Neurofilament Light Chain (NfL) as a Potential Biomarker of Treatment Response in Hereditary Transthyretin-Mediated Amyloidosis: Data from the Patisiran Global OLE Study

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Conclusions

- Patisiran treatment lowered levels of neurofilament light chain (NfL) in patients with hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, with polyneuropathy and led to sustained and durable improvement in neuropathy versus parent study baseline[1,2]
- NfL levels were lower in patients with less severe disease, supporting the potential relationship between NfL and disease activity in hATTR amyloidosis
- Significant reduction in NfL levels was observed when patisiran treatment was started in the Global Open-Label Extension (OLE) APOLLO-placebo group, even though modified Neuropathy Impairment Score+7 (mNIS+7) mainly stayed stable, highlighting the potential variance between this biologic indicator of nerve damage and the clinical indicators of neurologic impairment
  - NfL may reflect active neuronal damage at a specific point in time, whereas mNIS+7 reflects the burden of neurologic impairment[3]
- The NfL threshold of 37 pg/mL, which was previously reported to distinguish between healthy controls and patients with diagnosed hATTR amyloidosis with polyneuropathy,[3] would exclude many Phase 2 OLE patients and, therefore, underscores the need for further research into additional NfL level thresholds that may be age or disease severity-dependent
- Although the NfL levels of patients in the APOLLO-placebo group were decreased to a similar value with the APOLLO-patisiran group at 24 months in the Global OLE, their overall clinical burden remained higher, indicating the value of earlier intervention
- NfL levels may be useful for earlier diagnosis of polyneuropathy in patients with hATTR amyloidosis and for monitoring disease and treatment response over time

Background

hATTR Amyloidosis, Also Known As ATTRv Amyloidosis

- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease caused by variants in the *TTR* gene[4–8]
- Multisystem disease; majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[9–12]
- Affects ~50,000 people worldwide[8]
- Median survival of 4.7 years following diagnosis, with a reduced survival of 3.4 years for patients presenting with cardiomyopathy[13–16]
- Existing outcome measures for hATTR amyloidosis can be cumbersome to perform and difficult to use in clinical practice; additional measures could help to facilitate earlier diagnosis of hATTR amyloidosis and monitoring disease or treatment response

Patisiran

- Lipid nanoparticle-delivered RNAi therapeutic that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing variant and wild-type TTR proteins[17,18]
  - In the Phase 3 APOLLO study, patisiran demonstrated improvements on the primary endpoint of mNIS+7 (a composite measure of neuropathy), and all secondary endpoints (including quality of life [QOL]) vs placebo, with a positive benefit:risk profile in patients with hATTR amyloidosis with polyneuropathy[1]
  - Patisiran is approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy; specific indications vary by country/region[19–24]
- The long-term safety and efficacy of patisiran are being evaluated in the multicenter Global OLE study,[25] which enrolled patients who met eligibility criteria from the APOLLO study[1] and a Phase 2 OLE study[26]

NfL

- Elevated NfL plasma levels observed in central[27–30] and peripheral[31–34] nervous system diseases are thought to be due to damaged neurons releasing NfL into the circulation, thus making NfL a proximal biomarker for early nerve damage[35,36]
- Recent analyses, including the one from the APOLLO study, have identified NfL as a potential biomarker of neuronal injury in hATTR amyloidosis that may facilitate earlier diagnosis and monitoring of disease and treatment response[3,37–39]

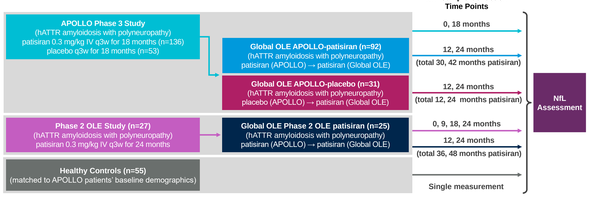
Objective

- To evaluate long-term change in NfL levels in response to patisiran at 12 and 24 months in the Global OLE study

Methods

- Patient samples were analyzed from the APOLLO study at baseline and 18 months, and from the Phase 2 OLE study at baseline, 9, 18, and 24 months (**Figure 1**)
- Patients who enrolled into the Global OLE are presented in one of three groups based on their participation in the parent studies:
  - **APOLLO-patisiran**: received patisiran for 18 months in APOLLO and continued receiving patisiran in the Global OLE
  - **APOLLO-placebo**: received placebo in APOLLO and started patisiran for the first time in the Global OLE
  - **Phase 2 OLE patisiran**: received patisiran for 24 months in the Phase 2 OLE and continued receiving patisiran in the Global OLE
- NfL levels were also measured at 12 and 24 months following parent study (APOLLO or Phase 2 OLE) completion in patients who rolled into the Global OLE
- NfL plasma levels were measured in duplicate in patients with hATTR amyloidosis with polyneuropathy, and in healthy controls, using the Quanterix Simoa platform

