Patisiran Global Open-Label Extension Study at 36 Months: Effect of Long-Term Treatment on Mortality and Ambulatory Function in Patients with hATTR Amyloidosis with Polyneuropathy

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September 4–8, 2022 || XVIII Meeting of the International Society of Amyloidosis (ISA) 2022

Oral Presentation OP044

Disclosures

Jonas Wixner, MD PhD

Relationships and Activities	Disclosure
Research Support	PI for trials by Akcea Therapeutics, Alnylam Pharmaceuticals, and Pfizer Inc., and SI for a trial by Intellia Therapeutics
Advisory Committee	Akcea Therapeutics, Alnylam Pharmaceuticals, and Pfizer Inc.
Consultant	Akcea Therapeutics, Alnylam Pharmaceuticals, Pfizer Inc.

Background and Rationale

hATTR Amyloidosis, also Known as ATTRv Amyloidosis

- A debilitating and fatal disease caused by variants in the *TTR* gene[1–5]

Disease Progression (Ambulation and Survival)

- Polyneuropathy is rapidly progressive without treatment; PND score worsens approximately every 18 months in patients with late-onset V30M and non-V30M disease,[6,7] and patients with early-onset V30M disease decline more slowly[6,8]
- In a study in patients of similar age and disease severity to those in the patisiran global OLE study (NCT02510261), median survival for untreated patients was 4.7 years following diagnosis[9]
  - Survival is further reduced in patients presenting with cardiomyopathy (median 3.4 years)[10] and patients with late-onset vs early-onset V30M disease[6,7]

Patisiran

- An RNAi therapeutic that reduces serum TTR levels by inhibiting hepatic synthesis of variant and wild-type TTR[11,12]
  - Approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy[13,14,a]
  - Efficacy and safety of patisiran were demonstrated in the Phase 3 APOLLO study,[b] where patisiran was able to halt or reverse polyneuropathy and improve QOL in the majority of patients[15]

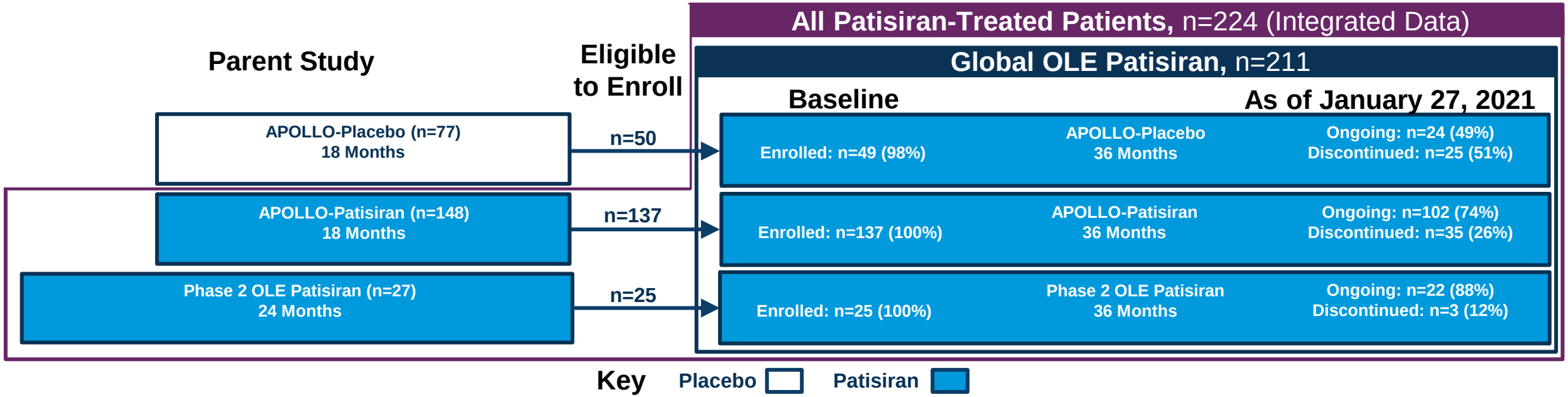
Objective

To describe the interim 36-month mortality and ambulatory status for patients with hATTR amyloidosis with polyneuropathy in the ongoing patisiran Global OLE study

