1/T2-weighted and axial T2-weighted anatomical scans of the cervical spinal cord, centred at the lesion level. Scans were performed in a supine, head-first position using 16-channel or 32-channel receive spine coils integrated into the table (appendix p 11–12).

Outcomes

The primary endpoint (analysed in the full analysis set) was the UEMS according to ISNCSCI (ranging from 0, no voluntary motor function, to 50, full voluntary motor function, in the upper extremities) with the difference between day 168 and baseline defining the primary outcome.[14] We analysed the following secondary endpoints

in the full analysis set: all other components of the ISNCSCI protocol, which were total motor score (ranging from 0, no voluntary motor function, to 100, normal voluntary motor function in the lower and upper extremities), lower extremity motor score (ranging from 0, no voluntary motor function, to 50, normal voluntary motor function in the lower extremities), total light touch score (ranging from 0, absent sensation, to 112, normal sensation), and total pinprick score (ranging from 0, absent sensation, to 112, normal sensation); the SCIM total score (ranging from 0, totally dependent, to 100, totally independent) including all subscores (self-care, respiration and sphincter, mobility); the GRASSP test (ranging from 0, absence of motor and sensory function in the upper extremities, to 232, normal) including all subscores (strength, sensation, prehension, ability, and prehension performance); and the WISCI (ranging from 0, not able to walk 10 m, to 20, able to walk 10 m without support) and all neurophysiological parameters. Few patients were able to perform the 6MWT and 10MWT at baseline, therefore, descriptive statistics of these secondary endpoints are not included. Results of all bladder assessments require further analyses and will be reported separately.

Safety was analysed by routine laboratory chemistry, vital signs, physical examinations, and the recording of adverse events and severe adverse events and was assessed in the safety analysis set, which is identical to the full analysis set. The unfavourable occurrence of spasticity was derived from adverse event reporting. Neuropathic pain was classified according to the International Spinal Cord Injury Pain Classification (ISCIP). For NG101 pharmacokinetics evaluation, CSF and serum were collected before each drug application (appendix p 18) and on day 84 post baseline.

In all participants who received at least one dose, NG101 concentrations in the CSF were quantified using ELISA with a specific mouse anti-NG101 monoclonal capture antibody. Serum NG101 concentrations were measured using ELISA with the minimal Nogo-A epitope peptide for capture and an anti-human IgG4-specific secondary antibody for detection (appendix p 11). The pharmacokinetics of NG101 in the CSF were extrapolated from the injected dose (45 mg; total adult CSF volume estimated at 130 mL) and the trough concentrations of NG101 measured 5 days after each injection. Half-lives were calculated using a linear half-life equation:

$$\ln[C] = \ln[C0] - k \times t$$

to determine the rate constant k assuming

$$(T_{1//2} \ln \frac{[2]}{k})$$

Animal studies suggest that anti-Nogo-A-enabled axon regeneration might facilitate motor recovery in people who have anatomically subtotal injuries with remaining tissue bridges, in whom preserved neuronal pathways can serve as substrates for regenerative processes to bypass the lesion site.[15] These preserved tissue bridges, identifiable through MRI scans, might correlate with improved electrophysiological and clinical outcomes.[16] Similarly, neurofilament light chain (NfL) has been associated with clinical impairment and worse functional outcomes in people with spinal cord injury.[17] Both measures were included in this study as exploratory not prespecified variables (appendix pp 11–12) and analysed in all participants with available data.

Statistical analysis

The power calculation was based on the mean UEMS changes in patients with cervical spinal cord injury recorded in the EMSCI trial network.[10] An expected mean difference of 6 points (target effect) from baseline to day 168 favouring NG101 (mean delta UEMS change of 14·3 for the placebo group and 20·3 for the NG101 group), a standard deviation of 10·8, a 20% dropout rate, and a 1:1 NG101:placebo allocation indicated that 132 participants in total would be sufficient to demonstrate superiority of NG101 over placebo with 80% power. During the study, challenges in recruitment and logistical issues caused by the COVID-19 pandemic prompted a protocol amendment, increasing the NG101:placebo allocation to 2:1 (approved by the ethics boards and implemented in protocol version 4.0, Oct 19, 2020). As a result, the target was adjusted to 78 NG101-treated patients (66% power), with the final placebo group size dependent on overall recruitment at the time of amendment implementation.

The treatment effects for the primary endpoint UEMS were defined as the group difference in UEMS change from baseline to day 168 post baseline. This parameter was specified as a fixed-effects time×treatment interaction in a normal linear mixed-effects model for UEMS recovery profiles (evaluated at baseline and days 30, 84, and 168 post baseline; appendix pp 13–14). The analysis across all patients in the full analysis set (ie, those who received at least one dose of NG101 or placebo) included a uniform model with a linear fixed-effect of time as a continuous variable, fixed-effect node-specific intercepts, and patient-specific correlated random intercepts and slopes, and a non-uniform model enhanced with URP node-specific recovery profiles by substituting patient-specific random slopes with fixed-effect, node-specific time slopes. A patient-specific random intercept captured correlations between repeated measurements in the enhanced version of the model, which was applied to both UEMS and predefined secondary endpoints. Data missing due to loss to follow-up were considered missing at random, with no imputation applied. Linear mixed models were fitted by restricted maximum likelihood, and 95% CIs were obtained from the limiting distribution without

