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 and Rationale

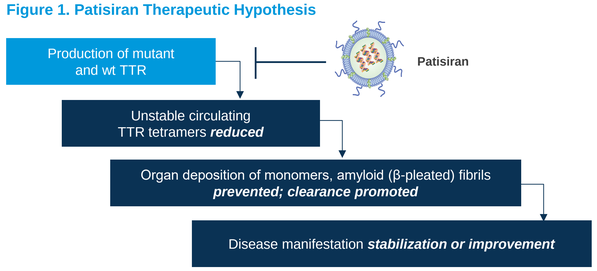
Hereditary Transthyretin-Mediated (ATTR) Amyloidosis

- Rare, progressively debilitating, life-threatening disease caused by a mutation in the *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 disease severity, 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 approved in certain countries globally[19–24] for the treatment of hereditary ATTR amyloidosis with polyneuropathy
  - Patisiran reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing mutant and wt TTR proteins[25,26] (**Figure 1**)
  - In the Phase 3 APOLLO study (NCT01960348), patisiran was able to halt or reverse polyneuropathy and improve QOL in the majority of patients[8]

Figure 1. Patisiran Therapeutic Hypothesis



Methods

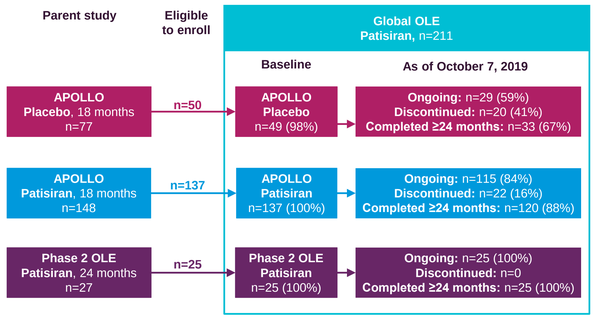
Global OLE Study Design

- Multicenter, international, OLE study to evaluate the long-term safety and efficacy of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy
- Patients who enrolled into the Global OLE are presented in one of three unique groups based on the parent study (**Figure 2**):
  - **APOLLO placebo**: received placebo in APOLLO and started patisiran for the first time in the Global OLE
  - **APOLLO patisiran**: received patisiran for 18 months in APOLLO and continued receiving patisiran 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

Objective

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

Figure 2. Transition of Eligible Patients to Global OLE



Results

Baseline Demographics and Disease Characteristics

- The Global OLE enrolled a broad patient population with a wide spectrum of disease severity (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics at Entry into the Global OLE

	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
Sex – male, n (%)	37 (76)	102 (74)	17 (68)	156 (74)
Mean time since hereditary ATTR 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

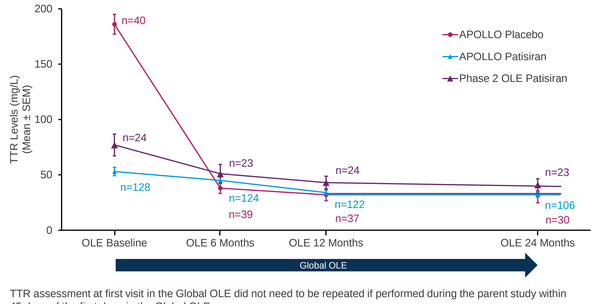
Serum TTR Levels in the Global OLE

- 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 (**Figure 3**)
- Reduction in serum TTR levels maintained with patisiran treatment in APOLLO and Phase 2 OLE groups with continued dosing in the Global OLE

Change in mNIS+7 Following 24 Months of Patisiran Treatment in the Global OLE

- APOLLO patisiran and Phase 2 OLE patisiran groups demonstrated durable improvement in polyneuropathy versus their 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]) (**Figures 4 and 5**)
- 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]) (**Figure 4**)

Figure 3. Serum TTR Levels (mg/L) Through 2 Years in the Global OLE (PD Analysis Set[a])



