Risk Factors for Mortality in Patients with Hereditary Transthyretin-Mediated Amyloidosis: Analysis of APOLLO and Global Open-Label Extension Studies

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Introduction

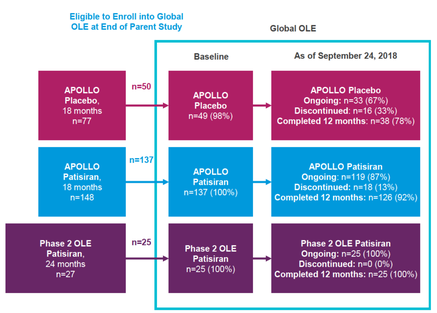
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, progressively debilitating, fatal disease caused by mutations in the transthyretin (*TTR*) gene that results in multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunction across these multiple organs[1–5]
- Non-specific heterogeneous clinical presentation[6,7]; the majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[6–11]
- Affects ~50,000 people worldwide[4]; median survival is 4.7 years following diagnosis, which is reduced to 3.4 years in patients presenting with cardiomyopathy[12–15]
- Previous studies have identified a range of risk factors for poor prognosis in patients with hATTR amyloidosis, including disease severity, older age, Val30Met mutation with late-onset disease (>50 years), and non-Val30Met *TTR* mutations[12,13,15–19]
- Among published studies in patients with ATTR amyloidosis, the estimated mortality rate ranges from 6.8 to 29 deaths per 100 patient-years[12,19–22]

Patisiran in hATTR Amyloidosis with Polyneuropathy

- Patisiran, a lipid nanoparticle-delivered RNA interference (RNAi) therapeutic, reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing mutant and wild-type (wt) TTR proteins[23,24]
- Patisiran is approved in select countries globally for the treatment of hATTR amyloidosis with polyneuropathy[25–27]
- The Phase 2 Open-Label Extension (OLE) (NCT01617967) was a multicenter, open-label, extension study of long-term patisiran treatment in patients with hATTR amyloidosis with polyneuropathy
- APOLLO (NCT01960348) was a Phase 3, randomized (2:1), placebo-controlled study of patisiran 0.3 mg/kg intravenously (IV) every 3 weeks in patients with hATTR amyloidosis with polyneuropathy[8,28]
  - In APOLLO, patisiran was able to halt or reverse polyneuropathy and improve quality of life at 18 months from baseline in the majority of patients[8]
- The Global OLE (NCT02510261) is an ongoing, multicenter, OLE study in patients with hATTR amyloidosis with polyneuropathy to evaluate long-term safety and efficacy of patisiran in which 99% of eligible patients enrolled (**Figure 1**)

Figure 1. Patient Disposition of the Global OLE Study



Objective

- To analyze baseline disease characteristics in patients enrolled in the APOLLO and Global OLE studies to identify risk factors for mortality in patients with hATTR amyloidosis with polyneuropathy

Methods

Mortality

- Number of deaths was collected during participation in the studies; deaths were adjudicated as cardiovascular (CV), non-CV, or unknown
- CV deaths were assigned into subcategories (e.g., fatal myocardial infarction, heart failure, sudden death, presumed CV death, fatal stroke, fatal pulmonary embolism, CV procedure-related death, and other CV death) where possible
  - Cardiac deaths were considered a subset of CV deaths excluding the subcategory of fatal stroke
- The cause of death was adjudicated according to the responsible underlying disease process rather than the immediate mechanism after review of available medical and hospitalization records
- Exposure-adjusted mortality rates were evaluated for patients in APOLLO (n=225) and among the integrated data for all patisiran patients (Phase 2 OLE, APOLLO, and Global OLE; n=224)

Statistical Analysis

- Univariate and multivariate Cox proportional hazards regression analyses were used to assess potential baseline prognostic factors including those listed below; analysis included survival data from APOLLO (n=225) and for all patisiran patients in the integrated APOLLO/Global OLE population (n=197)
  - Genotype (non-Val30Met vs Val30Met)
  - Familial amyloid polyneuropathy (FAP) stage (1, 2, 3)
  - *N*-terminal prohormone of brain-type natriuretic peptide (NT-proBNP; >3000 vs ≤3000 ng/L)
  - Age of disease onset, years (≥50 vs <50)
  - New York Heart Association (NYHA) functional class (I, II, III/IV)
  - Mean left ventricular (LV) wall thickness, cm (≥1.3 vs <1.3)
  - Cardiac subpopulation (yes vs no)
  - Age, years (≥65 vs <65)

