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

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For additional details go to PSTER 091.08 (Abstract 7441)

PSTR 091.02
Abstract 9690

BACKGROUND

BBB/BSCB dysfunction:

- Occurs early, including at presymptomatic stages of ALS, supporting barrier impairment as a potentially upstream contributor to disease initiation or progression and a therapeutic target *(Steinruecke, 2023)*.
- Intersects with mitochondrial dysfunction, astrocytic pathology, neuroinflammation, MMP activity, systemic inflammation and TDP-43 pathology, positioning the neurovascular unit at the convergence of multiple ALS disease mechanisms *(Steinruecke, 2023)*.
- Demonstrates pericyte loss, BSCB disruption and extravasation of blood-derived components, establishing neurovascular pathology as a feature of human disease - *in human ALS spinal cord (Winkler, 2013)*.
- Contributes to early motor-neuron degeneration, while restoration of barrier integrity delays motor-neuron impairment and degeneration, providing proof-of-concept in an ALS mouse model for barrier restoration as a therapeutic strategy *(Winkler, 2014)*.

Neuronal and synaptic dysfunction:

- Is characterized by excitotoxicity, excitatory–inhibitory imbalance and cortical hyperexcitability, thus, supports **neuroprotection** and **restoration of physiological neurotransmission** as complementary therapeutic strategies in ALS *(Arnold, 2024; Geevasinga, 2016)*.

NX210c represents a differentiated multimodal strategy **integrating BBB/BSCB repair, neuronal resilience and synaptic functional support**, with evidence of early barrier and neuronal excitability abnormalities supporting an intervention relevant to motor-neuron loss.

SEALS: PHASE 2 STUDY DESIGN

NIH 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

POPULATION SUMMARY

- **Sporadic ALS predominated** across group arms (80–90%)
- **Definite ALS** was the most common El Escorial category (55–61%)
- Baseline **ALSFRS-R scores were similar**
- **Serum NfL stratification successful;** the proportion patients with low v. high serum NfL were similar across groups
- Although **generally balanced**, **abnormal Qalb** was more frequent in the 10 mg/kg group (48.4%) than in the 5 mg/kg (19.4%) or placebo (30.0%) groups

Treatment Group	ALSFRS-R (median)	Range (min–max)	Definite ALS, n (%)	Probable ALS*, n (%)	Possible ALS, n (%)
5 mg/kg (NX210c)	40	29–45	19 (61.3%)	11 (35.5%)	1 (3.2%)
10 mg/kg (NX210c)	37	30–46	19 (61.3%)	12 (38.7%)	0 (0.0%)
Placebo	37	24–47	11 (55.0%)	5 (25.0%)	4 (20.0%)

* *Probable ALS includes Probable ALS and Probable Laboratory-Supported ALS*

Treatment Group	High NfL (>95 pg/mL), n (%)	Low NfL (≤95 pg/mL), n (%)	Mean Serum NfL (pg/mL)	Mean Qalb	Abnormal Qalb n (%)
5 mg/kg (NX210c)	9 (29.0%)	22 (71.0%)	78.29	6.5	6 (19.4%)
10 mg/kg (NX210c)	10 (32.3%)	21 (67.7%)	86.74	8.31	15 (48.4%)
Placebo	6 (30.0%)	14 (70.0%)	89.24	7.19	6 (30.0%)

KEY RESULTS

Safety & Tolerability up to week 16 (month 4)

Relation to IMP				
Unrelated	Unlikely	Possible	Probable	Related
183	46	65	6	22

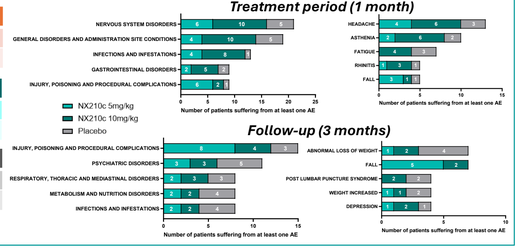
Severity			
Mild	Moderate	Severe	IRR*
223	50	21	28 (grade 1)

Seriousness (according to protocol definition)	
Non-serious	Serious
309	13

97.6% of participants received ≥11 of 12 planned doses

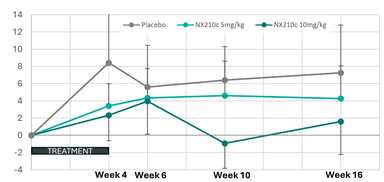
** IRR = infusion related reaction*

Most Frequent Adverse Events



Serum NfL

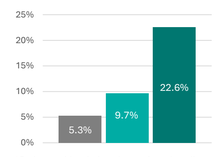
% Change from Predose mean±SEM



Predose value (pg/mL) [Mean ±SEM]: 5 mg/kg [83.27 ±6.75], 10 mg/kg [94.88 ±11.02], placebo [90.03 ±14.51]

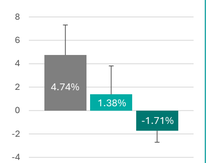
NfL&Qalb Responders*

% of Patients



**Patients with relative change from baseline to w6 of serum NfL≤-10% and relative change from screening to w6 of serum Qalb<0% are classified as "responders"*

