Neuropathy Progression in Patients with hATTR Amyloidosis: Analysis of the APOLLO Placebo Arm

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Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, 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 of 3.4 years for patients presenting with cardiomyopathy[6-8]
- Multisystem disease with heterogenous clinical presentation; amyloid accumulation often leads to dysfunction in multiple organs, including peripheral nervous system, heart, gastrointestinal tract, and kidneys[2,9,10]
- Limited treatment options are available with a continued high unmet medical need for new therapies
- Methods to access neuropathy progression in patients with hATTR amyloidosis include neuropathy impairment score + 7 (NIS +7), and the modified neuropathy impairment score + 7 (mNIS+7) (Figure 1)
  - Higher score indicates worsening of neuropathy[11]

Natural History of Neuropathy Progression

- Cross-sectional natural history study evaluating neuropathy progression in 283 hATTR amyloidosis patients calculated an estimated rate of mNIS+7 increase of 17.8 points/year[12]
- Additionally, a placebo-controlled randomized control trial evaluating diflunisal found a NIS+7 increase of 25.0 points in the placebo treated patients over two years[13]

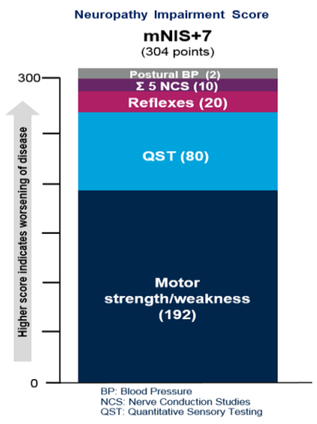
Patisiran

- Investigational RNAi therapeutic in development for the treatment of hATTR amyloidosis
- Patisiran demonstrated rapid and sustained reduction of mutant and wild-type TTR (wtTTR) by inhibiting the synthesis of disease-causing protein
- Phase 3 APOLLO Study: Patisiran demonstrated significant improvement in neuropathy (measured by mNIS+7) and Quality of Life (QOL) compared to placebo among patients with hATTR amyloidosis with polyneuropathy and was generally well-tolerated[14]
  - Patients in the placebo group experienced significant neuropathy progression at the end of this 18 month trial compared to baseline; 16% of patients withdrew from the study prior to completion due to progression

Objective

- Describe neuropathy progression in the placebo arm of the APOLLO study in patients with hATTR amyloidosis with polyneuropathy

Figure 1: mNIS+7



Methods

APOLLO Phase 3 Study Design

- Phase 3, randomized (2:1), double-blind study of patisiran 0.3mg/kg or placebo IV q3w in patients with hATTR amyloidosis with polyneuropathy[11,12]
- Primary endpoint change in mNIS+7 from baseline to 18 months
- Several additional endpoints were included to assess sensorimotor and autonomic neuropathy as well as other clinical manifestations of the disease; corresponding endpoint assessments included (Figure 2):
  - Sensorimotor neuropathy: Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN), Rasch-built Overall Disability Score (R-ODS), 10 Meter Walk Test (10-MWT), and Grip strength
  - Autonomic neuropathy: Composite Autonomic Symptom Score (COMPASS-31), modified Body Mass Index (mBMI), and Norfolk-QOL

Figure 2: APOLLO Assessments

	Sensorimotor Nerves	Autonomic Nerves
Clinical Manifestations[1-5]	• Loss of sensation • Muscle weakness • Impaired ambulation	• Orthostatic hypotension • Syncope/falls • Constipation/diarrhea • Urinary retention/UTIs
APOLLO Assessments	• mNIS+7 ○ NIS-W subdomain ○ QST subdomain ○ NIS-R subdomain • Norfolk-QOL • R-ODS Disability • 10-MWT • Grip strength	• mNIS+7 ○ Postural BP subdomain • Norfolk-QOL ○ Autonomic subdomain • mBMI • COMPASS-31

Neuropathy Impairment-Weakness (NIS-W), Neuropathy Impairment Score-Reflexes (NIS-R), Quantitative Sensory Testing (QST)