Results

Baseline Characteristics

- The patisiran clinical development program comprises one of the largest populations of patients with hATTR amyloidosis with polyneuropathy and included a majority of patients with the non-Val30Met genotype as well as patients with evidence of mixed phenotype, providing a robust dataset for both active and placebo treatment[8]
  - Baseline characteristics of the 225 patients enrolled in APOLLO and 211 patients enrolled in the Global OLE are shown in **Table 1**

Table 1. Baseline Characteristics and Exposure of Patients in APOLLO and the Global OLE

	APOLLO		Global OLE		
	Placebo (n=77)	Patisiran (n=148)	APOLLO Placebo (n=49)	APOLLO Patisiran (n=137)	Phase 2 OLE Patisiran (n=25)
Median (range) age, years	63 (34–80)	62 (24–83)	66 (36–78)	63 (26–84)	65 (31–79)
Genotype, n (%)					
Val30Met	40 (52)	56 (38)	24 (49)	56 (41)	18 (72)
Non-Val30Met	37 (48)	92 (62)	25 (51)	81 (59)	7 (28)
FAP stage, n (%)					
1	37 (48)	67 (45)	14 (29)	58 (42)	20 (80)
2	39 (51)	81 (55)	27 (55)	71 (52)	5 (20)
3	1 (1)	0	8 (16)	8 (6)	0
NYHA class, n (%)					
I	40 (52)	70 (47)	22 (45)	67 (49)	19 (76)
II	36 (47)	77 (52)	21 (43)	59 (43)	4 (16)
III	0	0	4 (8)	9 (7)	2 (8)
IV	0	0	2 (4)	2 (1)	0
Missing	1 (1)	1 (1)	0	0	0
Cardiac subpopulation[a], n (%)	36 (47)	90 (61)	–	–	–
Median (range) NT-proBNP, ng/L	563 (25–16,498)	474 (28–9,882)	868 (56–15,101)	375 (21–10,282)	166 (5–1,897)
NT-proBNP categories, n (%) >3,000 ng/L	9 (11.7)	20 (13.5)	10 (20.4)	14 (10.2)	0 (0)
Mean (SD) LV wall thickness, cm	1.6 (0.2)	1.7 (0.3)	1.5 (0.3)	1.5 (0.3)	1.2 (0.3)
Patisiran exposure					
Mean (SD) patisiran exposure, months[b]	0	17.7 (3.4) (n=148)	17.2 (8.8) (n=49)	19.8 (7.0) (n=137)	30.5 (2.1) (n=25)
Mean (SD) time since first dose, months[b]	0	17.7 (3.4) (n=148)	17.2 (8.8) (n=49)	36.0 (10.6) (n=148)	52.9 (9.2) (n=27)

[a]Patients with baseline LV wall thickness ≥1.3 cm and no medical history of aortic valve disease or hypertension qualified for the pre-defined cardiac subpopulation
[b]Global OLE data as of September 24, 2018

Risk Factors for Mortality

- Utilizing risk factors identified in literature, a univariate and multivariate analysis was executed using baseline data from the APOLLO study and integrated data from the APOLLO and Global OLE studies
  - Univariate analysis of baseline characteristics identified non-Val30Met genotype, elevated serum NT-proBNP (>3000 ng/L), and advanced neuropathy (FAP stage 2 vs 1; 3 vs 1) as the 3 most significant risk factors for mortality based on the APOLLO population
    - Age ≥65 years old and higher NYHA class were additional potential factors based on the integrated APOLLO and Global OLE population
  - In the multivariate analysis, non-Val30Met genotype, elevated serum NT-proBNP (>3000 ng/L), and advanced neuropathy (FAP stage 2 vs 1; 3 vs 1) were significantly associated with mortality in both the APOLLO and integrated APOLLO/Global OLE populations (**Table 2**)
    - Age ≥65 years old and higher NYHA class were insignificant because of their association with other factors

Table 2. Multivariate Cox Proportional Hazard Analysis of Risk Factors for Mortality[a]

