Neurofilament Light Chain as a Biomarker in Hereditary Transthyretin-Mediated Amyloidosis: 36-Month Data from the Patisiran Global Open-Label Extension

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Introduction

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- A rare, underdiagnosed, rapidly progressive, debilitating, and potentially fatal disease caused by a variant in the transthyretin (*TTR*) gene[1–5]
- hATTR amyloidosis is a multisystem disease with a heterogeneous clinical presentation
  - The majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[6–9]
  - Diagnosis is difficult and often delayed[10,11]
  - Monitoring of disease progression and treatment response is challenging[12–16]
- Identification of reliable biomarkers would be beneficial in order to facilitate early diagnosis of hATTR amyloidosis, and to monitor disease progression and treatment response

Neurofilament Light Chain (NfL)

- NfL is a known biomarker for nerve damage in multiple diseases[17,18]
- Elevated plasma NfL levels in many diseases presenting with neuropathy, including hATTR amyloidosis, are presumed to result from NfL release following neuroaxonal injury[19–28]

Abbreviations: ATTRv, hereditary transthyretin (v for variant); hATTR, hereditary transthyretin-mediated; NfL, neurofilament light chain; TTR, transthyretin.

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Introduction

Patisiran

- An RNAi therapeutic that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing variant and wild-type (wt) TTR proteins[1,2]
  - Approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy[3,4,a]
  - Efficacy and safety of patisiran were demonstrated in the Phase 3 APOLLO study (NCT01960348), where patisiran halted or reversed polyneuropathy (mNIS+7) and improved quality of life (Norfolk QOL-DN) in the majority of patients[5]
  - During APOLLO, treatment with patisiran also led to a decrease from baseline in NfL levels, whereas an increase from baseline was seen with placebo at 18 months[6]

Objective

- To evaluate long-term changes in NfL levels in patients treated with patisiran through 36 months of the patisiran Global OLE

[a]Specific indications vary by country/region.

Abbreviations: hATTR, hereditary transthyretin-mediated; mNIS+7, modified Neuropathy Impairment Score+7; NfL, neurofilament light chain; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; OLE, open-label extension; TTR, transthyretin; RNAi, RNA interference; wt, wild-type.

References: 1. Coelho et al. *N Engl J Med* 2013;369:819–29; 2. Suhr et al. *Orphanet J Rare Dis* 2015;10:109; 3. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. 2020. Available from: https://www.alnylam.com/wp-content/uploads/pdfs/ONPATTRO-Prescribing-Information.pdf (accessed May 27, 2020); 4. European Medicines Agency. Summary of product characteristics: ONPATTRO®. 2020. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf (accessed May 27, 2020); 5. Adams et al. *N Engl J Med* 2018;379:11–21; 6. Ticau et al. *Neurology* 2021;96:e412–22;

Methods

Global OLE Study Design

- Analysis of data from the Global OLE was conducted in 3 groups based on treatment in the APOLLO and Phase 2 OLE parent studies (**Figure 1**)
  - **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
- This analysis is based on a 36-month data cut-off point (January 27, 2021)
- All patients in the Global OLE received patisiran 0.3 mg/kg intravenously every 3 weeks, with plans to continue doing so for up to 5 years

