Impact of Patisiran on Norfolk Quality of Life Questionnaire Diabetic Neuropathy in Patients with Hereditary Transthyretin-Mediated Amyloidosis: Results from the Cardiac Subpopulation in the Phase 3 APOLLO Study

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Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Disease Overview and Introduction to Patisiran, an Investigational RNAi Therapeutic

- **hATTR Amyloidosis**
  - Rare, inherited, rapidly progressive, debilitating, life-threatening disease caused by mutations in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract[1-5]
  - Median survival 4.7 years following diagnosis[6]; reduced survival (3.4 years) for patients presenting with cardiomyopathy[6-8]

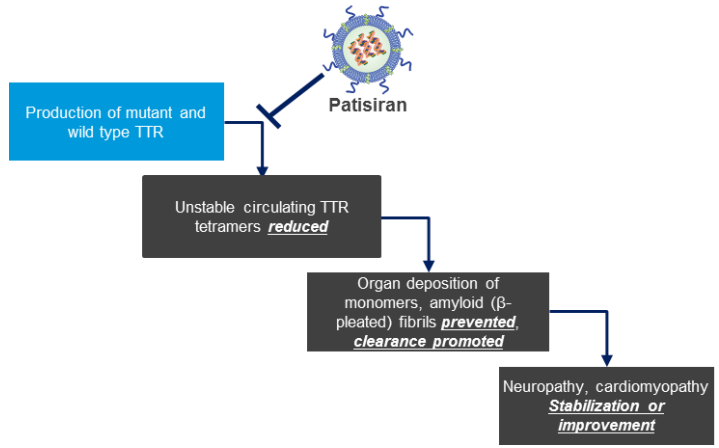
- Multisystem disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms[2,9,10]
  - Disease continuum includes patients who present with predominantly polyneuropathy symptoms (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many patients experience a variety of symptoms
    - Clinical manifestations (e.g., disease penetrance and rate of progression) is influenced by TTR genotype and geographical region

- Limited treatment options
  - Liver transplant for early-stage disease and TTR tetramer stabilizers
    - Tafamidis approved in EU for Stage 1 hATTR amyloidosis[11] and certain other countries outside U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[12]

- Continued high unmet medical need for novel therapeutics

- **Patisiran, an Investigational RNAi Therapeutic**
  - Lipid nanoparticle formulated RNAi, administered by IV infusion, targeting hepatic production of mutant and wild-type TTR

Patisiran Therapeutic Hypothesis



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Patisiran Phase 3 APOLLO Study

Study Design, Baseline Demographics and Characteristics

Patient Population
- hATTR amyloidosis with documented TTR mutation
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

ClinicalTrials.gov Identifier: NCT01960348

2:1 RANDOMIZATION†

Patisiran
0.3 mg/kg IV every 3 weeks*

or

Placebo
IV every 3 weeks*

Primary Endpoint
- Change in mNIS+7 from baseline at 18 months

Secondary Endpoints
- Norfolk QOL-DN
- R-ODS
- mBMI
- NIS-weakness
- 10-meter walk
- COMPASS-31

Select Exploratory Endpoints
- Cardiac assessments§: NT-proBNP, Troponin I‡, LV wall thickness, LV mass, Longitudinal strain, and LV ejection fraction

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

Cardiac subpopulation: patients with evidence of potential cardiac amyloid involvement prespecified as:
- Baseline LV wall thickness ≥ 13 mm
- No aortic valve disease or hypertension per medical history

	Cardiac Subpopulation (N=126)		Overall Population (N = 225)
	Placebo (N=36)	Patisiran (N=90)	
Median Age, years (range)	62 (43-80)	60 (24-79)	62 (24-83)
Gender, male	30 (83.3)	68 (75.6)	167 (74.2)
TTR Genotype, n (%)	**V30M:** 12 (33.3)	**V30M:** 22 (24.4)	**V30M:** 96 (42.7)
NIS, mean	68.7	60.9	59.3
FAP Stage, n (%)	**1:** 13 (36.1) 2: 23 (63.9)	**1:** 42 (46.7) **2:** 48 (53.3)	**1:** 104 (46.2) **2:** 120 (53.3) **3**: 1 (0.4)
PND Score, n (%)	**I:** 7 (19.4) **IIIA:** 12 (33.3) **II:** 12 (33.3) **IIIB:** 5 (13.9)	**I:** 24 (26.7) **IIIA:** 21 (23.3) **II:** 28 (31.1) **IIIB:** 17 (18.9)	**I:** 56 (24.9) **IIIA:** 63 (28.0) **II:** 66 (29.3) **IIIB:** 39 (17.3) **IV:** 1 (0.4)
NYHA Class, n (%)	**I:** 16 (44.4) **II:** 20 (55.6)	**I:** 34 (37.8) **II:** 56 (62.2)	**I:** 110 (48.9) **II:** 113 (50.2) **Missing:** 2 (0.9)

