Transthyretin Reduction with Patisiran in the APOLLO Phase 3 Study

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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]
  - Circulating TTR is a liver-derived tetrameric protein, the primary function of which is to transport vitamin A through binding of the retinol binding protein (RBP)-retinol complex; also plays minor role in binding thyroxine[6-10]
- Affecting approximately 50,000 people worldwide[5,11]; median survival of 4.7 years following diagnosis with a reduced survival (3.4 years) for patients presenting with cardiomyopathy[12-14]
- 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 heart can lead to cardiomyopathy
  - Disease penetrance and rate of progression may be influenced by TTR genotype[15]
- Limited treatment options are available; thus there is a continued high unmet medical need for novel therapeutic options

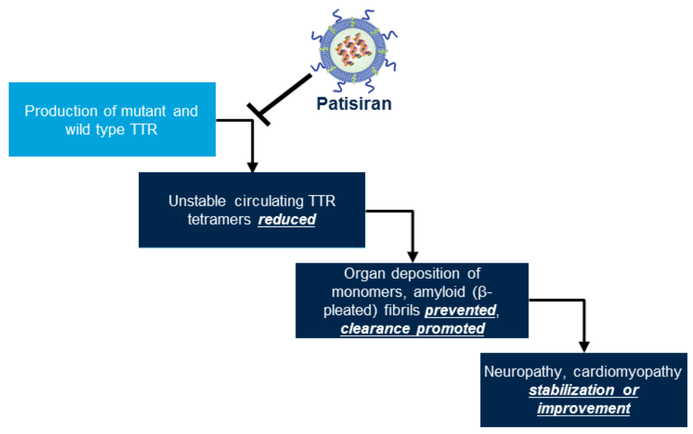
Patisiran

- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR (Figure 1)
- Phase 2: positive multi-dose results in patients with hATTR amyloidosis[16]
- Phase 2 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[17]
- Phase 3, APOLLO: study met the primary efficacy endpoint of modified Neuropathy Impairment Score (mNIS+7) and all secondary endpoints with favorable safety profile[18,19]
- Global-OLE: ongoing[20]

Objective

- Investigate degree of reduction for TTR, RBP, and vitamin A achieved in patients in the patisiran group in APOLLO

