Impact of Patisiran on Autonomic Neuropathy in Hereditary Transthyretin-Mediated Amyloidosis Patients

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

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

Background and Rationale

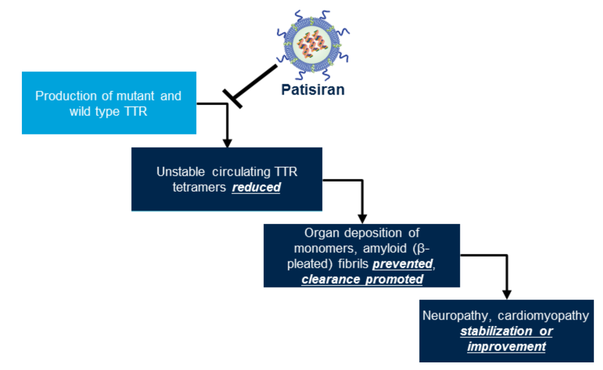
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- 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]
  - Disease penetrance and rate of progression may be influenced by TTR genotype[10]
- Accumulation of fibrils in nerves can lead to manifestations of polyneuropathy, including sensorimotor neuropathy and autonomic neuropathy, whereas accumulation in heart can lead to cardiomyopathy
- Autonomic dysfunction results in debilitating orthostatic hypotension, severe gastrointestinal symptoms (including early satiety, chronic nausea/vomiting, and both diarrhea and constipation leading to weight loss), bladder dysfunction with recurrent urinary tract infections, and cardiac arrhythmias[11]
- 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 Studies: positive multi-dose results in patients with hATTR amyloidosis[12]; 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[13]
- Phase 3, APOLLO: study met primary efficacy endpoint of modified Neuropathy Impairment Score (mNIS+7) and all secondary endpoints with favorable safety profile[14,15]
- Global-OLE: ongoing[16]

Figure 1: Patisiran Therapeutic Hypothesis



Objective

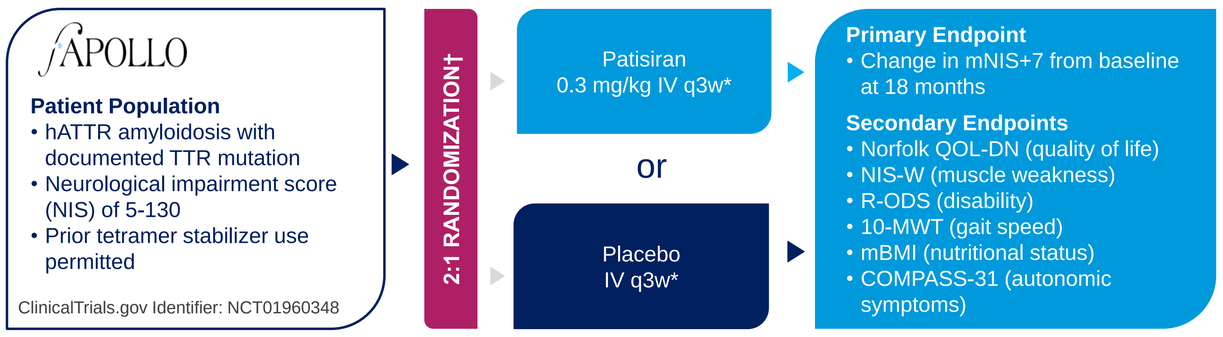
- Present data on measures of autonomic signs and symptoms in APOLLO, including postural blood pressure (BP), Norfolk Quality of Life-Diabetic Neuropathy questionnaire (Norfolk QOL-DN), and Composite Autonomic Symptom Score-31 (COMPASS-31)

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 the 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 indicated worsening of neuropathy (range 0 – 304)
  - Autonomic symptoms are evaluated by the postural BP component of mNIS+7[14]
- 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
- The Norfolk QOL-DN and the COMPASS-31 questionnaire were the secondary endpoints specific to autonomic symptoms[14]
  - Norfolk QOL-DN is a 35-item QOL questionnaire that is sensitive to small fiber, large fiber, and autonomic nerve function; higher score indicates worsening of QOL (range -4 – 136)
    - Five domains of Norfolk QOL-DN measure QOL pertinent to all aspects of polyneuropathy in hATTR amyloidosis, including large and small nerve fiber function, autonomic function, symptoms, and activities of daily living
    - Autonomic domain evaluates items related to GI denervation (e.g., postprandial vomiting, fluid reabsorption) and postural lightheadedness
  - COMPASS-31 is a measure of autonomic neuropathy symptoms, where a higher score indicates worsening of autonomic neuropathy symptoms (range 0-100)

