

Long-term Safety and Efficacy of Patisiran in Patients with hATTR Amyloidosis: Global OLE Study

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Dr. Michael Polydefkis reports the following disclosures as a consultant for Alnylam Pharmaceuticals, Ionis and Pfizer

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- **Rare, progressively debilitating, and fatal disease** caused by a mutation in the *TTR* gene that results in multisystem deposition of amyloid fibrils in nerves, heart, and gastrointestinal tract, leading to subsequent dysfunction across these multiple organs^{1–5}
 - The majority of patients develop a **mixed phenotype** of both polyneuropathy and cardiomyopathy^{6–9}
- Affects ~50,000 people worldwide⁵, with a **median survival of 4.7 years following diagnosis** and a reduced survival of 3.4 years for patients presenting with cardiomyopathy^{10–13}
 - Risk factors for poor prognosis include increasing age, non-V30M genotype with late-onset disease (>50 years), and presence of cardiac involvement^{11–13}
- Among published studies in patients with ATTR amyloidosis, the **exposure-adjusted mortality rate ranges from 6.8 to 29 deaths per 100 patient-years**^{12,14–17}

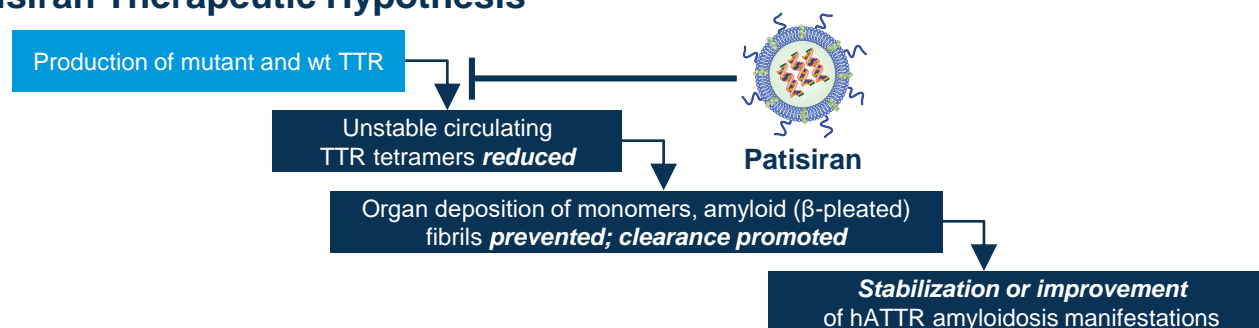
TTR, transthyretin

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. Castañón et al. *Heart Fail Rev* 2015;20:163–78; 11. Swiecicki et al. *Amyloid* 2015;22:123–31; 12. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 13. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 14. Maurer et al. *N Engl J Med* 2018;379:1007–16; 15. Ruberg et al. *Am Heart J* 2012;164:222–8 e1; 16. Berk et al. *JAMA* 2013;310:2658–67; 17. Arruda-Olson et al. *Amyloid* 2013;20:263–8

Patisiran: an RNAi Therapeutic

- Patisiran, a lipid nanoparticle-delivered RNAi therapeutic, reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing mutant and wt TTR proteins^{1,2}