Figure 1: Patisiran Therapeutic Hypothesis

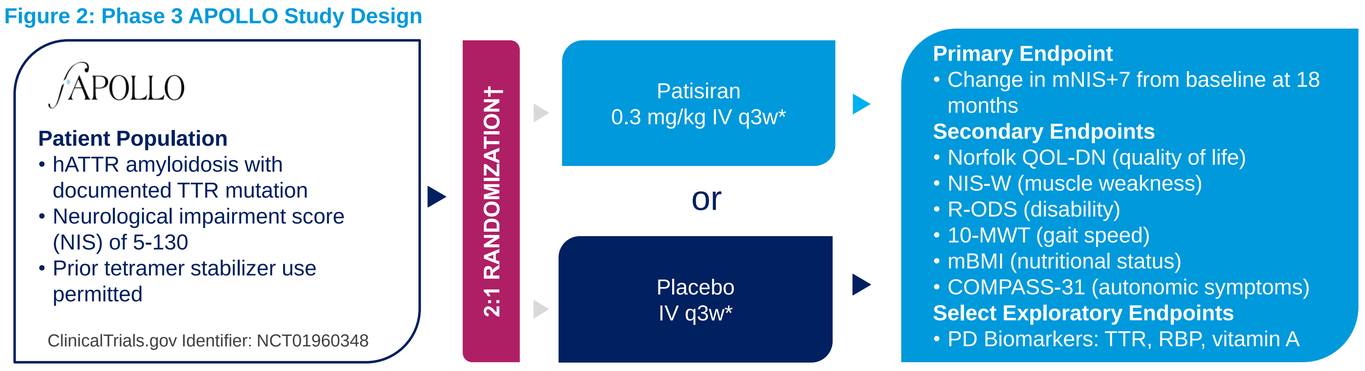


Methods

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)
- Primary endpoint was the change in the modified 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; autonomic symptoms are evaluated by the postural blood pressure (PBP) component of mNIS+7[18]
- Secondary endpoints are shown in Figure 2 and 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
- Exploratory endpoints included assessment of pharmacodynamics (PD) through measurements of serum TTR, RBP, and vitamin A levels
  - Serum TTR was assessed using ELISA and serum RBP was quantified using nephelometry
  - Blood samples for serum vitamin A levels were obtained prior to dosing with study drug and vitamin A supplementation, as applicable

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)
Serum TTR, mean (mg/L)	198.8	196.5
Serum RBP, mean (mg/dL)	3.85	3.89
Serum Vitamin A, mean (ug/dL)	37.0	37.8
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

Serum TTR Percent Reduction (Figure 3)

- In the patisiran group, the mean TTR percent reduction from baseline was 73.5% at Week 3 (Day 22, prior to second dose of patisiran) while the mean percent reduction at day 22 in the placebo group was 9.3%
- TTR percent reduction of >80% was maintained with patisiran over the duration of the study (Figure 3 and Table 2)
  - Mean TTR reduction was 82.6% and 84.3% at 9 and 18 months, respectively
  - The mean max serum TTR reduction over 18 months was 87.8%
- Similar TTR percent reduction was seen in both the V30M and non-V30M genotypes

Figure 3: Mean (+/- SEM) Serum TTR (ELISA) Percent Change over Time (mITT Population)

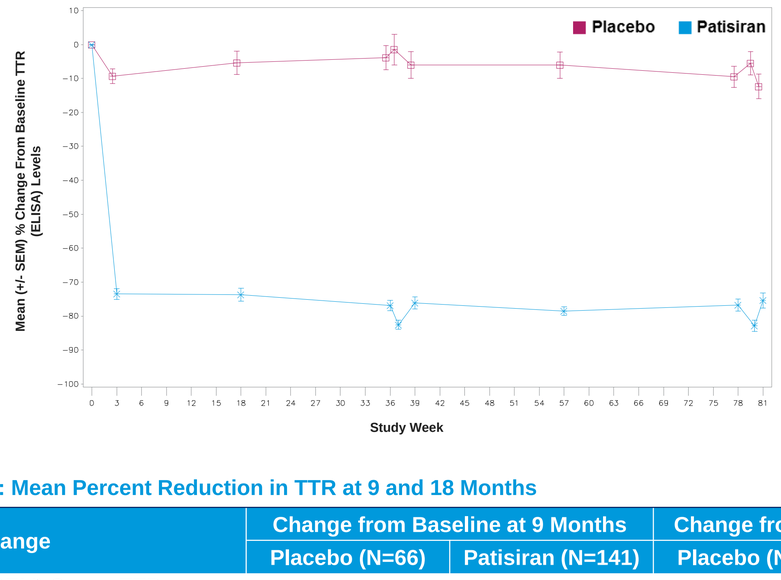


Table 2: Mean Percent Reduction in TTR at 9 and 18 Months

TTR Change	Change from Baseline at 9 Months		Change from Baseline at 18 Months	
	Placebo (N=66)	Patisiran (N=141)	Placebo (N=47)	Patisiran (N=130)
Mean (SEM) Serum TTR Percent Reduction	1.5% (4.5)	82.6% (1.4)	4.8% (3.4)	84.3% (1.5)

RBP Change over 18 Months (Figure 4)

- Mean serum RBP percent reduction was 47.1% and 46.6% at 9 and 18 months, respectively, in the patisiran group (Table 3)

Figure 4: Mean (+/- SEM) Retinol Binding Protein (mg/dL) Percent Change over Time (mITT Population)