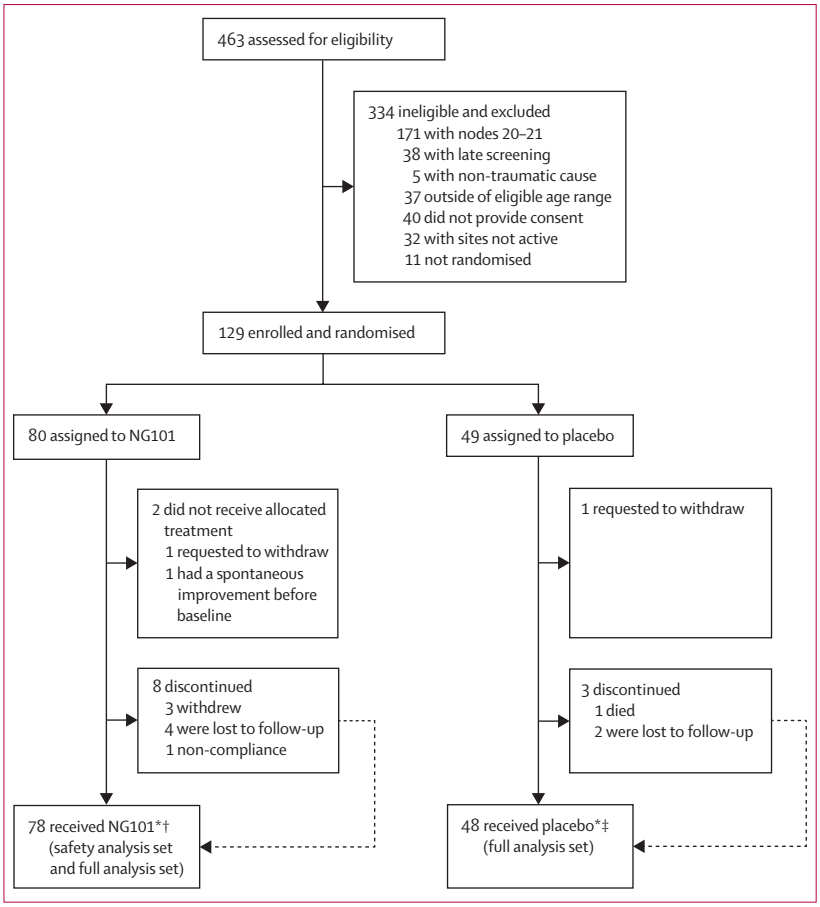

Figure 1: **Trial profile**
All patients who discontinued were part of the full analysis set. *Includes seven patients in the NG101 group and four in the placebo group who did not receive full dosing as per protocol (appendix p 20). †18 were enrolled within the 1:1 allocation period and 60 were enrolled within the 3:1 allocation period. ‡23 were enrolled within the 1:1 allocation period and 25 were enrolled within the 3:1 allocation period.

	Placebo group (n=48)	NG101 group (n=78)
Age, years		
Mean (SD)	47·25 (17·05)	45·63 (16·64)
Median (IQR)	52·00 (29·75–61·25)	50·50 (30·00–58·00)
Sex		
Female	8 (17%)	11 (14%)
Male	40 (83%)	67 (86%)
Participating country		
Switzerland (3 sites)	11 (23%)	18 (23%)
Germany (9 sites)	36 (75%)	55 (71%)
Spain (1 site)	1 (2%)	3 (4%)
Czechia (1 site)	0	2 (3%)
Time from injury to first injection, days		
Mean (SD)	23·81 (4·61)	21·78 (5·40)
Median (IQR)	25·00 (22·00–27·00)	23·00 (17·00–27·00)
Outcome cohorts		
Nodes 4–5*	3 (6%)	11 (14%)
Nodes 8–9*	3 (6%)	6 (8%)
Node 10	10 (21%)	12 (15%)
Node 13	16 (33%)	23 (30%)
Nodes 16–18*	16† (33%)	26 (33%)
AIS grade screening		
A	11 (23%)	26 (33%)
B	12 (25%)	14 (18%)
C	16 (33%)	21 (27%)
D	9 (19%)	17 (22%)
Neurological level of injury		
C1	0	0
C2	3 (6%)	11 (14%)
C3	10 (21%)	12 (15%)
C4	18 (38%)	39 (50%)
C5	14 (29%)	10 (13%)
C6	3 (6%)	5 (6%)
C7	0	1 (1%)
C8	0	0

Data are n (%), unless otherwise specified. URP-CTREE=unbiased recursive partitioning with conditional inference tree. AIS=American Spinal Injury Association Impairment Scale. *The small sample sizes in some of the individual nodes necessitated the combining of nodes 4–5, 8–9, and 16–18. Each of these combined nodes belong to the same final URP-CTREE branch (appendix p 17). †One participant in the placebo group with AIS B (eligible for node 8, 9, or 10 at screening) was incorrectly assigned to node 17.

Table 1: **Baseline characteristics (full analysis set)**

small-sample or multiplicity correction. The analysis code is presented in the appendix (p 13). Post-hoc analyses estimated subgroup-specific treatment effects for URP nodes using the same model with subgroup×time×treatment interactions. Additionally, the same model was used for a post-hoc analysis in patients with motor-complete and motor-incomplete spinal cord injury. A sensitivity analysis under relaxed model assumptions (non-normality of ordinal outcomes, non-linear time recovery profiles) is detailed in the appendix (pp 13, 14). For tissue bridge analysis, measurements of distances between the hyperintense intramedullary cyst and the spinal canal were aggregated to calculate the total width of preserved neuronal tissue, across all identifiable slices. To account for variations in spinal cord size, the sum of all tissue bridges was normalised by the number of slices displaying discernible tissue bridges, resulting in the mean preserved tissue bridges in millimetres.[18] For an exploratory post-hoc mass spectrometry-based proteome analysis,[19] CSF samples obtained at visit 3 (before the first intrathecal injection) were analysed. Wilcoxon rank sum tests compared the extent of preserved tissue bridges and NfL abundances between the cohorts of participants with motor-complete (nodes 4–5, 8–9, and 13 representing injury severities AIS A and B) and motor-incomplete spinal cord injury (nodes 10, 16–18 representing injury severities AIS C and D), and within these cohorts between NG101 and placebo treatment. Quantitative protein data for NfL were reported as normalised and log2 transformed label-free quantitation values representing the relative protein abundance.