Results

APOLLO Baseline Demographics

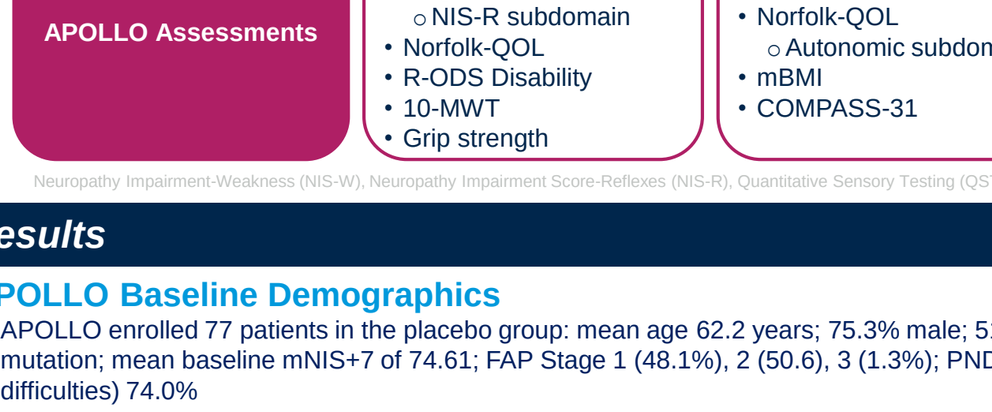
- APOLLO enrolled 77 patients in the placebo group: mean age 62.2 years; 75.3% male; 51.9% V30M mutation; mean baseline mNIS+7 of 74.61; FAP Stage 1 (48.1%), 2 (50.6), 3 (1.3%); PND>1 (walking difficulties) 74.0%

Measures of Neuropathy

mNIS+7

- Quantitative and referenced assessment to quantify motor, sensory, and autonomic components of the polyneuropathy in patients with hATTR amyloidosis
- At 9 and 18 months, neuropathy progression relative to baseline in patients on placebo was observed with an mNIS+7 LS mean increase (SEM) of 14.0 (2.1) and 28.0 (2.6) points, respectively
  - Neuropathy progression observed in patients with early and advanced neuropathy at baseline (Figure 3)
  - Neuropathy progression relative to baseline was observed with an increase across all components of mNIS+7: NIS-W of 17.93, NIS-R of 1.32, QST of 7.0, ∑5 NCS of 1.02, and Postural BP of 0.1

Figure 3: Neuropathy Progression Measured by mNIS+7 by NIS Quartiles in Placebo Group at Baseline, 9 and 18 months

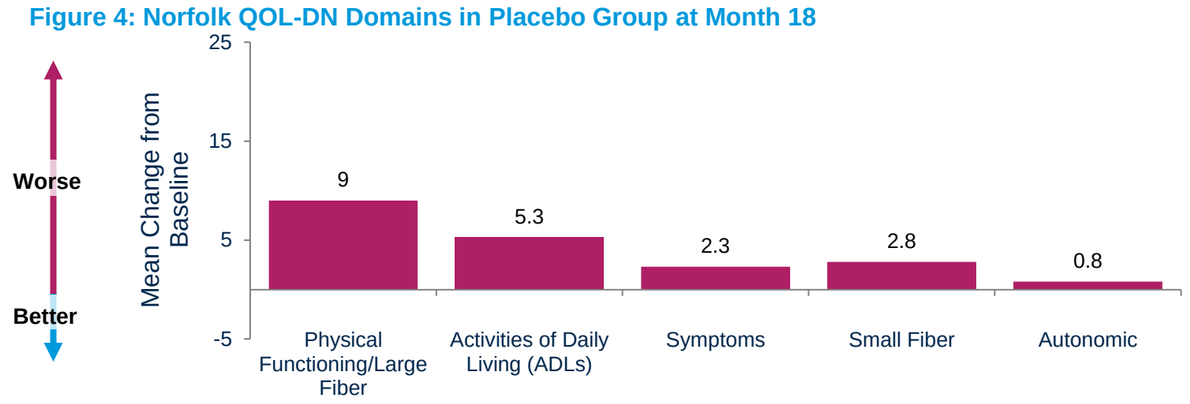


Norfolk QOL-DN

- 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)
- Patients on placebo had worsening QOL over time, demonstrated by a LS mean increase of 14.4 points at 18 months compared to baseline
- Disease worsening was observed across all five domains of Norfolk QOL-DN indicating progression of large and small nerve fiber neuropathy including autonomic neuropathy (Figure 4)

Results (Continued)

