Neurofilament Light Chain May Serve as a Biomarker in Hereditary Transthyretin-Mediated Amyloidosis

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Background

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis, Also Known As ATTRv Amyloidosis

- **Rare, rapidly progressive, debilitating, and potentially fatal disease caused by a variant in the *TTR* gene**[1–5]
  - Multisystem disease; majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[6–9]
  - Affects ~50,000 people worldwide[4]; median survival of 4.7 years following diagnosis, with a reduced survival of 3.4 years for patients presenting with cardiomyopathy[10–13]

Patisiran

- Lipid nanoparticle-delivered **RNAi therapeutic** that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing variant and wild-type (wt) TTR proteins[14–15]
  - In the **Phase 3 APOLLO study**, patisiran demonstrated improvements on the primary endpoint mNIS+7 and all secondary endpoints vs placebo with a positive benefit:risk profile in patients with hATTR amyloidosis with polyneuropathy[8]
  - Patients who met eligibility criteria from the **Phase 2 OLE and APOLLO studies** were able to roll over into the multicenter, international, **open-label extension (OLE) study** to evaluate the long-term safety and efficacy of patisiran
  - Patisiran is approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy[a,16–21]

[a]Specific indications vary by country/region

ATTRv, hereditary transthyretin (v for variant); hATTR, hereditary transthyretin-mediated; OLE, open-label extension; QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin; wt, wild-type

1. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 3. Adams et al. *Neurology* 2015;85:675–82; 4. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 5. Hawkins et al. *Ann Med* 2015;47:625–38; 6. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 7. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 8. Adams et al. *N Engl J Med* 2018;379:11–21; 9. Benson et al. *N Engl J Med* 2018;379:22–31; 10. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 11. Swiecicki et al. *Amyloid* 2015;22:123–31; 12. Castaño et al. *Heart Fail Rev* 2015;20:163–78; 13. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 14. Coelho et al. *N Engl J Med* 2013;369:819–29; 15. Suhr et al. *Orphanet J Rare Dis* 2015;10:109; 16. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use. 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf (accessed February 13, 2020); 17. European Medicines Agency. Summary of product characteristics: Onpattro 2 mg/mL concentrate for solution for infusion. 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf (accessed February 13, 2020); 18. Alnylam Pharmaceuticals Inc. Alnylam announces approval in Japan of ONPATTRO® for the treatment of hereditary ATTR amyloidosis with polyneuropathy. 2019. Available from: https://investors.alnylam.com/press-release?id=23886 (accessed February 13, 2020); 19. Canadian Agency for Drugs and Technologies in Health. Available from: https://www.cadth.ca/patisiran (accessed February 13, 2020); 20. Abbreviated information for health care professionals for ONPATTRO 10mg/5ml, concentrate for solution for infusion (Version September 2019). Available from: www.swissmedicinfo.ch (accessed February 13, 2020); 21. Alnylam Pharmaceuticals Inc. Alnylam Announces Approval in Brazil of ONPATTRO® for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy. Available from: https://investors.alnylam.com/press-release?id=24606

Background

Neurofilament Light Chain

- **Neurofilament light chain (NfL)** has been described extensively as a **biomarker of neuronal injury** across central nervous system diseases[1–4] and peripheral nervous system diseases[5–8]
  - Elevation of NfL has been identified in blood and thought to be released into circulation from damaged neurons, thus making it a **proximal biomarker for early nerve damage**[9,10]
  - Recent publications identified NfL as a **potential biomarker of neuronal injury in hATTR amyloidosis**[11,12]

Presentation objectives:

