# Global Open-label Extension: 24-month Data of Patisiran in Patients with hATTR Amyloidosis

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# Background

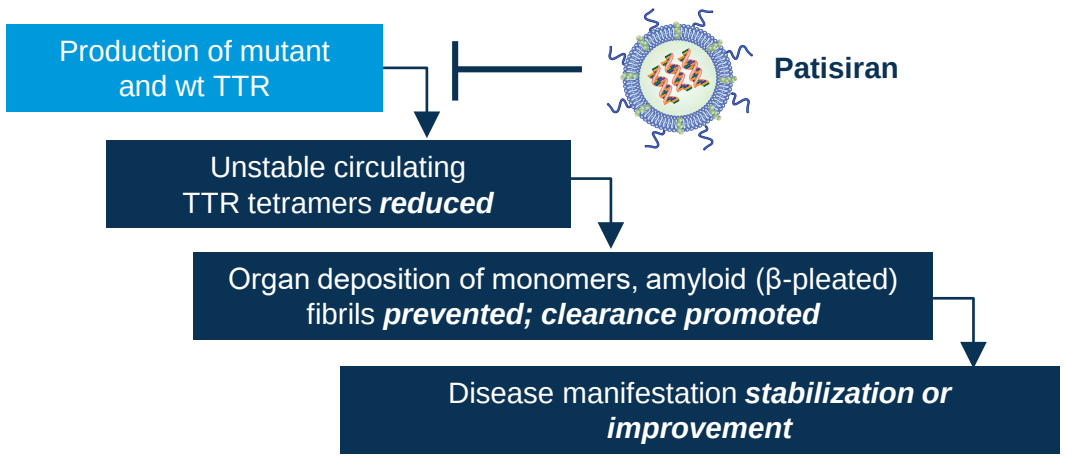
## Hereditary Transthyretin-Mediated (hATTR) Amyloidosis, Also Known As ATTRv Amyloidosis

- **Rare, rapidly progressive, 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 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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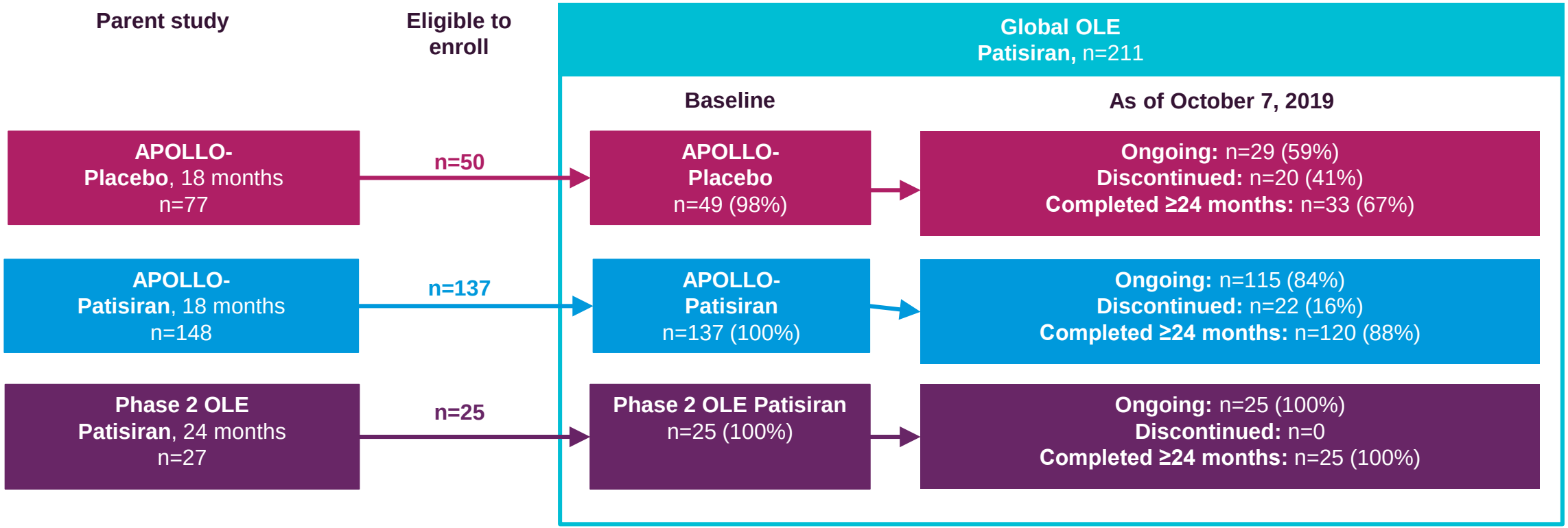
# Patisiran Global Open-Label Extension (OLE) Study

