Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, inherited, rapid progression, 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.
- Affecting approximately 50,000 people worldwide,
- median survival of 4.7 years following diagnosis with a reduced survival of 4.4 years for patients presenting with cardiomyopathy.
- Multisystem disease with heterogeneous clinical presentation; amyloid accumulation often leads to dysfunction in multiple organs, including peripheral nervous system, heart, gastrointestinal tract, and kidney.
- Limited treatment options are available with a continued high unmet medical need for new therapies.

Methods

APOLLO Phase 3 Design
- Phase 3, randomized (2:1), double-blind study of patisiran 0.3 mg/kg or placebo IV q2W in patients with hATTR amyloidosis with polyneuropathy
- Primary endpoint change in mNIS+7 from baseline to 18 months
- Several additional endpoints 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-Neuropathy Domain (Norfolk QOL-DN), Racz-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-DN

Results

APOLLO Baseline Demographics
- APOLLO enrolled 77 patients in the placebo group: mean age 62.2 years; 75.3% male; 51.9% TTRm mutation; mean baseline mNIS+7 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 neuropathy 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
- 36-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 worsened 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)

Additional Measures of Autonomic Neuropathy

COMPASS-31
- 31-item questionnaire used to evaluate patient reported autonomic symptoms
- Patients on placebo showed a mean worsening of autonomic neuropathy symptoms with an LS mean change of 2.4 points decrease from baseline to 18 months.
- Worsening of autonomic neuropathy was observed in all six domains of COMPASS-31 (Figure 8)

Summary
- Consistent with previously published natural history data, patients in the placebo arm of the APOLLO study 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 disability, 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.