Figure 4: Norfolk QOL-DN Domains in Placebo Group at Month 18

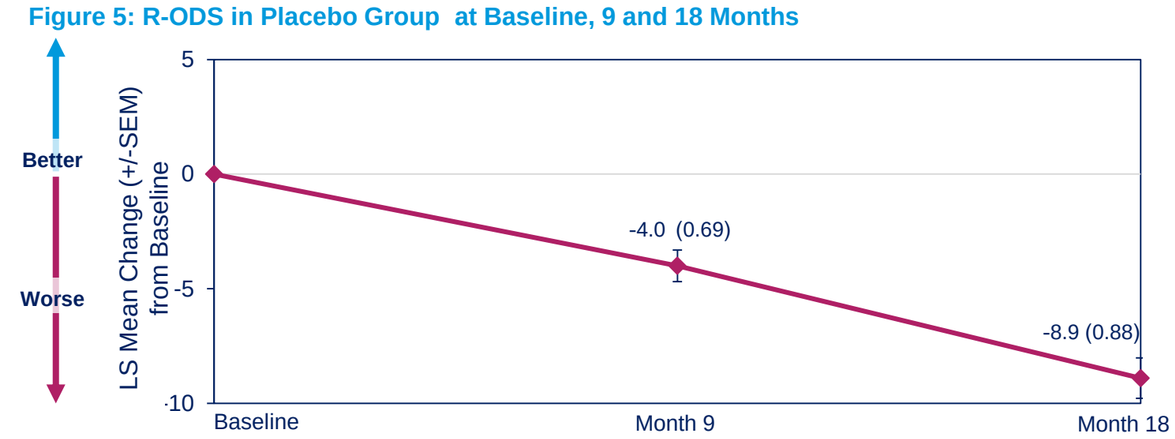


Additional Measures of Sensorimotor Neuropathy

R-ODS

- 24-item questionnaire used to capture activity and social participation (disability)
- Disability worsened relative to baseline at both 9 and 18 months (Figure 5)
- This accumulation of disability affected multiple different activities of daily living, ranging from reading a newspaper, eating, bathing and dressing to activities related to working such as walking, standing, taking public transportation, or carrying and putting down heavy objects

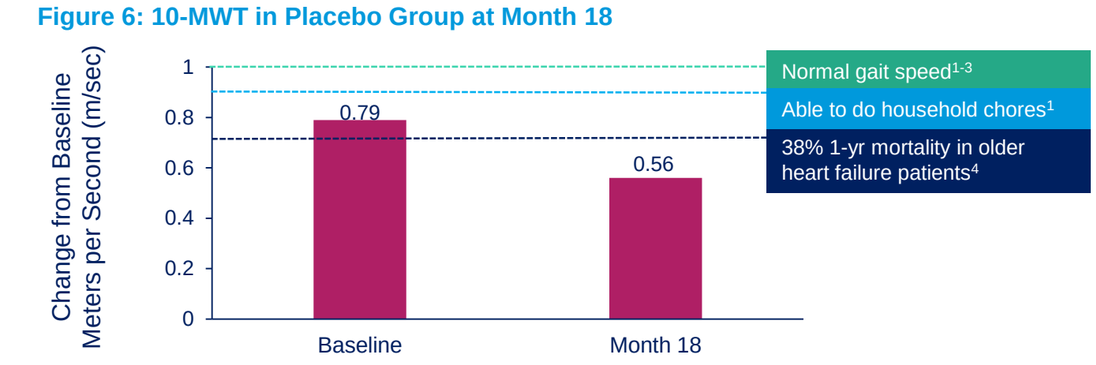
Figure 5: R-ODS in Placebo Group at Baseline, 9 and 18 Months



10-MWT

- Assessment of ambulation that measures gait speed
- Placebo-treated patients experienced a decline in gait speed at 18 months (LS mean change: -0.24m/sec), reflecting an approximately one-third reduction from baseline (Figure 6)

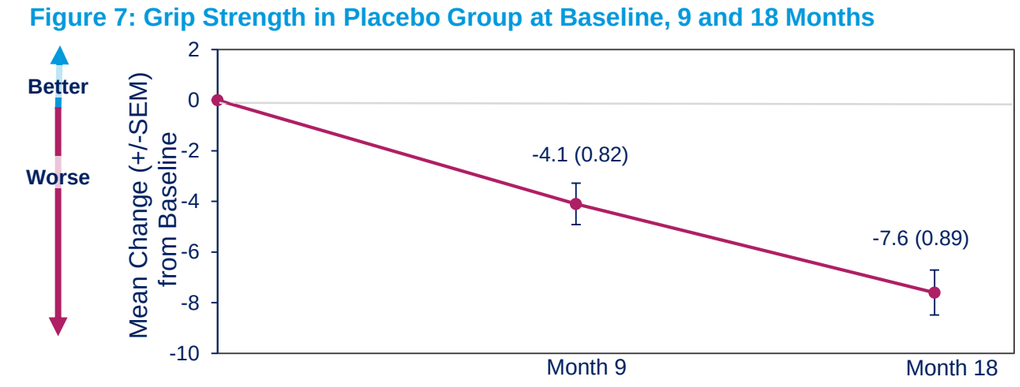
Figure 6: 10-MWT in Placebo Group at Month 18