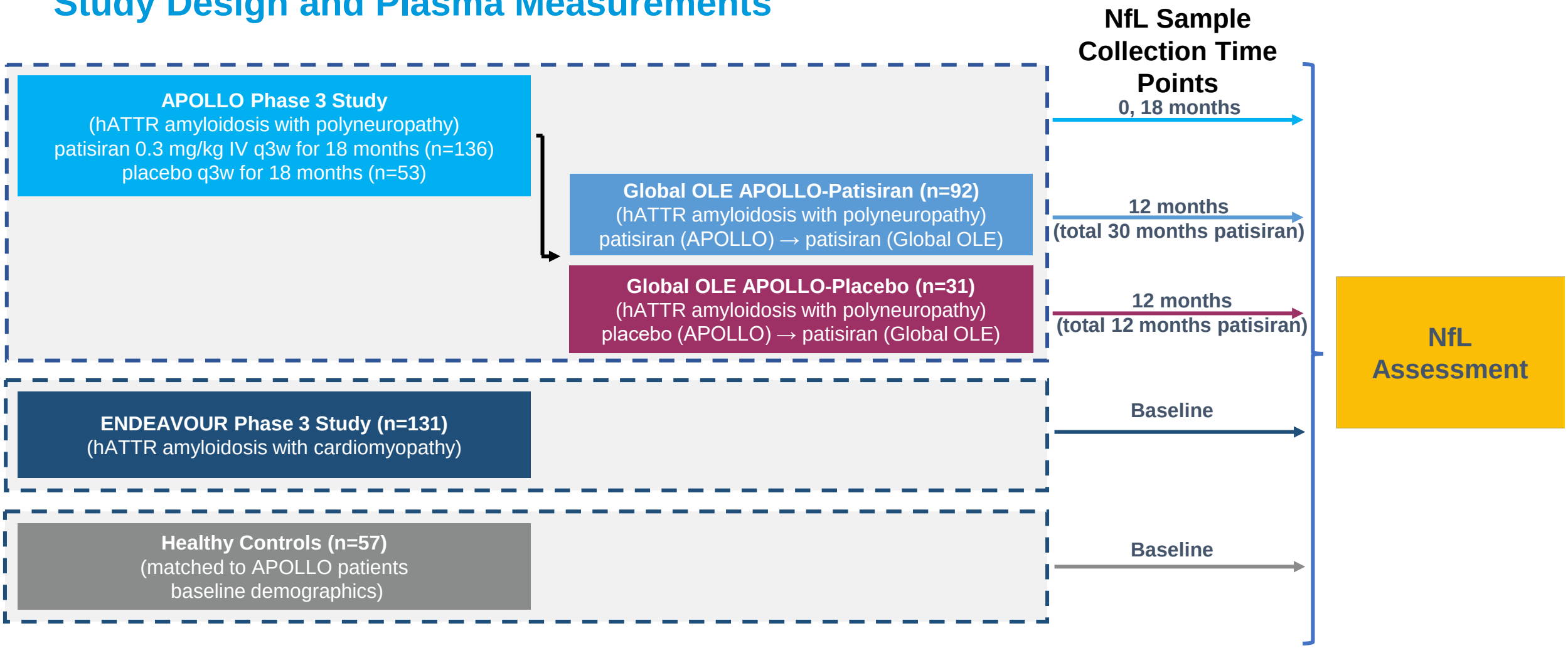
- Assess the longitudinal changes of NfL levels in patients with hATTR amyloidosis with polyneuropathy from APOLLO
  who have rolled over into the Global OLE
- Evaluate the potential for NfL to serve as a biomarker of neuronal damage in patients with hATTR amyloidosis with cardiomyopathy

hATTR, hereditary transthyretin-mediated; NfL, neurofilament light chain; OLE, open-label extension

1. Gunnarsson et al. *Ann Neurol* 2011;69:83–9; 2. Lewczuk et al. *Alzheimers Res Ther* 2018;10:71; 3. Lin et al. *Sci Rep* 2018;8:17368; 4. Byrne et al. *Lancet Neurol* 2017;16:601–9; 5. Bischof et al. *Ann Rheum Dis* 2018;77:1093–4; 6. Van Lieverloo et al. *J Peripher Nerv Syst* 2019. doi: 10.1111/jns.12319; 7. Mariotto et al. *J Peripher Nerv Syst* 2018; 23:174–7; 8. Sandelius et al. *Neurology* 2018;90:e518–24; 9. Lycke et al. *J Neurol Neurosurg Psychiatry* 1998;64:402–4; 10. Preische et al. *Nat Med* 2019;25:277–83; 11. Kapoor et al. *J Peripher Nerv Syst* 2019;24:314–19; 12. Maia et al. *Amyloid* 2020. Epub ahead of print