[a]Specific indications vary by country/region. [b]NCT01960348. **Abbreviations**: ATTRv, hereditary transthyretin (v for variant); hATTR, hereditary transthyretin-mediated; OLE, open-label extension; PND, polyneuropathy disability; QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin. **References**: 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. Mariani et al. *Ann Neurol* 2015;78:901–16; 7. Koike et al. *J Neurol Neurosurg Psychiatry* 2012;83:152–8; 8. Coutinho et al. *Amyloid and Amyloidosis* 1980;88–98; 9. Swiecicki et al. *Amyloid* 2015;22:123–31; 10. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 11. Coelho et al. *N Engl J Med* 2013;369:819–29; 12. Suhr et al. *Orphanet J Rare Dis* 2015;10:109; 13. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use; 14. 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 May 2022); 15. Adams et al. *N Engl J Med* 2018;379:11–21

Global OLE Study Design

- All patients received patisiran 0.3 mg/kg IV q3w, with plans to continue doing so for up to 5 years
- Three groups were analyzed based on patient enrollment and treatment in the parent studies at the Month 36 data cut-off (2021 January 27)
- At Month 36, the maximum duration of patisiran treatment varied by group
  - APOLLO-placebo: 36 months
  - APOLLO-patisiran: 54 months
  - Phase 2 OLE patisiran: 60 months



Abbreviations: IV, intravenous; OLE, open-label extension; q3w, every 3 weeks

