APOLLO, a Phase 3 Study of Patisiran for the Treatment of Hereditary Transthyretin-Mediated Amyloidosis: 18-Month Safety and Efficacy in Subgroup of Patients with Cardiac Involvement

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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 (3.4 years) for patients presenting with cardiomyopathy[6-8]
- Multi-systemic amyloid accumulation often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, gastrointestinal tract, and kidneys[2,9,10]
- 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 the heart can lead to cardiomyopathy
- Disease penetrance and rate of progression may be influenced by TTR genotype[11]
- Limited treatment options are available
- Continued high unmet medical need for novel therapeutic options

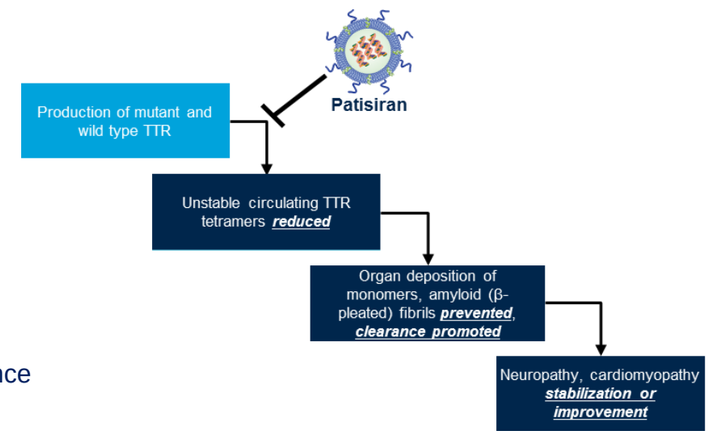
Patisiran

- 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[12]
- Phase 2 Open-Label Extension (OLE): trial completed with sustained mean serum TTR knockdown of 80%, 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 (mNIS+7) and all secondary endpoints with a favorable safety profile[14,15]
- Global-OLE: ongoing[16]

Objective

- Assess the effects of patisiran on cardiac structure and function in a pre-defined subpopulation of APOLLO patients with echocardiographic evidence of cardiac amyloid involvement at study entry

Figure 1: Patisiran Therapeutic Hypothesis

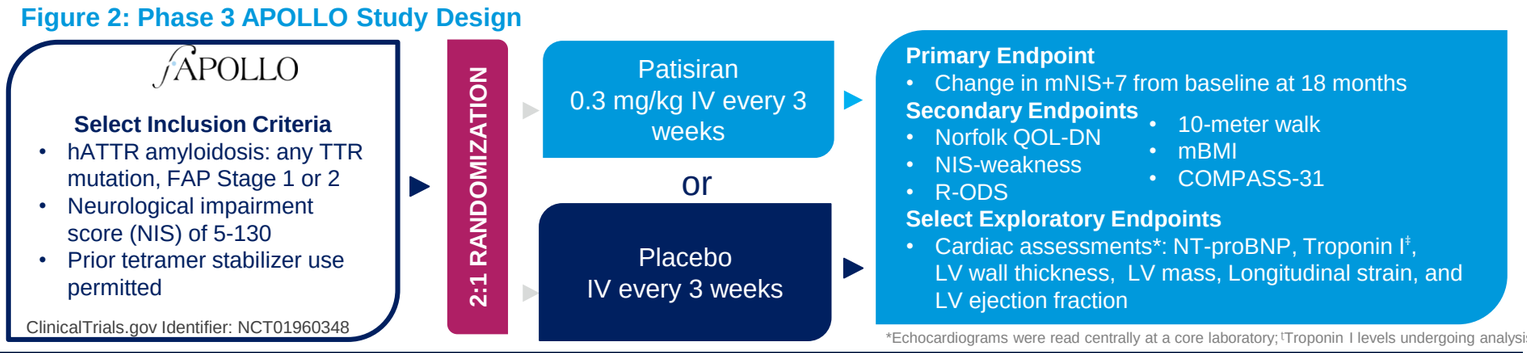


Methods

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)
- Cardiac efficacy evaluated in pre-defined cardiac subpopulation that included patients with baseline left ventricular (LV) wall thickness ≥13mm without possible confounding effects of aortic valve disease or hypertension
- Cardiac safety assessed in all patients (mITT population)
- Primary endpoint was the change in the modified Neuropathy Impairment Score (mNIS+7) from baseline at 18 months; secondary endpoints and exploratory endpoints are shown in Figure 2

Figure 2: Phase 3 APOLLO Study Design



*Echocardiograms were read centrally at a core laboratory; ‡Troponin I levels undergoing analysis

Results

APOLLO Baseline Demographics

- Overall, 225 patients with 39 different genotypes were enrolled in the APOLLO study, of which 126 (56%) qualified for the pre-defined cardiac subpopulation (Table 1)