Patisiran Therapeutic Hypothesis



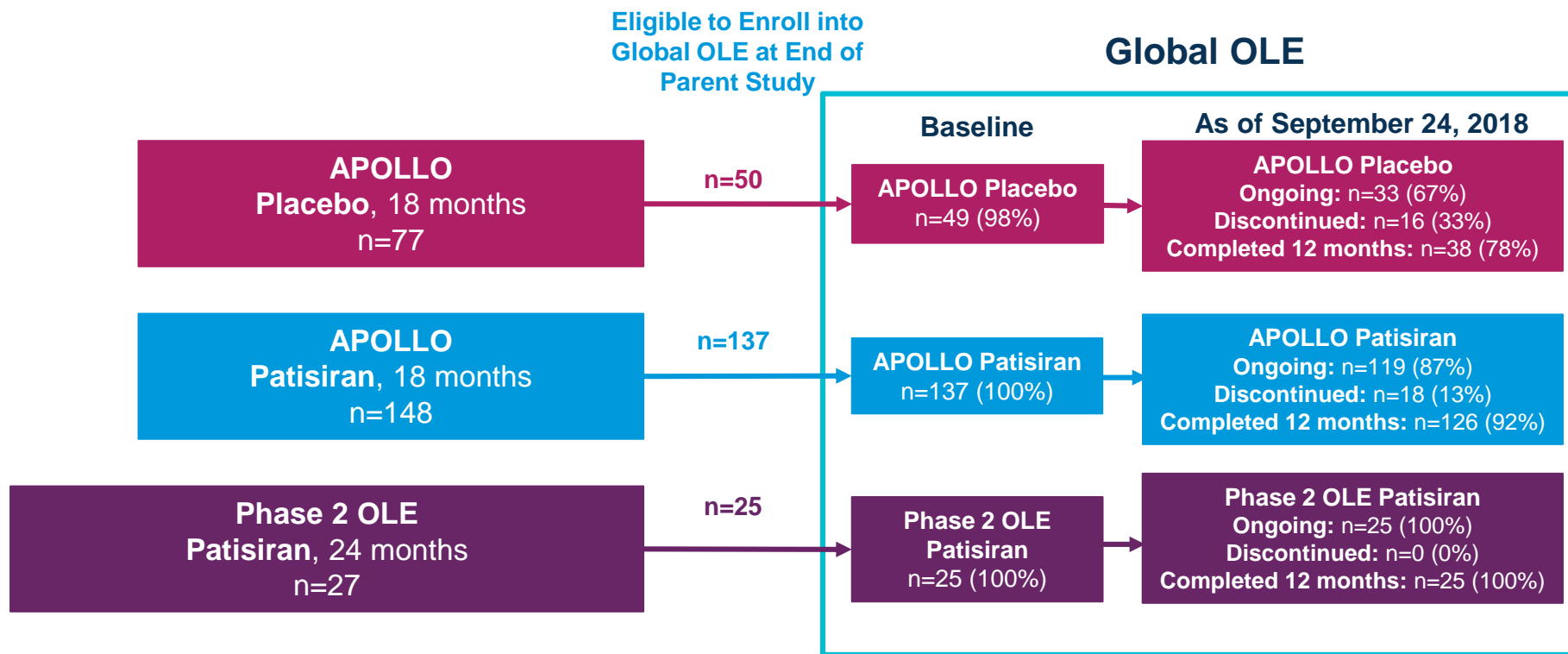
- Patisiran was investigated in a Phase 1 study in healthy volunteers³, and in patients with hATTR amyloidosis with polyneuropathy in a Phase 2 study,⁴ Phase 2 OLE study,^{5,6} and the pivotal Phase 3 APOLLO study⁷
- Patisiran is approved in the US for the treatment of the polyneuropathy of hATTR amyloidosis in adults, in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of hATTR amyloidosis with polyneuropathy⁸⁻¹⁰

EU, European Union; IV, intravenous; Open-label extension; RNAi, RNA interference; US, United States; wt, wild-type

1. Coelho et al. *N Engl J Med* 2013;369:819–29; 2. Suhr et al. *Orphanet J Rare Dis* 2015;10:109; 3. Coelho et al. *N Engl J Med* 2013;369:819–29; 4. Suhr et al. *Orphanet J Rare Dis* 2015;10:109; 5. Adams et al. *American Academy of Neurology (AAN) Congress* 2017. S27.004; 6. Alnylam Pharmaceuticals Inc. 2018. NCT01961921. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01961921?term=NCT01961921&rank=1>; 7. Adams et al. *N Engl J Med* 2018;379:11–21; 8. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf; 9. European Medicines Agency. Summary of product characteristics: 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf; 10. <http://investors.alnylam.com/news-releases/news-release-details/alnylam-announces-approval-japan-onpattro-treatment-hereditary>

Patisiran Global Open-Label Extension (OLE) Study

Study Design and Objectives



Objective: To describe the interim 12-month safety and efficacy data (as of September 24, 2018) for patients in the ongoing Global OLE study

Patisiran Global OLE Baseline

Broad Patient Population with a Wide Spectrum of Disease Severity

	APOLLO Placebo n=49	APOLLO Patisiran n=137	Phase 2 OLE Patisiran n=25	Global OLE Total n=211
Median age, years	66	63	65	64
Male, n (%)	37 (76)	102 (75)	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)	2.7 (1–8)	2.9 (0–21)
Genotype, n (%)				
V30M	24 (49)	56 (41)	18 (72)	98 (46)
Non-V30M	25 (51)	81 (59)	7 (28)	113 (54)
Region^b, n (%)				
North America	5 (10)	34 (25)	1 (4)	40 (19)
Western Europe	26 (53)	61 (45)	23 (92)	110 (52)
Rest of World	18 (37)	42 (31)	1 (4)	61 (29)