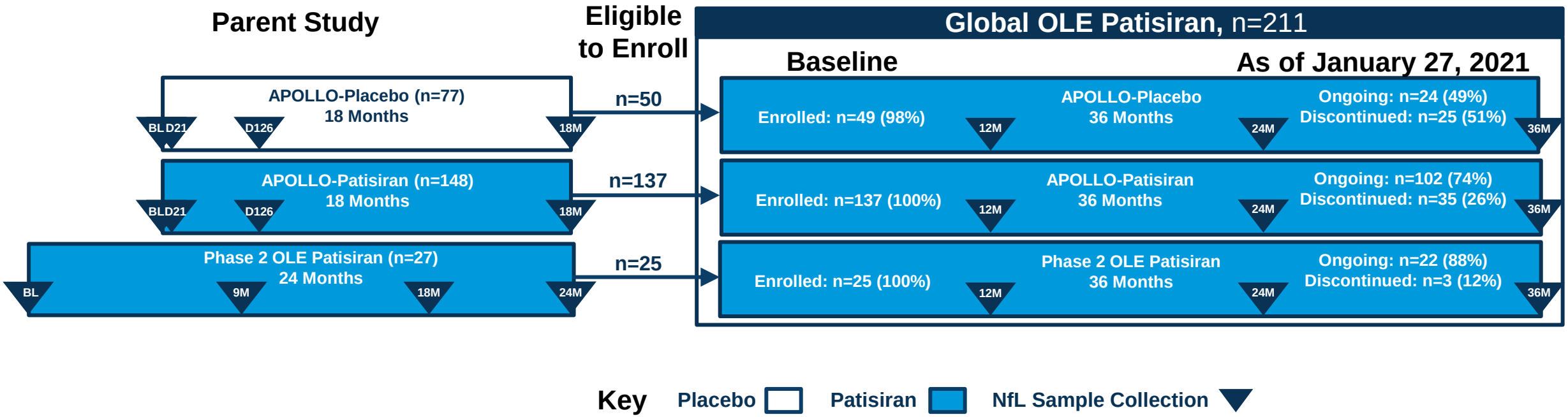
NfL Measurements

- The NfL analysis was post hoc
- NfL plasma levels were measured using the Quanterix Simoa platform in patients during the parent studies, and at 12, 24, and 36 months in the Global OLE
- A single NfL measurement was also made in healthy controls age and sex matched with the APOLLO population (n=55)

Abbreviations: NfL, neurofilament light chain; OLE, open-label extension.

Methods

Figure 1. Study Design



Abbreviations: BL, baseline; D, day; M, month; OLE, NfL, neurofilament light chain; open-label extension.

Results

Demographic and Disease Severity at Global OLE Baseline

- At Global OLE baseline, patients from the Phase 2 OLE had less advanced disease than either APOLLO group, and a higher proportion had the V30M genotype[1]
- The APOLLO-placebo group had characteristics associated with more severe disease, including a lower proportion of patients who were able to walk unaided[1]

Table 1. Global OLE Baseline Characteristics

	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
Male, n (%)	37 (76)	102 (74)	17 (68)	156 (74)
Mean time since hATTR 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)
Serum TTR, mean (SD)	**189 (59)**	**55 (47)**	**81 (52)**	89 (75)
mNIS+7 score[b], mean (min–max)	**101 (22–190)**	**75 (8–199)**	**46 (3–128)**	77 (3–199)
Norfolk QOL-DN score[c], mean (SD)	**73 (28)**	**55 (31)**	NA[d]	59 (31)
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)

Bold text highlights certain differences at baseline 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. [c]Norfolk QOL-DN, range −4 to 136; higher score indicates worsening QOL. [d]The Phase 2 OLE study did not assess Norfolk QOL-DN

Abbreviations: hATTR, hereditary transthyretin-mediated; mNIS+7, modified Neuropathy Impairment Score+7; NA, not available; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; OLE, open-label extension; PND, polyneuropathy disability; QOL, quality of life; SD, standard deviation; TTR, transthyretin.

