NX210c, an Innovative Peptide with Neurovascular and Peripheral Effects in ALS

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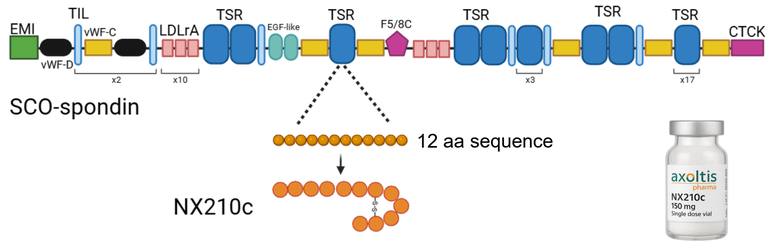
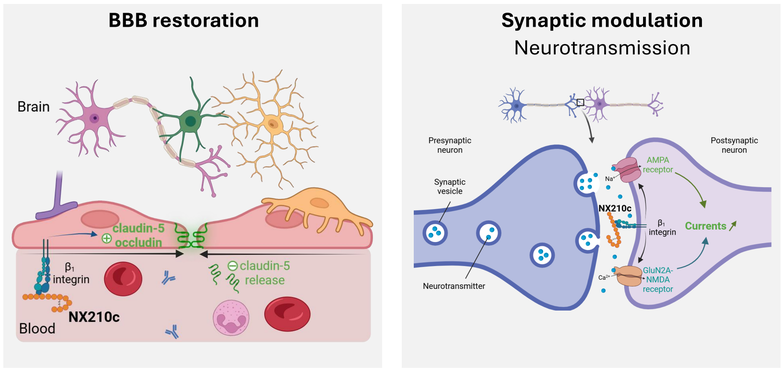
BACKGROUND

NX210c is a 12-amino acid peptide designed from subcommissural organ spondin (SCO-spondin), a glycoprotein essential for nervous system development. β1-integrin has been identified as its most important receptor. Increasing evidence suggests that disruption of blood-brain and blood-spinal cord barrier integrity (BBB and BSCB, respectively) may contribute to ALS pathophysiology, alongside other pathogenic mechanisms, leading to neuroaxonal loss. In this context, NX210c links activity across the neurovascular unit, extracellular matrix-cell interactions, and neural cells, thereby providing a unified basis for barrier stabilization and synaptic modulation.



NX210c Neurovascular and Synaptic modulation Related Properties



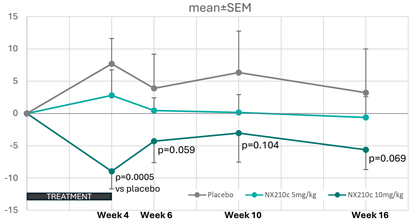
SEALS: A Randomized, Double-Blind, Placebo-Controlled **Phase 2** Study Evaluating **Efficacy and Safety** of **NX210c In Amyotrophic Lateral Sclerosis** (ALS) Patients NCT06365216

Population	ALS by El Escorial, **≤36 months** from symptoms, **SVC ≥55%**; generally well-balanced for a small study, representative of real-world ALS distributions
Number / Randomization	**82 patients randomized**, **3:3:2** (31pts at **5mg/kg**, 31pts at **10 mg/kg**, 20 pts at **Placebo**)
Stratification	Baseline NfL threshold set ≤95 pg/mL (low) or >95 pg/ml (high)
Treatment	**4-week IV dosing; 3 infusions per week;** nearly all patients were **receiving Riluzole**
Sampling	Blood (primary); lumbar punctures at screening and 2 weeks post-treatment; urine
Follow-up	**Core: safety, biomarkers** + clinical endpoints; *Extension: survival, time-to-event, clinical data*
Primary Endpoint	Change in biomarkers: serum NfL or Qalb ratio from pre-dose to Week 6
Secondary Endpoints	Function (ALSFRS-R, SVC); strength (dynamometry); biomarkers (blood/CSF/urine); safety & tolerability; progression & survival; QoL (ALSAQ-40); pharmacokinetics
Digital Twins	Synthetic placebo arm (of 62 actively dosed patients); statistical enrichment

Disclosure: all the authors are directly or indirectly employed by Axoltis Pharma

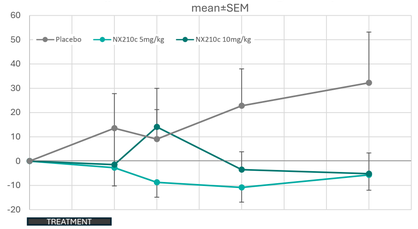
RESULTS - NEUROVASCULAR SYSTEM RELATED BIOMARKERS

Claudin-5 (plasma) – relative % change from predose
mean±SEM



Predose value (ng/mL) mean ±SEM:
placebo: 1.85 ±0.13; NX210c 5 mg/kg: 2.37 ±0.48; NX210c 10 mg/kg: 1.68 ±0.11

MMP-9 (plasma) –relative % change from predose
mean±SEM



Predose value (ng/mL) mean ±SEM:
placebo: 13.77 ±2.0; NX210c 5 mg/kg: 17.05 ±3.5; NX210c 10 mg/kg: 20.03 ±3.9

Target Engagement Biomarker

Claudin-5 is the tight junction protein highly enriched in brain microvascular endothelial cells and a critical determinant of blood–brain barrier integrity, although its expression is not restricted to the neurovascular unit. The initial reduction in plasma claudin-5 (Week 4, 10 mg/kg) suggests stabilization of endothelial tight junctions, consistent with engagement of pathways involved in neurovascular unit restoration.