Unadjusted 95% CIs and p values are reported for all treatment effect estimates. All analyses were performed using R (version 4.4.1 with the lme4 package[20]) and SAS (version 9.4). All data throughout this article are presented as absolute values with percentages, means with SDs medians with IQRs, or regression estimates with 95% CIs.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participants were screened for eligibility and randomised into the trial with repeated follow-up assessments over 168 days post baseline. Between May 20, 2019, and July 20, 2022, a total of 463 patients with acute traumatic cervical spinal cord injury were assessed for eligibility. 334 were deemed ineligible and excluded and 129 were enrolled and randomly assigned to either NG101 or placebo. 11 participants withdrew from the study after giving consent but before randomisation. 80 patients were assigned to the NG101 group and 49 were assigned to the placebo group. Two patients assigned to the NG101 group did not receive the allocated treatment (one requested to withdraw and one had a spontaneous improvement before baseline) and 78 patients were included in the full analysis set. One patient assigned to the placebo group requested to withdraw and 48 were included in the full analysis set (figure 1).

Of the 126 patients constituting the full analysis set, which is identical to the safety analysis set, seven patients in the NG101 group and four in the placebo group did not receive complete full dosing as per protocol (appendix p 20). The eight patients who discontinued in the NG101 group did so for the following reasons: three withdrew, one had non-compliance, and four were lost to follow-up. In the placebo group, one died and two were lost to follow-up. 126 patients were randomly assigned, dosed and included in the full analysis set with a median age of 51·5 years (IQR 30·0–60·0). 107 patients (85%) were male and 19 (15%) were female, with a predominant neurological injury level at C3, C4, or C5 (103 patients [82%]; table 1). All available data from these participants were included in the analyses. Stratification into the URP nodes (predicting UEMS outcomes at day 168), which are specified in respect to AIS grade distribution at screening within each node (appendix p 21), proceeded as planned, with the expected distribution across different UEMS outcome cohorts (appendix p 19). As anticipated, nodes 13 (subset of patients with motor-complete spinal cord injury), and nodes 10 and 16–18 (both together containing all patients with motor-incomplete spinal cord injury), contained the highest number of eligible patients, representing a typical sample for acute traumatic cervical spinal cord injury.

	Placebo group (n=48)	NG101 group (n=78)
Adverse events		
Number of participants with at least one adverse event	48 (100%)	73 (94%)
Number of distinct events	432	650
Action taken with study treatment		
Dose interrupted owing to adverse event	1 (2%)	3 (4%)
Dose reduced owing to adverse event	0	0
Dose not changed owing to adverse event	48 (100%)	71 (91%)
Drug withdrawn owing to adverse event	4 (8%)	4 (5%)
Adverse event considered to be related to intervention	6	9
Adverse event considered to be unrelated to intervention	4 (8%)	4 (5%)
Action taken with study treatment unknown	0	1 (1%)
Serious adverse events		
Number of participants with at least one serious adverse event	6 (13%)	11 (14%)
Number of distinct events	7	18
Seriousness criteria		
Death	1 (2%)	0
Life threatening	0	4 (5%)*
Requires or prolongs hospital stay	1 (2%)	5 (6%)
Disability or incapacity	1 (2%)	0
Otherwise important	3 (6%)	5 (6%)
Serious adverse event considered to be related to intervention	0	0
Serious adverse event considered to be unrelated to intervention	6 (13%	11 (14%)
Adverse events with more than 5% incidence in either group		
Infections and infestations	44 (92%)	65 (83%)
Nervous system disorders	32 (67%)	41 (53%)
Musculoskeletal and connective-tissue disorders	23 (48%)	33 (42%)
Skin and subcutaneous-tissue disorders	14 (29%)	36 (46%)
Injury, poisoning, and procedural complications	19 (40%)	21 (27%)
Gastrointestinal disorders	11 (23%)	24 (31%)
General disorders and administration-site conditions	15 (31%)	15 (19%)
Renal and urinary disorders	12 (25%)	16 (21%)
Psychiatric disorders	11 (23%)	14 (18%)
Respiratory, thoracic, and mediastinal disorders	10 (21%)	14 (18%)
Metabolism and nutrition disorders	10 (21%)	13 (17%)
Vascular disorders	6 (13%)	14 (18%)
Cardiac disorders	4 (8%)	8 (10%)
Blood and lymphatic system disorders	3 (6%)	6 (8%)
Ear and labyrinth disorders	5 (10%)	4 (5%)
Eye disorders	4 (8%)	4 (5%)
Reproductive system and breast disorders	2 (4%)	5 (6%)

*The following life-threatening serious adverse events were documented: asystolia, low cardiac output with depression of circulation, pulmonary infection or spontaneous pneumothorax, and coma. All four patients recovered before the end of the study. All four serious adverse events were assessed to be not related to the study drug.