Earlier Treatment Is Associated with Lower Disease Severity at Global OLE Baseline

- At Global OLE baseline, patients had a wide spectrum of disease severity[1]
  - The APOLLO-placebo group had characteristics associated with more severe disease, reflecting disease progression while on placebo in the parent study, and patients in the Phase 2 OLE patisiran group had the least advanced disease

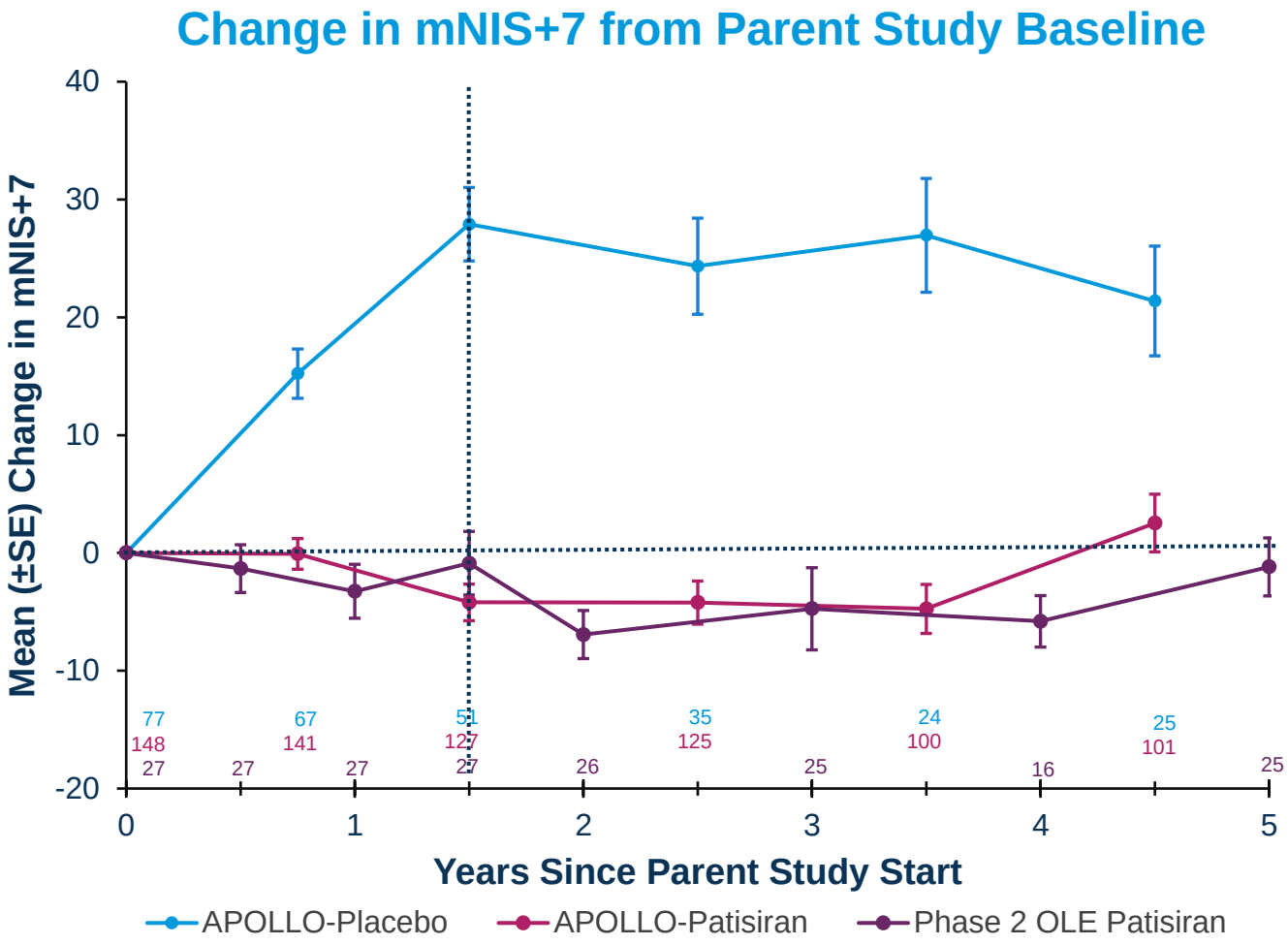
	APOLLO-Placebo (n=49)	APOLLO-Patisiran (n=137)	Phase 2 OLE Patisiran (n=25)	Global OLE Total Patisiran (n=211)
Median age, years	66	63	65	64
Male, n (%)	37 (76)	102 (74)	17 (68)	156 (74)
Mean time since hATTR amyloidosis diagnosis to first patisiran dose,[a] years (range)	**4.5 (2–18)**	2.5 (0–21)	2.8 (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)
NT-proBNP, ng/L, median (range)	**868 (56–15,101)**	**375 (21–10,282)**	**166 (5–1,897)**	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 certain 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. [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; LV, left ventricular; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NA, not applicable; NT-proBNP, *N*-terminal prohormone of brain-type natriuretic peptide; OLE, open-label extension; PND, polyneuropathy disability; QOL, quality of life SD, standard deviation; TTR, transthyretin. **Reference:** 1. Adams et al. *Lancet Neurol* 2021;20:49–59