Methods

Study Design and Plasma Measurements



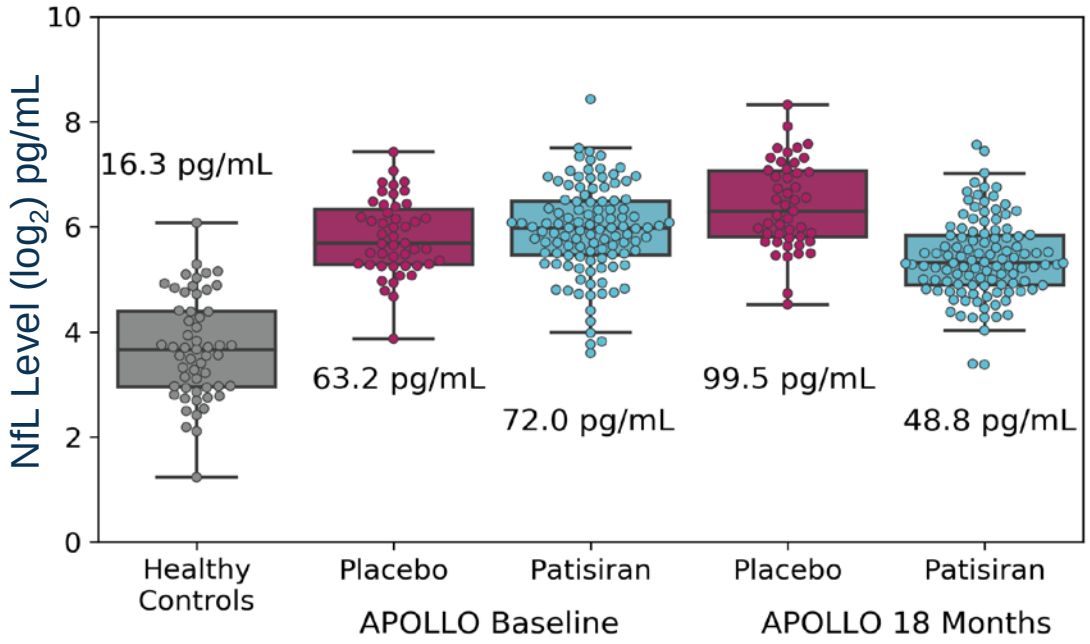
hATTR, hereditary transthyretin-mediated; IV, intravenous; NfL, neurofilament light chain; OLE, open-label extension; q3w, every three weeks

Results

NfL Levels Are Elevated in Patients with hATTR Amyloidosis with Polyneuropathy

- Patients with hATTR amyloidosis with polyneuropathy exhibited > **4-fold higher plasma NfL at baseline** relative to healthy controls ($p<0.0001$ log_2 scale)
- In APOLLO, patients randomized to **placebo** exhibited **significantly elevated NfL levels at 18 months** relative to baseline ($p<0.001$)
- In APOLLO, patients randomized to **patisiran** exhibited **significantly decreased NfL levels at 18 months** relative to baseline ($p<0.001$)

Levels of NfL in Healthy Controls (Grey) and Placebo- (Magenta) or Patisiran- (Blue) Treated Patients at Baseline and 18 Months



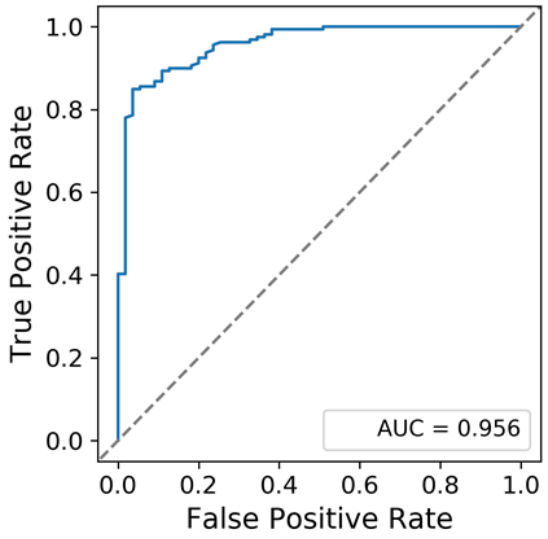
Numbers represent mean NfL levels; boxplots show the first quartile, median, and third quartile of the data; the whiskers are the minimum and maximum values within 1.5× the interquartile range