Table 2: **Overview of adverse events and serious adverse events in the safety analysis set**

The mean time from injury to first dosing was 21·78 days (SD 5·40) in the NG101 group and 23·81 days (4·61) in the placebo group. The DSMB considered the overall tolerability and feasibility of the intervention to be favourable. A comprehensive analysis of all 1082 adverse events and all 25 serious adverse events in the safety analysis set identified 15 adverse events (nine in the NG101 group and six in the placebo group)

	Placebo group		NG101 group		Delta (95% CI)
	Baseline	Day 168	Baseline	Day 168	
ISNCSCI categories					
LEMS	15·16 (20·99)	26·48 (24·61)	17·13 (23·10)	26·35 (25·88)	−1·6 (−4·43 to 1·23)
Total motor score	34·33 (28·51)	57·45 (37·14)	35·40 (34·52)	57·53 (41·43)	0·53 (−3·83 to 4·88)
Pin prick	36·82 (33·10)	49·37 (39·15)	36·27 (36·90)	48·84 (40·08)	1·14 (−4·16 to 6·44)
Light touch	62·93 (34·13)	74·06 (33·31)	56·00 (39·48)	68·01 (38·35)	0·75 (−4·11 to 5·61)
SCIM III					
SCIM total	14·69 (16·88)	45·20 (35·43)	16·88 (24·72)	51·52 (44·29)	4·35 (−0·60 to 9·31)
SCIM self-care	1·90 (4·60)	8·75 (8·80)	1·63 (4·68)	9·54 (10·70)	1·58 (0·13 to 3·03)
SCIM respiration and sphincter	10·67 (8·71)	22·08 (14·65)	11·38 (11·21)	24·32 (16·06)	1·92 (−0·9 to 4·73)
SCIM mobility	2·11 (5·70)	14·33 (14·80)	3·86 (11·23)	17·85 (20·16)	2·32 (−0·28 to 4·92)
WISCI					
Total	0·39 (3·64)	5·88 (10·55)	2·24 (7·72)	8·08 (12·56)	..
GRASSP					
GRASSP total	45·23 (33·53)	81·45 (44·78)	46·64 (44·91)	82·35 (58·75)	..
GRASSP strength	29·40 (21·55)	53·15 (31·07)	30·99 (29·45)	55·16 (39·84)	2·36 (−2·12 to 6·84)
GRASSP sensation	9·88 (9·52)	16·48(9·29)	9·37 (10·32)	14·25 (10·56)	−1·11 (−2·53 to 0·30)
GRASSP prehension ability	5·87 (7·45)	12·26(10·22)	6·21 (8·80)	13·07 (12·16)	1·00 (−0·69 to 2·69)
AIS grade					
A	10/48 (21%)	6/44 (14%)	24/78 (31%)	12/68 (18%)	..
B	12/48 (25%)	7/44 (16%)	15/78 (19%)	9/68 (13%)	..
C	13/48 (27%)	6/44 (14%)	18/78 (23%)	13/68 (19%)	..
D	13/48 (27%)	24/44 (55%)	21/78 (27%)	34/68 (50%)	..
E	0	1/44 (2%)	0	0	..
GRASSP prehension performance*					
Left	5·77 (8·11)	9·80 (8·55)	5·28 (9·19)	9·73 (9·43)	..
Right	5·68 (8·15)	10·19 (9·12)	5·64 (8·91)	9·93 (9·35)	..
NCV, normal ulnar compound motor action potential cMAP (≥6mV)†					
Left	18/42 (43%)	18/40 (45%)	30/74 (41%)	22/66 (33%)	..
Right	18/41 (44%)	15/40 (38%)	30/76 (39%)	23/66 (35%)	..
Tibial SSEP , preserved (>0μV)†					
Left	13/40 (33%)	14/36 (39%)	20/74 (27%)	21/65 (32%)	..
Right	16/41 (39%)	15/36 (42%)	22/75 (29%)	22/64 (34%)	..
C6 dSSEP, preserved (>0μV)†					
Left	24/41 (59%)	23/37 (62%)	29/74 (39%)	32/65 (49%)	..
Right	24/42 (57%)	27/38 (71%)	32/75 (43%)	32/64 (50%)	..
C8 dSSEP, preserved (>0μV)†					
Left	13/40 (33%)	17/38 (45%)	23/73 (32%)	26/65 (40%)	..
Right	16/42 (38%)	18/38 (47%)	23/75 (31%)	25/64 (39%)	..

Data are n/N (%) or mean (SD). Estimated secondary endpoints in the total cohort were analysed as prespecified in the statistical analysis plan in the same manner as the primary endpoint. Delta is defined as change from baseline to day 168. AIS=American Spinal Injury Association Impairment Scale. dSSEP=dermatomal somatosensory evoked potentials. ISNCSCI=International Standards for Neurological Classification of Spinal Cord Injury. GRASSP=Graded and Redefined Assessment of Strength, Sensibility and Prehension test. LEMS=lower extremity motor score. NCV=nerve conduction velocity. SCIM=Spinal Cord Independence Measure. SSEP=somatosensory evoked potentials. UEMS=upper extremity motor score. WISCI=Walking Index for Spinal Cord Injury. *Not assessed at baseline but on day 30 and day 168. †Not measured at baseline but at screening and day 168.

***Table 3*: Secondary outcomes**

potentially related to the treatment drug, with no related serious adverse events (table 2). Both treatment groups experienced similar numbers of adverse events (mean 8·3 [SD 6·4] per participant in the NG101 group and mean 9·0 [SD 6·1] in the placebo group), with no difference in the distribution of serious adverse events (seven serious adverse events in six [13%] patients in the placebo group, 18 serious adverse events in 11 [14%] patients in the NG101 group). Infections were the most common adverse event affecting 44 (92%) patients in the placebo group and 65 (83%) patients in the NG101 group. Spasticity of any severity was reported in 17 (22%) patients in the NG101 group and 21 (44%) patients in the placebo group. Moderate to severe spasticity was reported in

nine (12%) patients in the NG101 group and ten (21%) patients in the placebo group. Approximately one-third of participants in each treatment group (pain assessment at day 168 classified according to ISCIP was available from 67 participants in the NG101 group and 43 in the placebo group) reported neuropathic pain at day 168 post baseline: 21 (31%) in the NG101 group and 13 (30%) in the placebo group. Although no treatment-related fatalities were reported in the NG101 group, one fatality not related to treatment occurred in the placebo group.