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)

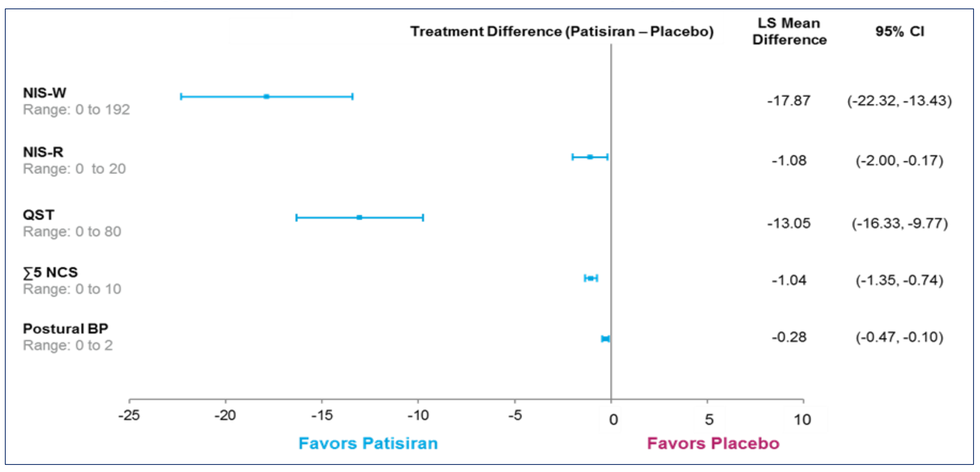
Demographics and Characteristic, n (%)	Placebo (N=77)	Patisiran (N=148)
Median Age, years (range)	63 (34, 80)	62 (24, 83)
Gender (Male)	58 (75.3)	109 (73.6)
V30M	40 (51.9)	56 (37.8)
Non-V30M†	37 (48.1)	92 (62.2)
NIS, mean (min, max)	57 (7.0, 125.5)	61 (6.0, 141.6)
PND Score		
I: preserved walking, sensory 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 in Total Score and Components

- LS mean change in mNIS+7 from baseline to month 18 was -6.0 for patisiran and 28.0 for placebo (LS mean difference of -34.0; $p=9.26 \times 10^{-24}$)
  - 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; $p=1.82 \times 10^{-15}$; improvement defined as <0 point increase from baseline to 18 months)
- At 18 months, improvement compared to placebo was seen for patisiran across all mNIS+7 components, including postural BP which had LS mean change (SEM) of -0.2 (0.05) for patisiran and 0.1 (0.08) for placebo (Figure 3)

Figure 3: Change from Baseline to Month 18 in mNIS+7 and Components



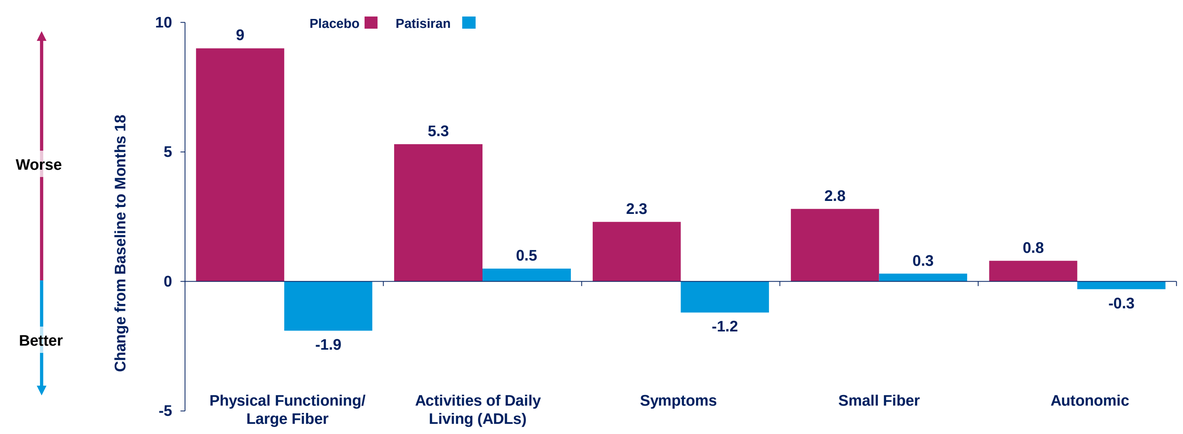
Norfolk QOL-DN: Change from Baseline to Month 18