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

Figure 4. Integrated Change in mNIS+7 from APOLLO and Global OLE[a]

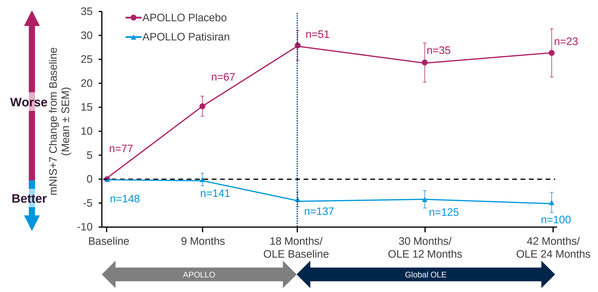
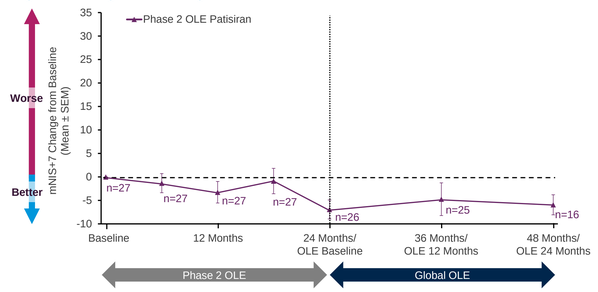


Figure 5. Integrated Change in mNIS+7 from the Phase 2 OLE and Global OLE[b]

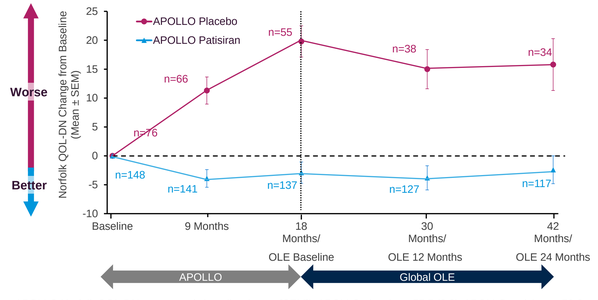


[a]For APOLLO patients initiating alternative hereditary ATTR amyloidosis treatment, mNIS+7 assessments after alternative treatment are treated as missing. APOLLO mNIS+7 parent study baseline (mean [SEM]): APOLLO placebo = 74.6 (4.2); APOLLO patisiran = 80.9 (3.4). [b]Phase 2 OLE mNIS+7 parent study baseline (mean [SEM]): 53.0 (6.9)

Change in Norfolk QOL-DN Following 24 Months of Patisiran Treatment in the Global OLE

- 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]) (**Figure 6**)
- 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]) (**Figure 6**)

Figure 6. Integrated Change in Norfolk QOL-DN from APOLLO and Global OLE[a]



[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

Summary of Overall Exposure

- As of October 7, 2019, across the patisiran clinical development program for hereditary ATTR amyloidosis with polyneuropathy, a total of 224 patients have been exposed to patisiran for periods up to 6 years with 13,691 doses administered (**Table 2**)
- Of these patients, 47% and 16% received patisiran for ≥4 years and ≥5 years, respectively

Table 2. Overall Exposure in the Global OLE

	APOLLO Placebo	APOLLO Patisiran	Phase 2 OLE Patisiran	Total
In Global OLE				
Number of patients	n=49	n=137	n=25	n=211
Mean exposure, months (range)	25.3 (1.3–46.2)	30.4 (1.3–51.4)	43.0 (35.4–46.9)	30.6 (1.3–51.4)
Cumulative number of doses	1691	5838	1487	9016
Since first dose of patisiran in any study[a]				
Number of patients	n=49	n=148	n=27	n=224
Mean exposure, 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 number of doses	1691	9578	2422	13691

[a]First dose in Phase 2 OLE, APOLLO, or Global OLE; integrated data across all patisiran-treated patients

Summary of Global OLE Safety (Table 3)