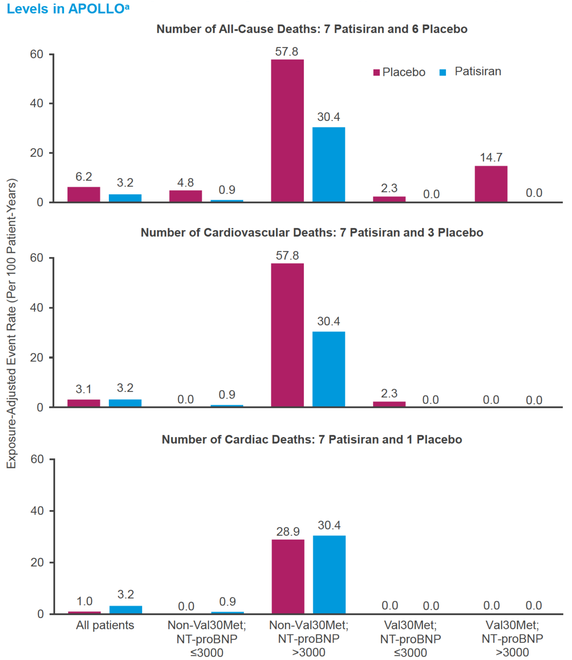
	APOLLO (n=225)		Integrated APOLLO/Global OLE (n=197)	
	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value
Genotype				
Non-Val30Met vs Val30Met	4.5 (1.0, 20.5)	5.1×10^{-2}	2.6 (1.0, 6.4)	4.3×10^{-2}
NT-proBNP, ng/L				
>3000 vs ≤3000	15.6 (4.8, 51.0)	5.3×10^{-6}	5.3 (2.4, 11.7)	3.5×10^{-5}
FAP stage[b]				
2 vs 1	9.9 (1.3, 76.9)	2.8×10^{-2}	4.5 (1.5, 13.1)	6.5×10^{-3}
3 vs 1	NA	NA	14.8 (3.5, 62.4)	2.5×10^{-4}

[a]Calculated as time from the first dose of either patisiran or placebo for APOLLO (or time from first dose of patisiran for integrated APOLLO/Global OLE) to death or censored at last known date alive; [b]In APOLLO, only 1 patient had FAP stage 3 and was therefore grouped with FAP stage 2 for the APOLLO analysis

APOLLO: Analysis of Exposure-Adjusted Mortality Rates by Baseline Risk Factors

- A higher percentage of patients with non-Val30Met and a higher percentage in the pre-defined cardiac subgroup were in the patisiran group (62%, 61%) compared with placebo (48%, 47%), respectively
- Of the identified mortality risk factors, an analysis of the baseline APOLLO population also showed that the proportion of patients with both non-Val30Met and elevated NT-proBNP was higher in the patisiran group (11.5%) compared with the placebo group (5.2%)
- Exposure-adjusted mortality rates were summarized by treatment arm and by subgroup defined by the combination of genotype and the other key risk factor NT-proBNP (**Figure 2**)
  - Patients with non-Val30Met and baseline NT-proBNP >3000 ng/L had a higher mortality rate compared with other patients, consistent with the Cox regression analysis
  - For non-Val30Met patients with elevated NT-proBNP (>3000 ng/L), the exposure-adjusted all-cause mortality rates (per 100 patient-years) was lower in the patisiran group (30.4) vs placebo (57.8)
  - The exposure-adjusted cardiac mortality rates (per 100 patient-years) were comparable between the patisiran (30.4) and placebo (28.9) groups

Figure 2. Exposure-Adjusted Mortality Rates by Genotype and Baseline NT-proBNP Levels in APOLLO[a]



[a]Of the patients in this analysis, 12/13 had severe neuropathy (FAP 2/3) at baseline

Integrated Analysis of All Patisiran-Treated Patients: Exposure-Adjusted Mortality Rates (Table 3)

- Among all patisiran-treated patients in the Phase 2 OLE, APOLLO, and Global OLE studies, the exposure-adjusted overall mortality rate per 100 patient-years was 4.8 and is at the lower end of the expected range estimated for patients with ATTR amyloidosis (6.8–29)[12,19–22]
  - Exposure-adjusted overall mortality rates and cardiac mortality rates per 100 patient-years were highest in patients from the APOLLO placebo group, whose disease had advanced during APOLLO, and lowest in patients from the Phase 2 OLE patisiran group who were treated the earliest in their disease

Table 3. Exposure-Adjusted Mortality Rates (All Patisiran-Treated Patients; n=224) in Global OLE