Figure 1. Study design with participants who had NfL levels measured, showing APOLLO and Phase 2 OLE enrollment in the Global OLE, and healthy controls



Results

Patient Demographics (Table 1)

- At Global OLE baseline, the Phase 2 OLE patisiran group had a higher proportion of patients with the V30M genotype and less severe disease than either APOLLO group, while the APOLLO-placebo group had the most severe disease burden of the three groups

Table 1. Patient demographics and disease characteristics at Global OLE baseline

	APOLLO-placebo (n=49)	APOLLO-patisiran (n=137)	Phase 2 OLE patisiran (n=25)	Global OLE Total patisiran (n=211)
Median age, years	66	63	65	64
Sex – male, n (%)	37 (76)	102 (74)	17 (68)	156 (74)
Mean time since hereditary ATTR amyloidosis diagnosis to first patisiran dose[a], years (range)	**4.5** (2–18)	**2.5** (0–21)	**2.8** (1–8)	3.0 (0–21)
Genotype, n (%)				
V30M	**24 (49)**	**56 (41)**	**18 (72)**	98 (46)
Non-V30M	**25 (51)**	**81 (59)**	**7 (28)**	113 (54)
mNIS+7 score[b], mean (min, max)	**101** (22–190)	**75** (8–199)	**46** (3–128)	77 (3–199)
PND score, n (%)				
0: No symptoms	0	1 (1)	0	1 (<1)
I: Preserved walking, sensory disturbances	7 (14)	32 (23)	10 (40)	49 (23)
II: Impaired walking but walk without stick/crutch	9 (18)	36 (26)	13 (52)	58 (27)
IIIA/B: Walk with 1 or 2 sticks/crutches	**25 (51)**	**60 (44)**	**2 (8)**	87 (41)
IV: Confined to wheelchair/bedridden	**8 (16)**	**8 (6)**	**0**	16 (8)
NT-proBNP, pg/mL, median (range)	**868 (56–15,101)**	**375 (21–10,282)**	**166 (5–1897)**	376 (5–15,101)
LV wall thickness, cm, mean (SD)	1.5 (0.3)	1.5 (0.3)	1.2 (0.3)	1.5 (0.3)

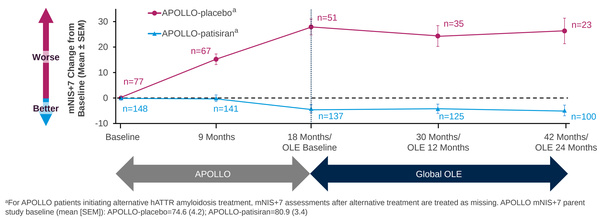
Bold text highlights specific baseline differences between groups
[a]First patisiran dose could have occurred in Phase 2 OLE, APOLLO, or Global OLE. [b]mNIS+7, range 0–304, higher score reflects greater impairment.

Global OLE Results: mNIS+7 (Figure 2)

- During the 18-month APOLLO and 24-month Phase 2 OLE parent studies, patisiran treatment was associated with an improvement in polyneuropathy, as measured by mNIS+7
- In the Global OLE,[2] the APOLLO-patisiran and Phase 2 OLE patisiran groups demonstrated that this improvement in polyneuropathy vs parent study baselines was durable, indicated by a mean negative change [SEM] in mNIS+7 at 24 months (–4.9 [2.1] from APOLLO baseline; –5.9 [2.1] from Phase 2 OLE baseline)
- Rapid polyneuropathy progression in the APOLLO-placebo group was halted upon patisiran treatment in the Global OLE (mean change in mNIS+7 [SEM] from Global OLE baseline at 24 months, +0.1 [3.3]); however, it did not return to parent study baseline values due to progression while on placebo in APOLLO
- Similar results were seen with QOL, as measured by Norfolk QOL-Diabetic Neuropathy (Norfolk QOL-DN) score

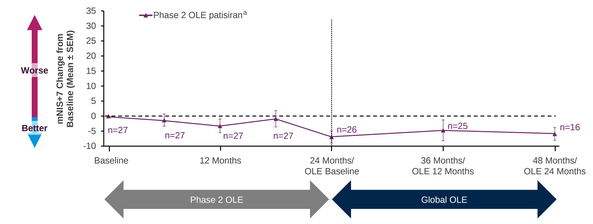
Figure 2. Integrated change in mNIS+7 in (A) APOLLO and Global OLE and (B) the Phase 2 OLE and Global OLE[2]

A.



[a]For APOLLO patients initiating alternative hATTR amyloidosis treatment, mNIS+7 assessments after alternative treatment are treated as missing. APOLLO mNIS+7 parent study baseline (mean [SEM]): APOLLO-placebo=74.6 (4.2); APOLLO-patisiran=80.9 (3.4)

Figure 2B.