Durable Efficacy of Patisiran at Global OLE Month 36

- 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 following initiation of patisiran; mean (SE) change from Global OLE baseline was –5.99 (3.60)
  - However, patients did not return to parent study baseline



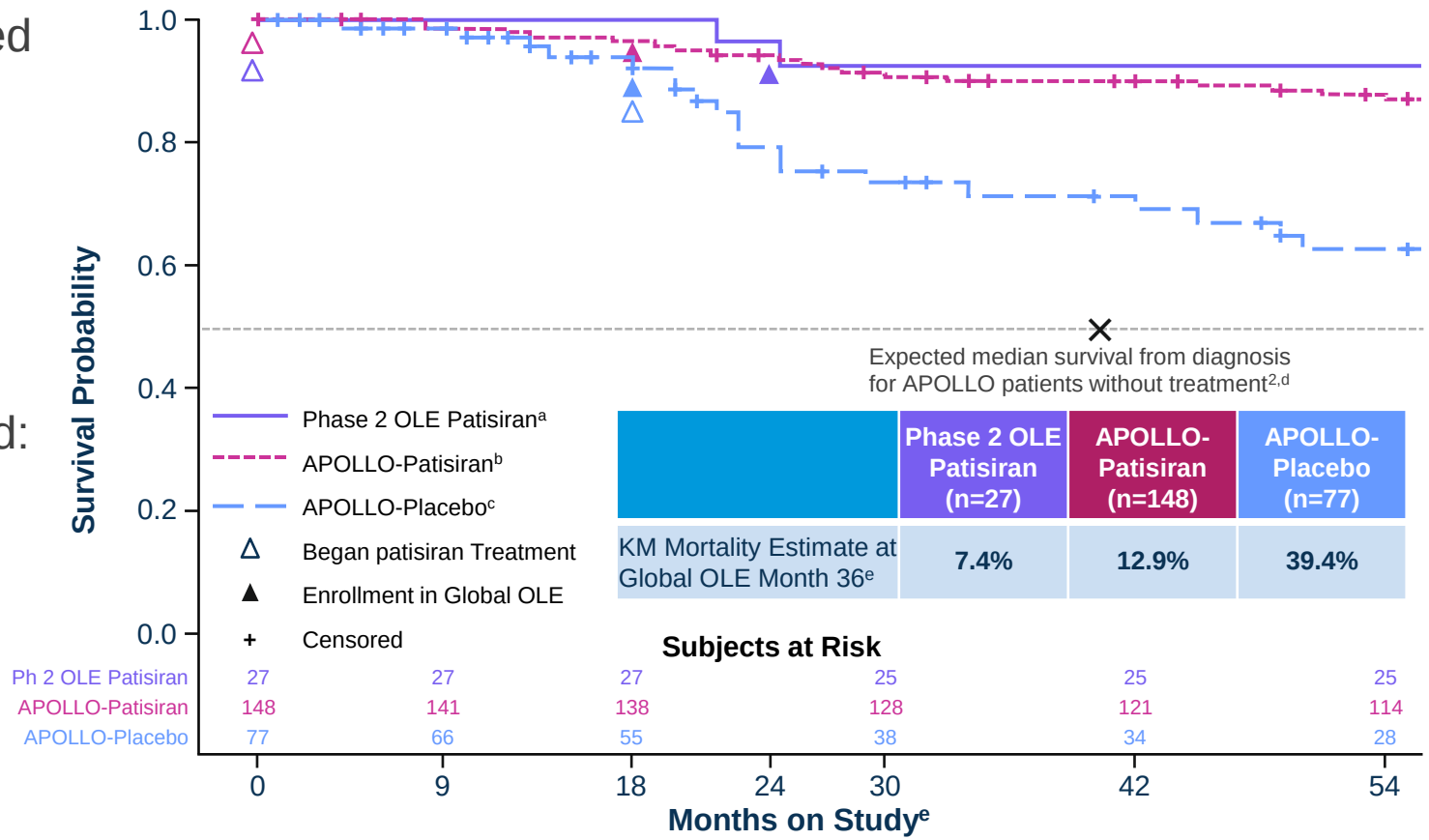
Mean (SD) mNIS+7 at parent study baseline was 74.6 (37.0) for the APOLLO-placebo group, 80.9 (41.5) for the APOLLO-patisiran group, and 53.0 (35.6) for the Phase 2 OLE patisiran group. **Abbreviations:** mNIS+7, modified Neuroimpairment Score+7; OLE, open-label extension; SE, standard error

Earlier Treatment is Associated with Lower Mortality

- Patients in the APOLLO-patisiran and Phase 2 OLE patisiran groups who received patisiran in their parent studies had:
  - Lowest disease burden at Global OLE baseline[1]
  - Lowest mortality rates

- Patients in the APOLLO-placebo group had:
  - Highest disease burden at Global OLE baseline[1]
  - Highest mortality rate that appeared to stabilize 6 months after treatment onset

Kaplan–Meier Product-Limit Survival Estimates



	Phase 2 OLE Patisiran (n=27)	APOLLO-Patisiran (n=148)	APOLLO-Placebo (n=77)
KM Mortality Estimate at Global OLE Month 36[e]	7.4%	12.9%	39.4%

[a]The Phase 2 OLE patisiran group received patisiran in the Phase 2 OLE for 24 months and continued patisiran in the global OLE. [b]APOLLO-patisiran received patisiran in APOLLO for 18 months and continued patisiran in the global OLE. [c]APOLLO-placebo received placebo in APOLLO for 18 months and started patisiran in the global OLE. [d]APOLLO patients were diagnosed 16.8 months prior to study baseline. Median survival from diagnosis of 4.7 years from hATTR amyloidosis diagnosis based on a natural history study of 266 patients. [e]Until censored or died. Patients were censored at the study withdrawal, 90 days past the last dose of patisiran, or at the last known alive date on or prior to data cut-off (January 27, 2021). Counting deaths within 90 days of last dose of study drug continues an established convention for patisiran mortality rates. **Abbreviations:** hATTR, hereditary transthyretin mediated; K-M, Kaplan-Meier; OLE, open-label extension. **References:** 1. Adams et al. *Lancet Neurol* 2021;20:49–59; 2. Swiecicki et al. *Amyloid* 2015;22:123–31