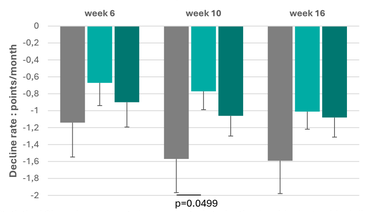
CSF NfL - % Change Predose to w6 ±SEM



Predose value (pg/mL) [Mean ±SEM]: 5 mg/kg [5607 ±436], 10 mg/kg [6982 ±781], placebo [5854 ±737]

ALS Functional Rating Scale - Revised Global score Slope

mean ±SEM



ALSFRS-R Global score Slope at week 16 by NfL level at predose

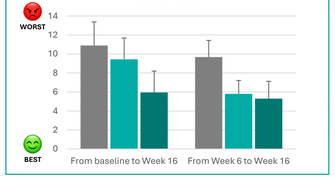
mean slope ±SEM

Subgroup	Placebo n	Placebo Mean ±SEM	Active Dose n	Active Dose Mean ±SEM	5mg/kg n	5mg/kg Mean ±SEM	10mg/kg n	10mg/kg Mean ±SEM
Low NfL (<95pg/ml)	14 /20	-1.32 ±0.34	43 /62	**-0.65 ±0.13**	22 /31	**-0.77 ±0.22**	21 /31	**-0.53 ±0.13**
p-value vs placebo				p=0.0716		p=0.1745		p=0.0623
High NfL (>95pg/ml)	6 /20	-2.21 ±1.04	19 /62	-1.94 ±0.34	9 /31	-1.61 ±0.45	10 /31	-2.23 ±0.51
p-value vs placebo				p=0.7423		p=0.9280		p=0.5187

Statistical Slope Assessment: 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)

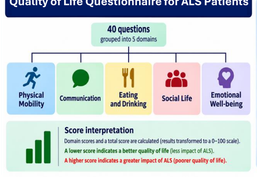
ALSAQ-40 absolute change (points/100)

mean ±SEM



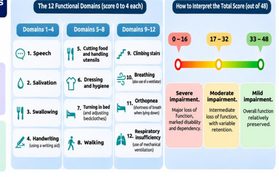
ALSAQ-40

Quality of Life Questionnaire for ALS Patients

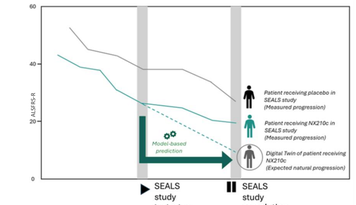


The ALSFRS-R Score

ALS Functional Rating Scale - Revised



IN SILICO RESULTS: DIGITAL TWIN ANALYSIS

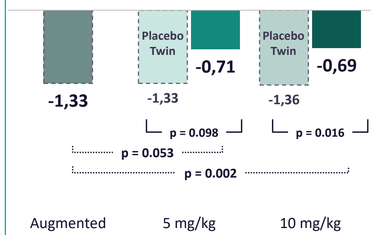


Digital Twin: from each patient's pre-study data, the model predicts the ALSFRS-R course without treatment. Twin vs observed slope gives a within-patient effect.

Model: trained on PRO-ACT; externally validated on BENEFIT-ALS and VITALITY-ALS (R^2 = 0.75 at 24 weeks). SEALS placebo patients closely represent their own twins (−1.24 vs −1.37 pts/month, p = 0.70).

20 real placebo + **62** Digital Twins of treated → **82** augmented placebo

ALSFRS-R Median Slope of Decline points/month



Solid brackets: arm vs its own Digital Twins (dashed bars; Wilcoxon). Dotted brackets: arm vs augmented placebo (Mann-Whitney). Not corrected for multiplicity.

Main slowest-declining subgroups

(univariate analysis)

Subgroup	N	Active Dose	Augm. placebo	p
King's stage 1	14/17	**−0.18**	−1.22	<0.001
Probable (El Escorial)	13/18	**−0.29**	−1.30	<0.001
Serum NfL ≤95 (BL)	36/50	**−0.29**	−1.24	<0.001
ALSFRS-R > median	32/37	**−0.37**	−1.21	<0.001

Median slope, pts/month; N = active/augmented placebo. 4 of 36 subgroup levels, selected on observed effect; Mann-Whitney p, not corrected for multiplicity.

CONCLUSION & NEXT STEPS

- NX210c shows a **good safety and tolerability** and **early efficacy signals** with a **favorable benefit/risk profile.** Although the prespecified primary endpoint of change in NfL or Qalb was non-significant, the **broader pattern of findings** warrants further clinical investigation.
- Conventional statistical analyses revealed:
  - Dose-dependent changes in serum and CSF NfL
  - A **higher proportion of responders in the active treatment arms** when both serum NfL and Qalb responders were assessed jointly,
  - A consistent pattern of **lesser decline in global ALSFRS-R slope in active treatment arms** during the core follow-up period through week 16, with **a trend toward statistical significance observed in patients comprising the low NfL stratum**
  - Complementary *in silico* analyses using digital-twins and augmented placebo provided added support for the observed treatment effects.
- Data from the study extension at Months 7 and 10 are pending analysis.
- Collectively, the **safety, biomarker, clinical, and model-supported evidence** generated thus far **supports continued clinical development of NX210c in ALS**, with the selected **dose and repeat-dosing regimens to be further evaluated** in a Phase 2b/3 study.

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