- 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
- 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 patisiran groups
    - APOLLO placebo patients had higher disease burden at Global OLE baseline

Table 3. 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)
AE	48 (98)	136 (99)	25 (100)	209 (99)
Severe AE	27 (55)	42 (31)	7 (28)	76 (36)
SAE	34 (69)	59 (43)	11 (44)	104 (49)
IRR	13 (27)	15 (11)	3 (12)	31 (15)
AE leading to study withdrawal	18 (37)	12 (9)	0	30 (14)
Death[a]	16 (33)	13 (9)[b]	0	29 (14)

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

Patisiran Exposure and Mortality Rates: Integrated Data

- 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 (**Table 4**)
  - This rate is at the lower end of the expected range for patients with ATTR amyloidosis (6.8–29 per 100 patient-years)[12,15–18]

Table 4. Integrated Exposure-Adjusted Mortality Rates

	APOLLO Placebo (n=49)	APOLLO Patisiran (n=148)	Phase 2 OLE Patisiran (n=27)	All Patisiran-treated Patients[c] (n=224)
Total patient-years exposure[a]	100.3	563.9	144.5	808.7
Deaths[b], 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]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. [b]Only deaths from the period of first dose of patisiran to 90 days after last dose are included. [c]The integrated safety population encompasses all patients exposed to patisiran. Data are recorded from first patisiran dose in either the APOLLO, Phase 2 OLE, or Global OLE studies until data cut-off. [d]Exposure-adjusted mortality rate is calculated as: (total number of deaths/total patient-years exposure) × 100

Conclusions

- 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
- Patients treated with patisiran early in their disease demonstrated sustained and durable improvement from baseline in polyneuropathy and QOL through 2 additional years 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 polyneuropathy progression and improved QOL following 24 months of patisiran treatment
  - Delay in treatment resulted in an increased disease burden compared with those patients receiving patisiran during the parent studies

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Abbreviations: AE, adverse event; ATTR, transthyretin-mediated; CI, confidence interval; IRR, infusion-related reaction; 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; QOL, quality of life; PD, pharmacodynamic; PND, polyneuropathy disability; RNAi, ribonucleic acid interference; SAE, serious adverse event; SD, standard deviation; SEM, standard error of the mean; TTR, transthyretin; wt, wild-type.

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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. 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. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 11. Swiecicki et al. *Amyloid* 2015;22:123–31; 12. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 13. Adams et al. *Ther Adv Neurol Disord* 2013;6:129–39; 14. Mariani et al. *Ann Neurol* 2015;78:901–16; 15. Maurer et al. *N Engl J Med* 2018;379:1007–16; 16. Ruberg et al. *Am Heart J* 2012;164:222–8.e1; 17. Berk et al. *JAMA* 2013;310:2658–67; 18. Arruda-Olson et al. *Amyloid* 2013;20:263–8; 19. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use. 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf (accessed February 13, 2020); 20. 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 February 13, 2020); 21. Alnylam Pharmaceuticals Inc. Alnylam announces approval in Japan of ONPATTRO® for the treatment of hereditary ATTR amyloidosis with polyneuropathy. 2019. Available from: https://investors.alnylam.com/press-release?id=23886 (accessed February 13, 2020); 22. Canadian Agency for Drugs and Technologies in Health. Available from: https://www.cadth.ca/patisiran (accessed February 13, 2020); 23. Swiss prescribing information. Abbreviated information for health care professionals for ONPATTRO 10mg/5ml, concentrate for solution for infusion (Version September 2019). Available from: www.swissmedicinfo.ch (accessed February 5, 2020); 24. Alnylam Announces Approval in Brazil of ONPATTRO® for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy. Available from: https://investors.alnylam.com/press-release?id=24606 (accessed March 23, 2020); 25. Coelho et al. *N Engl J Med* 2013;369:819–29; 26. Suhr et al. *Orphanet J Rare Dis* 2015;10:109.