- LS mean change from baseline to 18 months in Norfolk QOL-DN was -6.7 for patients on patisiran and 14.4 for patients on placebo (LS mean difference of -21.1; $p=1.10 \times 10^{-10}$)
  - 51.4% of patients in the patisiran group demonstrated improvement in Norfolk QOL-DN compared to 10.4% of patients on placebo (odds ratio: 10.0; $p=1.95 \times 10^{-10}$; improvement defined as <0 point increase from baseline to 18 months)

Norfolk QOL-DN: Change from Baseline to Month 18 in Individual Domains

- Patisiran demonstrated improvement across all domains of the Norfolk QOL-DN compared to placebo at 18 months (Figure 4)
- In the patisiran group, there was improvement in the autonomic domain with a change from baseline to month 18 of -0.3, compared to the placebo group which had a change from baseline to month 18 of 0.8

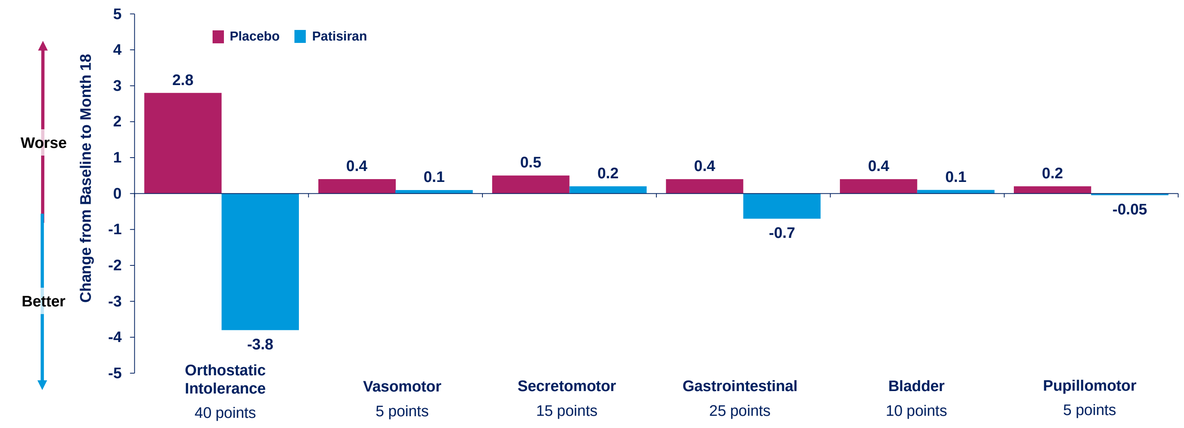
Figure 4: Change from Baseline to Month 18 in Norfolk QOL-DN Domains



COMPASS-31: Change from Baseline to Month 18

- LS mean change from baseline to 18 months was -5.3 for patients on patisiran and 2.2 for patients on placebo (LS mean difference of -7.5; p=0.0008)
- While all of the COMPASS-31 domains improved with patisiran relative to placebo, the orthostatic intolerance and gastrointestinal domains were impacted the most at 18 months, showing improvement relative to baseline in the patisiran group (Figure 5)

Figure 5: Change from Baseline to Month 18 in Domains of COMPASS-31



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 and quality of life relative to placebo and baseline, associated with improvement in multiple measures of autonomic symptoms and function
  - The improvement in dysautonomia included reduction of GI symptoms (e.g., diarrhea and constipation) and orthostatic intolerance (e.g., inability to stand upright)
- 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; BP, blood pressure; 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; NCS, Nerve Conduction Studies; NIS, Neuropathy Impairment Score; NIS-R; Neuropathy Impairment Score – Reflexes; NIS-W, Neuropathy Impairment Score – Weakness; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; PND, polyneuropathy disability; QST, Quantiative Sensory Testing; R-ODS, Rasch-built Overall Disabiity Scale; RNAi, RNA interference; SAE, serious adverse events; WT, wild type; 10-MWT, 10-Meter 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. Ando Y et al. Orphanet J Rare Dis. 2013;8:31; 12. Suhr OB et al. Orphanet J Rare Dis. 2015;10:109; 13. Adams et al. Neurology. 2017;88:15 Supplement S27.004 (NCT01961921); 14. Adams D et al. BMC Neurology. 2017:181; 15. Adams, D. Orphanet J Rare Dis. 2017, 12(Suppl 1):O9 – oral presentation EU ATTR; 02 Nov 17; 16. Clinicaltrials.gov: NCT02510261

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