Table 1: Baseline Demographics of the Pre-defined Cardiac Subpopulation

Characteristic, n (%)	Placebo (N=77)	Patisiran (N=148)
Cardiac Subpopulation	36 (46.8)	90 (60.8)
Median Age, years (IQR)	62 (57, 72)	60 (54, 66)
Gender (Male)	30 (83.3)	68 (75.6)
Non-V30M	24 (66.7)	68 (75.6)
V30M	12(33.3)	22 (24.4)
NYHA Class I	16 (44.4)	34 (37.8)
NYHA Class II	20 (55.6)	56 (62.2)
NT-proBNP (pg/mL)		
Median (IQR)	845.7 (373.2, 1581.7)	756.4 (285.4, 2432.4)
Geometric Mean (CV%)	711.1 (190.8)	726.9 (220.3)
Echocardiographic Parameters Median (IQR)		
LV Wall Thickness (mm)	16.2 (14.9, 17.9)	16.4 (14.8, 18.6)
Global Longitudinal Strain (%)	-15.5 (-18.0, -12.8)	-15.1 (-17.2, -12.6)
LV Mass (g)	243.7 (206.2, 341.0)	270.9 (216.0, 322.8)
Mean LVEF (%), (SD)	62.2 (8.6)	60.0 (9.9)

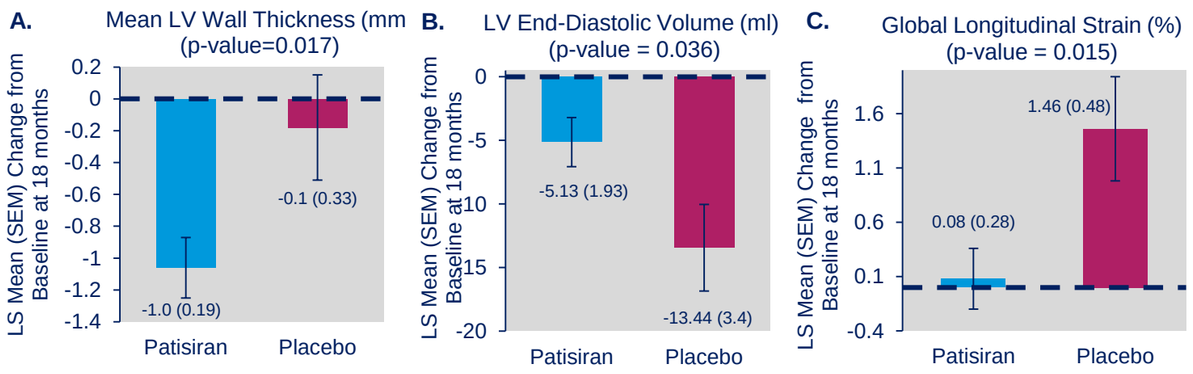
Blue, bolded text indicates ≥10% difference in either group

IQR, interquartile range; CV, Coefficient of variation; LV, left ventricular; LVEF, left ventricular ejection fraction; SD, standard deviation

Overall Improvement in Echocardiographic Parameters

- Patisiran treatment resulted in significant improvement in mean LV wall thickness, LV end-diastolic volume, and global longitudinal strain compared to placebo at 18 months (Figures 3A-C)
- Improvement was seen in additional echocardiographic parameters at 18 months: interventricular septum thickness, posterior wall thickness, LV relative wall thickness, cardiac output, and LV mass

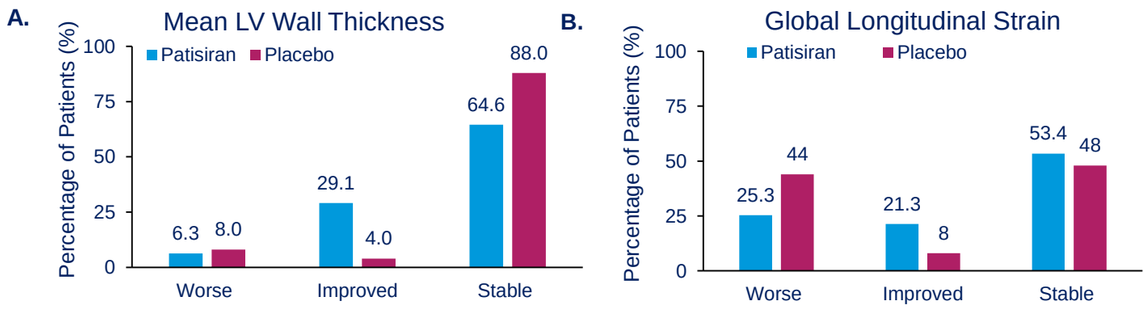
Figure 3: Select Echocardiographic Parameters Following 18 months of Treatment



Improvement in Mean LV Wall Thickness and Global Longitudinal Strain

- A greater proportion of patients in the patisiran group had a reduction in mean LV wall thickness >2 mm (Figure 4A) and absolute improvement in longitudinal strain of >2% (Figure 4B) compared with placebo (29.1% vs. 4.0% and 21.3% vs. 8.0%, respectively)
- Smaller proportion of patients in the patisiran group had an absolute worsening in global longitudinal strain of >2% at compared to placebo (25.3% vs. 44.0%, respectively) (Figure 4B)