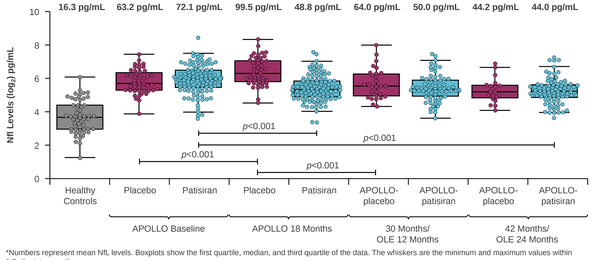
[a]Phase 2 OLE mNIS+7 parent study baseline (mean [SEM]): 53.0 (6.9)

Change in NfL Levels in the Global OLE

- At baseline, Phase 2 OLE patients had lower NfL levels (mean 32.9 pg/mL) than either APOLLO group (mean 72.1 pg/mL for patisiran and 63.2 pg/mL for placebo) (**Figure 3**); all patient groups had significantly higher NfL levels than healthy controls (mean 16.3 pg/mL)
- During APOLLO, there was a significant decrease in NfL levels from baseline in the patisiran group at 18 months (mean 48.8 pg/mL, p<0.001); in the Phase 2 OLE, NfL levels also decreased from baseline to 24 months (mean 29.6 pg/mL, p=0.19), but at a lesser degree than in APOLLO (**Figure 3**, **Figure 4**)
- In the Global OLE, the reduction in NfL levels from parent study baseline in both the APOLLO-patisiran and Phase 2 OLE patisiran groups following an additional 24 months of patisiran treatment was significant (APOLLO-patisiran, mean 44.0 pg/mL, p<0.001; Phase 2 OLE patisiran, mean 22.8 pg/mL, p<0.001) (**Figure 3**, **Figure 4**)
- During APOLLO, NfL levels increased significantly in the placebo group (mean 99.5 pg/mL; p<0.001) (**Figure 3A**), yet were significantly reduced following 12 months of patisiran treatment started in the Global OLE (mean 64.0 pg/mL, p<0.001)
  - The reduction of NfL levels in the APOLLO-placebo group continued at 24 months in the Global OLE (mean 44.2 pg/mL), to reach levels below the APOLLO baseline and to a similar level to the APOLLO-patisiran group

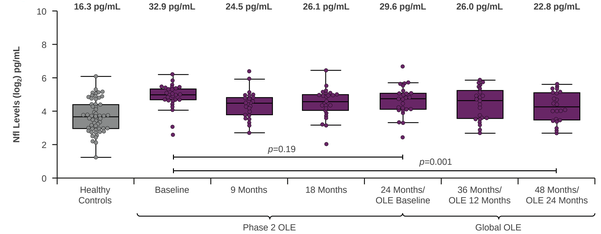
Figure 3. NfL levels in patients treated with patisiran in (A) APOLLO and Global OLE and (B) the Phase 2 OLE and Global OLE*

A.



*Numbers represent mean NfL levels. Boxplots show the first quartile, median, and third quartile of the data. The whiskers are the minimum and maximum values within 1.5× the interquartile range

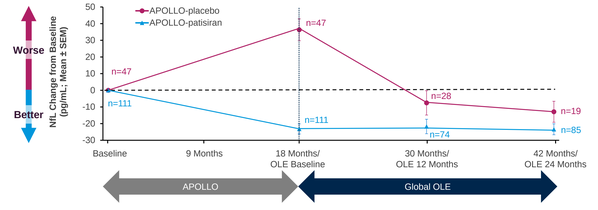
Figure 3B*.



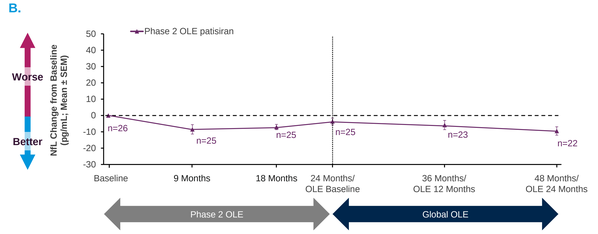
*Numbers represent mean NfL levels. Boxplots show the first quartile, median, and third quartile of the data. The whiskers are the minimum and maximum values within 1.5× the interquartile range

Figure 4. NfL levels from parent study baseline in patients in (A) APOLLO and Global OLE and (B) the Phase 2 OLE and Global OLE

A.



B.



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Abbreviations: ATTRv, hereditary transthyretin (v for variant); hATTR, hereditary transthyretin-mediated; IV, intravenous; LV, left ventricular; NfL, neurofilament light chain; OLE, Norfolk QOL-DN, Norfolk QOL-Diabetic Neuropathy; open-label extension; NT-proBNP , N-terminal prohormone of brain-type natriuretic peptide; PND, polyneuropathy disability; q3w, every 3 weeks; QOL, quality of life; RNAi, RNA interference; SD, standard deviation; SEM, standard error of the mean.

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