Long-Term Safety and Efficacy of Patisiran: Global Open-Label Extension 24-Month Data in Patients with Hereditary Transthyretin-Mediated Amyloidosis

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Background

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

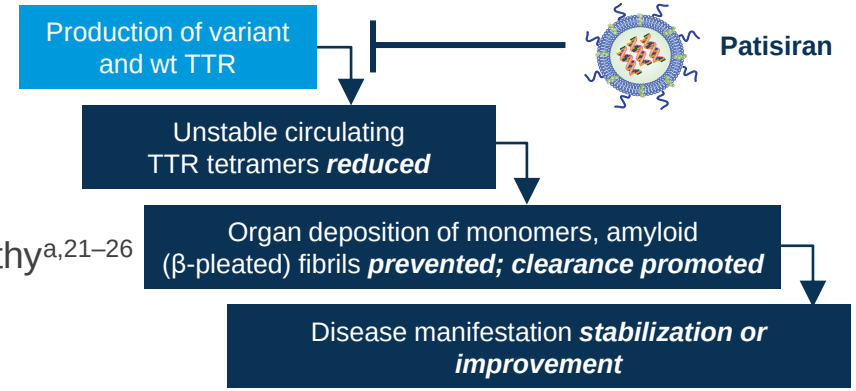
Rare, underdiagnosed, rapidly progressive, debilitating, and potentially fatal disease caused by a variant in the transthyretin (*TTR*) gene[1–5]

- **Multisystem disease**; the majority of patients develop a **mixed phenotype** of both polyneuropathy and cardiomyopathy[6–9]
- Risk factors for poor prognosis include advanced polyneuropathy, increasing age, non-V30M genotype, and presence of cardiac involvement[10–14]
- Among published studies in patients with ATTR amyloidosis, the **exposure-adjusted mortality rate ranges from 6.8–29 deaths per 100 patient-years**[12,15–18]

Patisiran

- **RNAi therapeutic** that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing variant and wild-type (wt) TTR proteins[19,20]
  - Approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy[a,21–26]
  - In the Phase 3 APOLLO study (NCT01960348), patisiran was able to **halt or reverse polyneuropathy** and **improve QOL** in the majority of patients[8]

Patisiran Therapeutic Hypothesis



[a]Specific indications vary by country/region

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

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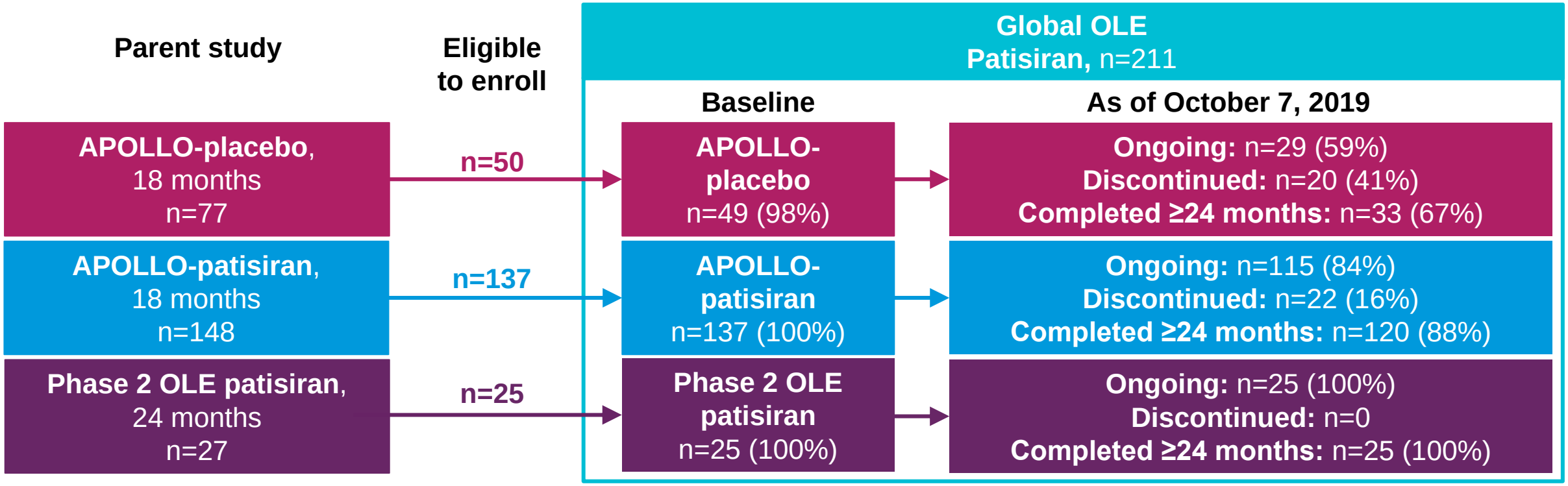
Patisiran Global Open-Label Extension (OLE) Study

