Neurofilament Light Chain in ATTR Amyloidosis with Cardiomyopathy: Analysis from the Phase 3 APOLLO-B Study

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Conclusions

- **Baseline neurofilament light chain (NfL) levels were elevated compared with matched healthy controls in patients with transthyretin amyloidosis (ATTR; hereditary or wild-type) with cardiomyopathy (ATTR-CM) in APOLLO-B, with a substantial proportion of patients having higher than reference levels of NfL at baseline, despite exclusion of patients with a polyneuropathy disability (PND) score > II**
- **Patients with elevated NfL levels had greater neuropathy impairment at baseline than those with normal levels**
- **NfL levels decreased with patisiran treatment over 24 months in the patisiran arm of the APOLLO-B study, and between 12 and 24 months after the placebo patients started patisiran treatment**
- **These findings collectively indicate that a substantial percentage of patients with ATTR-CM, including wild-type ATTR (ATTRwt), can have a mixed phenotype of CM and polyneuropathy (PN)**
- **Further validation of these results is required, particularly in ATTR-CM populations including patients with PND scores > II and where other potential causes of increased NfL levels are accounted for more systematically**

Introduction

Transthyretin Amyloidosis (ATTR)

- A rapidly progressive and often fatal disease caused by accumulation of toxic transthyretin (TTR) amyloid fibrils in multiple organs and tissues, including the nervous system and heart[1–3]
  - The two types of ATTR are hereditary ATTR (ATTRv), in which variants in the *TTR* gene result in misfolded TTR protein, and ATTRwt, in which wild-type TTR protein misfolds without a variant in the gene[1]
- ATTRv often presents with a mixed phenotype of PN and CM[4,5]

Neurofilament Light Chain (NfL)

- A well-characterized biomarker of neuroaxonal damage[6]
- NfL levels are found to be significantly higher in patients with ATTRv compared with healthy controls, and show a correlation with disease severity measures such as Neuropathy Impairment Score[6]
- Plasma NfL levels decreased in patients with ATTRv-PN who were treated with the RNA interference therapeutics patisiran and vutrisiran in the Phase 3 APOLLO and HELIOS-A studies, respectively[7,8]
  - NfL is considered as a biomarker of nerve damage in ATTRv-PN, with potential utility in earlier diagnosis and monitoring of disease progression and treatment response[7,8]

APOLLO-B Study

- The APOLLO-B study (NCT03997383) is evaluating the efficacy and safety of patisiran in patients with ATTR-CM[9]
- Patients treated with patisiran demonstrated sustained benefit across functional capacity, health status, and quality-of-life endpoints over the 12-month double-blind (DB)[9] and open-label extension (OLE)[10] periods of the study
- Patisiran was well tolerated[9,10]

Objectives

- This post hoc analysis aims to assess the potential of NfL as a biomarker of PN in patients with ATTR-CM, and the effect of patisiran on NfL levels in this patient population

Methods

Phase 3 APOLLO-B Study

- APOLLO-B is an international, randomized, placebo-controlled study in patients with ATTR-CM (ATTRv or ATTRwt), evaluating patisiran in a 12-month DB period followed by an ongoing OLE[9,10]
  - Patients enrolled in the trial were aged 18–85 years with a diagnosis of ATTR-CM
  - Patients with PND scores > II were excluded
  - Approximately 25% of patients received background tafamidis treatment
- Data cutoff for NfL analysis was August 14, 2023

Analysis of NfL Levels

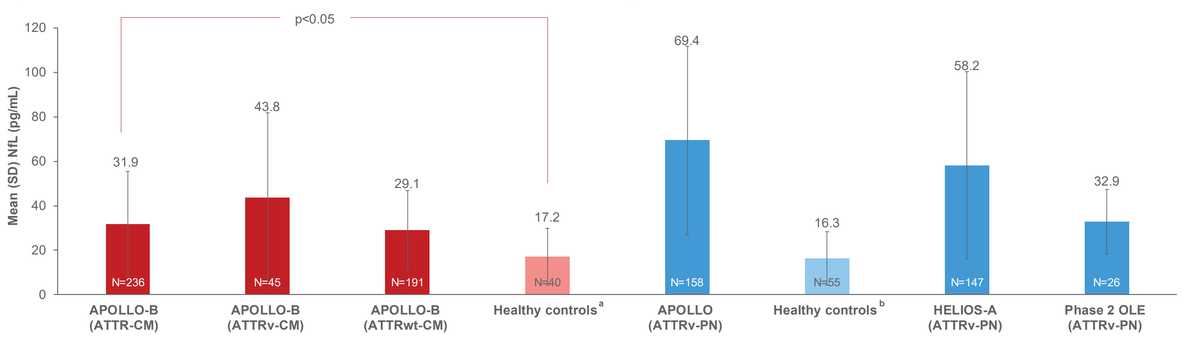
- Serum NfL was measured by SIMOA® immunoassay at baseline, Month 12 (end of DB period), and Month 24 (Month 12 of the OLE period) in patients from APOLLO-B who consented to the exploratory analysis and indicated not having other neurologic diseases when asked to list other factors that could contribute to their neuropathy, other than ATTR (e.g., diabetes, chemotherapy)
- Baseline NfL levels were compared with two sets of reference values (Mayo Clinic Laboratory[11] and University of Basel NfL Reference Database[12]), and with levels in age- and sex-matched healthy controls, as well as patients from patisiran clinical trials in ATTRv-PN (NCT01960348 [APOLLO], NCT03759379 [HELIOS-A], and NCT01961921 [Phase 2 OLE])
  - Patients were classified as having high NfL if levels were greater than the Mayo Clinic reference value for the corresponding age range[11] or above the 95th percentile age- and body mass index-adjusted z-scores, as calculated from the University of Basel database[12]
- The proportions of patients with baseline PND scores 0, 1, or 2, and baseline mean Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire scores were summarized according to high or normal baseline NfL levels