Bold text highlights specific baseline difference between groups

^aFirst patisiran dose could have been in the Phase 2 OLE, APOLLO, or Global OLE; integrated data across all patisiran-treated patients (APOLLO placebo n=49; APOLLO patisiran n=148; Phase 2 OLE n=27; total patisiran n=224)

^bNorth America: USA, CAN; Western Europe: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; Rest of World: Eastern Europe: BGR, CYP, TUR; Asia: JPN, KOR, TWN; Central and South America: MEX, ARG, BRA

Patisiran Global OLE Baseline

Baseline Disease Characteristics Demonstrate Higher Disease Burden in Patients with Delayed Patisiran Treatment

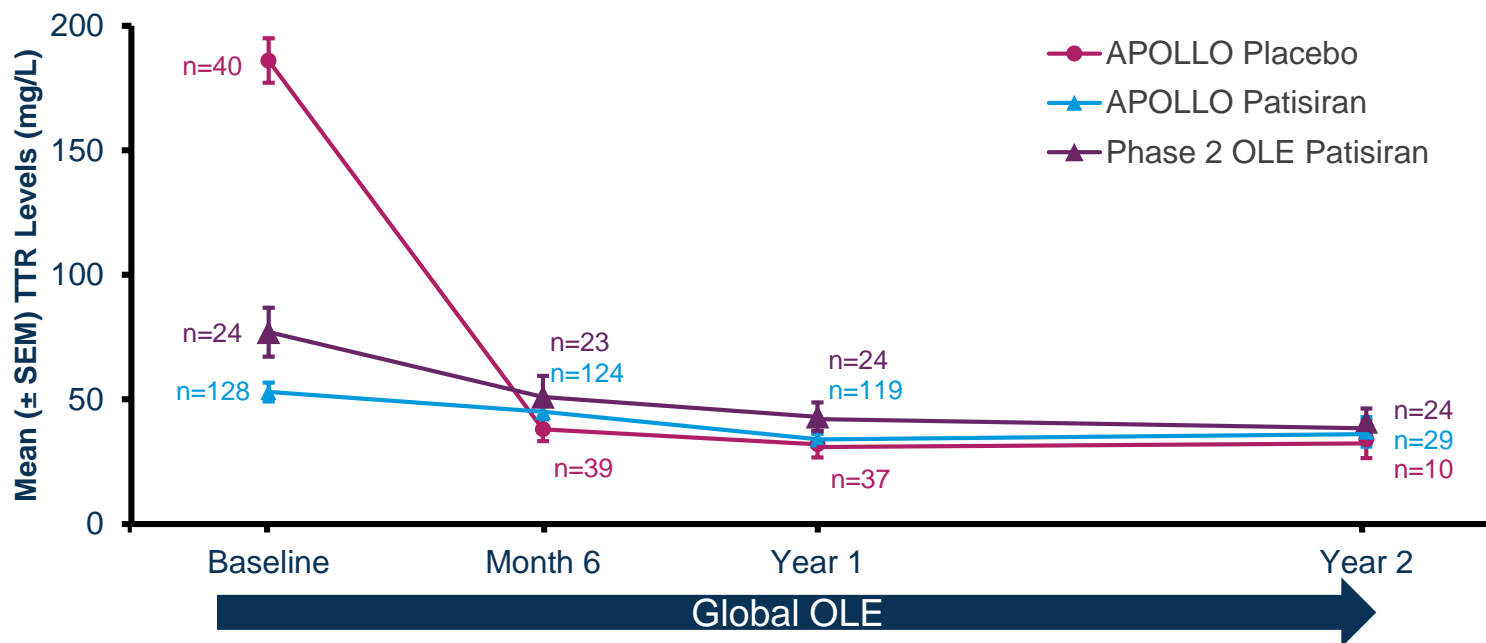
	APOLLO Placebo n=49	APOLLO Patisiran n=137	Phase 2 OLE Patisiran n=25	Global OLE Total n=211
PND score, n (%)				
0: no symptoms	0	1 (1)	0	1 (<1)
I: preserved walking, sensory disturbances	7 (14)	32 (23)	10 (40)	49 (23)
II: impaired walking but walk without stick/crutch	9 (18)	36 (26)	13 (52)	58 (27)
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)
	101	75	46	77
mNIS+7 score, mean (min, max)	(22, 190)	(8, 199)	(3, 128)	(3, 199)
NYHA classification, n (%)				
I: no symptoms	22 (45)	67 (49)	19 (76)	108 (51)
II: symptoms with ordinary physical activity	21 (43)	59 (43)	4 (16)	84 (40)
III: symptoms with less than ordinary physical activity	4 (8)	9 (7)	2 (8)	15 (7)
IV: symptoms at rest	2 (4)	2 (1)	0	4 (2)
	868	375	166	376
Median NT-proBNP, ng/L (range)	(56–15,101)	(21–10,282)	(5–1897)	(5–15,101)
Mean LV wall thickness, cm (SD)	1.5 (0.3)	1.5 (0.3)	1.2 (0.3)	1.5 (0.3)