	APOLLO Placebo/ Global OLE (n=49)	APOLLO Patisiran/ Global OLE (n=148)	Phase 2 OLE Patisiran/ Global OLE (n=27)	All Patisiran-Treated Patients (n=224)
Total patient-years exposure	68.6	442.2	118.6	629.4
All-cause deaths[a], n (%)	13 (27)	15 (10)	2 (7)	30 (13)
Exposure-adjusted total mortality rate, deaths per 100 patient-years[b] (95% CI)	18.9 (10.4, 31.2)	3.4 (2.0, 5.4)	1.7 (0.3, 5.2)	4.8 (3.3, 6.7)
Cardiac deaths[a], n (%)	6 (12)	11 (7)	1 (4)	18 (8)
Exposure-adjusted cardiac mortality rate, deaths per 100 patient-years[b] (95% CI)	8.7 (3.5, 17.7)	2.5 (1.3, 4.3)	0.8 (0.1, 3.7)	2.9 (1.7, 4.4)

[a]Deaths within 90 days of last dose of patisiran; [b]Exposure-adjusted mortality rate is calculated as: (total number of deaths/total patient-years exposure)×100; For each patient, exposure in years is defined as: (last dose date of study drug – first dose date of drug+91)/365.25; The total patient-year exposure time is calculated as the sum of each patient's time using the minimum of the duration of exposure in years or follow-up in years; Data as of September 24, 2018

Conclusions

- The patisiran development program comprises the largest clinical trial population of patients with hATTR amyloidosis with polyneuropathy and included a majority of patients with the non-Val30Met genotype as well as patients with evidence of mixed phenotype
- Elevated NT-proBNP levels, severe neuropathy, and non-Val30Met genotype were identified as the 3 most significant risk factors for mortality in patients with hATTR amyloidosis with polyneuropathy and are consistent with those described in the literature
- In APOLLO, the exposure-adjusted all-cause mortality rates were lower in patisiran-treated patients compared with placebo
  - Further analysis by baseline risk factors demonstrated no imbalance of exposure-adjusted CV or cardiac mortality rates between the treatment groups
- Overall exposure-adjusted mortality rates in the integrated patisiran experience are at the lower end of the expected range for patients with ATTR amyloidosis[12,19–22]
  - Exposure-adjusted mortality rates were highest in patients with delayed patisiran treatment and more advanced disease than those who had the longest patisiran exposure (>4 years) and began treatment in earlier disease stages
- These identified risk factors and results underscore the importance of earlier clinical suspicion of hATTR amyloidosis in order to diagnose and treat patients earlier in their disease course

Abbreviations: CI, confidence interval; CV, cardiovascular; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated; IV, intravenously; LV, left ventricular; NA, not available; NT-proBNP, *N*-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; TTR, transthyretin; wt, wild-type. **Acknowledgments:** Editorial assistance in the development of the poster was provided by Adelphi Communications Ltd, UK, funded by Alnylam Pharmaceuticals.
Funding: This study was sponsored by Alnylam Pharmaceuticals. **References:** 1. Adams et al. *Neurology* 2015;85:675–82; 2. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 3. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 4. Hawkins et al. *Ann Med* 2015;47:625–38; 5. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 6. Damy et al. *Amyloid* 2016;23:194–202; 7. Conceição et al. *J Peripher Nerv Syst* 2016;21:5–9; 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. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 11. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 12. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 13. Swiecicki et al. *Amyloid* 2015;22:123–31; 14. Castaño et al. *Heart Fail Rev* 2015;20:163–78; 15. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 16. Coelho et al. *Neurology* 2018;91:e1999–e2009; 17. Rapezzi et al. *Amyloid* 2006;13:143–53; 18. Connors et al. *Amyloid* 2011;18(Suppl. 1):157–9; 19. Berk et al. *JAMA* 2013;310:2658–67; 20. Maurer et al. *N Engl J Med* 2018;379:1007–16; 21. Ruberg et al. *Am Heart J* 2012;164:222–8 e1; 22.Arruda-Olson et al. Amyloid 2013;20:263–8; 23. Coelho et al. *N Engl J Med* 2013;369:819–29; 24. Suhr et al. *Orphanet J Rare Dis* 2015;10:109; 25. 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; 26. 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; 27. Alnylam Pharmaceuticals. Alnylam Announces Approval in Japan of ONPATTRO® for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy. 2019. Available from: http://investors.alnylam.com/news-releases/news-release-details/alnylam-announces-approval-japan-onpattror-treatment-hereditary; 28. Adams et al. *BMC Neurol* 2017;17:181.