Changes in Neuropathy Stage in Patients with Hereditary Transthyretin-Mediated Amyloidosis Following Treatment with Patisiran, an Investigational RNAi Therapeutic: An Analysis from the Phase 3 APOLLO Study

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Background and Rationale

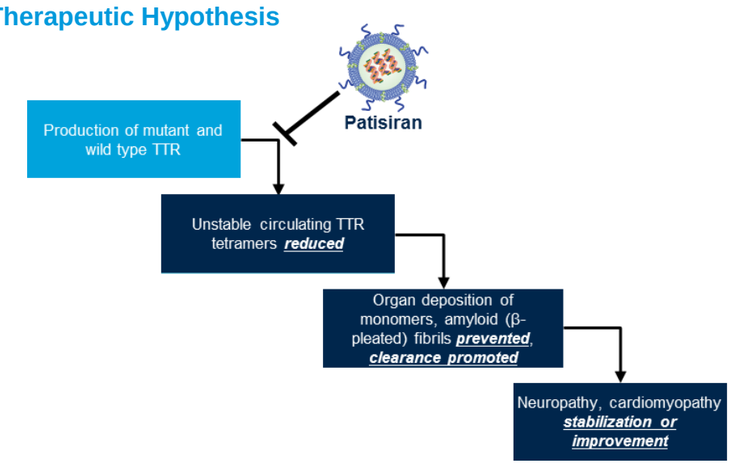
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- 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 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 favorable safety profile[14,15]
- Global-OLE: ongoing[16]

Figure 1: Patisiran Therapeutic Hypothesis



Objective

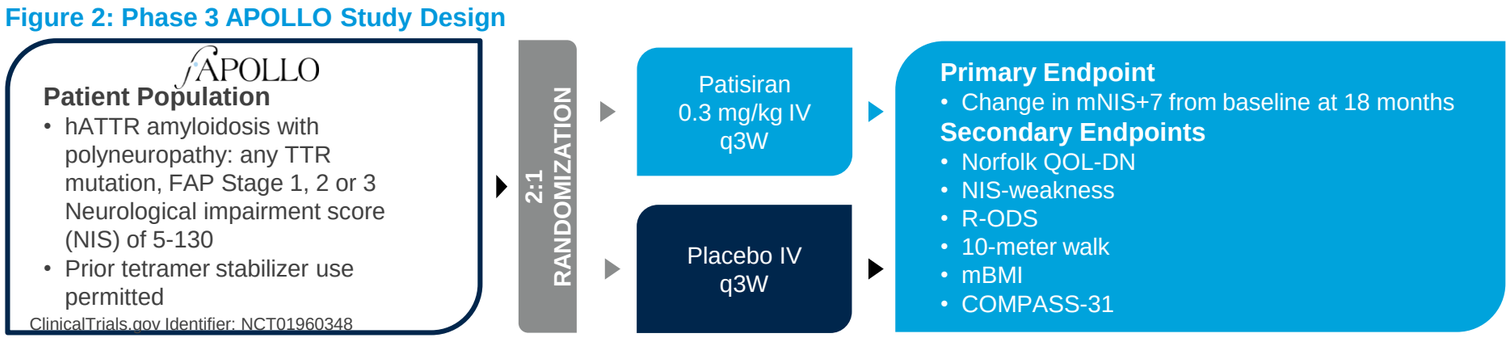
- Describe the change in the polyneuropathy disability (PND) scores and familial amyloidotic polyneuropathy (FAP) Stage following 18 months of treatment with patisiran or placebo in APOLLO

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 Neuropathy Impairment score (mNIS+7) from baseline at 18 months; secondary endpoints are shown in Figure 2
- Exploratory endpoints included the polyneuropathy disability (PND) score and FAP stage, measures utilized to assess hATTR patient ambulation[17]

Figure 2: Phase 3 APOLLO Study Design



Results

APOLLO Enrollment

- Patients enrolled had 39 different mutations and were divided into the following groups: North America, Western Europe and Rest of World (Table 1)

Table 1: Baseline Demographics

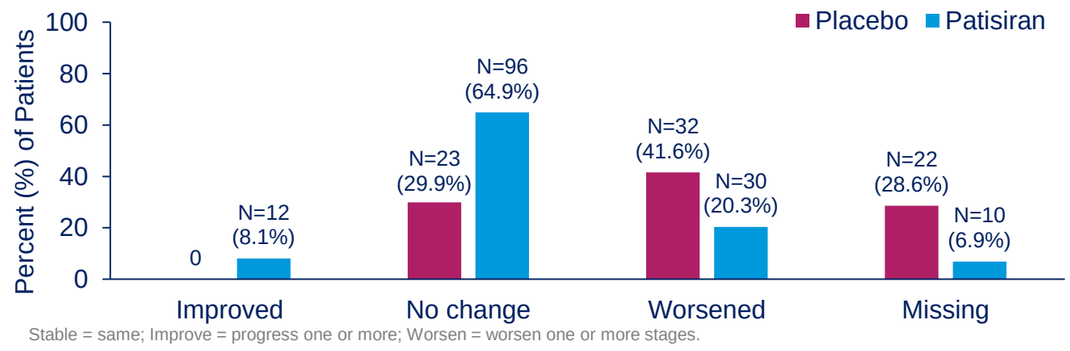
Characteristic, n (%)	Placebo (N=77)	Patisiran (N=148)
Median Age, years (range)	63 (34, 80)	62 (24, 83)
Gender (Male)	58 (75.3)	109 (73.6)
V30M	40 (51.9)	56 (37.8)
NonV30M[t]	37 (48.1)	92 (62.2)
NIS, Mean (min, max)	57 (7.0, 125.5)	61 (6.0, 141.6)
<50	35 (45.5)	62 (41.9)
≥50 - <100	33 (42.9)	63 (42.6)
≥100	9 (11.7)	23 (15.5)
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

[t]Represents 38 different mutations including A97S, T60A, E89Q, S50R, S77Y, D38A, F64L, and V122I.

