Association of Phosphorylated Neurofilament Heavy Chain (pNF-H) Levels With Motor Function Achievement in Individuals With Spinal Muscular Atrophy (SMA) Treated With Nusinersen

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Objective: To assess phosphorylated neurofilament heavy chain (pNF-H) levels in individuals from nusinersen clinical trials with presymptomatic (most likely to develop Type I/II), infantile-onset (has or most likely to develop Type I/II) or later-onset SMA (has or most likely to develop Type II/III) and volunteers without SMA and investigate the association with motor function (MF) achievement in nusinersen-treated individuals with SMA.

Background: Neurofilaments (NF) are neuronal cytoskeleton components released into interstitial fluid following axonal damage/neuronal degeneration. Elevated NF levels have been detected in neurodegenerative disorders.

Design/Methods: pNF-H plasma levels were evaluated using the ProteinSimple™ SimplePlex ELLA immunoassay. MF responses in infantile-onset SMA included 1) improvement in ≥1 HINE-2 category and more categories improving than worsening or 2) ≥4-point CHOP INTEND improvement. MF responses in later-onset SMA included 1) ≥3-point HFMSE improvement, 2) ≥2-point RULM improvement, or 3) attainment of ≥1 WHO motor milestone. Receiver Operating Characteristic (ROC) curves and logistic regression analyses assessed pNF-H levels and MF achievement associations.

Results: Baseline pNF-H levels were higher in individuals with SMA (n=302) than age-matched individuals without SMA (n=34). In nusinersen-treated individuals with SMA, plasma pNF-H levels declined during the nusinersen loading period and then stabilized at lower levels through latest observed visits (infantile-onset SMA: Day 302; later-onset SMA: Day 456). The percentage change from baseline in pNF-H levels at nusinersen loading end (Day 64 or 85) predicted MF response at Day 302 (infantile-onset SMA; HINE-2: AUC=74%, CHOP INTEND: AUC=92%) and at Day 456 (later-onset SMA; HFMSE: AUC=73%, RULM: AUC=76%, WHO: AUC=86%) after controlling for age of first dose and disease duration, respectively.

Conclusions: pNF-H levels were elevated at baseline in individuals with SMA; however, nusinersen treatment reduced pNF-H levels to lower levels. The percentage change in pNF-H levels at the completion of nusinersen loading appears to predict subsequent MF response. Further evaluation is warranted.