Impact of Patisiran on Overall Health Status in hATTR Amyloidosis: Results from the APOLLO Trial

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Background and Rationale

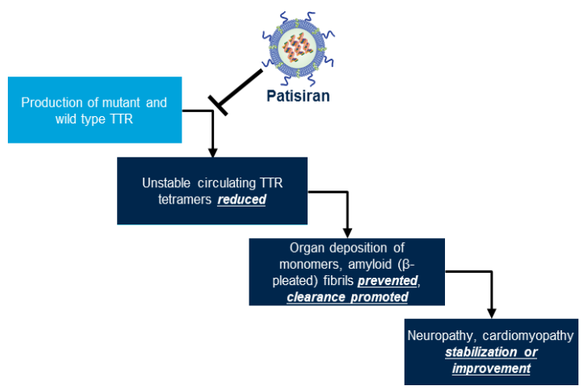
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- 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 gastrointestinal 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 the peripheral nervous system, heart, gastrointestinal tract, and kidneys[2,9,10]
- More than 120 pathologic TTR mutations have been identified, with V30M mutation as the most common worldwide[11]
- Limited treatment options, such as tetramer stabilizers, are available; continued high unmet medical need for novel therapeutic options

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 (Figure 1)
- Phase 3, APOLLO: study met the primary efficacy endpoint of modified Neuropathy Impairment Score (mNIS+7) and all secondary endpoints with favorable safety profile[12,13]

Figure 1: Patisiran Therapeutic Hypothesis



Objective

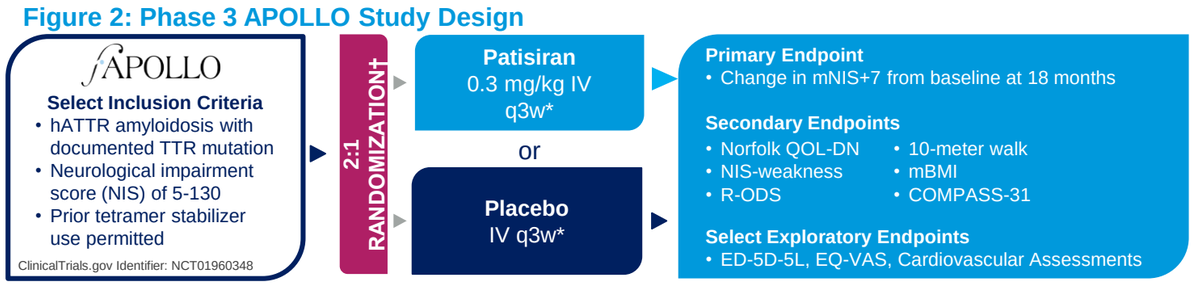
- Evaluate the impact of patisiran on overall health in patients enrolled in APOLLO

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[12,13] (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 polyneuropathy in patients with hATTR amyloidosis; higher score indicates worsening neuropathy (range 0 – 304)
- Norfolk Quality Of Life - Diabetic Neuropathy (Norfolk QOL-DN) questionnaire was the key secondary endpoint sensitive to small fiber, large fiber, and autonomic nerve function
  - Range of possible scores is -4 to 136; decrease from baseline score represents improvement in QOL
- Overall health status was an exploratory endpoint assessed using EuroQOL-5-dimension 5-level (EQ-5D-5L) and EuroQOL visual analogue scale (EQ-VAS)
  - EQ-5D-5L is a standardized measure of health status based on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
  - EQ-VAS is a patient's global impression of their overall health and is evaluated on a scale of 0 (worst possible health) to 100 (best possible health)
  - Preservation was defined as no change in score and improvement was defined as decrease in score from baseline
- Endpoints were analyzed using the MMRM method in the mITT population

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

- 225 patients with hATTR amyloidosis with polyneuropathy from 44 sites in 19 countries enrolled between December 2013 and January 2016 (Table 1)

Table 1: APOLLO Baseline Demographics and Disease Characteristics

Demographic, n (%)	Placebo (N=77)	Patisiran (N=148)
Median Age, years (range)	63 (34, 80)	62 (24, 83)
Gender, males	58 (75.3)	109 (73.6)
hATTR Diagnosis		
Years since hATTR diagnosis, mean (min, max)	2.6 (0.0, 16.5)	2.4 (0.0, 21.0)
TTR Genotype		
V30M	40 (51.9)	56 (37.8)
nonV30M‡	37 (48.1)	92 (62.2)
Previous tetramer stabilizer use	41 (53.2)	78 (52.7)
NIS^, Mean (min, max)	57 (7.0, 125.5)	61 (6.0, 141.6)
<50	35 (45.5)	62 (41.9)
≥50 - <100	33 (42.9)	63 (42.6)
≥100	9 (11.7)	23 (15.5)
Cardiac Subpopulation#	36 (46.8)	90 (60.8)