Stabilization or Improvement of PND Score

- Greater proportion of patients in the patisiran group had a stable or improved PND score relative to baseline compared with placebo at 18 months (Figure 3); improvement was only seen in the patisiran group
  - Among patisiran-treated patients, improvement in PND score was observed across all baseline severities (PND I – IIIb)
  - Of patients who improved in PND score (8.1%), 83% had an improvement from PND IIIa/b to PND I, corresponding to a requiring walking aid to ability to perform unimpaired ambulation
  - Of the 30 patients on patisiran with a worsening PND stage, most worsened by 1 PND stage (25 patients; 83%), while 3 patients (10%) worsened by 2 PND stages and 2 (7%) worsened by 3 PND stages
- Among the patients randomized to placebo, none demonstrated an improvement in PND score, while 29.9% showed no change and 41.6% worsened
  - Of the 32 patients on placebo with a worsening PND score, half of the patients worsened by 1 PND level, and the other half worsened by 2 PND levels
- Larger percentage of placebo patients compared to patisiran patients had missing data at 18 months as a result of a higher study withdrawal rate

Figure 3 Shift in PND Score from Baseline to 18 months

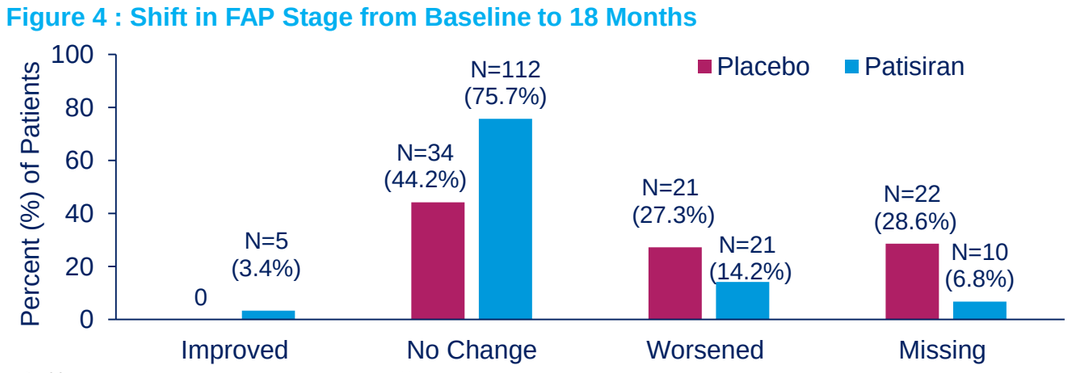


Stable = same; Improve = progress one or more; Worsen = worsen one or more stages.

Stabilization or Improvement of FAP Stage

- Greater proportion of patients in the patisiran group had a stable or improved FAP stage relative to baseline compared with placebo (Figure 4); improvement was only seen in the patisiran group
  - 117 patients (79.1%) in the patisiran group had stable or improved FAP stage compared with 32 (44.2%) in the placebo group
- Larger percentage of placebo patients compared to patisiran patients had missing data at 18 months as a result of a higher study withdrawal rate in placebo patients

Figure 4 : Shift in FAP Stage from Baseline to 18 Months



Stable = same; Improve = progress one or more; Worsen = worsen one or more stages.

Safety for Overall Population:

- Majority of AEs were mild or moderate in severity
  - Instances of peripheral edema did not result in any treatment discontinuations and decreased over time
  - The majority of infusion-related reactions (IRRs) were mild in severity with no severe, life-threatening or serious IRRs
  - Further, IRRs decreased over time and led to treatment discontinuation in 1 patient

Table 2. APOLLO Safety and Tolerability

Type of Adverse Event, n (%)	Placebo (N=77)	Patisiran (N=148)
Adverse event (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

- APOLLO, the largest controlled study of patients with hATTR amyloidosis with polyneuropathy to date, is representative of the global patient population and included patients with various stages of polyneuropathy
- Patisiran treatment preserved ambulation in a larger proportion of patients compared to placebo and even improved ambulation, with some patients going from requiring walking aids to unassisted walking at 18 months; these results were consistent with the improvement in 10-meter walk test gait speed observed in the patisiran group compared to placebo[15]
- Patisiran was generally well tolerated, with safety events similar in both groups
- These data further support the clinical benefit of patisiran compared to placebo in preserving or improving ambulation in patients with hATTR amyloidosis

Composite autonomic symptom score-31; mBMI, modified Body Mass Index; mNIS+7, Modified Neuropathy Impairment Score + 7; NIS; Neuropathy Impariments Score; NIS-W; Neuropathy Impairment Score – Weakness; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; COMPASS-31, 10-MWT, 10-Minute Walk Test; NYHA, New York Heart Association; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disabiity Scale; RNAi, RNA interference; WT, wild type.; AE, adverse events; SAE, searious adverse events; 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; 17. Slaes-Luis ML et al. Muscle Nerve. 1991; 14:377-378. Disclosures: Pritesch J Gandhi, Marianne Sweetser, Jhing Chen, Sunita Goyal and Jared Gollob are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.h

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