Long-Term Use of Patisiran, an Investigational RNAi Therapeutic, in Patients with Hereditary Transthyretin-Mediated Amyloidosis: Baseline Demographics and Interim Data from Global Open Label Extension Study

Ole B. Suhr[1], Alejandra Gonzalez-Duarte[2], William O'Riordan[3], Chih-Chao Yang[4], Taro Yamashita[5], Arnt Kristen[6], Ivaylo Tournev[7], Hartmut Schmidt[8], Teresa Coelho[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], David Adams[14]

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

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

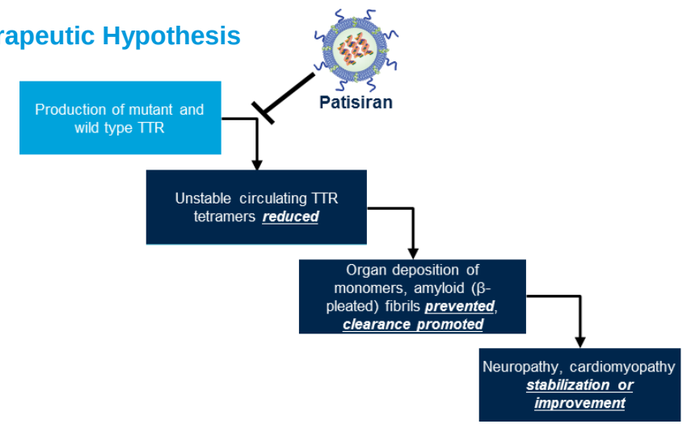
Patisiran

- 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 with polyneuropathy[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]

Objective

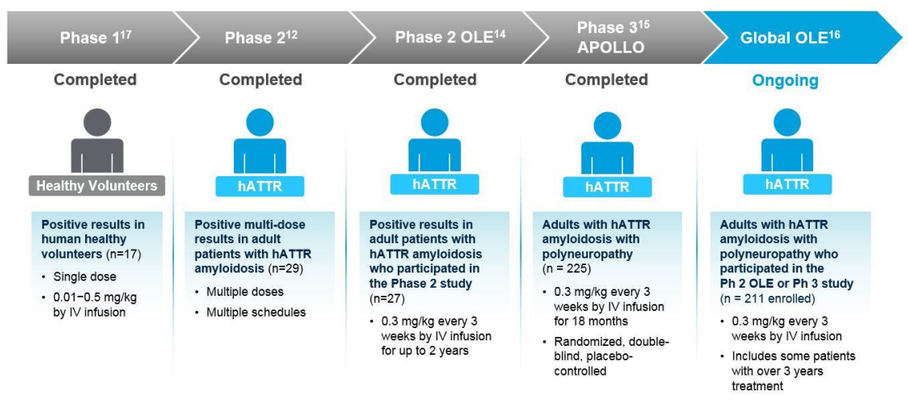
- Evaluate the baseline demographics as well as interim long term safety and efficacy in the Global OLE study

Figure 1: Patisiran Therapeutic Hypothesis



Methods

Figure 2: Patisiran Clinical Development Program



Global OLE Study Design

- Multicenter, international, OLE study to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis with polyneuropathy (Figure 2)
- Patients with hATTR amyloidosis who completed the Phase 2 OLE and Phase 3 APOLLO patisiran studies and met eligibility criteria were able to roll over and continue receiving patisiran 0.3mg/kg IV q3W for up to 5 years
- Safety assessments include monitoring for AEs (including serious AEs [SAEs]), clinical laboratory tests such as: hematology, clinical chemistry, urinalysis; measurement of anti-drug antibodies (if clinically indicated); vital signs; physical examinations; and ophthalmology examinations
- Complete set of efficacy assessments will be done at 52 weeks, followed by more limited assessments yearly until study completion
- Assessments include: effects on neurologic impairment (mNIS+7), Quality of Life (Norfolk QOL-DN), disability, ambulation, mBMI, grip strength, autonomic symptoms, cardiac endpoints and serum TTR levels
  - mNIS+7 is a highly standardized, quantitative, and referenced assessment to quantify motor, sensory and autonomic components of the polyneuropathy in patients with hATTR amyloidosis[14]

Results

Global OLE Enrollment

- 186 of 187 (99%) patients who completed the APOLLO study and were eligible for the Global OLE study, and 25 patients from the Phase 2 OLE study, enrolled in the Global OLE study
  - Mean baseline NIS and mNIS+7 were 64 (range: 0-162) and 77 (range: 3-199), respectively and PND I: 0.5%, PND II: 28%, PND IIIA: 20%, PND IIIB: 21%, and PND IV: 8%.