Study Design and Objective



Objective: To describe the interim 24-month efficacy and safety data (as of October 7, 2019) for patients in the ongoing Global OLE study

OLE, open-label extension

Patisiran Global OLE Baseline and Results

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 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)	**186 (56)**	**53 (43)**	**77 (48)**	84 (71)
mNIS+7 score[b], mean (range)	**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, 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. [c]Norfolk QOL-DN, range −4 to 136; higher score indicates worsening of QOL. [d]The Phase 2 OLE study did not assess Norfolk QOL-DN

Durable Reduction in Serum TTR Levels with Patisiran Treatment

Robust, sustained serum TTR reduction in APOLLO-placebo group upon patisiran treatment, mean (SD) TTR reduction of 79% (17%) at Month 6 maintained through 24 months

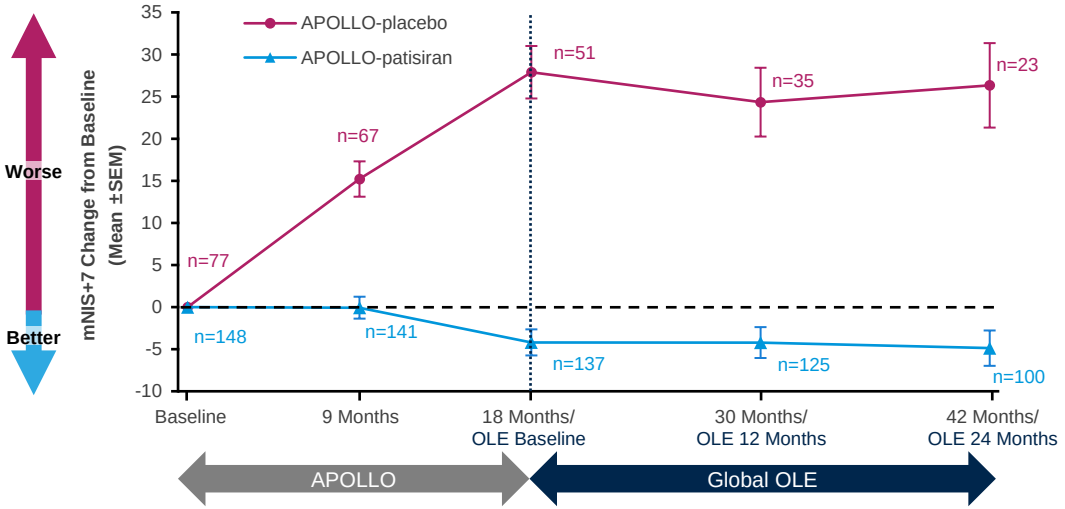
Reduction in serum TTR levels maintained with patisiran treatment in APOLLO and Phase 2 OLE groups with continued dosing in the Global OLE

hATTR, hereditary transthyretin-mediated; LV, left ventricular; mNIS+7, modified Neuropathy Impairment Score +7; NA, not applicable; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NT-proBNP, *N*-terminal prohormone of brain-type natriuretic peptide; OLE, open-label extension; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin

