APOLLO Phase 3 Study: Impact of Baseline Neuropathy Severity on Response to Patisiran

Laura Obici[1], Teresa Coelho[2], David Adams[3], Alejandra González-Duarte[4], William O'Riordan[5], Chih-Chao Yang[6], Michael Polydefkis[7], Arnt Kristen[8], Ivaylo Tournev[9], Hartmut Schmidt[10], John Berk[11], Kon-Ping Lin[12], Pritesh J Gandhi[13], Marianne Sweetser[13], Tim Lin[13], Jared Gollob[13], and Ole Suhr[14]

[1]Fondazione IRCCS Policlinco San Matteo, Pavio, Italy; [2]Hospital de Santo António, Porto, Portugal; [3]National Reference Center for FAP (NNERF)/ APHP/ INSERM U 1195/ CHU Bicêtre, Le Kremlin Bicêtre, France; [4]Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico City, Mexico; [5]eStudy Site, La Mesa, CA, USA; [6]National Taiwan University Hospital, Taipei, Taiwan; [7]Johns Hopkins, Baltimore, MD, USA; [8]Heidelberg University Hospital, Heidelberg, Germany; [9]University Multiprofile Hospital for Active Treatment, Sofia, Bulgaria; [10]University Hospital Muenster, Muenster, Germany; [11]Amyloid Treatment and Research Program, Boston University, Boston, MA, USA; [12]Taipei Veterans General Hospital, Taipei, Taiwan; [13]Alnylam Pharmaceuticals, Cambridge, MA, USA; [14]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, multisystem, life-threatening disease caused by a mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and GI tract[1-5]
  - Affecting approximately 50,000 people worldwide[5,6]; median survival of 4.7 years following diagnosis with a reduced survival (3.4 years) for patients presenting with cardiomyopathy[7-9]
- Accumulation of fibrils in nerves can lead to manifestations of polyneuropathy, including peripheral neuropathy, autonomic dysfunction, and motor weakness causing fine and gross motor impairments whereas accumulation in heart can lead to cardiomyopathy
  - Disease penetrance and rate of progression may be influenced by TTR genotype[10]
- Limited treatment options are available; thus there is a continued high unmet medical need for novel therapeutic options

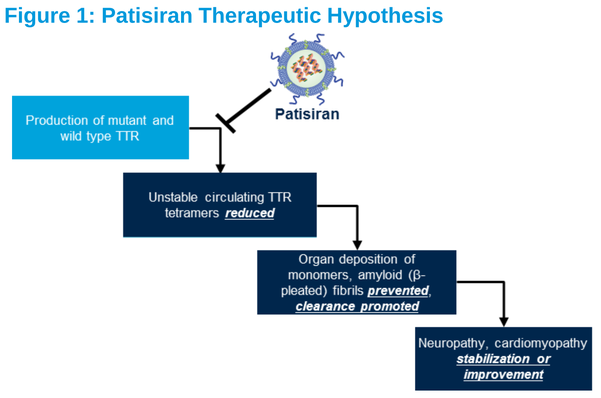
Patisiran

- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR (Figure 1)
- Phase 2: positive multi-dose results in patients with hATTR amyloidosis[11]
- Phase 2 Open-Label Extension (OLE): trial completed with sustained mean serum TTR percent reduction of 82%, patisiran generally well tolerated, and mean 7.0-point decrease in mNIS+7 at 24 months[12]
- Phase 3, APOLLO: study met the primary efficacy endpoint of modified Neuropathy Impairment Score (mNIS+7) and all secondary endpoints with favorable safety profile[13,14]
- Global-OLE: ongoing[15]

Objective

- Describe the mNIS+7 response by baseline Neuropathy Impairment Score (NIS) quartile to demonstrate the impact of patisiran across a broad range of neuropathy severity