Risk Factors for Mortality in the Global OLE

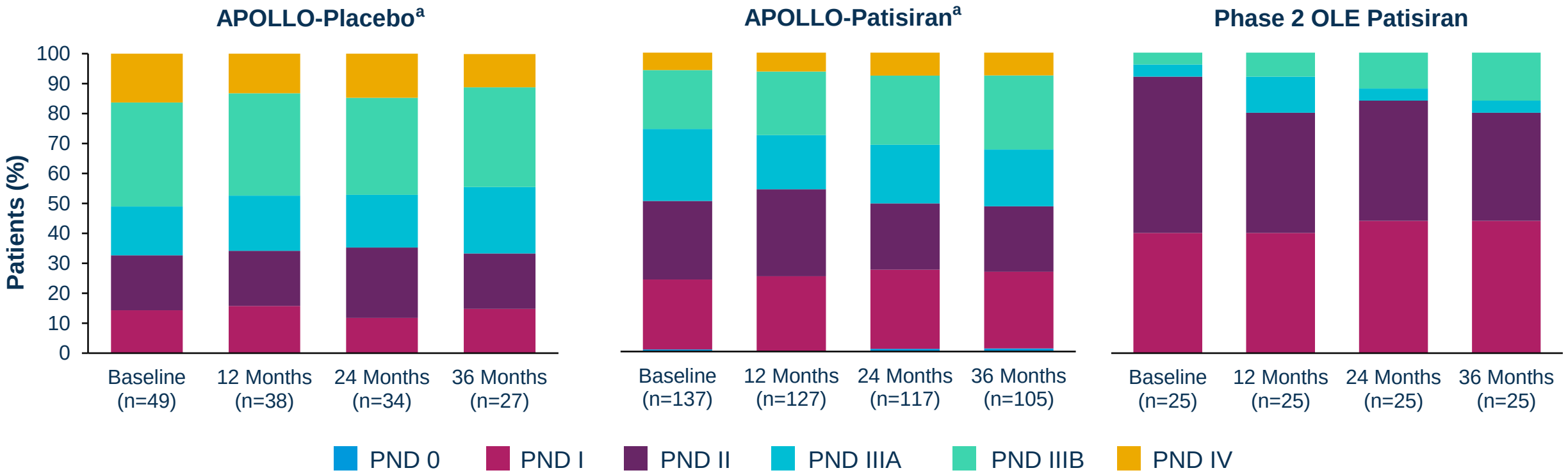
- Analysis of all patisiran-treated patients by potential risk factors for survival demonstrated a range of disease severity at first patisiran dose (data on file)
- Randomization to placebo in the parent study, NT-proBNP >3000 ng/L, and NYHA Class >1 were independent risk factors for mortality
- Earlier treatment and less advanced cardiac disease had a significant impact on survival

Characteristics at First Dose of Patisiran	All Patisiran-Treated Patients (n=224)[a]	
	Hazard Ratio (95% CI)	P-value
Parent Study Treatment[b]		
Placebo vs Patisiran	6.50 (2.82, 14.97)	**<0.0001**
NT-proBNP		
>3000 ng/L vs ≤3000 ng/L	7.52 (2.93, 19.28)	**<0.0001**
NYHA Classification		
II/III/IV vs I	2.55 (1.10, 5.89)	**0.0286**
Genotype		
Non-V30M vs V30M	1.78 (0.83, 3.84)	0.1401
FAP Stage		
3 vs 1/2	1.97 (0.63, 6.16)	0.2421
Mean LV Wall Thickness, cm		
≥1.3 cm vs <1.3 cm	1.02 (0.29, 3.61)	0.9728

[a]Multivariate Cox proportional hazards analysis was conducted at 36-month data cut-off using factors that were significant in a univariate model. In the multivariate Cox regression model, all 6 terms were included as effects. Survival time was calculated as time from first dose of patisiran to death or last known alive date on or before data cut-off (January 27, 2021). [b]This variable shows the effect of delayed treatment onset of 18 months. **Abbreviations:** CI, confidence interval; FAP, familial amyloid polyneuropathy; LV, left ventricular; NT-proBNP, *N*-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association, OLE, open-label extension