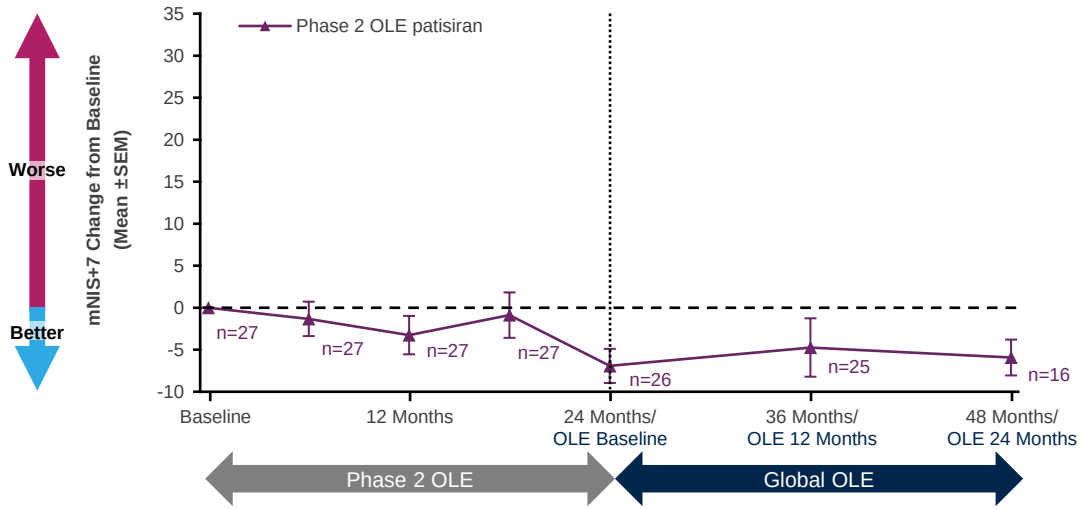
Integrated mNIS+7 Results

Durable Improvement 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[b]



APOLLO-patisiran and Phase 2 OLE groups demonstrated durable improvement in polyneuropathy versus parent study baselines, indicated by mean negative changes from baseline in mNIS+7 (mean change [SEM] from APOLLO baseline, –4.9 [2.1] and from Phase 2 OLE baseline, –5.9 [2.1])

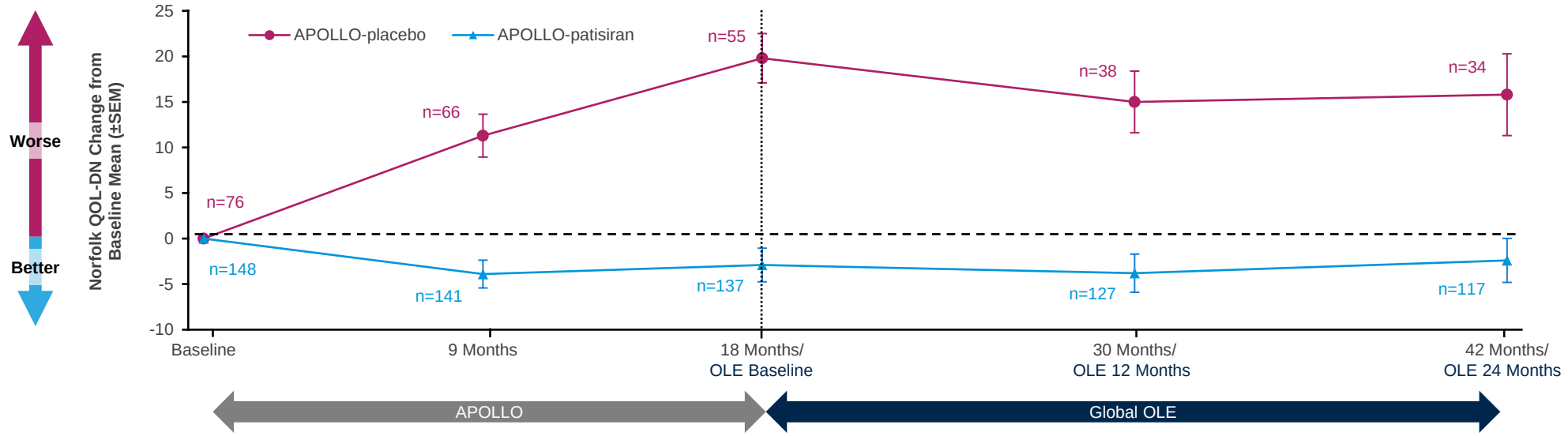
Rapid polyneuropathy progression in APOLLO-placebo group halted once patisiran treatment was initiated and after 24 months in the Global OLE (mean change [SEM] from Global OLE baseline, +0.1 [3.3]); however, patients did not return to parent study baseline (mean change [SEM] from APOLLO baseline, +26.3 [5.0])