Figure 1: Patisiran Therapeutic Hypothesis

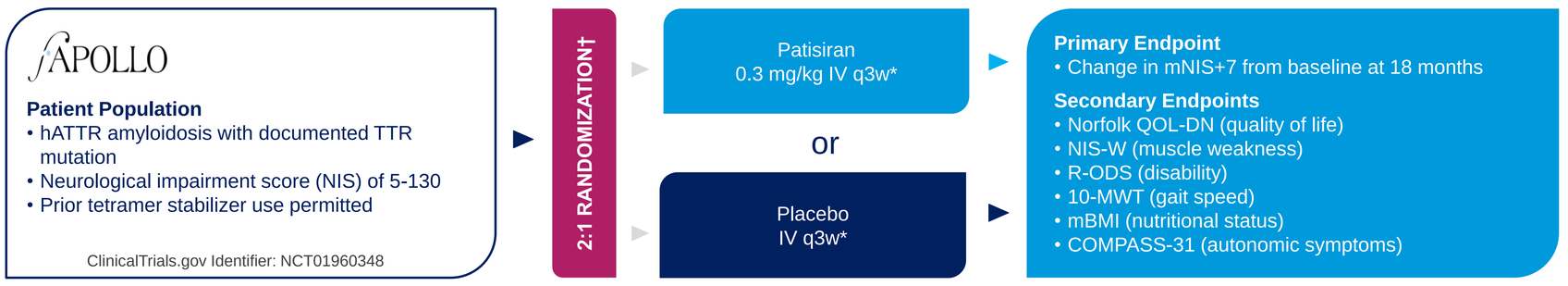


Methods

Phase 3 Study Design

- Multi-center, international, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy (Figure 2)
- Primary endpoint was change in mNIS+7 from baseline at 18 months
  - mNIS+7 is a quantitative and referenced assessment to quantify motor, sensory, and autonomic components of the polyneuropathy in patients with hATTR amyloidosis; higher score indicates worsening neuropathy (range 0 – 304)[13]
- Secondary endpoints were chosen to assess the burden of disease in these patients including quality of life, motor strength, disability, gait speed, nutritional status, and autonomic symptoms

Figure 2: Phase 3 APOLLO Study Design



†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous use
*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine)

Results

APOLLO Baseline Demographics and Disease Characteristics

- Overall, 225 patients were enrolled in the APOLLO study with median age 62 years (24 – 83), 74.2% males, and 42.7% V30M (Table 1)
- Patients were enrolled globally from 44 sites in 19 countries: 21% in North America, 44% in Western Europe and 36% in Rest of World

Table 1: Baseline Demographics and Disease Characteristics (mITT Population)

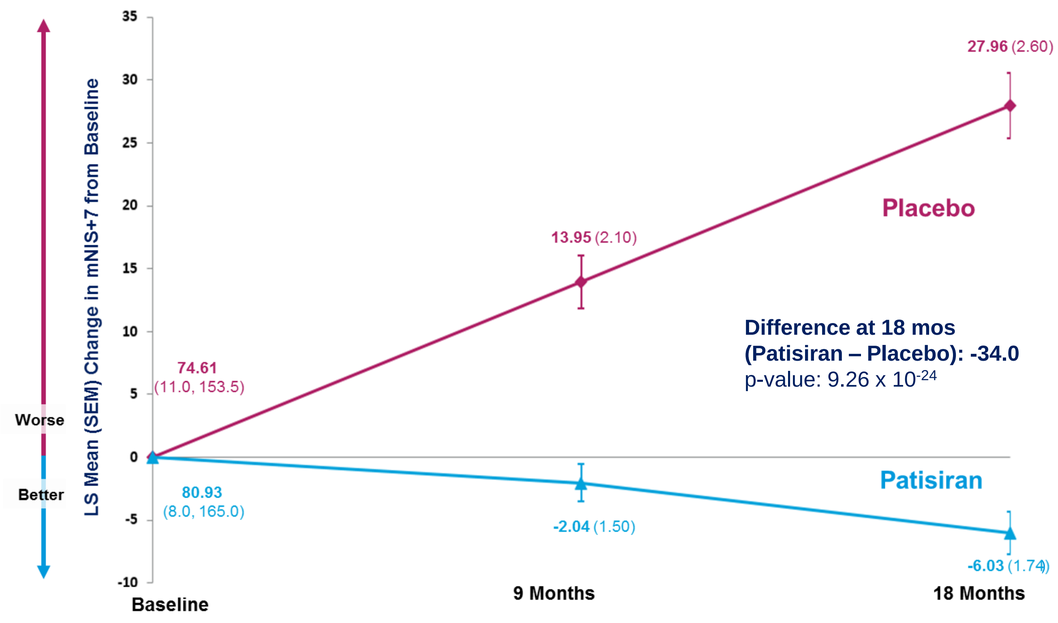
Demographics and Characteristics, n (%)	Placebo (N=77)	Patisiran (N=148)
Median Age, years (range)	63 (34, 80)	62 (24, 83)
Gender (Male)	58 (75.3)	109 (73.6)
V30M	40 (51.9)	56 (37.8)
Non-V30M†	37 (48.1)	92 (62.2)
NIS, mean (min, max)	57 (7.0, 125.5)	61 (6.0, 141.6)
PND Score		
I: preserved walking, sensory disturbances	20 (26.0)	36 (24.3)
II: impaired walking but can walk without stick or crutch	23 (29.9)	43 (29.1)
IIIa: walk with 1 stick or crutch	22 (28.6)	41 (27.7)
IIIb: walk with 2 sticks or crutches	11 (14.3)	28 (18.9)
IV: confined to wheelchair or bedridden	1 (1.3)	0
FAP Stage		
1: unimpaired ambulation	37 (48.1)	67 (45.3)
2: assistance with ambulation required	39 (50.6)	81 (54.7)
3: wheelchair bound or bedridden	1 (1.3)	0