hATTR, hereditary transthyretin-mediated; NfL, neurofilament light chain

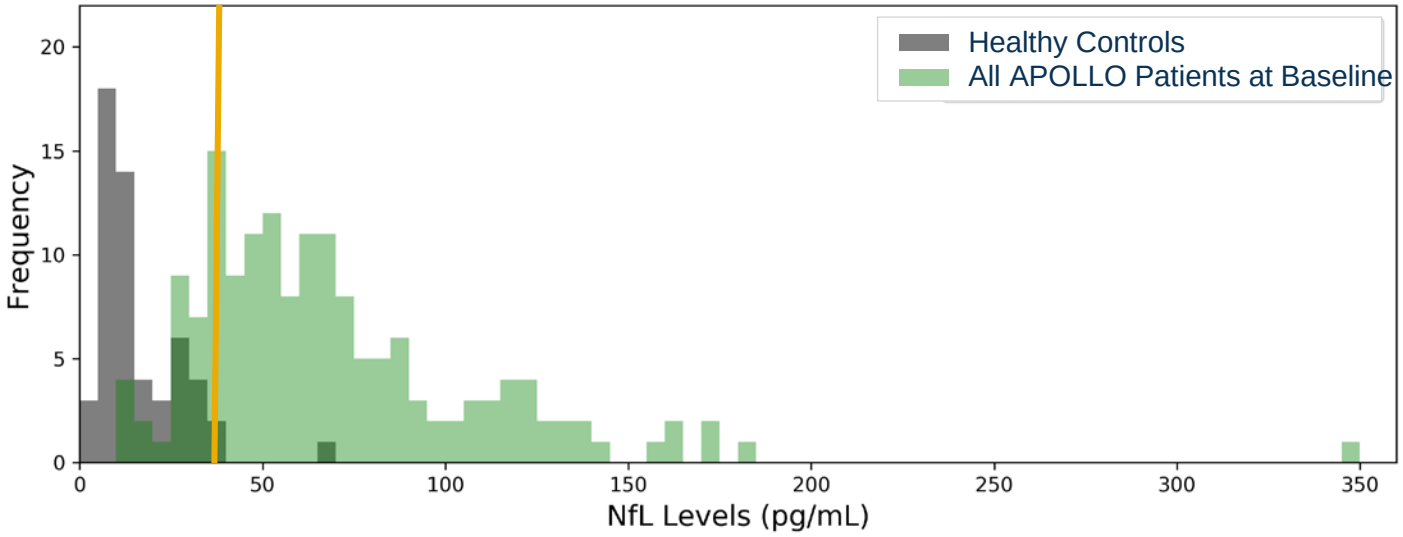
Results

Elevated NfL Levels in Patients with hATTR Amyloidosis with Polyneuropathy

- A threshold of 37 pg/mL for plasma NfL is suggested by the data (true positive rate=84.9%; false positive rate=3.7%) to distinguish between healthy controls and patients with hATTR amyloidosis with polyneuropathy



Receiver Operator Curve (ROC) Analysis Using Levels of NfL in Healthy Controls or APOLLO Patients at Baseline (Regardless of Subsequent Treatment)