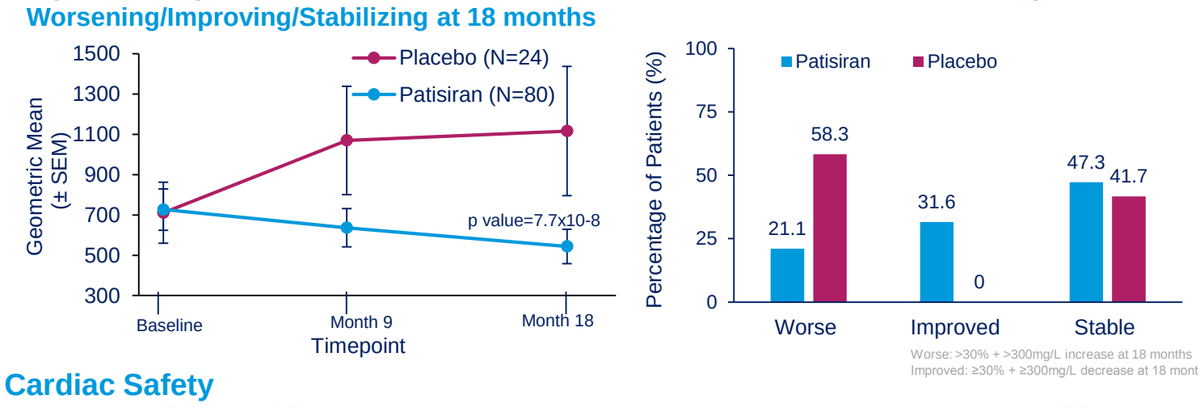
Figure 4: Mean LV Wall Thickness and Global Longitudinal at 18 Months



Improvement in NT-proBNP Levels and Gait Speed

- Patisiran significantly lowered NT-proBNP relative to placebo at 18-months with a greater proportion of patients in the patisiran group improving and a lower proportion worsening (Figure 5)
- Patisiran had a favorable effect on 10-MWT gait speed, demonstrating an increase of 0.35 m/s (95% CI 0.242, 0.466) compared with placebo

Figure 5: NT-proBNP Levels Over 18 Months and Percent of Patients with NT-proBNP Worsening/Improving/Stabilizing at 18 months



Cardiac Safety

- Cardiac AEs and SAEs occurred at similar frequency in both treatment groups in the mITT population (Table 2)
- Frequency and causes of deaths between placebo and patisiran arm were similar and consistent with natural history

Table 2: Safety and Tolerability Over 18 Months of Treatment in the mITT Population

Type of Adverse Event, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Cardiac Disorders SOC AEs	28 (36.4)	42 (28.4)
Cardiac Disorders SOC SAEs	10 (13.0)	20 (13.5)
Cardiac Arrhythmias (HGLT)	22 (28.6)	28 (18.9)
Torsades de Pointes SMQ[t]	14 (18.2)	8 (5.4)
Cardiac Failure SMQ (narrow)^	8 (10.4)	14 (9.5)
Deaths	6 (7.8)	7 (4.7)

SOC, System Organ Class; HGLT, high-level group term; SMQ, standardized MedDRA queries
[t] Events were summarized using a standard MedDRA query for events that may be associated with Torsades; it does not mean that these are confirmed events of Torsades. No events of Torsades have been reported.
^Events included: congestive cardiac failure, acute and chronic cardiac failure, pulmonary edema, cardiogenic shock, right ventricular failure

Summary

- APOLLO, the largest controlled study of patients with hATTR amyloidosis with polyneuropathy to date and representative of the global patient population, had a significant percentage (56%) of patients with echocardiographic evidence of cardiac amyloid involvement at study entry (cardiac subpopulation)
- In the cardiac subpopulation, treatment with patisiran for up to 18 months resulted in significant improvement relative to placebo in measures of cardiac structure and function, including reduction of ventricular wall thickness and improvement in global longitudinal strain
- At 18 months, patisiran treatment led to significant reduction in NT-proBNP, observed as early as 9 months, with patients showing an overall improvement compared to the majority of placebo patients who worsened
- Patisiran treatment led to clinically significant improvement in functional status as measured by 10-MWT gait speed relative to placebo, and was generally well tolerated
- Collectively, these data suggest patisiran may halt or reverse the progression of cardiomyopathy due to hATTR amyloidosis

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 Impairments Score; NIS-W; Neuropathy Impairment Score – Weakness; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; NT-proBNP, N-terminal of pro-Brain Natriuretic Peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disability Scale; RNAi, RNA interference; SAE, serious adverse events; WT, wild type.; 10-MWT, 10-Minute 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. Swiecicki PL, et al. Amyloid 2015;22(2):123-31; 7. Sattianayagam AJ, et al. Eur Heart J 2012;33;1120; 8. Gertz MA, et al. Mayo Clin Proc 1992;67(5):428-40; 9. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 10. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748; 11. Mariani LL et al. Ann Neurol. 2015;78(6):901-16; 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;17:181; 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, Jihong Chen, Sunita Goyal and Jared Gollob are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.