The statistical analysis of the full analysis set applying the uniform model across all 126 patients showed no significant change in UEMS from baseline to day 168 post baseline between treatment groups (group difference 1·37 [95% CI –1·44 to 4·18]; for the placebo group, mean 19·20 [SD 11·78] at baseline and mean 30·91 [SD 15·49] at day 168; for the NG101 group, mean 18·23 [SD 15·14] at baseline and mean 31·31 [19·54] at day 168), and the confidence interval excluded the target delta change of six UEMS points.

Of the secondary endpoints that were analysed in the same manner as the primary endpoint according to the statistical analysis plan (SCIM total score and subscores of self-care, respiration and sphincter management, and mobility; GRASSP subscores of strength, sensation, and prehension ability; total motor score; and total light touch and pinprick score), the only significant improvement (without multiplicity correction) was in the SCIM self-care subscore, with a difference in SCIM self-care change from baseline to day 168 post baseline of 1·58 (95% CI 0·13–3·03) between treatment groups (table 3; appendix p 28). The difference between treatment groups was even more pronounced in nodes 16–18, containing participants with motor-incomplete injury (delta SCIM self-care 3·77 [95% CI 1·22–6·32]; appendix p 28). All analysed secondary endpoints and their descriptive statistics as prespecified in the statistical analysis plan are listed in table 3.

CSF NG101 concentrations measured 5 days after each intrathecal injection indicated low trough levels, reflecting the antibody CSF half-life of approximately 10–11 h (figure 2A; appendix pp 15–16, 26, 31–32). Antibodies not retained in tissue appeared incrementally in the serum over 30 days (figure 2B). However, simulated kinetics showed high antibody concentrations in the CSF immediately following each injection (figure 2C). Although most patients exhibited low CSF concentrations 5 days post-injection, some displayed higher concentrations, probably due to differences in CSF circulation or antibody metabolism. A post-hoc analysis suggested better UEMS recovery in patients with motor-incomplete injury and higher CSF NG101 concentrations compared with people with motor-incomplete injury and lower CSF concentrations (appendix p 15, 26), indicating possible variable underdosing between injections (appendix pp 15–16, 31–32).