[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). [b]Phase 2 OLE mNIS+7 parent study baseline (mean [SEM]): 53.0 (6.9)
mNIS+7, modified Neuropathy Impairment Score +7; OLE, open-label extension; SEM, standard error of the mean

Integrated Norfolk QOL-DN Results

Durable Improvement in Patients with Longest Patisiran Experience

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



Durable improvement in QOL observed in the APOLLO-patisiran group compared with parent study baseline after additional 24 months of patisiran treatment in the Global OLE (mean change [SEM] from APOLLO baseline, –2.4 [2.4])

Improved QOL was observed in APOLLO-placebo patients over 24 months of patisiran treatment (mean change [SEM] from Global OLE baseline, –4.1 [3.3]); however, patients did not return to APOLLO study baseline due to progression on placebo during APOLLO (mean change [SEM] from APOLLO baseline, +15.8 [4.5])

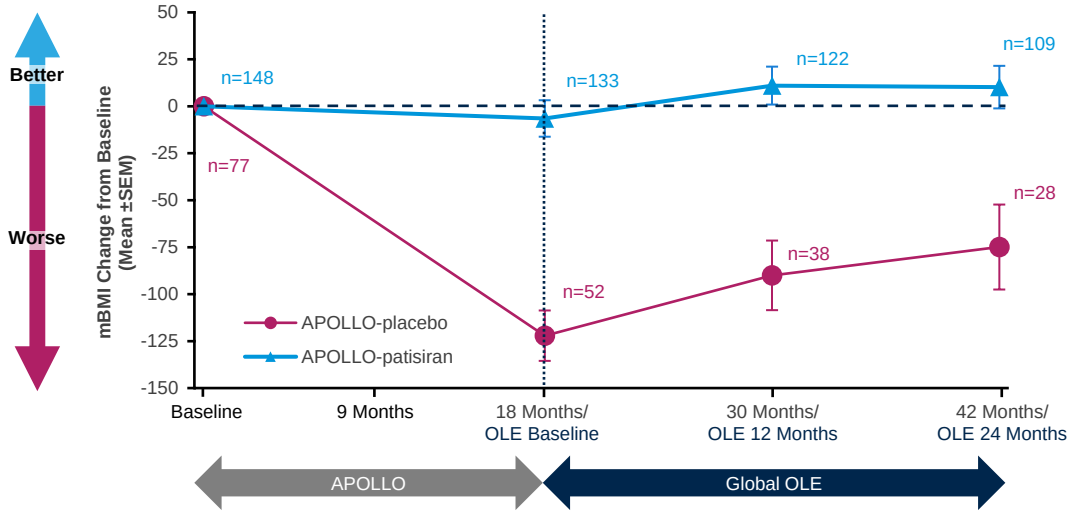
[a]APOLLO Norfolk QOL-DN parent study baseline (mean [SEM]): APOLLO placebo=55.5 (2.8); APOLLO patisiran=59.6 (2.3). Norfolk QOL-DN was not administered in the Phase 2 OLE and therefore change over time was not evaluated

Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; OLE, open-label extension; QOL, quality of life; SEM, standard error of the mean