†Represents 38 different mutations, with 5 most common including A97S, T60A, E89Q, S50R, and S77Y

mNIS+7: Change from Baseline to Month 18

- Compared to baseline, patients treated with patisiran had an improvement in neuropathy as measured by mNIS+7 (LS mean change: -6.0 points), while placebo patients worsened (LS mean change: + 28.0 points); benefit in mNIS+7 was seen in patisiran compared to placebo as early as 9 months (Figure 3)
- 56.1% of patients in the patisiran group demonstrated improvement in mNIS+7 compared to 3.9% of patients on placebo; odds ratio: 39.9; p=1.82 x 10^{-15}; improvement defined as <0 point increase from baseline to 18 months

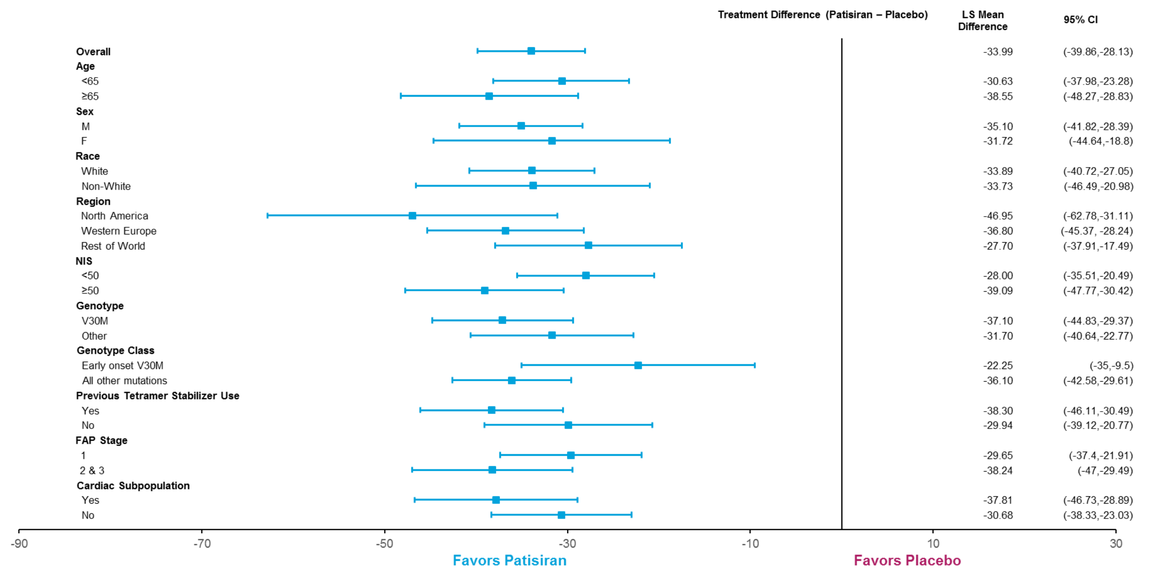
Figure 3: mNIS+7 LS Mean Change from Baseline



mNIS+7: Change from Baseline in Pre-Defined Subgroups

- A consistent treatment effect on mNIS+7 was observed across all pre-defined subgroups which included age, sex, race, region, baseline NIS, genotype, previous tetramer stabilizer use, FAP stage, and cardiac subpopulation (Figure 4)

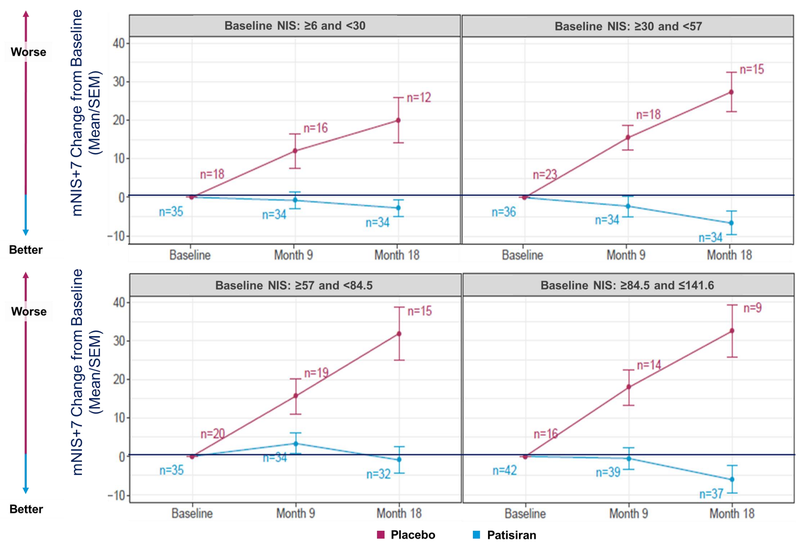
Figure 4: Change from Baseline to Month 18 in Overall mNIS+7 and Subgroups



