Patisiran, an Investigational RNAi Therapeutic for Patients with Hereditary Transthyretin-Mediated Amyloidosis: Regional and Genotypic Subgroup Analyses from the APOLLO Study

Teresa Coelho[1], David Adams[2], Alejandra Gonzalez-Duarte[3], William O'Riordan[4], Chih-Chao Yang[5], Taro Yamashita[6], Arnt Kristen[7], Ivaylo Tournev[8], Hartmut Schmidt[9], John Berk[10], Kon-Ping Lin[11], Peter Dyck[12], Pritesh J. Gandhi[13], Marianne Sweetser[13], Jihong Chen[13], Sunita Goyal[13], Jared Gollob[13], Ole B. Suhr[14]

[1]Hospital de Santo António, Porto, Portugal, [2]National Reference Center for FAP (NNERF)/ APHP/ INSERM U 1195/ CHU Bicêtre, Le Kremlin Bicêtre, France, [3]Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, [4]eStudy Site, La Mesa, United States, 5National Taiwan University Hospital, Taipei, Taiwan, [6]Kumamoto University Hospital, Kumamoto, Japan,[7]Heidelberg University Hospital, Heidelberg, Germany.[8]University Multiprofile Hospital for Active Treatment, Sofia, Bulgaria, [9]University Hospital Muenster, Muenster, Germany, [10]Amyloid Treatment and Research Program, Boston University, Boston, United States, [11]Taipei Veterans General Hospital, Taipei, Taiwan, [12]Mayo Clinic Hospital, Rochester, United States), [13]Alnylam Pharmaceuticals, Cambridge, United States, [14]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

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 which can vary by geographical region[11]
- Limited treatment options are available
- Continued high unmet medical need for novel therapeutic options

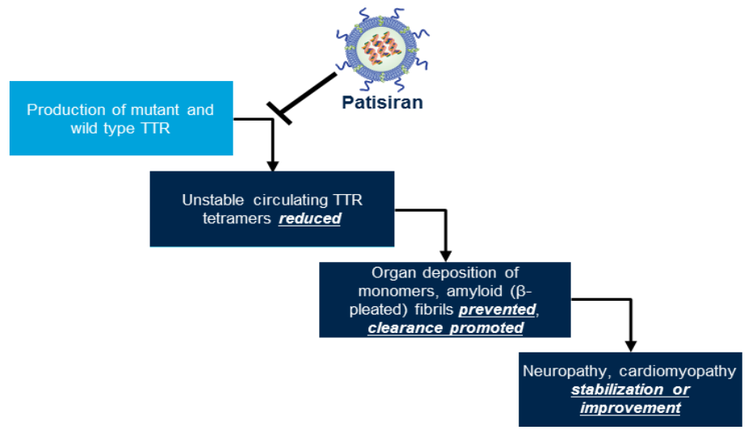
Patisiran

- 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

- Evaluate the impact of patisiran across geographical regions and in patients with Val30Met (V30M) and nonV30M mutations

Figure 1: Patisiran Therapeutic Hypothesis

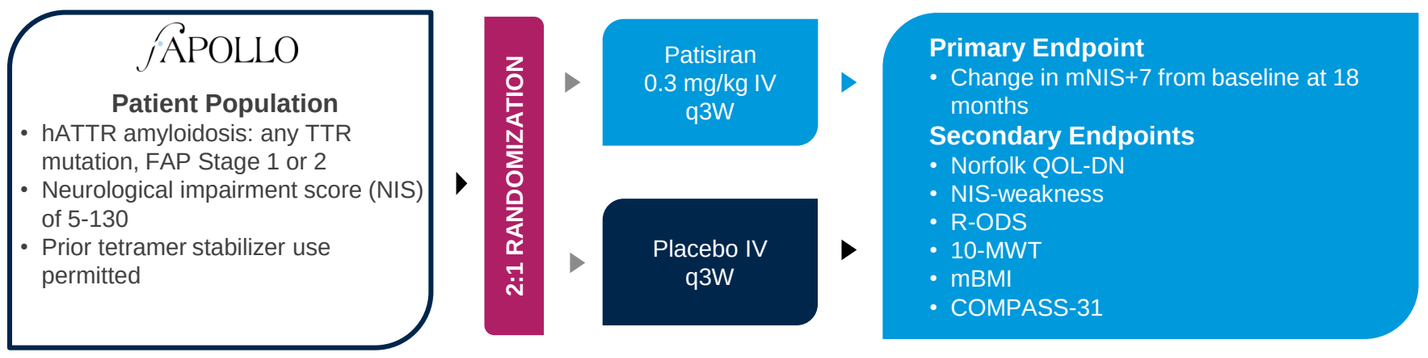


Methods

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 Neuropathy Impairment Score (mNIS+7) from baseline at 18 months; secondary endpoints are shown in Figure 2
  - mNIS+7 is a quantitative and referenced assessment to quantify motor, sensory and autonomic components of the polyneuropathy in patients with hATTR amyloidosis; higher score is indicative of worsening of neuropathy[14]
  - Norfolk QOL-DN is a 35-point patient reported outcome scale used to evaluate subjective perceptions of neuropathy symptoms sensitive to small fiber, large fiber, and autonomic nerve function; higher score is indicative of worsening quality of life[17]

