Neurofilament Light Chain As a Biomarker in Patients With Hereditary Transthyretin Amyloidosis With Polyneuropathy

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Neuro FeeL

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Conclusions

- NeuroFeeL is a single-center, observational study that evaluates NfL as a potential biomarker for diagnosis and monitoring of asymptomatic *TTR* variant carriers and patients with ATTRv-PN
- These baseline analyses represent a first descriptive step of the study and provide an overview of NfL levels at study baseline according to disease characteristics and severity
- Consistent with the natural history of ATTRv, baseline NfL levels were elevated in patients with ATTRv-PN compared with asymptomatic *TTR* variant carriers and increased progressively with disease severity in patients with ATTRv-PN; NfL levels demonstrated correlations with parameters such as NIS, CMAP/SNAP, and troponin I
- Higher NfL levels vs reference values observed in asymptomatic carriers and individuals with low NIS scores indicate that NfL may be useful as a biomarker to detect nerve damage before the onset of symptomatic disease
- Ongoing longitudinal analyses at 12- and 24-month timepoints are planned to further explore the value of NfL as a biomarker of disease onset in carriers and of disease progression in patients with ATTRv-PN

Key takeaway

NfL levels are significantly higher in patients with ATTRv-PN compared with asymptomatic *TTR* variant carriers, and also correlate with multiple measures of disease severity in patients with ATTRv-PN

Introduction

Hereditary ATTR (ATTRv)

- ATTRv is a progressive, debilitating, and fatal disease caused by *TTR* gene variants resulting in misfolded pathogenic TTR accumulating as amyloid fibrils in nerves, heart and other systems[1–3]
- Manifestations of ATTRv present as polyneuropathy (ATTRv-PN), cardiomyopathy (ATTRv-CM), or a mixed phenotype[2,4,5]
- The predominant manifestations of ATTRv-PN are sensory, motor, and autonomic neuropathy but symptoms are often diverse, which can delay diagnosis[2]
- Identifying sensitive biomarkers to aid early detection of active disease onset in asymptomatic *TTR* variant carriers and monitoring progression in patients with ATTRv-PN remains an unmet need that may be key to improving patient outcomes

Neurofilament Light Chain (NfL)

- NfL is a well-characterized biomarker of neuronal damage across a range of neurological conditions, with emerging evidence supporting its relevance in ATTRv-PN[6–8]
  - Plasma NfL levels have been shown to be elevated in patients with ATTRv-PN compared with carriers or healthy controls[7,9] and show positive correlations with disease activity measures such as PND score and NIS[8,9]
- RNAi therapeutics vutrisiran and patisiran, which are approved for the treatment of ATTRv-PN, decreased NfL levels in phase 3 studies of patients with ATTRv-PN[7,10]
- NfL has the potential to serve as a biomarker for early diagnosis, disease monitoring, and treatment response

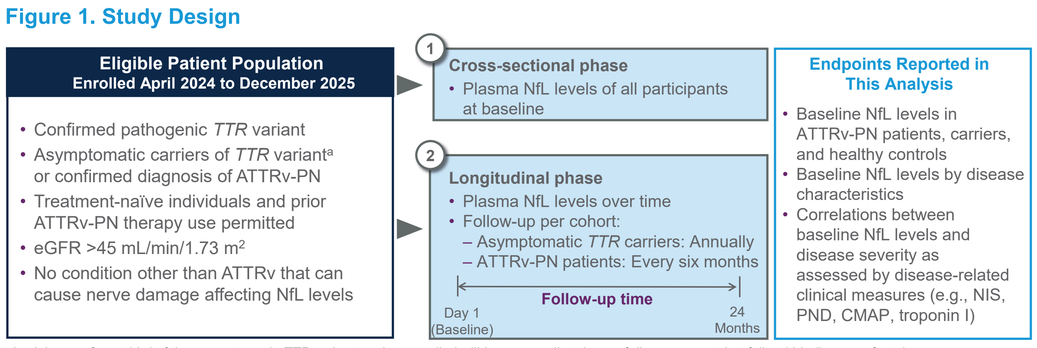
Objective

- The NeuroFeeL study aims to investigate the potential of NfL as a biomarker for early detection of disease onset in carriers and for monitoring disease progression and treatment response in patients with ATTRv-PN
- This initial analysis evaluates baseline NfL levels according to baseline status (carrier vs active disease) and characteristics, and assesses the relationship between NfL levels and disease activity parameters