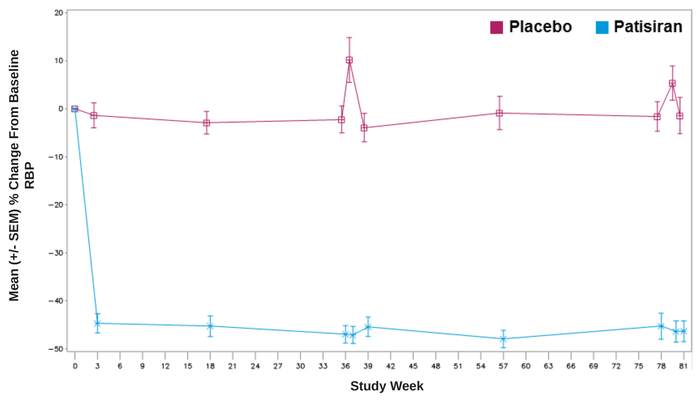


Table 3: Mean Percent Reduction in RBP at 9 and 18 Months

RBP Change	Change from Baseline at 9 Months		Change from Baseline at 18 Months	
	Placebo (N=65)	Patisiran (N=137)	Placebo (N=46)	Patisiran (N=129)
Mean (SEM) Serum RBP Percent Reduction	-10.2% (4.7)	47.1% (1.8)	-6.3% (3.5)	46.6% (2.3)

Vitamin A Change over 18 Months (Figure 5)

- In the patisiran group, mean vitamin A percent reduction was 66.1% and 67.0% at 9 and 18 months, respectively (Table 4)

Figure 5: Mean (+/- SEM) Vitamin A (ug/dL) Percent Change over Time (mITT Population)

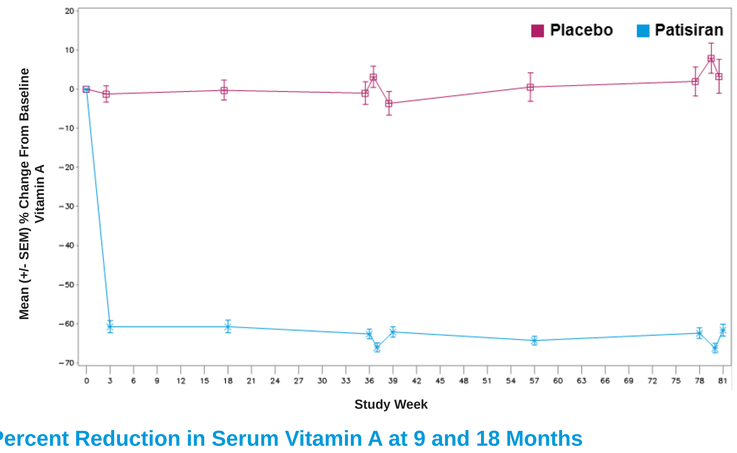


Table 4: Mean Percent Reduction in Serum Vitamin A at 9 and 18 Months

Vitamin A Change	Change from Baseline at 9 Months		Change from Baseline at 18 Months	
	Placebo (N=66)	Patisiran (N=137)	Placebo (N=47)	Patisiran (N=127)
Mean (SEM) Serum Vitamin A Reduction	-3.2% (2.7)	66.1% (1.1)	-8.8% (3.8)	67.0% (1.2)

Safety and Tolerability

- Majority of adverse events (AEs) were mild or moderate in severity (Table 5)
  - 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
- No clinical manifestations of vitamin A deficiency or thyroid disorders

Table 5: 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 robust and durable serum TTR reduction throughout 18 months, with consistent reductions in RBP and vitamin A
  - Similar effect on TTR reduction seen in V30M and non-V30M genotypes
- 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; one treatment discontinuation due to these events
  - No clinical manifestations of vitamin A deficiency

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 Impariments Score; NIS-W, Neuropathy Impairment Score – Weakness; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Polyneuropathy Questionnaire; 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-Meter Walk Test; 95% CI, 95% Confidence Interval.

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