Table 1: Baseline Demographics

Previous Treatment Group	APOLLO Placebo N=49	APOLLO Patisiran N=137	Phase 2 OLE Patisiran N=25	Global OLE Total N=211
Mean Age (years)	63.5 (11.02)	61.0 (12.1)	58.5 (15.1)	61.3 (12.28)
Age by Categories, n (%)				
18-64 years	22 (44.9)	74 (54.0)	12 (48.0)	108 (51.2)
65-74 years	20 (40.8)	51 (37.2)	10 (40.0)	81 (38.4)
≥75 years	7 (14.3)	12 (8.8)	3 (12.0)	22 (10.4)
Male, n (%)	37 (75.5)	102 (74.5)	17 (68.0)	156 (73.9)
Genotype, n (%)				
V30M	24 (49.0)	56 (40.9)	18 (72.0)	98 (46.4)
nonV30M	25 (51.0)	81 (59.1)	7 (28.0)	113 (53.6)
Region*, n (%)				
North America	5 (10.2)	34 (24.8)	1 (4.0)	40 (19.0)
Western Europe	26 (53.1)	61 (44.5)	23 (92.0)	110 (52.1)
Rest of World	18 (36.7)	42 (30.7)	1 (4.0)	61 (28.9)
Concurrent TTR Tetramer Stabilizer Use, n (%)	3 (6.1)	0	13 (52.0)	16 (7.6)
Tafamidis	1 (2.0)	0	12 (48.0)	13 (6.2)
Diflunisal	2 (4.1)	0	1 (4.0)	3 (1.4)

*__North America__: USA, CAN; __Western Europe__: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; __Rest of world__: *Eastern Europe*: BGR, CYP, TUR; Asia: JPN, KOR, TWN; *Central & South America:* MEX, ARG, BRA

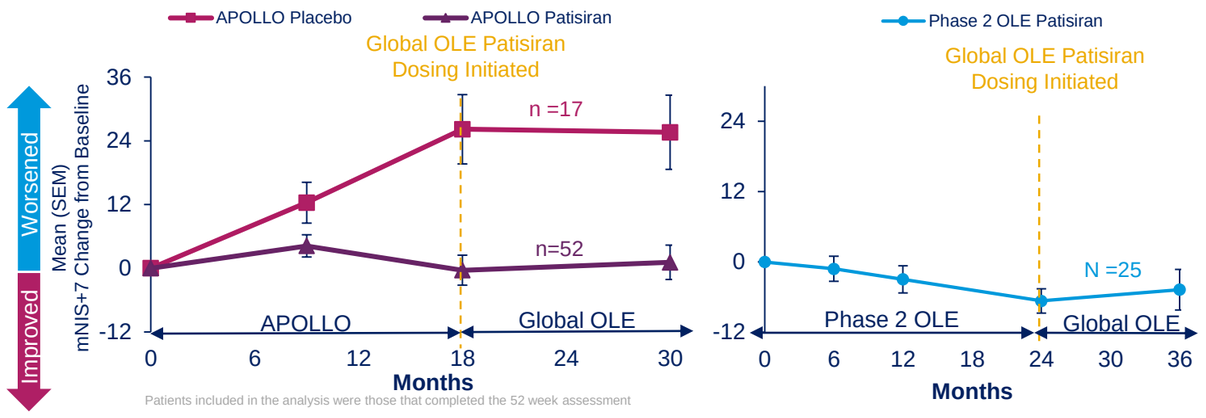
Table 2: Baseline Characteristics, n (%)