Bold text highlights specific baseline difference between groups

Patisiran Global OLE Results

Durability of Reduction in Serum TTR Levels with Patisiran Treatment

Serum TTR Levels (mg/L) through 2 Years in the Global OLE



Robust, sustained reduction in mean serum TTR in the APOLLO placebo group upon treatment with patisiran in the Global OLE, with a mean (SD) TTR reduction of 79% (17%) at Month 6

Reduction in serum TTR levels maintained with patisiran treatment in the APOLLO and the Phase 2 OLE groups with continued dosing in the Global OLE

TTR assessment at first visit in the Global OLE did not need to be repeated if performed during the parent study within 45 days of the first dose in the Global OLE

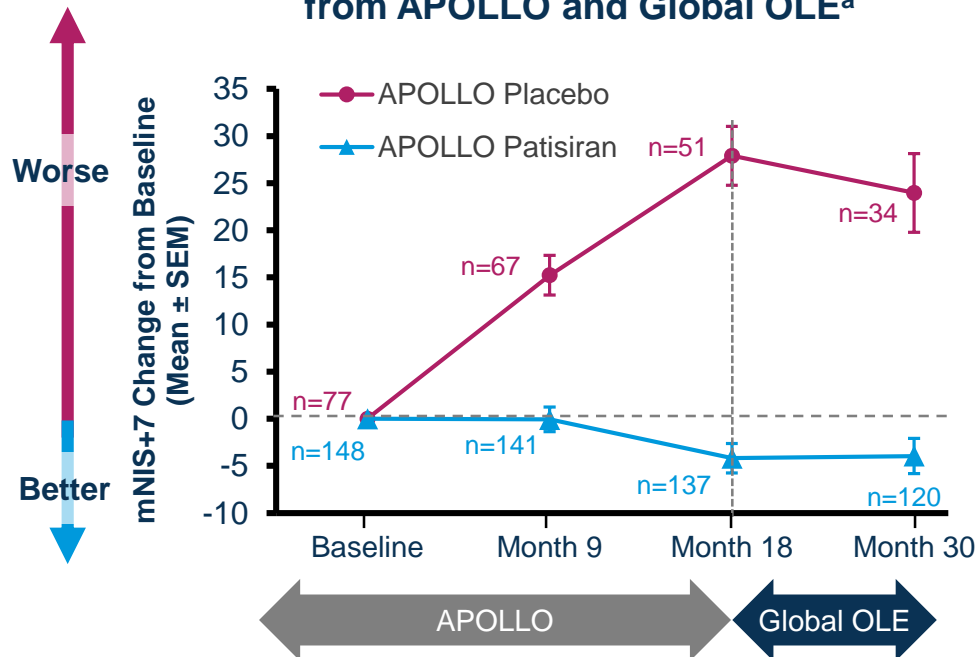
Note: PD analysis set includes all patients who received ≥1 dose of patisiran in this study and had both baseline and ≥1 post-baseline PD assessment; for a patient who received patisiran in the parent study, if >45 days elapsed between the last dose of patisiran in the parent study and the first dose of patisiran in this study, the patient was excluded from the PD analysis set