Methods

NeuroFeeL Is a Single-Center, Observational, French Study Evaluating NfL As a Biomarker in Asymptomatic *TTR* Variant Carriers and Patients with ATTRv-PN

Figure 1. Study Design



[a]A minimum of one-third of the asymptomatic *TTR* variant carriers enrolled will have a predicted age of disease onset that falls within 5 years of study enrollment.

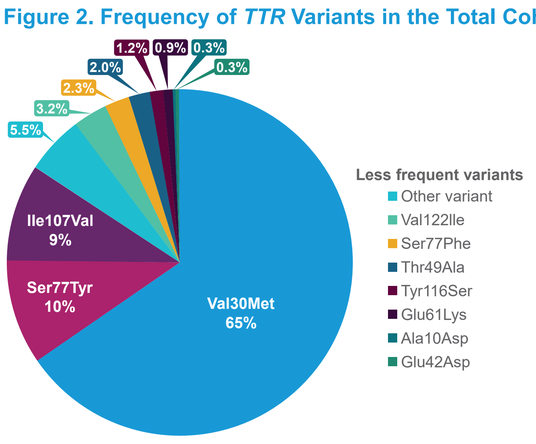
- All patient data except NfL levels will be extracted from medical records or collected as part of routine clinic visits
- All NfL measurements, using the Meso Scale Discovery electrochemiluminescence immunoassay, were performed on blood samples collected as part of routine clinic visits; levels were compared to the normal levels expected in the general population by using existing reference ranges and databases for the Quanterix Simoa assay

Results

Baseline Demographics and Characteristics

- In total, 184 (53%) patients with ATTRv-PN and 160 (47%) asymptomatic *TTR* variant carriers (n=57 with predicted age of disease onset [PADO] <5 years from age at enrollment or having passed age of onset; n=89 with PADO >5 years from age at enrollment; n=14 unknown) were included in the analysis
- At enrollment, patients with ATTRv-PN were older than carriers (median [range] age: 61 [49–73] vs 49 [35–57] years), more frequently male (65% vs 41%), and had higher total NIS scores (mean [SD] 28.2 [29.2], n=137 vs 2.3 [4.4], n=73)

Figure 2. Frequency of *TTR* Variants in the Total Cohort



- A wide spectrum of *TTR* variants (>10) was represented, with Val30Met being the most frequent variant (224/343; 65%; **Figure 2**)
- Frequency of specific *TTR* variants was generally similar in the patients with ATTRv-PN and the carriers
- At diagnosis, 35% (64/184) of patients with ATTRv-PN had polyneuropathy, 61% (112/184) had a mixed phenotype, and 4% (8/184) had predominant cardiomyopathy
- In patients with ATTRv-PN, 37.5% (69/184) presented with early-onset (<50 years) Val30Met disease

- At baseline, patient characteristics were consistent with the ATTRv disease spectrum (**Figure 3**); patients with ATTRv-PN showed sensory and motor neuropathic involvement (94.6% with PND ≥1) whereas carriers showed no neurological involvement (87.5% with PND = 0)
- **Figure 4** demonstrates the range of treatments patients with ATTRv-PN are receiving at study enrollment

Figure 3. Disease Severity at Baseline in the Total Cohort Based on PND Scores

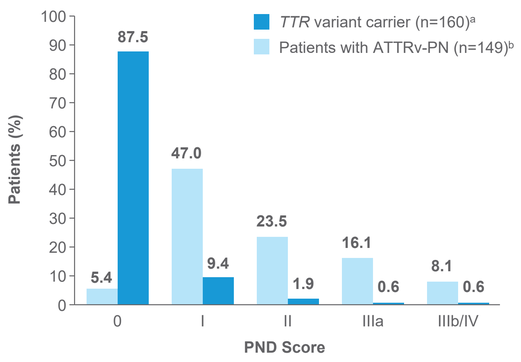
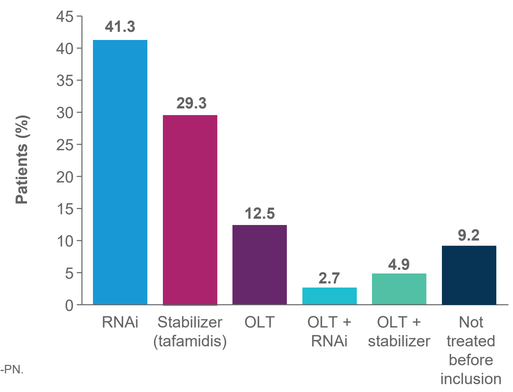