Ambulatory Function Is Maintained After Initiation of Patisiran

- Most patients remained ambulatory (PND <IV) and the majority of patients stabilized or improved in PND score over time in the Global OLE in all 3 groups
  - Greater proportions of the APOLLO-patisiran and Phase 2 OLE patisiran groups (55.5% and 80.0%, respectively) stabilized or improved in PND score from Global OLE baseline than the APOLLO-placebo group (42.9%)
- Patients in the Phase 2 OLE patisiran group, who had the least advanced disease at Global OLE baseline, had the best ambulatory function at Month 36 in the Global OLE (most patients at PND ≤II)



[a]Missing patients excluded; patients with no post-baseline PND assessments were counted as missing. **Abbreviations**: OLE, open-label extension; PND, polyneuropathy disability

Patisiran Global OLE Safety

- The majority of patients enrolled in the Global OLE have received patisiran for at least 54 months; some have received patisiran for up to 7 years
- The majority of AEs were mild or moderate in severity
- The most common treatment-related AEs were IRRs
  - IRRs were mild or moderate and occurred more often in patients newly-treated with patisiran (APOLLO-placebo) and decreased in frequency over time, consistent with APOLLO
  - There were no discontinuations due to IRRs
- Deaths were reported in 35 patients in the Global OLE
  - The proportion of deaths in the APOLLO-placebo group was higher than in the APOLLO-patisiran and Phase 2 OLE patisiran groups
- The safety profile of patisiran was acceptable and consistent with prior Global OLE analyses,[1,2] suggesting that it remains stable over time

Exposure and Overall Safety in the Global OLE

Patients with ≥1 Event, n (%)	APOLLO-Placebo (n=49)	APOLLO-Patisiran (n=137)	Phase 2 OLE Patisiran (n=25)	Global OLE Total Patisiran (n=211)
Exposure in Global OLE				
Mean exposure, months (range)	32.5 (1.3–61.3)	42.3 (1.3–60.7)	56.7 (45.6–60.1)	41.7 (1.3–61.3)
Cumulative no. of doses	2224	8188	1959	12371
Safety				
AE	49 (100)	137 (100)	25 (100)	211 (100)
Severe AE	30 (61.2)	56 (40.9)	7 (28.0)	93 (44.1)
SAE	37 (75.5)	72 (52.6)	12 (48.0)	121 (57.3)
IRR	13 (26.5)	16 (11.7)	4 (16.0)	33 (15.6)
AE leading to study withdrawal	19 (38.8)	14 (10.2)	0	33 (15.6)
Death[a]	18 (36.7)	16 (11.7)	1 (4.0)	35 (16.6)

Data as of interim cut-off 27 January, 2021. [a]All deaths summarized, including deaths due to AEs that are not treatment emergent. **Abbreviations:** AE, adverse event; IRR, infusion-related reaction; OLE, open-label extension; SAE, serious adverse event. **References:** 1. Adams et al. *Lancet Neurol* 2021;20:49–59; 2. Adams et al. Oral presentation 2020 ISA Online event

Summary

- At Month 36 in the ongoing 5-year Global OLE, treatment with patisiran continued to prevent polyneuropathy progression in the APOLLO-patisiran and Phase 2 OLE patisiran groups
  - Halting of disease progression among APOLLO-placebo patients upon initiation of patisiran in the Global OLE was sustained to Month 36

- Patients who received patisiran treatment earlier, in the APOLLO-patisiran and Phase 2 OLE patisiran groups, experienced greater survival

- The therapeutic benefit of patisiran on ambulatory function, first demonstrated in APOLLO, was sustained and was greatest in groups that initiated patisiran treatment earlier with a lower disease burden

- While all patients experienced clinical benefit with patisiran treatment, delaying treatment resulted in lower survival and worse ambulatory function, highlighting the substantial impact of earlier diagnosis and treatment with patisiran in patients with hATTR amyloidosis with polyneuropathy

Abbreviations: hATTR, hereditary transthyretin mediated; OLE, open-label extension

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the APOLLO, Phase 2 OLE, and Global OLE studies

Evaluation of Potential Risk Factors for Mortality at the First Dose of Patisiran