SEM, standard error of the mean

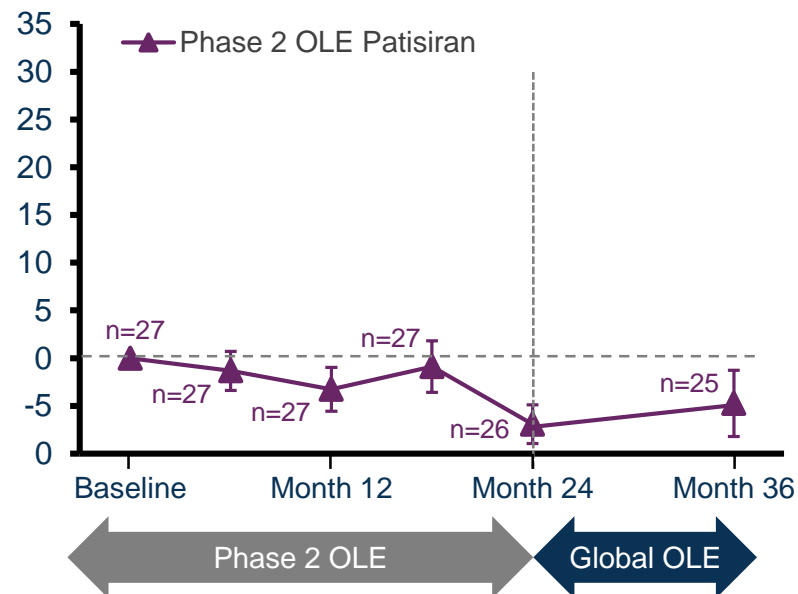
Patisiran Global OLE Results

Durable Improvement in mNIS+7 in Patients with Longest Patisiran Experience

Integrated Change in mNIS+7 from APOLLO and Global OLE^a



Integrated Change in mNIS+7 from the Phase 2 OLE and Global OLE



APOLLO patisiran and Phase 2 OLE groups demonstrated **durable improvement in neuropathy** versus their parent study baselines, as demonstrated by mean negative change from baseline in mNIS+7

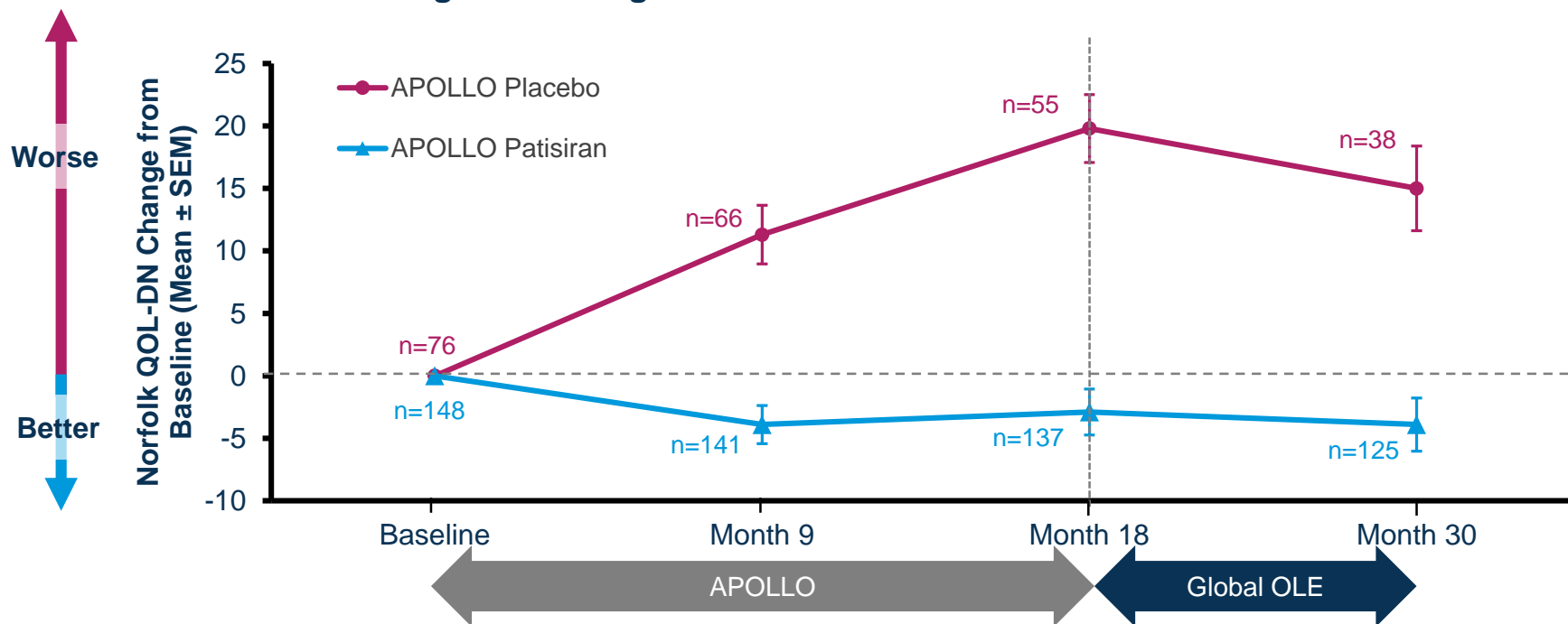
Rapid trajectory of disease progression among APOLLO placebo patients **halted once patisiran treatment was initiated** in the Global OLE, however patients did not return to parent study baseline