## 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

## 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 (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,** 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

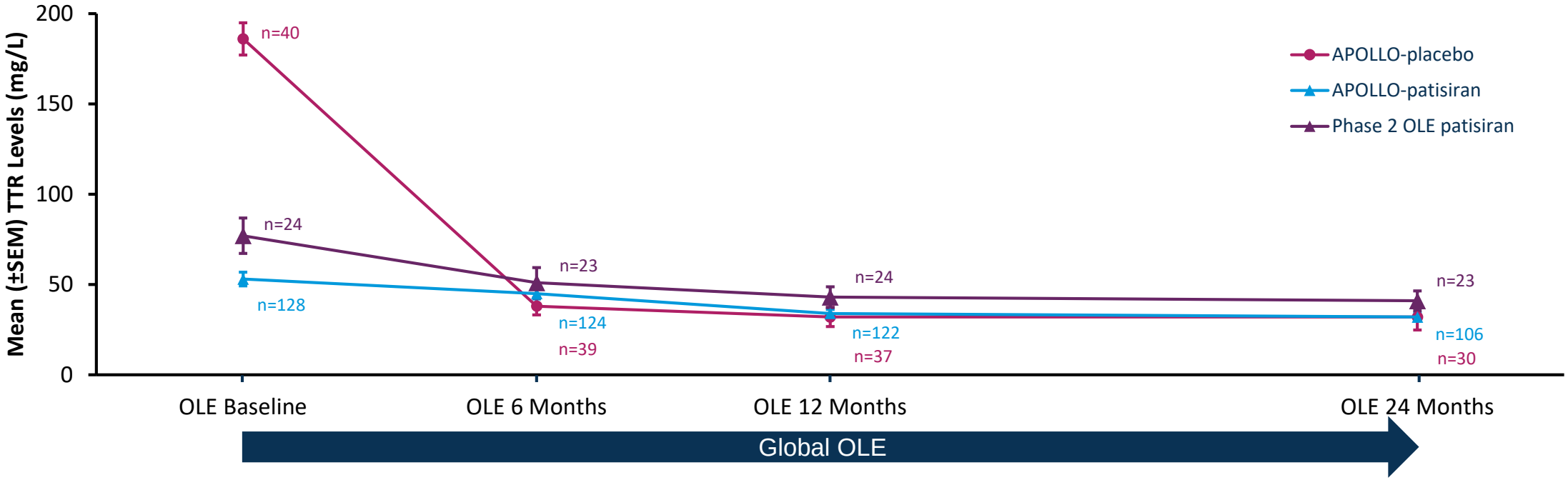
[a]First patisiran dose could have occurred in Phase 2 OLE, APOLLO, or Global OLE. [b]mNIS+7, range 0–304; higher score reflects greater impairment. [c]Norfolk QOL-DN, range −4 to 136; higher score indicates worsening of QOL. [d]The Phase 2 OLE study did not assess Norfolk QOL-DN

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; SD, standard deviation; TTR, transthyretin