Figure 2: Phase 3 APOLLO Study Design

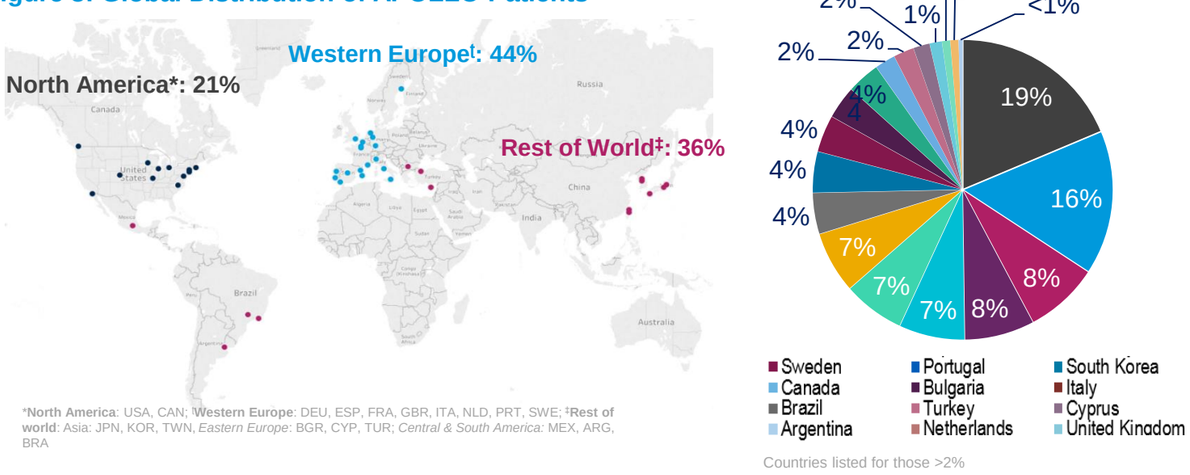


Results

APOLLO Baseline Demographics

- 225 patients with hATTR amyloidosis from 44 sites in 19 countries enrolled between December 2013 and January 2016 (Figure 3)
- Mean age: 60.5 years (24-83), males 74%, cardiac involvement (defined as patients with baseline left ventricular (LV) wall thickness ≥13mm and no medical history of aortic valve disease or hypertension) 65%

Figure 3: Global Distribution of APOLLO Patients



*North America: USA, CAN; ‡Western Europe: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; ‡Rest of world: Asia: JPN, KOR, TWN, *Eastern Europe*: BGR, CYP, TUR; *Central & South America:* MEX, ARG, BRA

Countries listed for those >2%

APOLLO Regions and Genotypes

- Patients enrolled had 39 different mutations and were divided into the following groups: North America, Western Europe and Rest of World (Figure 3, Table 1)

Table 1: Baseline Characteristics for Region and Genotype Subgroups

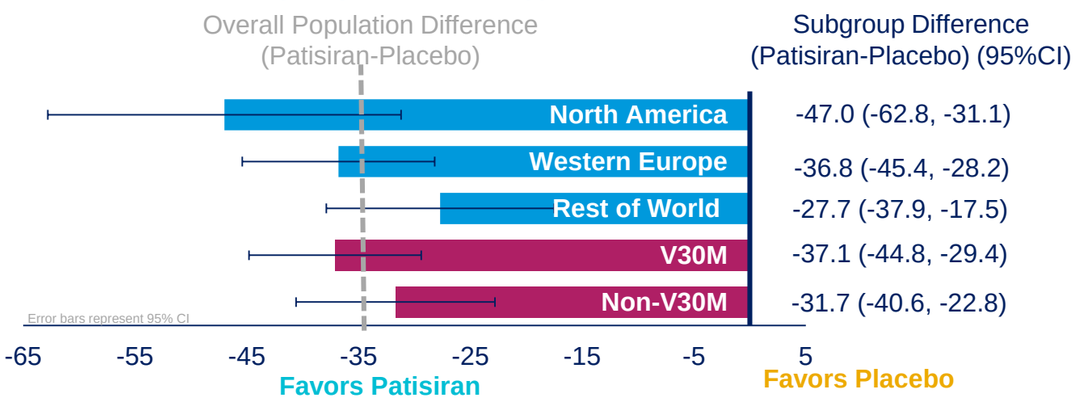
Characteristic, n (%)		Placebo (N=77)	Patisiran (N=148)	Overall (N=225)
Region	North America	10 (13.0)	37 (25.0)	47 (20.9)
	Western Europe	35 (46.8)	62 (41.9)	97 (43.6)
	Rest of World	31 (40.3)	49 (33.1)	80 (35.6)
Genotype	V30M	39 (51.9)	56 (37.8)	95 (42.7)
	Non-V30M	37 (48.1)	92 (62.2)	129 (57.3)