†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 tetramer stabilizer 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)

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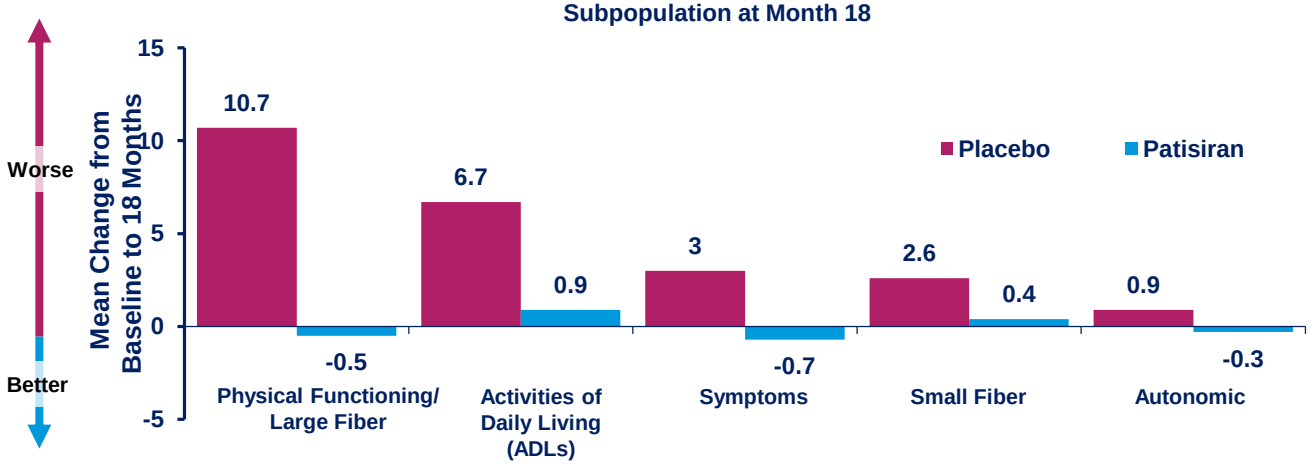
Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline in Overall and Individual Domains in the Prespecified Cardiac Subpopulation at Month 18

- **Norfolk QOL-DN**: 35-item QOL questionnaire sensitive to small fiber, large fiber, and autonomic nerve function
- At month 18, patisiran demonstrated statistically significant improvement compared to placebo in the overall Norfolk QOL-DN in the entire APOLLO patient population (p=1.95 x 10-10)
- At month 18, improvement seen in the prespecified cardiac subpopulation was consistent with the improvement seen in the entire APOLLO population (p=1.65 x 10-6)
- This improvement in QOL at 18 months in patients on patisiran was related to strength, digestive health, ability to perform everyday activities, and steadiness on their feet

Change from Baseline in Individual Domains of the Norfolk QOL-DN in the Prespecified Cardiac Subpopulation at Month 18



		Cardiac Subpopulation			
LS Mean		Placebo (N=23)	Patisiran (N=79)	Treatment Difference (Pati - PBO)	P-Value
Norfolk QOL-DN	Baseline score, mean	62.0	60.9		
	CFB to 18 mos	**20.4**	**-2.6**	**-23.0**	**1.65×10^{-6}**

Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; QOL, quality of life; LS, least squares; pati, patisiran; PBO, placebo; CI, confidence interval; CFB, change from baseline

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Patisiran Phase 3 APOLLO Study Results

Cardiac Safety and Summary

Cardiac Safety

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

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

- hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening, often fatal disease with high morbidity and mortality and limited therapeutic options
- Treatment with patisiran improved QOL compared to placebo in hATTR amyloidosis patients with evidence of cardiac involvement
- These results are consistent with the outcomes in the overall population, showing that patisiran provided clinical benefit to patients with hATTR amyloidosis with both polyneuropathy and cardiomyopathy
- Patisiran showed an encouraging safety and tolerability profile

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