Reference: 1. Adams et al. *Lancet Neurology* 2021;20:49–59

Results

NfL Levels in APOLLO and the Global OLE

- At APOLLO baseline, mean (SE) NfL levels were comparable between the patisiran (72.0 [4.3] pg/mL) and placebo groups (63.2 [4.7] pg/mL)[1] (**Table 2**)
- A significant difference between the groups was first apparent at Day 126 of APOLLO (mean [SE] 82.2 [5.0] pg/mL [APOLLO-placebo], 51.6 [2.9] pg/mL [APOLLO-patisiran]; estimated difference [95% CI] 30.6 pg/mL [21.8, 42.0])[1] (**Table 2, Figure 2**)
- In the APOLLO-placebo group:
  - NfL levels significantly increased during the APOLLO study while patients were receiving placebo[1]
  - Upon initiation of patisiran in the Global OLE, the APOLLO-placebo group experienced a significant reduction in NfL levels through 36 months ($p<0.0001$), to a similar level as that of the APOLLO-patisiran group
- In the APOLLO-patisiran group:
  - NfL levels significantly decreased following treatment with patisiran in the APOLLO study[1]
  - Reduction in NfL levels was maintained following 36 months of additional patisiran treatment in the Global OLE

Abbreviations: NfL, neurofilament light chain; OLE, open-label extension; SE, standard error.

References: 1. Ticau et al. Poster at the American Academy of Neurology (AAN) Virtual Annual Meeting April 17–22, 2021.

Results

Table 2. NfL Levels from Parent Study Baseline in Patients in APOLLO and Global OLE

Timepoint	APOLLO-Placebo		APOLLO-Patisiran		Healthy Controls[a]	
	n	Mean (SE), pg/mL	n	Mean (SE), pg/mL	n	Mean (SE), pg/mL
APOLLO Baseline	47	63.2 (4.7)	111	72.0 (4.3)	55	16.3 (1.6)
APOLLO Day 21	46	66.9 (4.9)	104	73.8 (4.7)		
APOLLO Day 126	47	82.2 (5.0)	106	51.6 (2.9)		
APOLLO 18 Months/Global OLE Baseline	47	99.5 (8.8)	111	48.8 (2.8)		
Global OLE 12 Months	28	64.0 (9.7)	76	50.1 (3.7)		
Global OLE 24 Months	24	42.8 (5.0)	87	44.0 (3.0)		
Global OLE 36 Months	15	39.9 (5.1)	72	44.8 (2.7)		

[a]Healthy controls were age and sex matched to the APOLLO population and were not matched to the Phase 2 OLE population

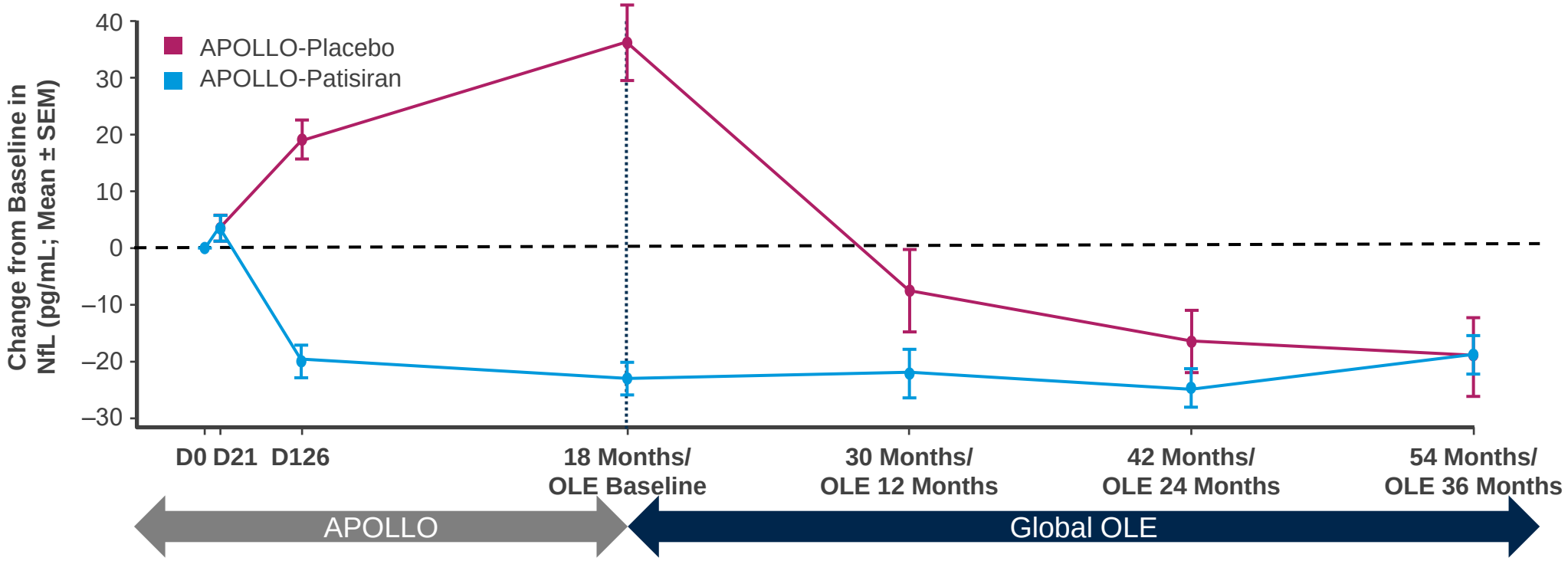
Abbreviations: NfL, neurofilament light chain; OLE, open-label extension; SE, standard error.