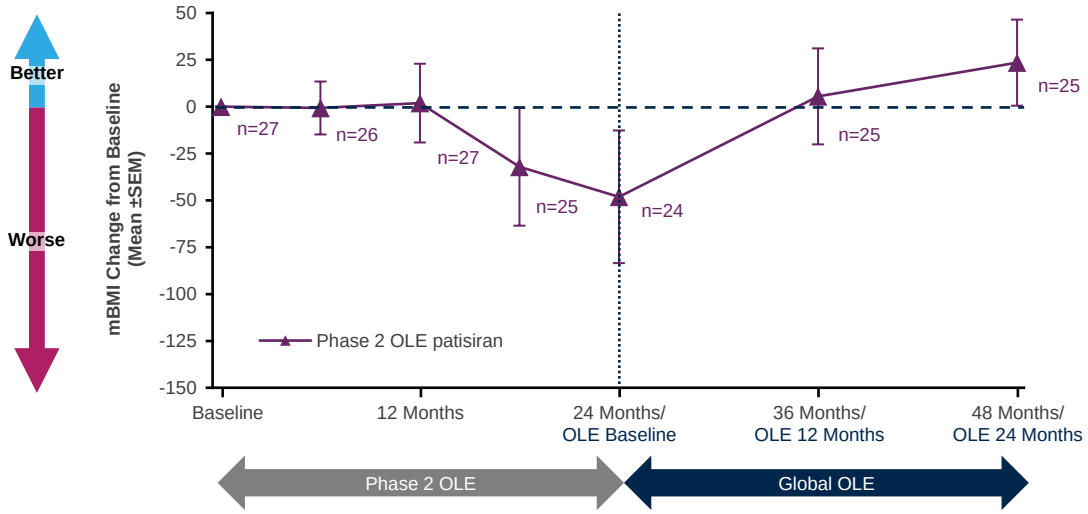
Integrated mBMI Results

Nutritional Status Maintained in Patients with Longest Patisiran Experience

Integrated Change in mBMI from APOLLO and Global OLE[a]



Integrated Change in mBMI from the Phase 2 OLE and Global OLE[b]



APOLLO-patisiran and Phase 2 OLE groups maintained nutritional status compared with parent study baseline after additional 24 months of patisiran treatment in the Global OLE (mean change [SEM] from APOLLO baseline, 10.2 [11.3] and from Phase 2 OLE baseline, 23.5 [23.0])

An improvement in mBMI was seen among APOLLO-placebo patients once patisiran was initiated in the Global OLE (mean change [SEM] from Global OLE baseline, 37.1 [24.8]); however, their mBMI did not return to APOLLO baseline value due to deterioration experienced while on placebo during APOLLO (mean change [SEM] from APOLLO baseline, –74.9 [22.6])

[a]For APOLLO patients initiating alternative hATTR amyloidosis treatment, mBMI assessments after alternative treatment are treated as missing. APOLLO mBMI parent study baseline (mean [SEM]): APOLLO-placebo=989.9 (24.4); APOLLO-patisiran=969.7 (17.3). [b]Phase 2 OLE mBMI parent study baseline (mean [SEM]): 1030.5 (32.5)
mBMI, modified body mass index; OLE, open-label extension; SEM, standard error of the mean

Patisiran Global OLE Exposure and Safety

In the Global OLE **the majority of AEs were mild or moderate**

- Most common treatment-related AEs were mild or moderate IRRs
  - **IRRs occurred more often in patients newly treated with patisiran** (APOLLO-placebo) and their frequency decreased over time, consistent with APOLLO
- There were **no serious IRRs or discontinuations due to IRRs**
- **Deaths were reported in 29 patients** in the Global OLE; **none were considered related to patisiran** by the investigators and causes were consistent with natural history of disease
  - The **proportion of deaths in the APOLLO-placebo group was higher** than in the APOLLO-patisiran and Phase 2 OLE groups
  - APOLLO-placebo patients had higher disease burden at Global OLE baseline

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)	25.3 (1.3–46.2)	30.4 (1.3–51.4)	43.0 (35.4–46.9)	30.7 (1.3–51.4)
Cumulative no. of doses	1691	5838	1487	9016
Safety				
AE	48 (98.0)	136 (99.3)	25 (100.0)	209 (99.1)
Severe AE	27 (55.1)	42 (30.7)	7 (28.0)	76 (36.0)
SAE	34 (69.4)	59 (43.1)	11 (44.0)	104 (49.3)
IRR	13 (26.5)	15 (10.9)	3 (12.0)	31 (14.7)
AE leading to study withdrawal	18 (36.7)	12 (8.8)	0	30 (14.2)
Death[a]	16 (32.7)	13 (9.5)[b]	0	29 (13.7)