Figure 4. Treatment at the Time of Inclusion in Patients With ATTRv-PN



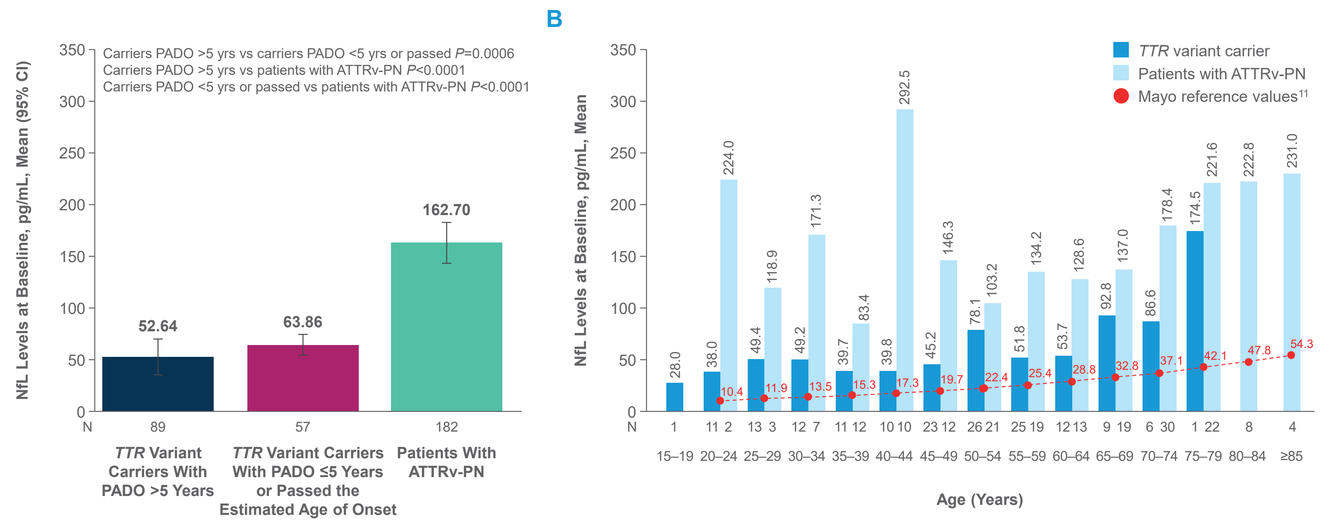
[a]In carriers with PND >1, gait impairment is attributable to comorbid conditions unrelated to ATTRv-PN.
[b]PND assessment was not available in 35 patients with ATTRv-PN.

Results (Cont'd)

Baseline Assessment of NfL Levels

- At baseline, the NfL levels were significantly higher in patients with ATTRv-PN than in asymptomatic *TTR* variant carriers (mean [SD] 162.7 [134.2] pg/mL [n=182] vs 56.6 [64.7] pg/mL [n=160]; *P*<0.0001)
- NfL levels were significantly lower in the *TTR* variant carriers with PADO of >5 years vs those with PADO <5 years or already having passed the estimated age of onset (*P*=0.0006; **Figure 5A**)
- Baseline NfL levels in patients with ATTRv-PN were higher than in asymptomatic *TTR* variant carriers across all age categories; both were higher than the reference values (**Figure 5B**)
- In carriers, NfL levels were greater with increasing age, consistent with the general trend with NfL levels; patients with ATTRv-PN demonstrated an overall trend for increasing NfL levels with age from >50 years onward