Results

NfL Levels in APOLLO and the Global OLE

- At Global OLE 36 months, NfL levels remained significantly lower than parent study baseline for both the APOLLO-placebo group (p<0.02) and the APOLLO-patisiran group (p<0.0001) (**Figure 2**)

Figure 2. Change in NfL Levels from Parent Study Baseline in Patients in APOLLO and Global OLE



Abbreviations: D, day; NfL, neurofilament light chain; OLE, open-label extension; SEM, standard error of the mean.

Results

NfL Levels in Phase 2 OLE and the Global OLE

- In the Phase 2 OLE, NfL levels decreased from baseline to 24 months with patisiran treatment[1] (**Figure 3, Table 3**)
- At the end of Global OLE 36 months, NfL levels in Phase 2 OLE patisiran patients remained lower than parent study baseline
  - Throughout the parent Phase 2 OLE study and for 36 months during the Global OLE, NfL levels were lower than both APOLLO groups

Table 3. NfL Levels from Parent Study Baseline in Patients in Phase 2 OLE and Global OLE

	Phase 2 OLE Patisiran		Healthy Controls[a]	
Timepoint	**n**	**Mean (SE) (pg/mL)**	**n**	**Mean (SE), pg/mL**
Phase 2 Baseline	26	32.9 (2.8)	55	16.3 (1.6)
Phase 2 Month 9	25	24.5 (3.3)		
Phase 2 Month 18	25	26.1 (3.2)		
Phase 2 Month 24/Global OLE Baseline	25	29.6 (4.0)		
Global OLE Month 12	23	26.0 (3.4)		
Global OLE Month 24	23	23.0 (2.7)		
Global OLE Month 36	19	26.1 (2.7)		

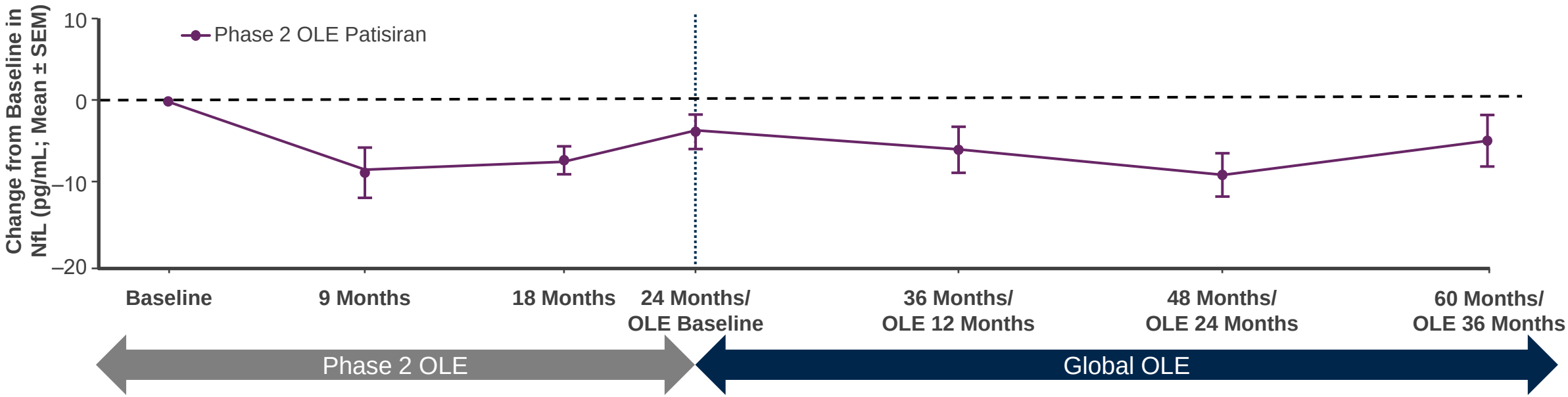
[a]Healthy controls were age and sex matched to the APOLLO population and were not matched to the Phase 2 OLE population