^aFor APOLLO patients initiating alternative hATTR amyloidosis treatment, mNIS+7 assessments after alternative treatment are treated as missing

Patisiran Global OLE Results

Durable Improvement in Norfolk QOL-DN in Patients with Longest Patisiran Experience

Integrated Change in Norfolk QOL-DN from APOLLO and Global OLE



Durable improvement in QOL observed in the APOLLO patisiran group compared with parent study baseline, after additional 12 months of patisiran treatment in the Global OLE

APOLLO placebo patients experienced an **improvement in QOL** over the 12 months of patisiran treatment; however, their QOL did not return to their baseline values due to the deterioration experienced while on placebo during APOLLO

Patisiran Global OLE Safety

Summary of Safety

Among patients exposed to patisiran (n=224), 46% and 16% have received patisiran for ≥ 3 years and ≥ 4 years, respectively

Majority of AEs were mild or moderate

- Most common related AEs were mild or moderate IRRs
 - IRRs occurred more often in patients newly treated with patisiran (APOLLO placebo) and decreased over time, consistent with the APOLLO study
- No serious IRRs or discontinuations due to IRRs

None of the deaths were considered related to patisiran; causes were consistent with natural history of hATTR amyloidosis

- Majority of patients had known risk factors for poor prognosis
- Overall exposure-adjusted mortality rate for patients who received ≥ 1 dose of patisiran across the integrated data^c was 4.8 per 100 patient-years, based on 30 deaths and 629 patient-years of cumulative exposure
 - This rate is lower than the expected range for patients with ATTR amyloidosis (6.8–29 per 100 patient-years)^{1–5}

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 n=211
AE	48 (98)	131 (96)	25 (100)	204 (97)
Severe AE	23 (47)	35 (26)	3 (12)	61 (29)
SAE	28 (57)	48 (35)	6 (24)	82 (39)
IRR	13 (27)	10 (7)	2 (8)	25 (12)
AE leading to study withdrawal	15 (31)	11 (8)	0	26 (12)
Death ^a	13 (27)	10 (7) ^b	0	23 (11)

Integrated Exposure Adjusted Mortality Rates^c

	APOLLO Placebo n=49	APOLLO Patisiran n=148	Phase 2 OLE Patisiran n=27	Global OLE Total n=224
Deaths ^d , n (%)	13 (27)	15 (10)	2 (7)	30 (13)
Exposure-Adjusted Mortality Rate (CI), deaths per 100 patient-years	18.9 (10.4, 31.2)	3.4 (2.0, 5.4)	1.7 (0.3, 5.2)	4.8 (3.3, 6.7)

^aAll deaths summarized, including deaths due to AEs that are not treatment-emergent; ^bIn this group, 1 additional patient with breast cancer died 6.5 months after withdrawing from the study;

^cIntegrated data: Phase 2 OLE, APOLLO, and Global OLE; ^dIncludes all deaths reported within 3 months after the last dose of patisiran

AE, adverse event; CI, confidence interval; IRR, infusion-related reaction; SAE, serious adverse event

1. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 2. Maurer et al. *N Engl J Med* 2018;379:1007–16; 3. Ruberg et al. *Am Heart J* 2012;164:222–8 e1; 4. Berk et al. *JAMA* 2013;310:2658–67; 5. Arruda-Olson et al. *Amyloid* 2013;20:263–8

Patisiran Global OLE

Summary

- Patients in the Global OLE represent those with the longest treatment with an RNAi therapeutic, including **patients receiving >4 years of patisiran**
- The **safety profile remained consistent with previous studies** and patisiran continues to show a positive benefit:risk profile
- Patients treated with patisiran early in their disease demonstrated **sustained and durable improvement from baseline in neuropathy and QOL** through an additional year of treatment in the Global OLE
- Despite marked disease progression while receiving placebo during the 18-month APOLLO study, **treatment with patisiran in previously untreated patients halted disease progression and improved neuropathy and QOL following 12 months of patisiran treatment**
 - Delay in treatment resulted in these patients accumulating greater disease burden compared with those patients receiving patisiran during the parent studies

Acknowledgments

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