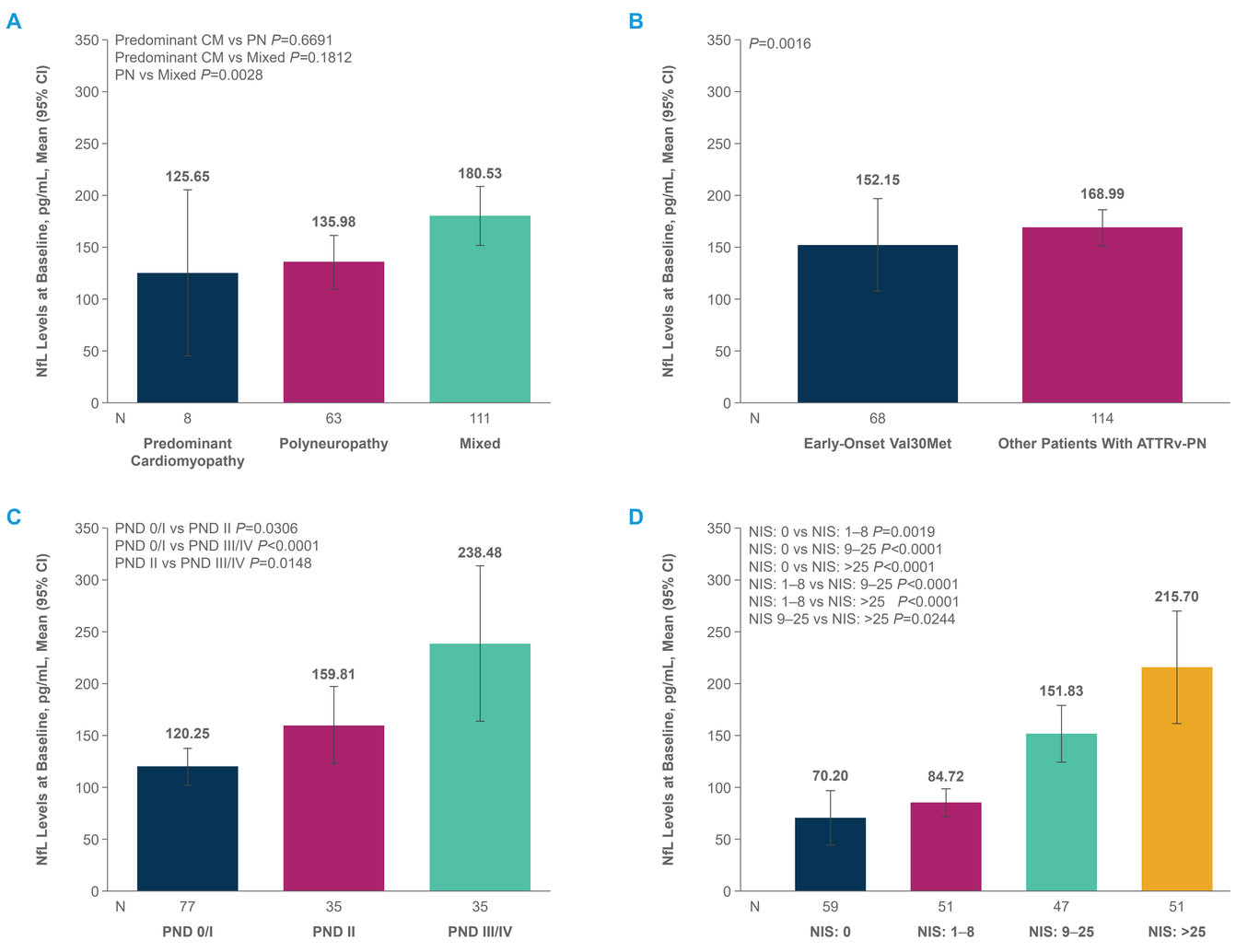
Figure 5. Baseline NfL Levels by A) Cohort Subgroup and B) Age Category in the Total Cohort