Abbreviations: NfL, neurofilament light chain; OLE, open-label extension; SE, standard error.

Reference: 1. Ticau et al. Poster at the American Academy of Neurology (AAN) Virtual Meeting April 17-22, 2021

Results

Figure 3. Change in NfL Levels from Parent Study Baseline in Patients in Phase 2 OLE and Global OLE



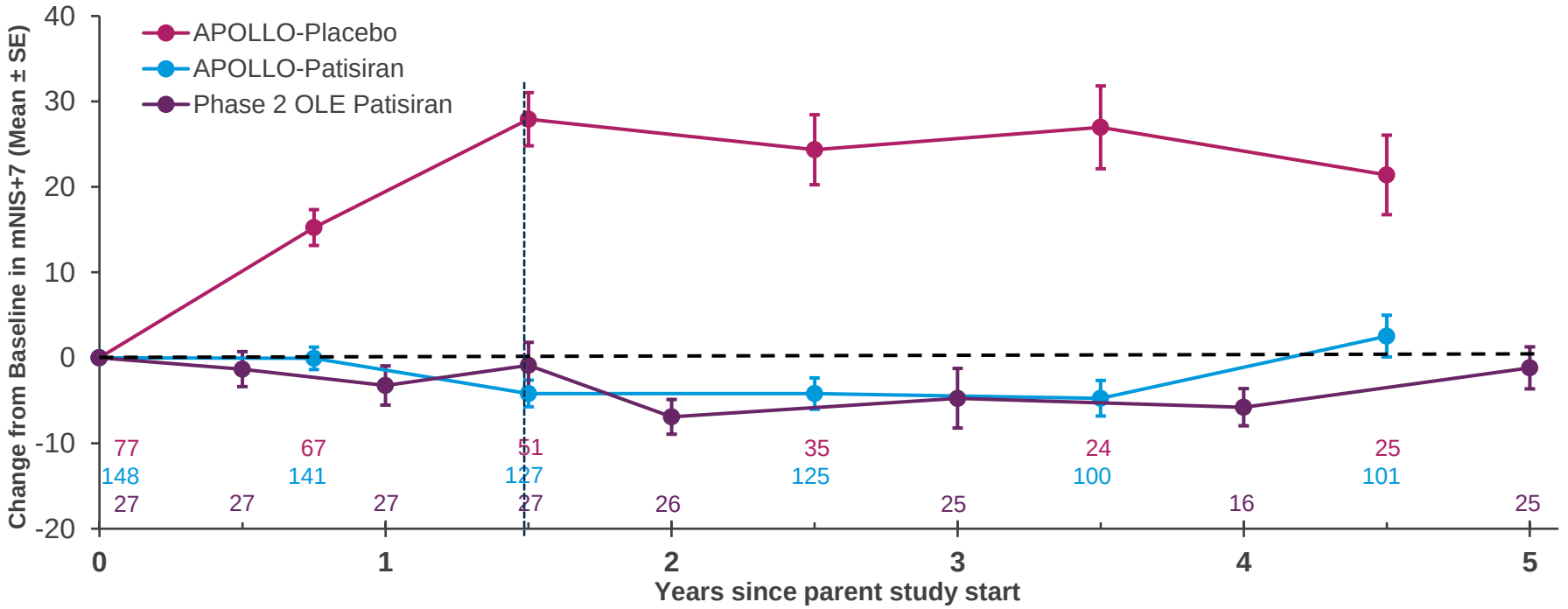
Abbreviations: NfL, neurofilament light chain; OLE, open-label extension; SEM, standard error of the mean.