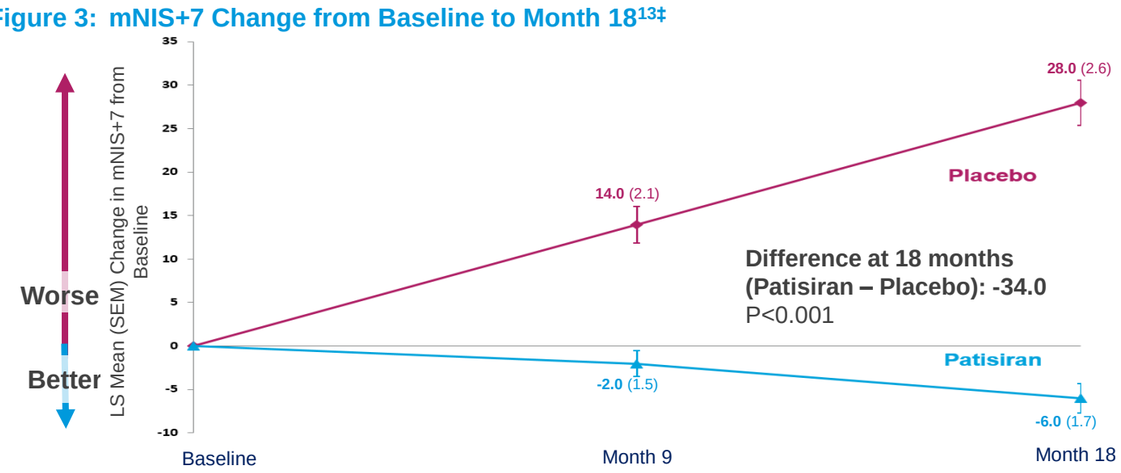
‡Represents 38 different TTR mutations
^Neuropathy Impairment Score is a composite score of lower limbs, upper limbs and cranial nerves measuring weakness, sensation, and reflexes (range: 0-244)
#Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 13 mm and no aortic valve disease or hypertension in medical history)

Results (continued)

Primary Endpoint: mNIS+7

- Statistically significant improvement in neuropathy, as measured by change from baseline in mNIS+7, was seen for patisiran relative to placebo at 18 months, with a LS mean difference of
- -34.0 (3.0) points (Figure 3)

Figure 3: mNIS+7 Change from Baseline to Month 18‡



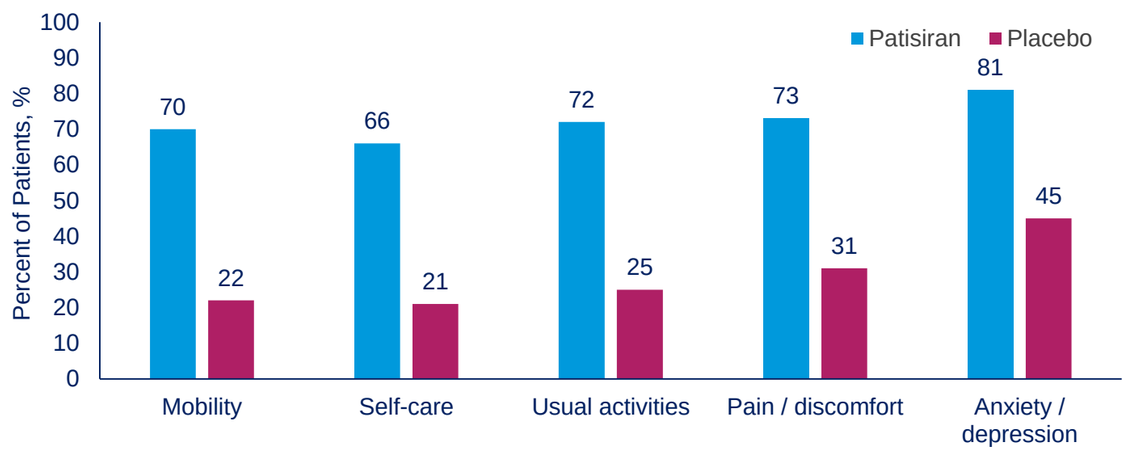
Secondary Endpoint: Norfolk QOL-DN

- Patisiran treatment led to statistically significant improvements in Norfolk QOL-DN compared with placebo at 18 months, with an LS mean (SEM) difference of -21.1 (3.1) points
- Patients on placebo had worsening QOL over time, demonstrated by a LS mean (SEM) 14.4 (2.7) point increase in Norfolk QOL-DN compared with baseline, while patisiran group improved compared with baseline with an LS mean (SEM) change of -6.7 (1.8) points at 18 months