Results

Baseline NfL Levels

- Overall, 236 patients (45 with ATTRv and 191 with ATTRwt) with ATTR-CM in APOLLO-B had baseline NfL data and indicated no other factors contributing to neuropathy
- Mean baseline NfL for the overall population of APOLLO-B was significantly higher than matched external healthy controls (31.9 vs 17.2 pg/mL; p<0.05; **Figure 1**)
  - Baseline NfL levels in APOLLO-B were lower than those in the APOLLO study in ATTRv-PN, and comparable to those in the Phase 2 OLE of patisiran (NCT01961921)[13] in which patients with ATTRv-PN with relatively early-stage disease were included (**Figure 1**)

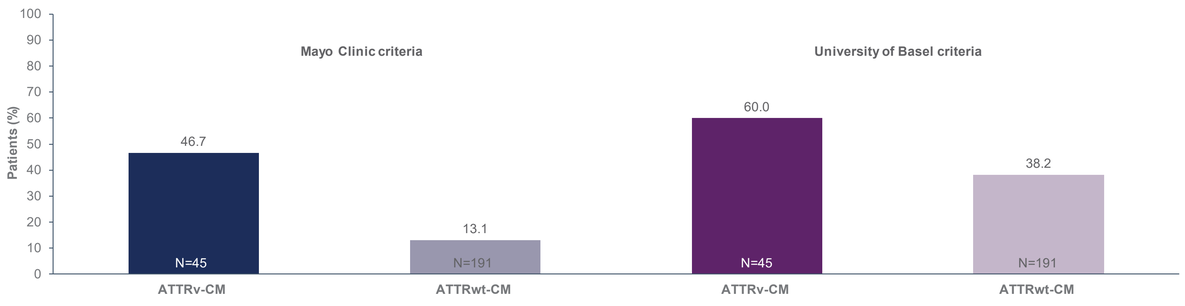
Figure 1. Baseline NfL Levels in APOLLO-B, Healthy Controls, and Other Clinical Studies



[a]Matched to APOLLO-B; [b]Matched to APOLLO

- A substantial percentage of patients had elevated baseline NfL according to Mayo Clinic and University of Basel reference values (**Figure 2**)

Figure 2. Proportion of Patients with Elevated Baseline NfL According to Reference Levels



- A greater proportion of patients with PND scores 1 or 2 and numerically higher Norfolk QoL-DN scores were observed in the high baseline NfL (both criteria) group, compared with the normal baseline NfL population (**Table 1**)