Results

Durable Efficacy of Patisiran at Global OLE 36 Months (Figure 4)

- In the APOLLO-patisiran and Phase 2 OLE patisiran groups, mNIS+7 remained stable from parent study baseline; mean (SE) change from parent study baseline was 2.53 (2.45) and –1.18 (2.46), following 4.5 and 5 years of treatment, respectively
- In the APOLLO-placebo group, a decrease in mNIS+7 was observed from Global OLE baseline (mean [SE] change at 36 months: –5.99 [3.60]); however, patients did not return to parent study baseline

Figure 4. Change in mNIS+7 from Parent Study Baseline



Mean (SD) mNIS+7 at parent study baseline was 74.6 (37.0) for the APOLLO-placebo group, 80.9 (41.5) for the APOLLO-patisiran group, and 53.0 (35.6) for the Phase 2 OLE patisiran group

Abbreviations: mNIS+7, modified Neuropathy Impairment Score+7; OLE, open-label extension; SD, standard deviation; SE, standard error.

Summary

- In the APOLLO, Phase 2 open-label extension (OLE), and Global OLE studies, treatment with patisiran lowered neurofilament light chain (NfL) levels in patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy
  - This reduction in NfL levels was maintained to 36 months in the Global OLE for all groups
- In the APOLLO study, an increase in modified Neuropathy Impairment Score+7 (mNIS+7) was associated with an increase in NfL levels in the placebo group, but upon initiation of patisiran treatment in the Global OLE, mNIS+7 stabilized and NfL levels decreased to a level significantly lower than Global OLE baseline and parent study baseline at Global OLE 36 months
- Alongside sustained reduction in NfL levels, treatment with patisiran continued to prevent polyneuropathy progression in the APOLLO-patisiran and Phase 2 OLE patisiran groups at Global OLE 36 months, which constitutes a total treatment duration of 4.5 and 5 years, respectively
  - Halting of disease progression among APOLLO-placebo patients upon initiation of patisiran in the Global OLE was also sustained to 36 months
- These results demonstrate the potential utility of NfL as a biomarker of active nerve damage in hATTR amyloidosis with polyneuropathy, and support continued evaluation of NfL to monitor disease progression and treatment response as an adjunct to clinical assessments

Abbreviations: hATTR, hereditary transthyretin-mediated; mNIS+7, modified Neuropathy Impairment Score+7; NfL, neurofilament light chain; OLE, open-label extension.

Disclosures

- **Disclosures:** EA, ST, and PN are employed by Alnylam Pharmaceuticals, and report ownership of Alnylam Pharmaceuticals shares. MP reports participation in clinical trials sponsored by Akcea, Alnylam Pharmaceuticals, and Pfizer, and consultancy fees from Akcea, Alnylam Pharmaceuticals, Biogen-Idec, Pfizer, and Vertex Pharmaceuticals. DA reports participation in clinical trials sponsored by Akcea and Alnylam Pharmaceuticals, and consultancy fees from Alnylam Pharmaceuticals, Eidos, and Pfizer. MMR reports participation in a clinical trial sponsored by Ionis, and consultancy fees from Akcea, Alnylam Pharmaceuticals, and Ionis

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Abbreviations: GPP3, Good Publication Practice version 3.