# Population Pharmacokinetic (PK) And Pharmacodynamic (PD) Analyses Of Multiple Intravenous Infusions Of NX210c Peptide In Healthy Elderly Volunteers (HEVs)

**PRESENTER:**
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## *BACKGROUND*

- NX210c is a promising cyclic peptide with potential therapeutic implications in neuronal protection, particularly for ALS
- NX210c derived its origin from the brain's SCO-spondin
- NX210c showcases beneficial properties including neuroprotection and factors that may affect neurotransmission and the blood-brain barrier

## *OBJECTIVES*

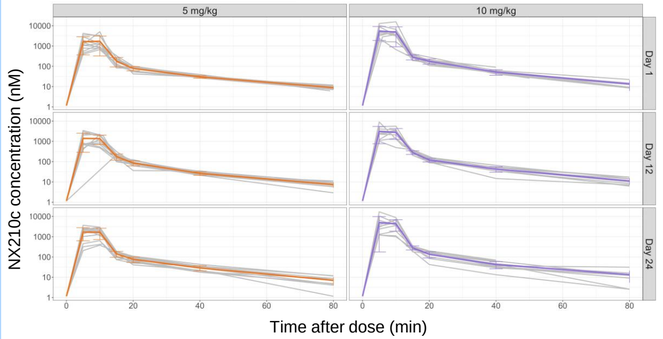
- Characterize and quantify NX210c PK in humans after repeated administrations
- Assess NX210c impact on Neurofilament light chain formation (NfL), a relevant biomarker in ALS

## *DATA & METHODS*

- Data from AXO-CLI-210c-02 double-blind, randomized, placebo-controlled, Multiple Ascending Dose (MAD) study on HEVs
- 29 HEVs (18 males, 11 females, average age 68.8 years)
- 3 treatment arms: placebo (n=6), 5 mg/kg (n=12), 10 mg/kg (n=11)
- NX210c administered *via* intravenous infusions over 10 minutes, thrice weekly for four weeks (26 days in total)
- PK samples collected on days 1, 12 and 24
- NfL measurements performed on days -1 (baseline), 12, 26 and 40 (follow-up)
- PK/PD analysis performed within a nonlinear mixed effects modeling approach using the SAEM algorithm implemented in Monolix

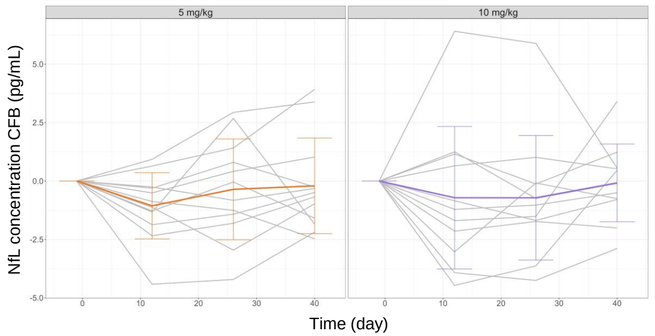
NX210c PK profiles showed **no accumulation** between days, with a rapid distribution and elimination.

Observed NX210c profiles




NfL levels showed a large inter-individual variability, with a slight **decrease at days 12 and 26**, with a return to baseline levels at day 40.

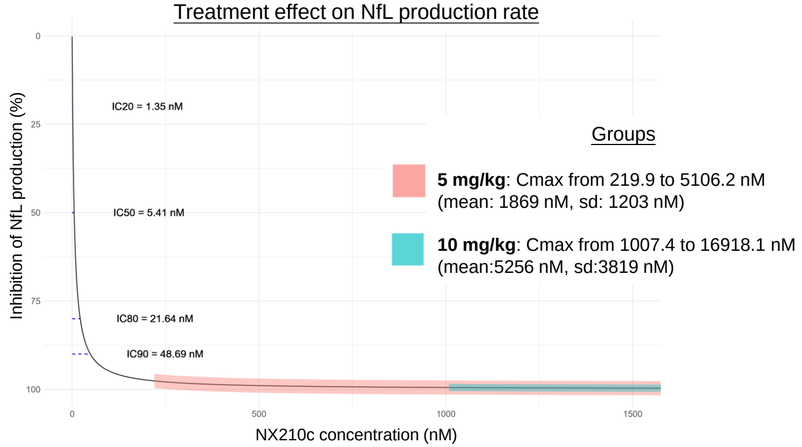
Observed plasma NfL change from baseline




*Grey lines are individual profiles, solid colored lines are mean profiles, intervals are built using the standard deviation values in each group*

A **2-compartments Wagner TMDD** model best described NX210c PK data. Its effect on NfL levels was described with an **indirect Imax model, inhibiting NfL production**.

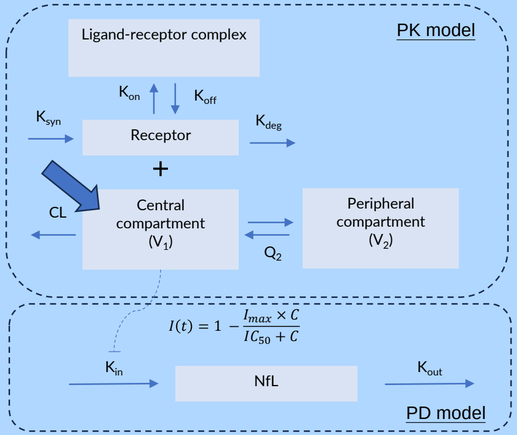
Treatment effect on NfL production rate



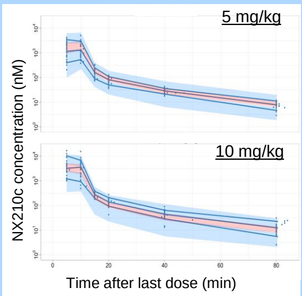

Simulations suggest that the two NX210c peptide dose groups are able to **inhibit NfL production**.

## *RESULTS*

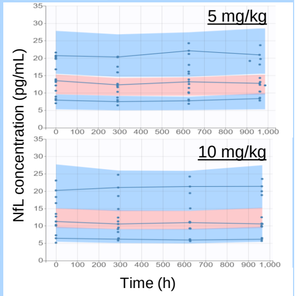
- Time-concentration profiles of NX210c are best described with a two-compartments Wagner TMDD model
- NX210c impact on NfL levels is best described using an indirect Imax response model, with inhibition of NfL production upon treatment
- PK and PD models are validated using standard GoF plots and Visual Predictive Checks (VPCs)
- IC50 value determined to be 5.41 nM, IC90 of 48.69 nM




VPC for PK




VPC for PD




*Blue dots are observations, solid blue lines correspond to the 5%, 50% and 95% of observations. Pink and blue areas correspond respectively to the 90% confidence interval of median, 5% and 95% of simulations.*

These analysis results support the **selection of the doses of 5 mg/kg and 10 mg/kg** for the **upcoming Phase II trial in ALS patients**. Selection of these dose regimens was further validated by analyses of additional informative biomarkers which will be described in a subsequent publication.

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