Relationship Between Disease Characteristics, Severity, and NfL Levels

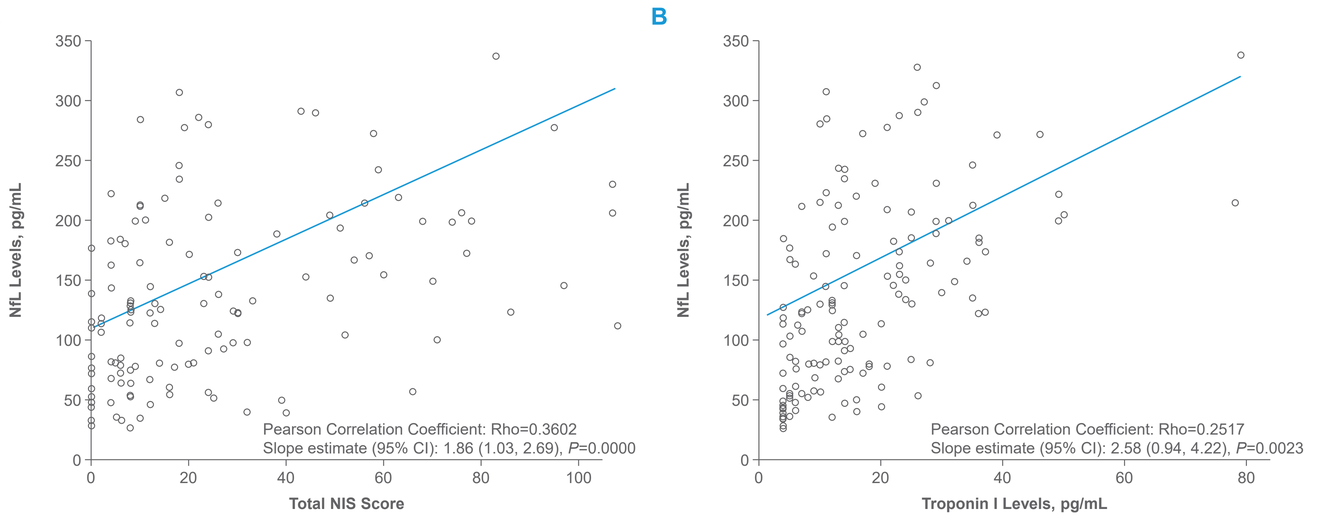
- In patients with ATTRv-PN, baseline NfL levels were higher in patients with a mixed phenotype than polyneuropathy alone or predominant cardiomyopathy (**Figure 6A**) and were lower in patients with early-onset Val30Met disease than in those with other *TTR* variants (**Figure 6B**)
- Higher NfL levels were observed with increasing PND score in patients with ATTRv-PN (**Figure 6C**), and with higher NIS scores in the total study cohort, including patients with very low NIS scores (**Figure 6D**), consistent with worsening disease severity and increased neuronal damage

Figure 6. Baseline NfL Levels in Patients With ATTRv-PN According to A) Phenotype, B) Early-Onset Val30Met vs Other *TTR* Variants, and C) PND Score and D) in the Total Cohort According to NIS Quartiles



- In patients with ATTRv-PN, NfL levels were moderately but significantly correlated with NIS and troponin I, parameters related to polyneuropathy and cardiomyopathy, respectively (**Figure 7**)
  - Electroneuromyography measures, CMAP and SNAP also demonstrated a moderate negative correlation with NfL levels

Figure 7. Univariate Linear Regression Correlations Between Baseline NfL Levels in Patients With ATTRv-PN and Disease Severity Parameters A) NIS, and B) Troponin I



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If you are seeking additional scientific information related to Alnylam therapeutics, non-US HCPs should contact medinfo@alnylam.com. US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com.

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Abbreviations: ATTRv, hereditary transthyretin amyloidosis; ATTRv-CM, ATTRv with cardiomyopathy; ATTRv-PN, ATTRv with polyneuropathy; CI, confidence interval, CM, cardiomyopathy; CMAP, compound muscle action potential; eGFR, estimated glomerular filtration rate; HCP, healthcare professional; NfL, neurofilament light chain; NIS, Neuropathy Impairment Score; OLT, orthotopic liver transplant; PADO, predicted age of disease onset; PN, polyneuropathy; PND, polyneuropathy disability; RNAi, RNA interference; SD, standard deviation; SNAP, sensory nerve action potential; TTR, transthyretin; yrs, years.