mNIS+7 Change by Baseline NIS Quartile

- In a post-hoc analysis, patients were grouped into quartiles based on baseline NIS scores: ≥6 - <30, ≥30 - <57, ≥57 - <84.5, and ≥84.5 - <141.6; mean mNIS+7 change in baseline was calculated for each quartile by treatment group
- Within each baseline NIS quartile (Figure 5), mNIS+7 worsened in the placebo group, with mean changes from baseline at 18 months of 20.0, 27.4, 31.9, and 32.5 points going from lowest (less severe disease) to highest (more severe disease) quartiles
- In the patisiran group, mNIS+7 improved or remained stable within each quartile, mean change of -2.8, -6.6, -1.0, and -6.0 points at 18 months from lowest to highest quartiles, demonstrating benefit in patients with either early or advanced neuropathy at baseline

Figure 5: Mean mNIS+7 Change by Baseline NIS Quartile



Safety and Tolerability

- Majority of adverse events (AEs) were mild or moderate in severity (Table 2)
  - Peripheral edema (22.1% placebo, 29.7% patisiran): decreased over time; did not result in treatment discontinuation
  - Infusion-related reactions (IRRs) (9.1% placebo, 18.9% patisiran): majority mild with no severe or serious IRRs, decreased over time, 1 patient discontinued treatment
  - No safety concerns with regard to hematology including platelets, hepatic, or renal dysfunction

Table 2: APOLLO Safety and Tolerability

Type of Adverse Event‡, n (%)	Placebo (N=77)	Patisiran (N=148)
AE	75 (97.4)	143 (96.6)
Severe AE	28 (36.4)	42 (28.4)
Serious adverse event (SAE)	31 (40.3)	54 (36.5)
AE leading to treatment discontinuation	11 (14.3)	7 (4.7)
AE leading to study withdrawal	9 (11.7)	7 (4.7)
Death	6 (7.8)	7 (4.7)

‡Patients that experienced at least 1 event

Summary

- hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening, often fatal disease with high morbidity and mortality and limited therapeutic options
- Patisiran treatment resulted in significant improvement in polyneuropathy relative to placebo with positive effects observed across a wide range of baseline neuropathy severity
- Patisiran showed an encouraging safety and tolerability profile
  - Mortality rate trended lower in the patisiran group vs placebo group
  - Key patisiran safety findings include mild to moderate peripheral edema and IRRs; only one treatment discontinuation due to these events
  - No safety signals with regard to thrombocytopenia, hepatic or renal dysfunction

AE, adverse events; COMPASS-31, Composite Autonomic Symptom Score-31; LS mean, Least Squares mean; mBMI, modified Body Mass Index; GI, Gastrointestinal; mNIS+7, Modified Neuropathy Impairment Score + 7; NIS, Neuropathy Impariment Score; NIS-W; Neuropathy Impairment Score – Weakness; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disability Scale; RNAi, RNA interference; SAE, serious adverse events; WT, wild type; 10-MWT, 10-Mieter Walk Test; 95% CI, 95% Confidence Interval

References: 1. Hanna M. Curr Heart Fail Rep. 2014;11(1):50-57; 2. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540; 3. Adams D et al. Neurology. 2015;85(8):675-682; 4. Damy T et al. J Cardiovasc Transl Res. 2015;8(2):117-127; 5. Hawkins PN et al. Ann Med. 2015;47(8):625-638; 6. Plante-Bordeneuve. J Neurol. 2014;261:1227–33; 7. Swiecicki PL et al. Amyloid. 2015;22(2):123-31; 8. Sattianayagam AJ et al. Eur Heart J. 2012;33;1120; 9. Gertz MA et al. Mayo Clin Proc. 1992;67(5):428-40; 10. Mariani LL et al. Ann Neurol. 2015;78(6):901-16; 11. Suhr OB et al. Orphanet J Rare Dis. 2015;11:109; 12. Adams et al. Neurology. 2017;88:15 Supplement S27.004 (NCT01961921); 13. Adams D et al. BMC Neurology. 2017;17:181; 14. Adams, D. Orphanet J Rare Dis. 2017, 12(Suppl 1):O9 – oral presentation EU ATTR ; 02 Nov 17; 15. Clinicaltrials.gov: NCT02510261

Disclosures: Pritesh J Gandhi, Marianne Sweetser, Tim Lin, and Jared Gollob are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.

Alnylam® PHARMACEUTICALS