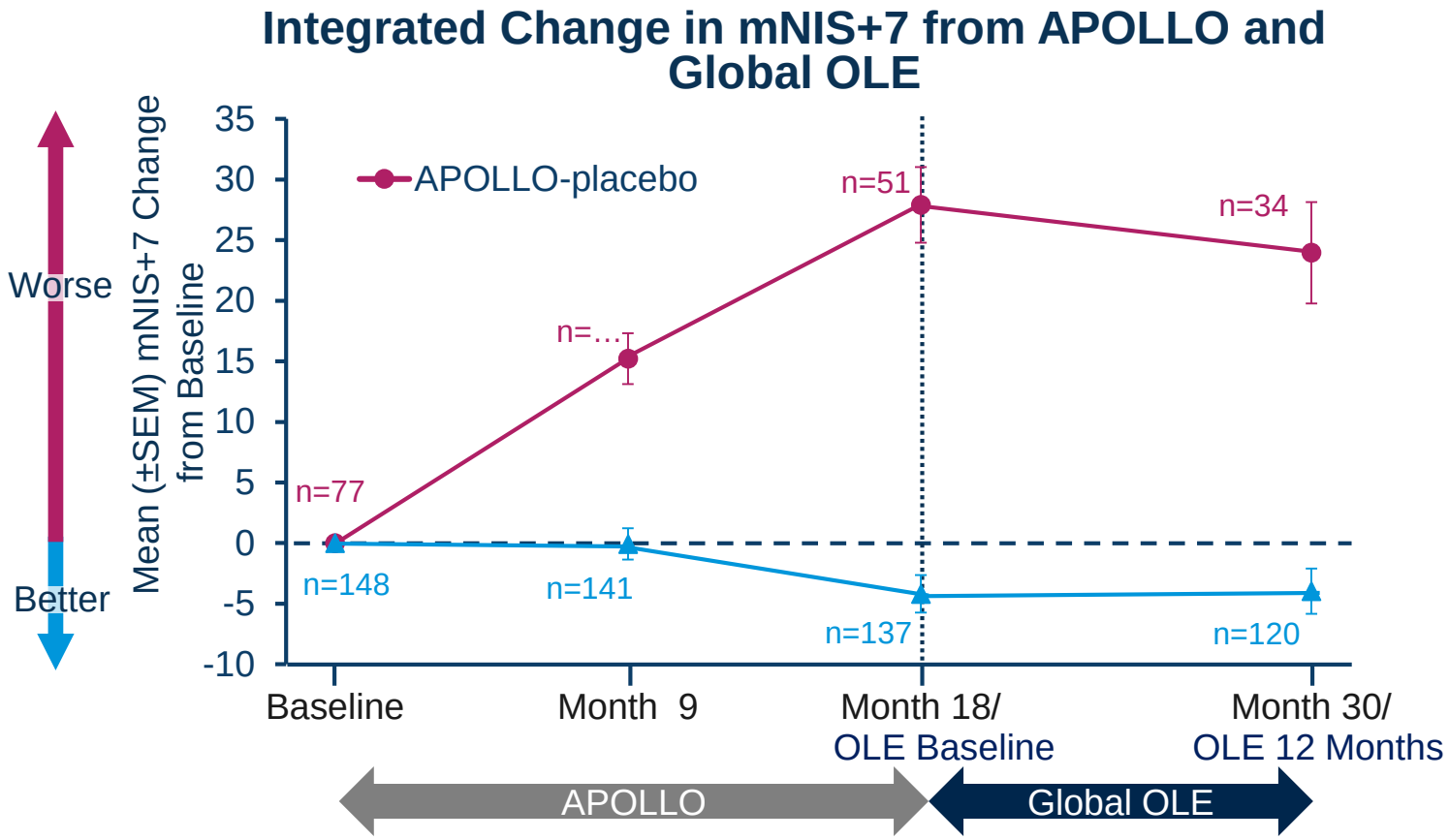
Histogram of NfL Levels in Healthy Controls (Grey) or APOLLO Patients at Baseline (Green; Regardless of Subsequent Treatment); the Proposed Threshold to Differentiate between the Two Populations, 37 pg/mL NfL, Is Shown by a Vertical Orange Line

AUC, area under the curve; hATTR, hereditary transthyretin-mediated; NfL, neurofilament light chain; ROC, receiver operator curve

Results

Improvement in Polyneuropathy Following Patisiran Treatment in the Global OLE

- After 12 months of additional patisiran treatment in the Global OLE, APOLLO-patisiran patients demonstrated **durable improvement in neuropathy versus their parent-study baselines**, as seen by mean negative change from baseline in modified neuropathy impairment score+7 (mNIS+7)
- Rapid trajectory of polyneuropathy progression among the APOLLO-placebo patients halted once patisiran treatment was initiated in the Global OLE, with **an improvement in mNIS+7 score over the 12 months they received patisiran** in the Global OLE