Exploratory Endpoint: EQ-5D-5L

- At 18 months, patients on patisiran showed an overall improvement in EQ-5D-5L by an LS mean difference of 0.20 points compared to patients on placebo; improvement was evident at 9 months (LS mean difference between groups: 0.09 points) in favor of patisiran
- A larger proportion of patients on patisiran than placebo, respectively, showed preservation or improvement in EQ-5D-5L relative to baseline in each domain (Figure 4)

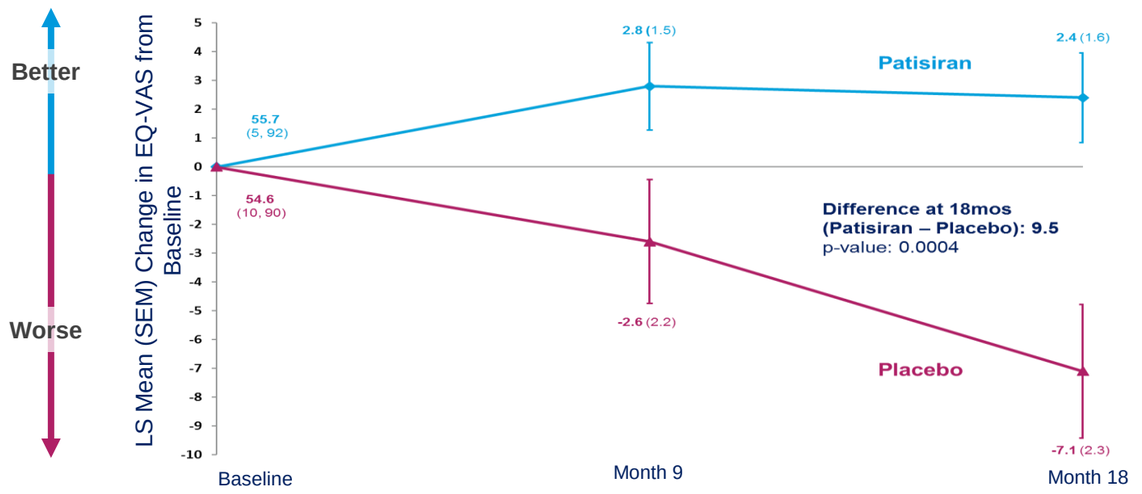
Figure 4: Preservation or Improvement in EQ-5D domains from Baseline to 18 months



Exploratory Endpoint: EQ-VAS

- Overall health, measured by EQ-VAS, improved (2.4 average point increase) in patients on patisiran whereas EQ-VAS declined (7.1 average point decrease) in patients on placebo indicating a 9.5 point difference (Figure 5) in favor of patisiran

Figure 5: Change in EQ-VAS from Baseline to 18 months



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

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
- Patients in the patisiran group in APOLLO consistently experienced improvement in overall health status as measured by EQ-5D-5L and EQ-VAS
- A greater number of patisiran patients reported preservation or improvement in EQ-5D-5L domains compared to placebo treated patients
- Improvement in overall health status in patients treated with patisiran was consistent with improvement in other measures of efficacy such as mNIS+7 and Norfolk QOL-DN
- Patisiran showed an encouraging safety and tolerability profile

Abbreviations: COMPASS-31, Composite Autonomic Symptom Score-31; mBMI, modified Body Mass Index; mNIS+7, Modified Neuropathy Impairment Score + 7; NIS; Neuropathy Impariments Score; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; 10-MWT, 10-Meter Walk Test; RNAi, RNA interference; WT, wild-type: EQ-5D, European Quality of Life-5 Dimensions; EQ-VAS, EuroQoL visual analogue scale; EQ-5D-5L, EuroQoL 5 dimensions-5L; MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; TTR, transthyretin; R-ODS, Rasch-built overall disability scale; V30M, Val30Met; q3W, every 3 weeks; LS, least squares; SEM, standard error of the mean
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