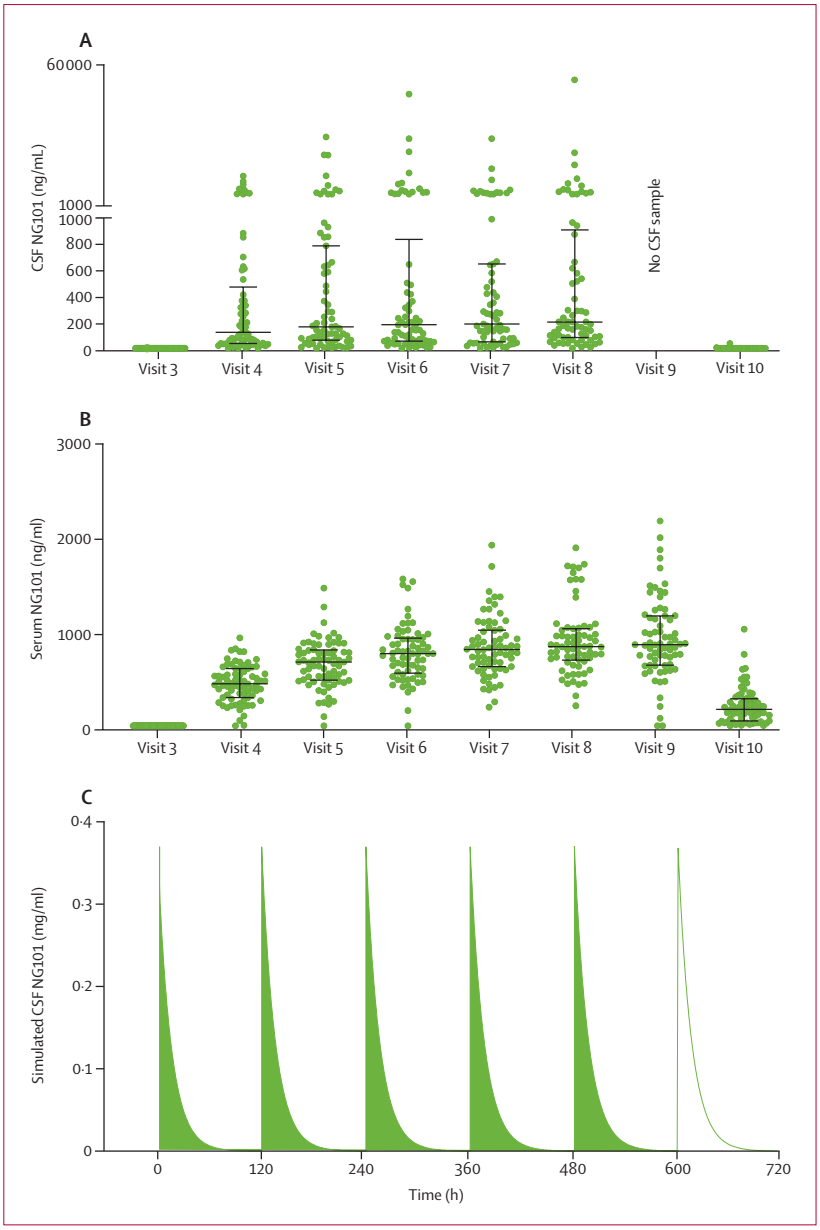

Figure 2: **Pharmacokinetics of NG101** CSF trough concentration of NG101 for all dosed patients 5 days after each intrathecal injection; data are presented as median (95% CI). The y-axis is split into a lower part (range 0–999 ng/mL; 3 log fold change) and an upper part (range 1000–60 000 ng/mL; 0·5 log fold change). (B) Serum trough concentrations of NG101 for all dosed patients; data are presented as median (95% CI). Visit 3: baseline to before first injection; visits 4–7: trough concentrations of NG101 5 days after each injection; visit 10: 59 days after the last injection. (C) Simulation of the CSF NG101 concentration over 30 days and six intrathecal injections using the half-life and the initial concentration of 45 mg/130 mL CSF. The final peak is extrapolated.

The application of a non-uniform model accounting for non-uniform recovery profiles in predefined outcome cohorts (URP nodes) also did not demonstrate significant differences in UEMS recovery between treatment groups (UEMS change 2·13 [95% CI –0·09 to 4·35]; appendix p 21). However, analysis of individual outcome cohorts (URP nodes) showed a significant treatment

effect in node 10 (delta UEMS 6·02 [95% CI 1·14 to 10·89]), which contains only patients with motor-incomplete injury (appendix pp 21–22, 28–29).

Post-hoc analysis of all patients allocated to nodes 10 and 16–18, which included all 63 participants with motor-incomplete spinal cord injury (AIS C or D), is hereafter referred to as the motor-incomplete cohort. In this cohort, NG101 treatment was associated with a greater neurological recovery (delta UEMS 4·40 [95% CI 1·32–7·47]) and functional recovery (delta SCIM self-care 4·16 [1·95–6·36]; appendix pp 23, 24, 28). The greater improvement in SCIM self-care in NG101-treated participants with motor-incomplete spinal cord injury (nodes 10, 16–18) might have contributed to greater functional independence: in the motor-incomplete cohort, 32% (eight of 25) of placebo-treated versus 18% (seven of 38) of NG101-treated participants stayed in the lowest category of independence (n=15) at day 168. Conversely, 45% (17 of 38) of NG101-treated versus 28% (seven of 25) of participants in the placebo group reached the highest category (n=24) of independence at day 168 (appendix pp 25, 30).

We did a post-hoc exploratory neuroimaging substudy that included the 103 participants who had undergone MRI at screening (mean 17·2 days [SD 6·9] days since date of injury) to assess the extent of preserved neuronal tissue. 23 patients did not undergo MRI at screening either due to organisational or medical reasons. Of those 103 patients, 13 (13%) were excluded from this analysis due to metal artifacts (six patients) or motion artifacts or poor image quality (seven patients), resulting in 90 participants included in this analysis. The median extent of preserved tissue bridges at screening was 0·85 mm (IQR 0–2·2) in patients with motor-complete spinal cord injury, compared with 1·9 mm (IQR 1·2–2·8; p=0·0030) in patients with motor-incomplete injury. Tissue bridge preservation at screening was balanced between treatment groups in both motor-complete (all participants allocated to nodes 4–5, 8–9, and 13, representing injury severities AIS A and B; placebo group: 1·3 mm [IQR 0–2·7]; NG101 group: 0·8 mm [IQR 0–1·7]) and motor-incomplete (all participants allocated to nodes 10 and 16–18, representing injury severities AIS C and D) cohorts (placebo group: 2·1 mm [IQR 1·4–2·9]; NG101 group: 1·6 mm [IQR 0·9–2·5]) with no significant differences (appendix p 27).

In a final post-hoc exploratory analysis, baseline CSF relative NfL abundance as a marker of CNS tissue damage measured with mass spectrometry were significantly higher in patients with motor-complete spinal cord injury (median 4·5 [IQR 4·1–5·0]) than in those with motor-incomplete spinal cord injury (median 4·1 [IQR 3·8–4·3]; p=0·0080). Within both the motor-complete cohort (placebo group: NfL 4·5 [IQR 3·7–5·0]; NG101 group: NfL 4·5 [IQR 4·2–5·1]) and the motor-incomplete cohort (placebo group: NfL 4·0 [IQR 3·9–4·3]; NG101 group: NfL 4·1 [IQR 3·8–4·1]), NfL concentrations were balanced without significant differences between treatment groups (appendix p 27).

Discussion

In this multicentre, randomised, placebo-controlled phase 2b clinical trial of NG101 in acute cervical spinal cord injury, the primary and most secondary endpoints were not met in the overall cohort. Treatment proved feasible and was well tolerated in this vulnerable and complex patient population, confirming phase 1 findings.[7] The secondary endpoint of SCIM self-care showed significant improvement in the overall cohort treated with NG101. The SCIM items related to upper extremity motor recovery most relevant for patients with cervical spinal cord injury are concentrated within the self-care domain. Although the absolute SCIM self-care change of 1·58 did not reach the proposed minimally clinically important differences of 4·2 defined for motor-complete (AIS A/B) patients, or 6·0 defined for motor-incomplete (AIS C/D) patients,[21] the shift towards a more favourable SCIM self-care outcome in NG101-treated participants is encouraging. With its emphasis on complex behaviours involving the whole upper limb, the SCIM self-care subscore reflects the function of all upper extremity myotomes C5–T1, and thus, is likely to be more sensitive than the GRASSP test in the present cohort of patients with predominantly C3–C5 lesions. By contrast, the only other comparable measure of upper limb function, the GRASSP prehension ability subscore, which is focused on distal arm and hand function and thus requires more caudal myotome (C8-T1) function to achieve higher scores, did not show significant improvement.