North America: USA, CAN; **Western Europe**: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; **Rest of world**: Asia: JPN, KOR, TWN, *Eastern Europe*: BGR, CYP, TUR; *Central & South America:* MEX, ARG, BRA

Improvement in mNIS+7 Following Patisiran Treatment

- APOLLO had an average mean mNIS+7 (SD) at baseline of 74.6 (37.0) and 80.9 (41.5) for placebo and patisiran groups, respectively
- Overall, patisiran demonstrated significant improvement in mNIS+7 compared to placebo with an LS mean change from baseline (patisiran-placebo) (95% CI) of -33.9 (-39.86,-28.13) at 18 months, which was consistent within each subgroup (Figure 4)

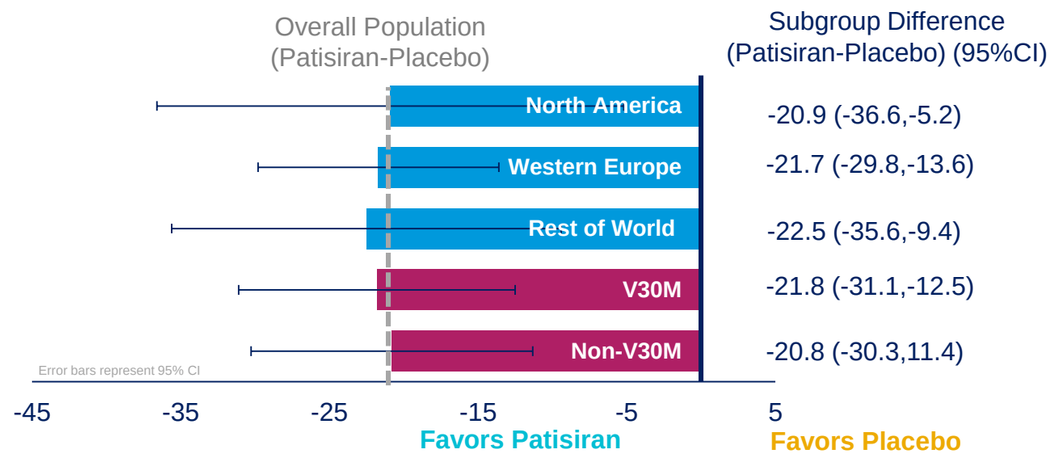
Figure 4: Difference between Patisiran and Placebo in mNIS+7 Change from Baseline to Month 18 by Region and Genotype



Improvement in Norfolk QOL-DN Following Patisiran Treatment

- Significant improvement was observed following patisiran treatment within each subgroup compared to placebo (Figure 5) and consistent with the overall population which showed a LS mean change from baseline (patisiran-placebo) (95% CI) of -21.1 (-27.24, -15.01)

Figure 5: Norfolk QOL-DN Change from Baseline to Month 18 in Region and Genotype Subgroups



Safety of Overall Population:

- Safety and tolerability for the entire APOLLO population is shown in Table 2
- Majority of AEs were mild or moderate in severity
  - Instances of peripheral edema did not result in any treatment discontinuations and did decrease over time
  - Majority of infusion-related reactions (IRRs) were mild with no severe, life-threatening or serious IRRs; IRRs decreased over time and led to treatment discontinuation in one patient
  - No differences in the AE and SAE profiles of patisiran were evident based on geographic region or genotype
- None of the deaths were considered related to study drug and causes of death (e.g., cardiovascular, infection) were consistent with natural history

Table 2: Safety and Tolerability at 18 months

Type of Adverse Event, number of patients (%)	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)

Summary

- APOLLO, the largest controlled study of patients with hATTR amyloidosis with polyneuropathy to date, is representative of the global patient population
- Patisiran demonstrated a consistent benefit over placebo for both mNIS+7 and Norfolk QOL-DN in all subgroups regardless of region or genotype
- Patisiran was generally well tolerated, with safety events similar in both groups

AE, adverse events; COMPASS-31, Composite Autonomic Symptom Score-31; LS mean, least squares mean; 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; NYHA, New York Heart Association; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disability Scale; SAE, serious adverse events; RNAi, RNA interference; 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; 17. Vinik EJ et al. Diabetes Technol Ther. 2005; 7(3): 497-508. Disclosures: Pritesch J Gandhi, Marianne Sweetser, Jihong Chen, Sunita Goyal and Jared Gollob are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.