Data as of interim cut-off October 7, 2019. [a]All deaths summarized, including deaths due to AEs that are not treatment-emergent. [b]In this group, 1 additional patient with breast cancer died 6.5 months after withdrawing from the study

AE, adverse event; IRR, infusion-related reaction; OLE, open-label extension; SAE, serious adverse event

Patisiran Exposure and Mortality Rates

Integrated Data

- As of October 7, 2019, across the clinical development program, a total of 224 patients with hATTR amyloidosis with polyneuropathy **have been exposed to patisiran for periods up to 6 years** with 13,691 doses administered
- **Exposure-adjusted mortality rate for patients who received ≥1 dose of patisiran was 4.3 per 100 patient-years** (95% CI 3.1, 5.9), based on 35 deaths and 808.7 patient-years of cumulative exposure
  - This **rate is at the lower end of the expected range** for patients with ATTR amyloidosis (6.8–29 per 100 patient-years)[1–5]

Integrated Exposure-Adjusted Mortality Rates*

	APOLLO-placebo (n=49)	APOLLO-patisiran (n=148)	Phase 2 OLE Patisiran (n=27)	All Patisiran-treated Patients[a] (n=224)
Mean exposure since first dose of patisiran in any study, months (range)	25.3 (1.3–46.2)	45.9 (0.7–70.0)	64.4 (19.3–71.7)	43.6 (0.7–71.7)
Cumulative no. of doses	1691	9578	2422	13,691
Total patient-years exposure[b]	100.3	563.9	144.5	808.7
Deaths[c], n (%)	16 (33)	17 (11)	2 (7)	35 (16)
Exposure-adjusted mortality rate (95% CI), deaths per 100 patient-years[d]	16.0 (9.4, 25.1)	3.0 (1.8, 4.7)	1.4 (0.2, 4.3)	4.3 (3.1, 5.9)

[a]The integrated safety population encompasses all patients exposed to patisiran. Data are recorded from first patisiran dose in either the APOLLO, Ph 2 OLE, or Global OLE studies until data cut-off. [b]For each patient, exposure in years is defined as: (last dose date of study drug – first dose date of study drug + 91)/365.25. Total patient-year exposure time is calculated as the sum of each patient's time using minimum of exposure in years or follow-up in years. [c]Only deaths from the period of first dose of patisiran to 90 days after last dose are included. [d]Exposure-adjusted mortality rate is calculated as: (total number of deaths/total patient-years exposure) × 100

*integrated exposure-adjusted mortality rates were performed as post hoc analyses

CI, confidence interval; hATTR, hereditary transthyretin-mediated

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

Conclusions

Summary

- Patients in the Global OLE represent those with the longest treatment with an RNAi therapeutic, including **patients receiving ≥5 years of patisiran**
- There were **no new safety concerns or signals**; the **safety profile remained consistent with previous studies** and patisiran continues to show a positive benefit:risk profile
- Through an additional 24 months of treatment in the Global OLE, patients treated with patisiran earlier in their disease continued to demonstrate maintained efficacy and **reversal of polyneuropathy from parent study baseline**, as measured by mNIS+7
  - Similarly, patients treated with patisiran earlier in their disease demonstrated **sustained and durable improvement from parent study baseline in QOL** (evaluated by Norfolk QOL-DN), and **maintained nutritional status** (evaluated by mBMI)
- Despite marked disease progression while receiving placebo during the 18-month APOLLO study, **treatment with patisiran in previously untreated patients halted polyneuropathy progression and improved QOL and mBMI following 24 months of patisiran treatment**
  - Delay in treatment resulted in the accumulation of greater disease burden in these patients compared with those patients receiving patisiran during the parent studies and may negatively impact survival

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mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; OLE, open-label extension; QOL, quality of life; RNAi, ribonucleic acid interference