These overall findings, along with positive effects in URP nodes corresponding to patients with motor-incomplete spinal cord injury (AIS C or D), prompted a post-hoc analysis in this group. The analysis suggested better UEMS recovery in motor-incomplete patients with cervical spinal cord injury treated with NG101 than in those who received placebo. This UEMS improvement in NG101-treated participants with motor-incomplete spinal cord injury might have contributed to increased functional independence, resulting in higher gains in activities of daily living (SCIM self-care), a key goal for patients with cervical spinal cord injury and their caregivers.

Patients with acute traumatic cervical spinal cord injury are vulnerable to multiple medical complications. Nevertheless, the type and extent of adverse events and serious adverse events observed in this study confirmed the favourable safety profile of NG101 and its intrathecal route of administration seen during phase 1.[7] Specifically, increased frequencies of neuropathic pain and spasticity, which could be considered as potential side effects of aberrant axonal regeneration, were not observed in patients with cervical spinal cord injury treated with NG101. Rates of spasticity in NG101-treated patients were

about half those observed in the placebo group, suggesting that neuronal repair induced by NG101 is not complicated by the development of disproportionate spasticity, and might even be beneficial, in line with observations from animal studies.[22] The favourable safety profile in the present study is consistent with studies in participants with amyotrophic lateral sclerosis and relapsing multiple sclerosis, in which up to 15 mg/kg intravenously administered antibody to Nogo-A (ozanezumab) was not associated with any adverse events or serious adverse events.[23] Similarly, up to 200 mg intrathecally injected soluble Nogo-Receptor-Fc decoy was well tolerated by patients with chronic spinal cord injury.[24]

Previous studies in acute spinal cord injury have tended to rely on broad efficacy endpoints (AIS conversion rate or total motor scores) and had less sensitive stratification protocols than used here.[25] The URP stratification protocol targeting UEMS scores at baseline and expected UEMS outcomes[10] developed within a European network of specialised spinal cord injury centres, allowed for data-driven stratification of participants resulting in a balanced distribution of injury severities across treatment groups. Besides exclusion due to a predicted ceiling effect, participants are representative of the patients with traumatic cervical spinal cord injury in terms of injury severity and UEMS outcomes (appendix p 19). Excluding patients predicted to experience a ceiling effect due to a naturally high degree of spontaneous UEMS recovery might have enhanced the sensitivity of this trial to treatment effects.

CSF and serum measurements, along with simulated CSF kinetics, indicated that NG101 has a half-life of about 10 h in the CSF, consistent with previous studies on antibodies with different targets and the (AXER-204) Nogo-A receptor decoy.[24,26] The reasons for inter-individual variability remain unclear, but variations in CSF flow dynamics, antibody elimination, or metabolic differences are possible explanations. Although the high CSF NG101 concentrations shortly after injection might have provided effective target coverage, higher dosing could be considered in future trials.

This clinical trial included comprehensive exploratory substudies combining clinical assessments and biomarker analyses to gain additional insights into factors associated with therapeutic effects. Tissue bridges, which are anatomical correlates of preserved neuronal pathways,[15] were significantly larger in patients with motor-incomplete injuries than in those with complete spinal cord injury. This finding aligns with experiments in monkeys treated with antibodies to Nogo-A, in which increased axonal sprouting through preserved tissue was linked to better clinical and functional outcomes.[27,28] The association between preserved tissue bridges and neurological or functional recovery is not surprising as axonal repair requires a structural substrate.[9] A recent study targeting the same pathway with a soluble Nogo-receptor-Fc decoy administered intrathecally showed a trend towards responsiveness in the treatment group among a small cohort of patients with chronic cervical spinal cord injury.[24] Notably, this trend was also observed in participants with incomplete injuries (AIS B, C, and D), aligning with the findings presented in this study.

Complementing the MRI data, CSF NfL concentrations in the subacute stage (3–4 weeks post injury) provide additional objective evidence of more severe neural tissue damage in patients with motor-complete spinal cord injury compared with those with motor-incomplete spinal cord injury, corroborating previous studies that showed a correlation between NfL concentrations and injury severity within the first few days after traumatic spinal cord injury.[29] These biomarkers, alongside standardised clinical assessments, might help ensure the even distribution of structural damage between treatment groups in clinical trials. Future prediction models that incorporate both clinical and biomarker assessments could enhance the selection and stratification of patients with spinal cord injury who are most likely to benefit from neuroregenerative therapies.

Although our findings are encouraging and support further studies, this clinical trial has limitations. As a phase 2 study, it was not designed to demonstrate efficacy. The inclusive protocol based on URP-based prediction models allowed a broad inclusion spectrum reflecting the heterogeneity of acute cervical spinal cord injury, while excluding patients likely reaching a ceiling effect including patients with motor-complete injury (AIS A or B). Given evidence that neuroregeneration benefits from a substrate of intact neural tissue, inclusion of patients with complete injuries could have masked a treatment response in the participants with incomplete spinal cord injury—a hypothesis supported by significant UEMS and SCIM self-care treatment responses in post-hoc analyses. More robust treatment effects might have been masked by the possible intermittent underdosing of NG101 implied by our pharmacokinetic analyses.

This study showed no evidence of efficacy of anti-Nogo-A treatment with NG101 across the entire population, including patients with motor-complete injury, regarding the primary endpoint UEMS. Post-hoc analyses in the subgroup of patients with motor-incomplete spinal cord injury suggested superior UEMS recovery in NG101-treated participants, which was linked to greater independence in performing essential daily tasks at 6 months. Determining whether these findings can be replicated will require assessment in appropriately powered clinical trials.