# Patisiran Global OLE Results

## Durable Reduction in Serum TTR Levels with Patisiran Treatment

### Serum TTR Levels (mg/L) through 24 Months in the Global OLE (PD Analysis Set[a])




**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

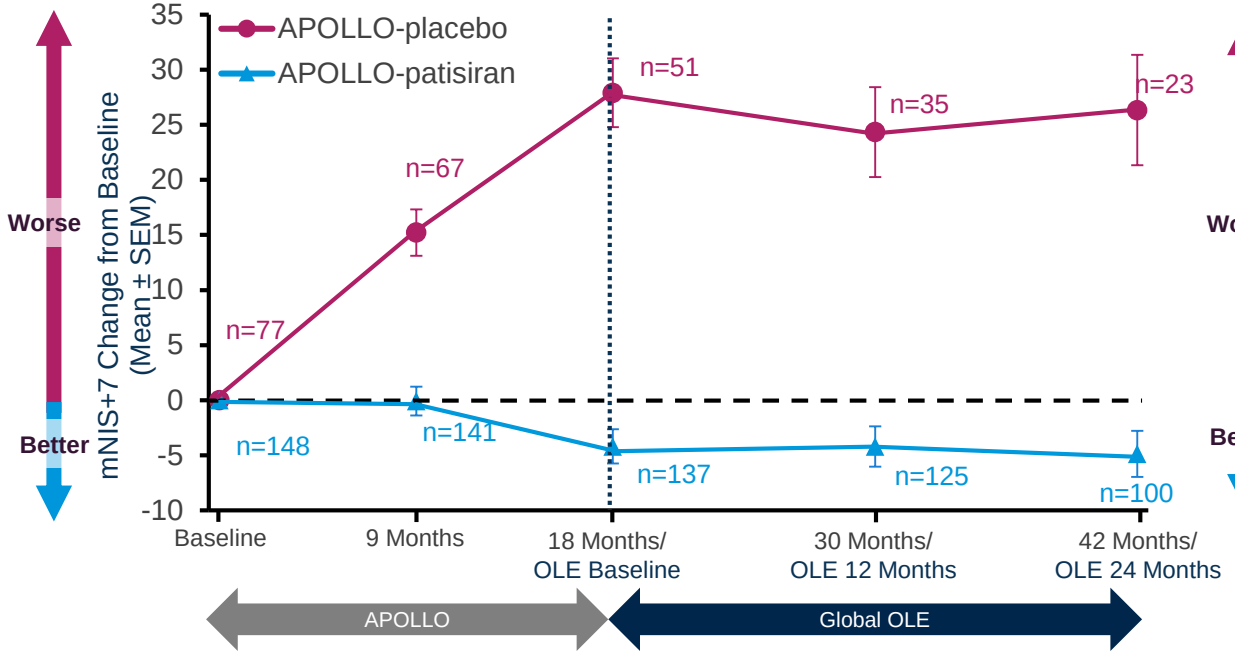
TTR assessment at first visit in the Global OLE did not need to be repeated if performed during the parent study within 45 days of the first dose in the Global OLE. [a]PD analysis set includes all patients who received ≥1 dose of patisiran in this study and had both baseline and ≥1 post-baseline PD assessment; 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

OLE, open-label extension; PD, pharmacodynamic; SD, standard deviation; SEM, standard error of the mean; TTR, transthyretin