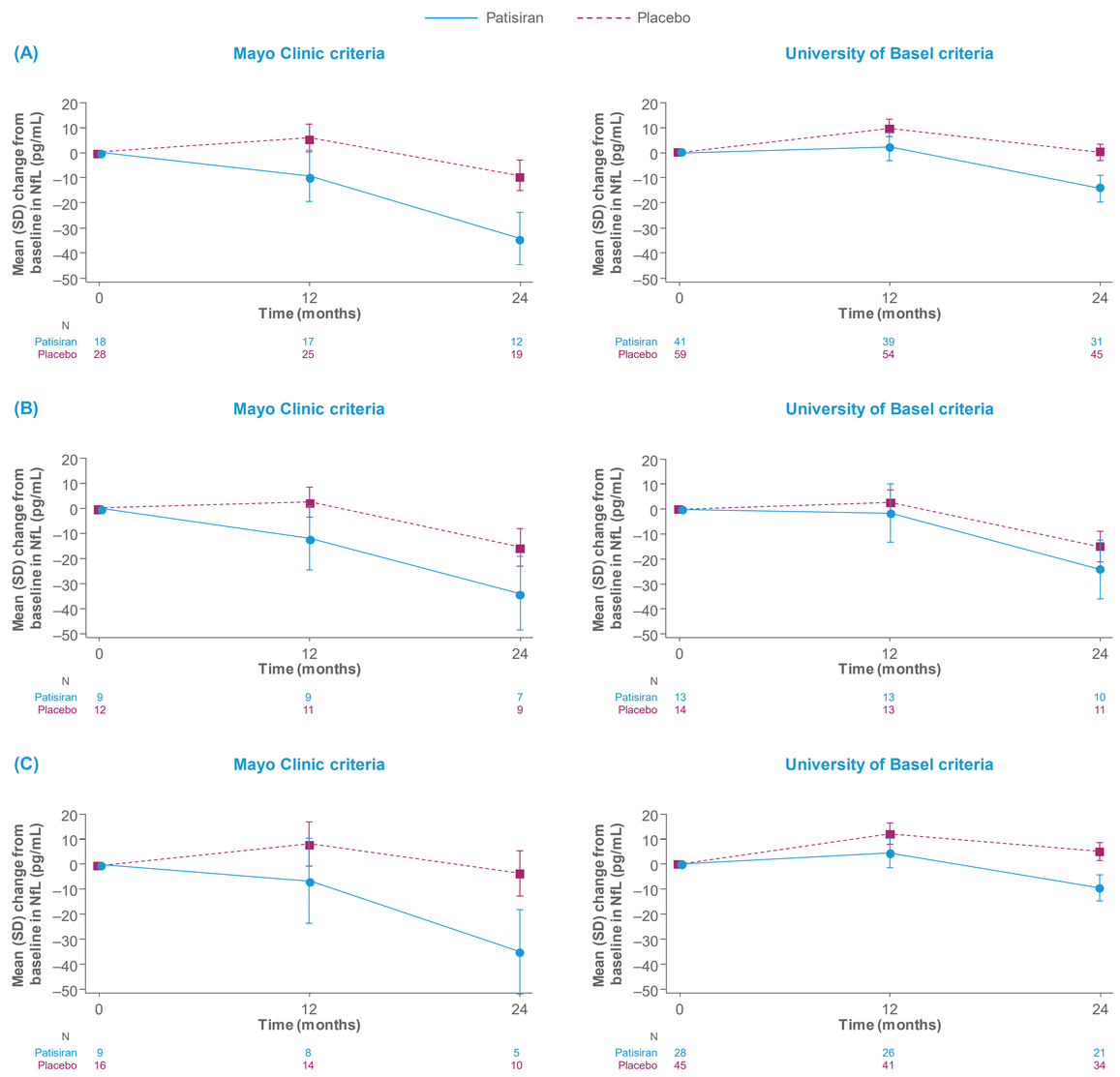
Table 1. PND and Norfolk QoL-DN Questionnaire Scores at Baseline According to Elevated and Normal Baseline NfL

	Baseline NfL according to reference levels							
	Mayo Clinic criteria				University of Basel criteria			
	High		Normal		High		Normal	
	Patisiran N=18	Placebo N=28	Patisiran N=99	Placebo N=91	Patisiran N=41	Placebo N=59	Patisiran N=76	Placebo N=60
PND, n (%)								
0	5 (27.8)	14 (50.0)	56 (56.6)	61 (67.0)	20 (48.8)	35 (59.3)	41 (53.9)	40 (66.7)
1	9 (50.0)	12 (42.9)	36 (36.4)	26 (28.6)	17 (41.5)	22 (37.3)	28 (36.8)	16 (26.7)
2	4 (22.2)	2 (7.1)	7 (7.1)	4 (4.4)	4 (9.8)	2 (3.4)	7 (9.2)	4 (6.7)
Norfolk QoL-DN score, mean (SD)	30.1 (16.5)	22.2 (19.4)	17.1 (16.0)	15.9 (15.3)	25.3 (18.9)	20.0 (17.3)	15.7 (14.4)	14.8 (15.4)

Impact of Patisiran Treatment on NfL Levels

- In the overall APOLLO-B population with high NfL levels at baseline according to both reference criteria, a decrease in NfL was observed in patisiran-treated patients at Month 24, which reached significance in the analysis according to University of Basel criteria (p=0.025) (**Figure 3A**)
  - Patisiran's impact on NfL levels was greater between Months 12 and 24 compared with between baseline and Month 12
  - Following initiation of patisiran treatment at Month 12, patients randomized to placebo at baseline demonstrated reduced NfL levels at Month 24
- Similar trends in response to patisiran were observed when the ATTRv and ATTRwt populations were analyzed separately (**Figures 3B and 3C**), with a significant decrease from baseline in NfL levels observed in patisiran-treated patients at Month 24 in the ATTRwt population according to University of Basel criteria (p=0.0292)

Figure 3. Change from Baseline in NfL Levels in Patients with High Baseline NfL According to Reference Levels in the Overall (A), ATTRv (B), and ATTRwt (C) Populations



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Disclaimer: Patisiran is not approved for the treatment of ATTR-CM in the US, but ANSM has granted approval for the compassionate use of patisiran in France for patients with ATTR-CM failing tafamidis 61 mg

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Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv, hereditary transthyretin amyloidosis; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; ATTRwt, wild-type transthyretin amyloidosis; ATTRwt-CM, wild-type transthyretin amyloidosis with cardiomyopathy; ATTRv-CM, hereditary transthyretin amyloidosis with cardiomyopathy; CM, cardiomyopathy; DB, double-blind; NfL, neurofilament light chain; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; OLE, open-label extension; PN, polyneuropathy; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin

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