Contributors

NWeid and AC were involved in study concept and design; had a major role in acquisition, analysis, and interpretation of data; drafting and revision of the manuscript for content; had full access to and verified the data; were part of the steering committee, and were the study medical directors. RA had a major role in acquisition of data, drafting and revision of the manuscript for content, and was part of the steering

committee. DM had a major role in acquisition of data, drafting and revision of the manuscript for content, and was part of the steering committee. KRö, FR, MBa, MH-G, MSa, JB, KRe, MA, AB, and JK had a major role in acquisition of data, and drafting and revision of the manuscript for content. MBo was involved in study concept and design, analysis and interpretation of data, and drafting and revision of the manuscript for content. KB, LF, MH, KM, MAM, and PSS were involved in analysis and interpretation of data and drafting and revision of the manuscript for content. TK was involved in interpretation of data and drafting and revision of the manuscript for content. MSe was involved in data collection, quality control of the data, analysis and interpretation of data, and drafting and revision of the manuscript for content. AH, MSc, CSc, CSi, BS, and TW was involved in study concept and design, analysis and interpretation of data, and drafting and revision of the manuscript for content. BR was involved in analysis and interpretation of data, had full access to and verified the data, was and was involved with drafting and revision of the manuscript for content. RR was involved in study concept and design, analysis and interpretation of data, and drafting and revision of the manuscript for content. NWeis was involved in analysis and interpretation of data and drafting and revision of the manuscript for content. PF and TH were involved in study concept and design, analysis and interpretation of data, had full access to and verified the data, and were involved in drafting and revision of the manuscript for content. MES was involved in study concept and design, analysis and interpretation of data, had full access to and verified the data, was involved in drafting and revision of the manuscript for content, and was a member of the steering committee. All authors confirm they had full access to the data in the study if they so wished and accept responsibility for the decision to submit for publication.

Declaration of interests

NWeid, RA, DM, MSa, KRö, KRe, MBa, MH-G, JB, MA, AB, JK, KB, KM, TW, NWeis, PF, TH, and AC received funding (European Commission Grant Agreement 681094 or Wings for Life) for conduction of work presented in this manuscript through their individual institutions. KB and KM additionally received funding for the ProDi project (ID 111.08.03.05–133974) from the Ministry of Culture and Science of the German State of North Rhine-Westphalia and from the Deutsche Forschungsgemeinschaft (DFG), German Research Foundation) under project ID 510957753 through the Ruhr University Bochum. AH received funding for participation in scientific conferences from the European Commission, Wings for Life, and Heidelberg University Hospital. RR received funding from the European Multicenter Study about Spinal Cord Injury (EMSCI) and serves unpaid as the Chair of the International Standards Committee and Board Member of the American Spinal Injury Association (ASIA). CSc serves unpaid as a member of ASIA. NWeis is supported by the Swiss State Secretariat for Education, Research and Innovation under contract number 15.0137 through the Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. He received additional grants for the projects "Early stage neuroimaging and behavioural biomarkers of PD progression and underlying mechanisms (IronSleep)" (funded by the German Federal Ministry for Education and Research in the framework of EU Joint Programme—Neurodegenerative Disease Research [JPND2021–650–135])", "The comprehensive microstructural human connectome (COMIC): from long-range to short-association fibers" (funded by the German Research Foundation (DFG) and "Evolution of Hominoid Brain Connectomics " (funded by the MPS). He holds a patent on acquisition of MRI data during spoiler gradients (Patent US 10,401,453 B2). He participates in the following Committees: Steering committee, National Institutes of Health (NIH) BRAIN Initiative U24 grant (NexGen) 7T scanner at University of California, Berkeley, USA; Member and Chair, Scientific Advisory Board of Leibniz Institute for Neurobiology, Magdeburg, Germany; Member Board of Trustees, Fraunhofer Institute for Electronic Nano Systems (ENAS), Chemnitz, Germany; Member Advisory Committee for P41 Center grant "Center for Mesoscale Mapping" (P41EB030006), MGH/HST Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA; Member of the UK Biobank Imaging Enhancement Monitoring Group. His employers, the Max Planck Institute for Human Cognitive and Brain Sciences and Wellcome Centre for Human Neuroimaging, have institutional research agreements with Siemens Healthcare. AC is a member of the Scientific Advisory Board of the Wings for Life Foundation, Salzburg, Austria and the International Foundation for Research in Paraplegia, Zurich, Switzerland. All other authors declare no competing interests.

Data sharing

The study protocol and statistical analysis plan are available in the appendix. Deidentified participant data underlying the results reported in this Article will be made available to investigators upon request to the corresponding author beginning 12 months and ending 36 months after publication, following approval upon reasonable request by the Nogo Inhibition in Spinal Cord Injury steering board.

Acknowledgments

We thank Novartis Pharma, Basel, Switzerland for providing the anti-Nogo-A antibody drug substance (ATI355). This investigator-initiated trial was funded by grants from the EU programme Horizon2020 (grant agreement number 681094—NISCI), Swiss State Secretariat for Education, Research and Innovation, Wings for Life (Salzburg), the Swiss Paraplegic Foundation, and the project CeNeReg of Wyss Zurich (University of Zurich and Eidgenössische Technische Hochschule Zurich). NWeis received funding from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; —project no. 347592254 [WE 5046/4–2]); from the Federal Ministry of Education and Research) under support code 01ED2210 and from the BMBF (01EW1711A & B) in the framework of ERA-NET NEURON. We thank the members of the Data Safety and Monitoring Board.

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