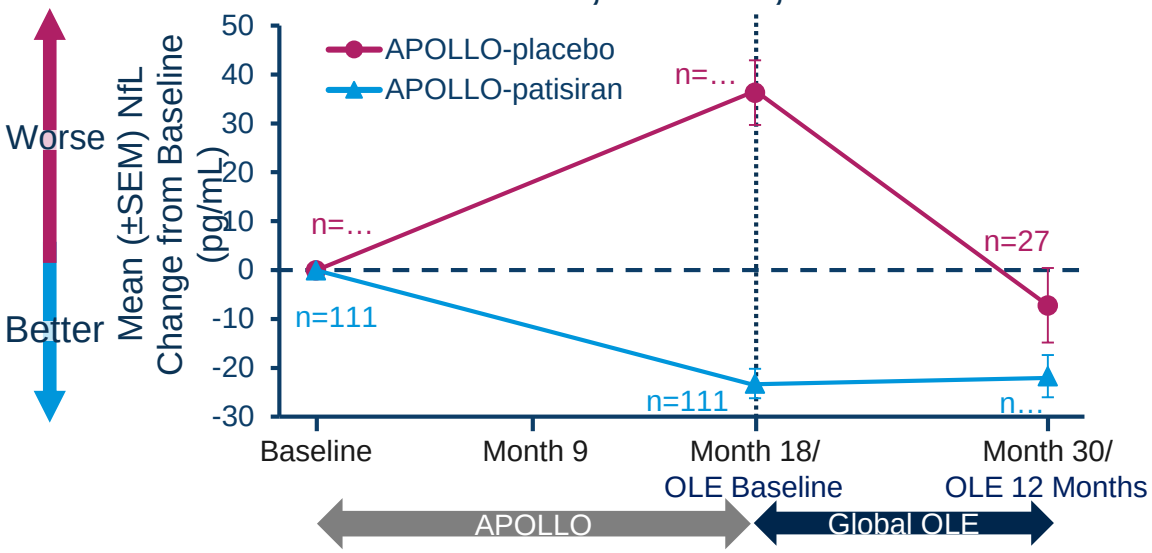
mNIS+7, modified neuropathy impairment score+7; OLE, open-label extension; SEM, standard error of the mean.

Results

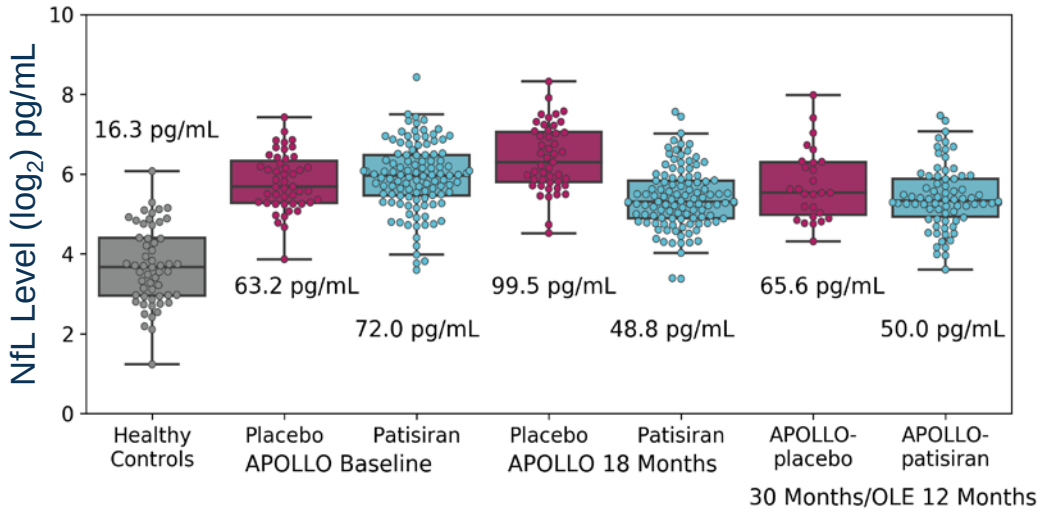
NfL Decreases in Patients who Switch from Placebo to Patisiran in the Global OLE

- NfL levels **remained steady after 12 months in the Global OLE** for the APOLLO-patisiran patients (mean 48.8 pg/mL vs 50.0 pg/mL)
- NfL levels **decreased significantly after 12 months of patisiran treatment** in the APOLLO-placebo patients (mean 99.5 pg/mL *vs* 65.6 pg/mL; p-value<0.001)

Integrated Change in NfL from APOLLO and Global OLE Studies at Baseline, Month 18, and Month 30[a]



Plasma NfL Levels of Healthy Controls and Patients from the APOLLO and Global OLE Studies at Baseline, 18 Months, and 30 Months[a]