Intra group Analysis by paired T-test for absolute change from predose to Month 4: 5mg/kg: p=0.514 ; 10mg/kg: p=0.030 ; Active Dose: p=0.044 ; placebo: p=0.965

Reduced Matrix Remodeling

A reduction in **plasma MMP-9 activity** (matrix metalloproteinase-9) may contribute to the preservation of BBB integrity by limiting the proteolytic degradation of extracellular matrix components and key tight junction proteins, including claudin-5, which are essential for maintaining endothelial cell–cell adhesion and restricting paracellular permeability.

Intra group Analysis by paired T-test for absolute change from predose to Month 4: 5mg/kg: p=0.082 ; 10mg/kg: p=0.085 ; Active Dose: p=0.014 ; placebo: p=0.518

Taken together, **decreases** in plasma **claudin-5 and MMP-9** provide mechanistic support for **NX210c effect on β1 integrin-mediated** neurovascular unit stabilization.

- A reduction in **plasma Homocysteine** (HCY) was observed from predose at End of Treatment (**% change from predose to week 4; mean±SEM; Placebo +1.08±3.31; 5mg/kg -2.65±1.93; 10mg/kg -4.66±2.77, p=0.032 for 10mg/kg vs placebo**). Elevated plasma HCY, even at moderately increased concentrations, has been associated with endothelial dysfunction, oxidative stress, neuroinflammation, BBB disruption. NX210c may interact with HCY through thiol–disulfide exchange.
- The reduction in **CSF S100β** levels may indicate attenuated astrocytic reactivity and reduced glial-associated stress, potentially reflecting CNS homeostasis.
- **Qalb** (CSF-to-serum albumin ratio) showed high variability. About 33% of SEALS patients had values above the published normal range for age (Castellazzi et al., *Fluids Barriers CNS*, 2020).

CSF S100β from baseline to Week 6

Mean ±SEM	Placebo	Active Dose	5mg/kg	10mg/kg
Predose value (ng/mL)	4.23 ±0.28	5.20 ±0.41	5.43 ±0.73	4.96 ±0.39
Week 6 (ng/mL)	4.45 ±0.46	4.45 ±0.17	4.30 ±0.27	4.58 ±0.20
Relative change %	**+5.07 ±8.09**	**-5.59 ±2.63**	**-8.43 ±4.26**	**-2.75 ±3.08**

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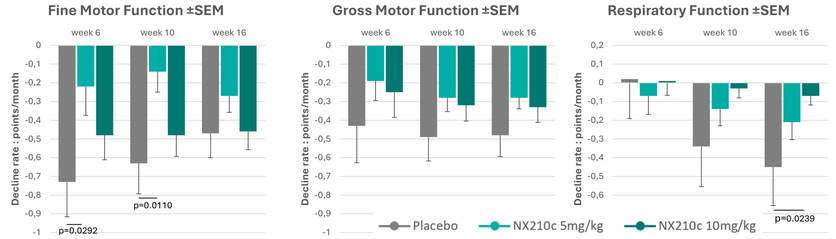
RESULTS – FUNCTIONAL ASSESSMENTS AT PERIPHERAL SITE

ALS Functional Rating Scale– Revised (ALSFRS-R) slope of decline - subscores



Assessment of studentized residuals (graphical diagnostics (histogram and normal Q-Q plot) indicated no substantial deviation from normality; minor departures were limited to the distribution tails. Levene's test indicated no evidence of heterogeneity of variances across treatment groups (Slope V13: p=0.6606 ; Slope V14: p=0.4078 ; Slope V15: p=0.3610)

The ALSFRS-R slope measures the rate of functional decline over time in patients with ALS, expressed as the change in ALSFRS-R score per month. A less negative slope indicates slower disease progression.

Hand-Held Dynamometry (HHD)
Relative change (%) from baseline to Week 16 (= 4 months) (mean ±SEM)

% of change from baseline to Month 4	Left side				Right side			
	Placebo	Active dose	5mg/kg	10mg/kg	Placebo	Active dose	5mg/kg	10mg/kg
Elbow flexion	**-36.11** ±11.56	**-22.09** ±7.17	-9.23 ±12.41	-35.91 ±5.75	**-37.41** ±8.70	**-17.30** ±7.42	-3.94 ±12.78	-32.15 ±5.64
Wrist extension	**-21.58** ±9.48	**-20.22** ±8.23	-6.05 ±14.23	-36.01 ±6.16	**-30.58** ±9.18	**-22.56** ±7.53	-9.03 ±12.37	-37.64 ±7.10
Knee extension	**-13.70** ±11.11	**-4.74** ±8.76	+8.90 ±16.06	-18.86 ±5.69	**-24.17** ±13.86	**+17.14** ±18.84	+12.27 ±15.88	+22.35 ±35.49
Ankle dorsiflexion	**-30.81** ±11.10	**-13.15** ±7.08	-7.07 ±13.01	-19.44 ±5.19	**-35.04** ±11.60	**-16.84** ±7.08	-8.48 ±12.92	-25.50 ±5.15

At week 16, a trend is observed to **a lower decrease** in HHD from baseline in the **active dose arms versus placebo.** HHD measures muscle strength using a portable device that records the force produced during a muscle contraction.

CONCLUSION – PERSPECTIVES

The **SEALS study** provides encouraging findings and **a favorable benefit/risk profile**, supporting the further clinical development of NX210c in ALS, including those relevant to other neurodegenerative diseases:

- **Biological and functional effects**: Effects observed on biomarkers of neurovascular unit function and peripheral functional assessments.
- **Therapeutic potential**: Supports further investigation of NX210c in ALS and other neurodegenerative diseases involving neurovascular unit dysfunction.
- **Next steps**: Optimize the treatment regimen, particularly by **evaluating repetition of 4-week treatment courses to sustain the observed clinical effect**.

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