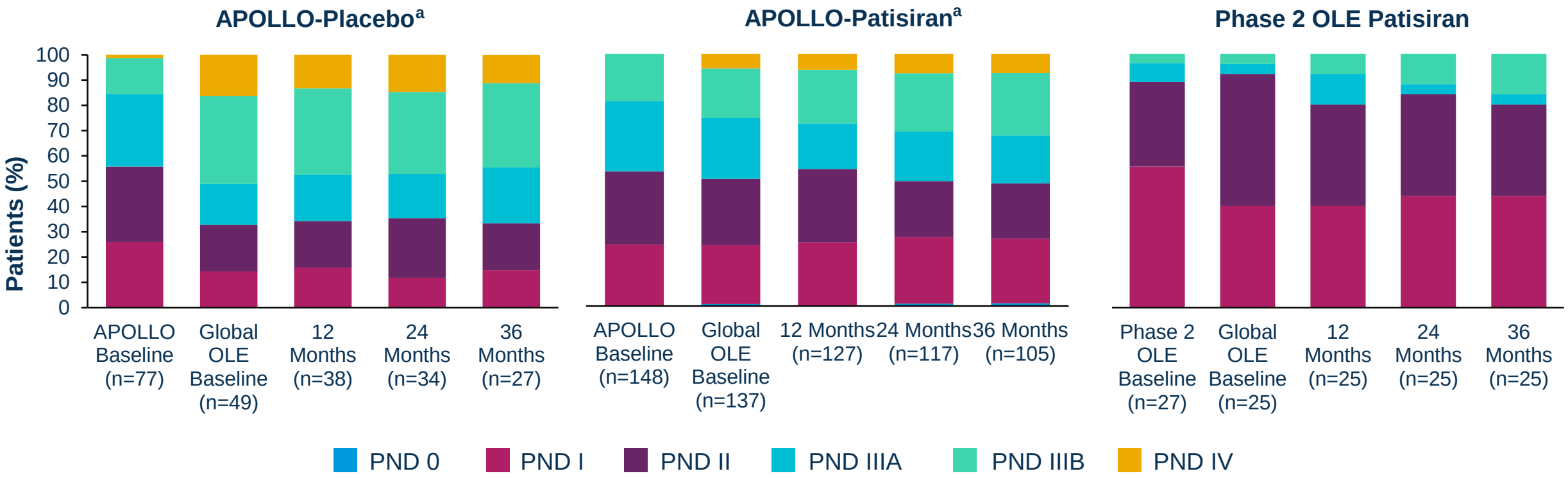
- Analysis of all patisiran-treated patients by potential risk factors for survival, demonstrated a range of disease severity at first patisiran dose

Characteristics at First Dose of Patisiran	All Patisiran-treated Patients (n=224)
NT-proBNP	
≤3000 ng/L	184 (82.1%)
>3000 ng/L	18 (8.0%)
Missing	22 (9.8%)
FAP Stage	
1	105 (46.9%)
2	111 (50.0%)
3	8 (3.6%)
Genotype	
Early onset V30M[a]	30 (13.4%)
Late onset V30M	70 (31.3%)
Not V30M	124 (55.4%)
LV wall thickness	
<1.3 cm	45 (20.1%)
≥1.3 cm	175 (78.1%)
Missing	4 (1.8%)
Age	
<65 years	122 (54.5%)
≥65 years	102 (45.5%)

Characteristics at First Dose of Patisiran	All Patisiran-treated Patients (n=224)
Age at disease onset	
<50 years	57 (25.4%)
≥50 years	140 (62.5%)
Missing[b]	27 (12.1%)
NYHA Classification	
I	111 (50.0%)
II	105 (46.9%)
III	4 (1.8%)
IV	2 (0.9%)
Missing	2 (0.9%)
Cardiac subpopulation[c]	
Yes	123 (54.9%)
No	101 (45.1%)
First treatment assignment	
Patisiran	175 (78.1)
Placebo	49 (21.9%)

[a]Identified as diagnosis or onset of earliest symptom related to amyloidosis at age <50 years. [b]Variable was not collected in the Phase 2 OLE. [c]Determined at baseline of parent study. **Abbreviations:** FAP, familial amyloid polyneuropathy; LV, left ventricular, NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association, OLE, open-label extension

Ambulatory Function From Parent Study to Global OLE Month 36



[a]Missing patients excluded; patients with no post-baseline PND assessments were counted as missing. **Abbreviations**: OLE, open-label extension; PND, polyneuropathy disability.