[a]One individual with NfL levels of 747 pg/mL at 18 months and a cerebral stroke at 17 months was excluded from the analysis
NfL, neurofilament light chain; OLE, open-label extension; SEM, standard error of the mean

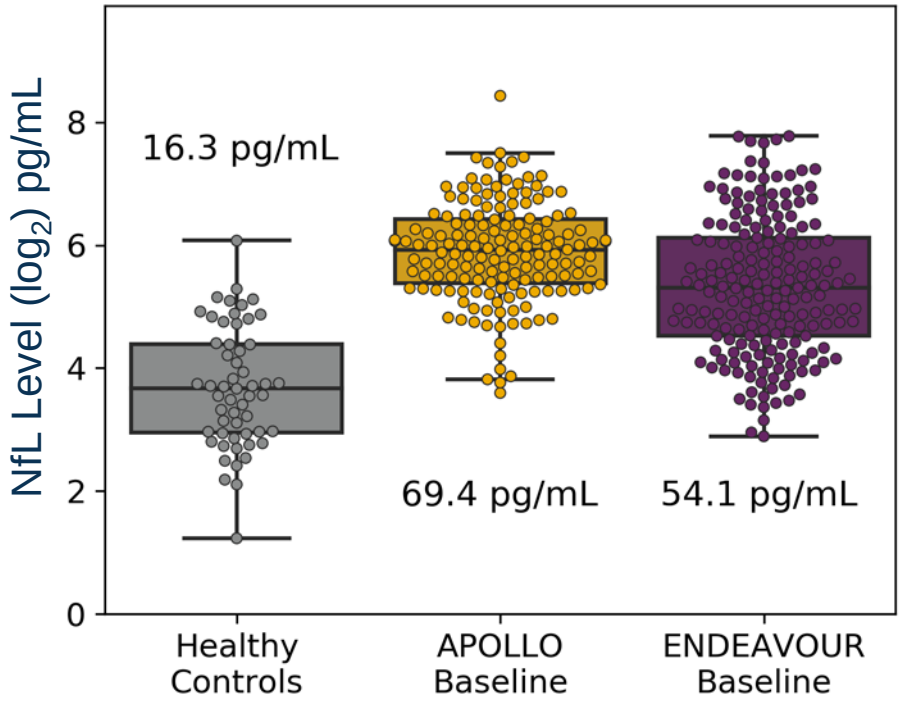
Numbers represent mean NfL levels; boxplots show the first quartile, median, and third quartile of the data; the whiskers are the minimum and maximum values within 1.5x the interquartile range

Results

NfL Levels in Patients with hATTR Amyloidosis with Cardiomyopathy

- NfL levels were measured at baseline in patients enrolled in a Phase 3 study of hATTR amyloidosis with cardiomyopathy (ENDEAVOUR)
- **Levels of NfL were significantly elevated in these patients relative to healthy controls** (mean 54.1 pg/mL vs 16.3 pg/mL; p<0.001)

Levels of NfL in Healthy Controls, APOLLO, and ENDEAVOUR Patients at Baseline



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

hATTR, hereditary transthyretin-mediated; NfL, neurofilament light chain

Conclusions

- NfL is a **well-described biomarker for neuronal damage** and may serve as a biomarker of nerve damage and polyneuropathy resulting from TTR amyloid deposition
- **Patisiran treatment lowers levels of NfL in patients with hATTR amyloidosis with polyneuropathy**, though not back to levels observed in healthy controls
  - **Degree of NfL lowering is sustained following the initial reduction** observed upon treatment initiation and remains consistent over the duration of treatment
- Patients initially enrolled in the APOLLO-placebo group demonstrated a **lowering of NfL levels once they began receiving patisiran treatment** during the Global OLE, though the **reduction was not to the same level observed in patients receiving patisiran earlier in their disease course**
- **Elevated NfL levels were also observed in patients with hATTR amyloidosis with cardiomyopathy** relative to healthy controls, **suggesting presence of nerve damage**, regardless of predominant manifestation
- This analysis may further establish NfL as a potential biomarker of neuronal injury in hATTR amyloidosis

hATTR, hereditary transthyretin-mediated; NfL, neurofilament light chain; OLE, open-label extension; TTR, transthyretin