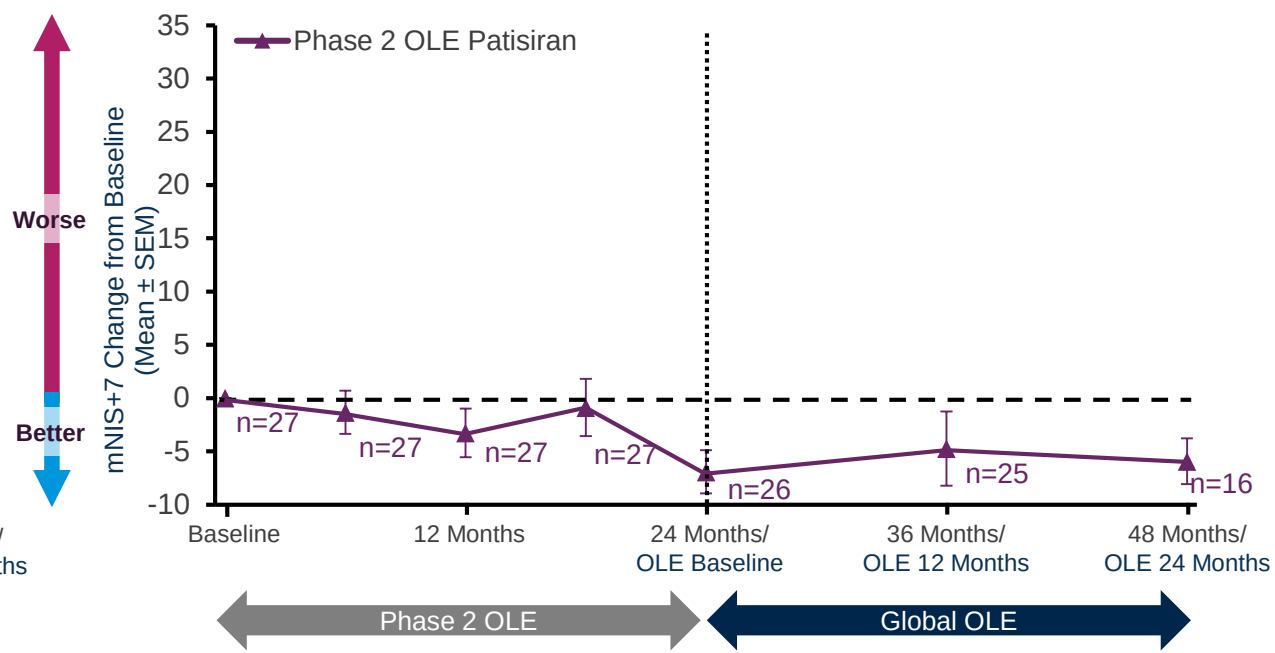
# Integrated mNIS+7 Results

## Durable Improvement in Patients with Longest Patisiran Exposure

### 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])

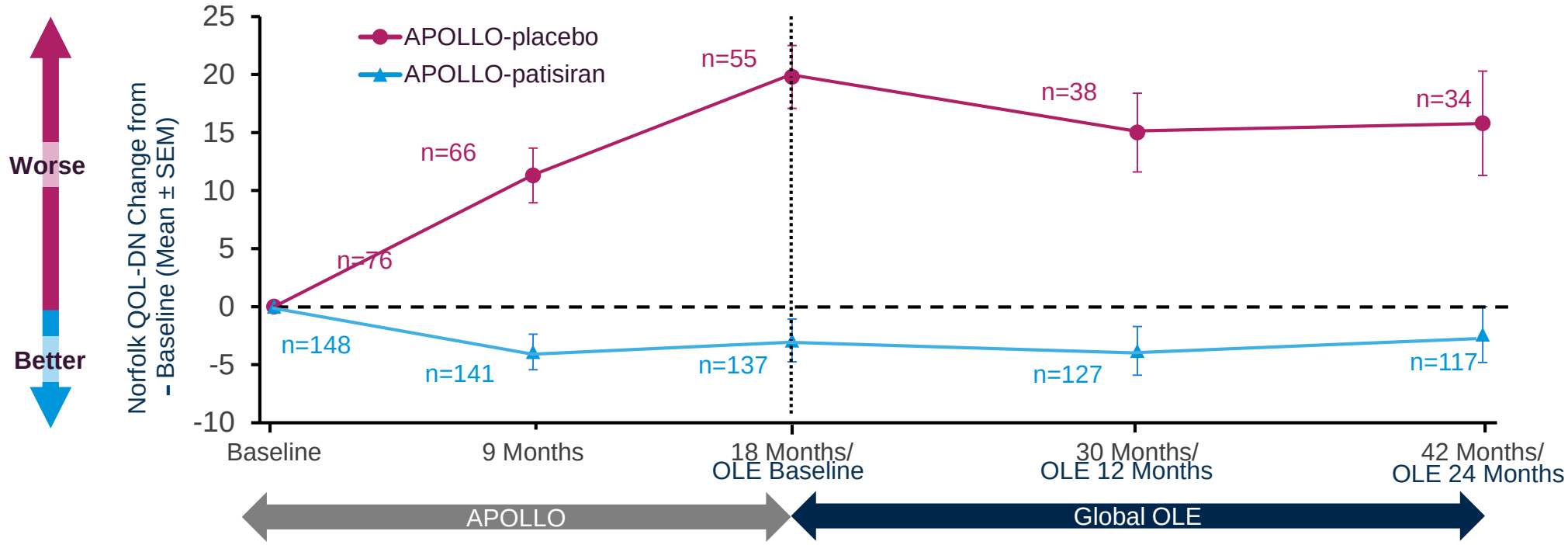
[a]For APOLLO patients initiating alternative hATTR amyloidosis treatment, mNIS+7 assessments after alternative treatment are treated as missing. APOLLO mNIS+7 parent study baseline (mean [SEM]): APOLLO placebo=74.6 (4.2); APOLLO patisiran=80.9 (3.4). [b]Phase 2 OLE mNIS+7 parent study baseline (mean [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 Norfolk QOL-DN 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

# 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 (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

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

# Patisiran Global OLE

## 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 **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,** as evaluated by Norfolk QOL-DN
- 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 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

***Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the Global OLE study***

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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