Grip Strength

- Patients on placebo observed an LS mean change of -7.6 kg in grip strength over 18 months
- Worsening of grip strength and demonstration of upper extremity weakness were observed as early as 9 months (Figure 7)

Figure 7: Grip Strength in Placebo Group at Baseline, 9 and 18 Months

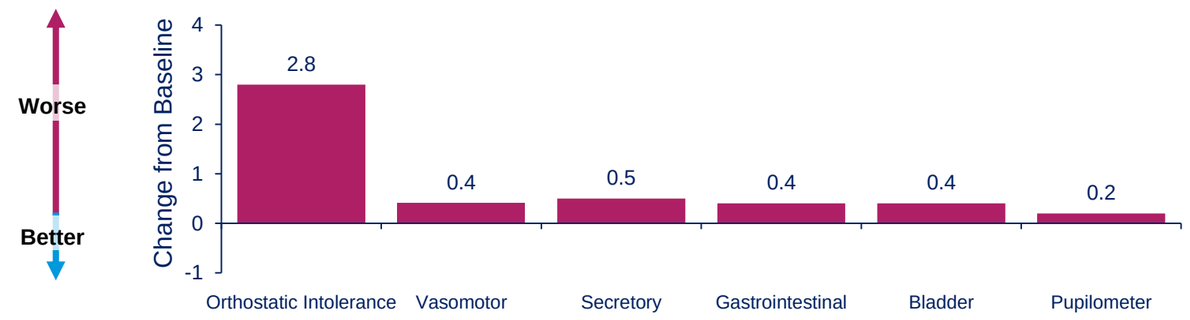


Additional Measures of Autonomic Neuropathy

COMPASS-31

- 31-item questionnaire used to evaluate patient reported autonomic neuropathy symptoms
- Patients on placebo showed a mean worsening of autonomic neuropathy symptoms with an LS mean change of 2.24 points decrease from baseline to 18 months
- Worsening of autonomic neuropathy was observed in all six domains of COMPASS-31 (Figure 8)

Figure 8: COMPASS-31 Domains in Placebo Group at Month 18



mBMI

- mBMI measurement used to accurately reflect nutritional status[15] in patients with low fluid retention
- Patients on placebo had worsening mBMI over time as demonstrated with a LS mean change of 119.4 kg/m^2 in mBMI at 18 months compared to baseline

Summary

- Consistent with previously published natural history data, patients in the placebo arm of the APOLLO experienced significant neuropathy progression at the end of this 18 month trial compared to baseline
- Across a variety of measures of sensorimotor and autonomic neuropathy, placebo patients with hATTR amyloidosis with polyneuropathy experienced substantial impairment, leading to worsening symptoms and decreased functional ability
- The rapid disease progression observed across all dimensions of polyneuropathy underscores the need for early administration of an effective therapy for patients with hATTR amyloidosis to prevent disability and morbidity accumulation

Abbreviations: hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; COMPASS-31, Composite Autonomic Symptom Score-31; mBMI, modified Body Mass Index; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; 10-MWT, 10-Meter Walk Test; PND, Polyneuropathy Disability; mNIS+7, Modified Neuropathy Impairment Score + 7; NIS; Neuropathy Impairments Score; NIS-R, Neuropathy Impairment Score – Reflexes; NCS, Nerve Conduction Studies; EQ-5D, European Quality of Life-5 Dimensions; R-ODS, Rasch-built overall disability scale; NIS-W, Neuropathy Impairment Score - Weakness; QST, Quantitative Sensory Testing; UTI, Urinary Tract Infections; RNAi, RNA interference; siRNA, small interfering ribonucleic acid; WT, wild-type; q3W, every 3 weeks; LS, least squares; SEM, standard error of the mean.

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