Previous Treatment Group	APOLLO Placebo	APOLLO Patisiran	Phase 2 OLE Patisiran	Global OLE Total
Familial Amyloidotic Polyneuropathy (FAP) Stage				
1	14 (28.6)	58 (42.3)	20 (80.0)	92 (43.6)
2	27 (55.1)	71 (51.8)	5 (20.0)	103 (48.8)
3	8 (16.3)	8 (5.8)	0	16 (7.6)
Polyneuropathy Disability (PND) Score				
0	0	1 (0.7)	0	1 (0.5)
I	7 (14.3)	32 (23.4)	10 (40.0)	49 (23.2)
II	9 (18.4)	36 (26.3)	13 (52.0)	58 (27.5)
IIIA	8 (16.3)	33 (24.1)	1 (4.0)	42 (19.9)
IIIB	17 (34.7)	27 (19.7)	1 (4.0)	45 (21.3)
IV	8 (16.3)	8 (5.8)	0	16 (7.6)
Neuropathy Impairment Scores mean (min, max)				
mNIS+7	101 (22,190)	75 (8,199)	46 (3,128)	77 (3,199)
NIS	82 (12,158)	62 (2,162)	36 (0,88.6)	64 (0,162)

Interim mNIS+7 Results Indicate Neuropathy Stabilization Following 52 Weeks of Patisiran Treatment on Global OLE

- As of the December 1, 2017 data cut: 44% of patients completed the 52 week assessment (APOLLO placebo, N=17, APOLLO patisiran, N=52, Phase 2 OLE Patisiran, N=25); neuropathy improvement or stabilization was observed in all groups (Figure 3)
- Patients in the APOLLO placebo group who had previously shown disease progression,[15] showed disease stabilization with a mean change (SEM) of -0.58 (2.98)

Figure 3: Longitudinal Analysis of mNIS+7 Change on Parent Study (APOLLO or Phase 2 OLE) and Global OLE



Patients included in the analysis were those that completed the 52 week assessment

Preliminary Long-term Safety Data:

- In the Global OLE Study, patients were treated with patisiran (overall mean 12 months) for an additional 11 or 21 months (APOLLO patisiran and Phase 2 patisiran, respectively) or newly treated for 10 months (APOLLO placebo), representing 211 patient-years and 3,506 doses
- Most common related AEs were mild or moderate infusion related reactions (10.4%) (Table 3)
- 2 patients with related SAEs: 1 patient with an event of phlebitis secondary to drug extravasation, cellulitis and hypotension; and 1 patient with abdominal discomfort who withdrew from the study (Table 3)
- Causes of death were consistent with natural history and none considered related to study drug (Table3)

Table 3: Safety in Patients Treated with Patisiran for up to 48 months, n (%)

Previous Treatment Group	APOLLO Placebo	APOLLO Patisiran	Phase 2 OLE Patisiran	Global OLE Total
Adverse Event (AE)	45 (91.8)	119 (86.9)	25 (100.0)	189 (89.6)
AE Related to Study Drug	22 (44.9)	30 (21.9)	7 (28.0)	59 (28.0)
Severe AE	16 (32.7)	19 (13.9)	3 (12.0)	38 (18.0)
Severe AE Related to Study Drug	1 (2.0)	1 (0.7)	0	2 (0.9)
Serious Adverse Event (SAE)	19 (38.8)	30 (21.9)	6 (24.0)	55 (26.1)
SAE Related to Study Drug	2 (4.1)	0	0	2 (0.9)
AE Leading to Study Withdrawal	9 (18.4)	7 (5.1)	0	16 (7.6)
Study Drug Related AE Leading to Study Withdrawal	1 (2.0)	0	0	1 (0.5)
Death	7 (14.3)	4 (2.9)	0	11 (5.2)

Patients included above had at least 1 event matching the group criteria

Summary

- Nearly all eligible patients from the previous patisiran studies enrolled in the Global OLE study including 99% of patients who completed APOLLO and all those eligible from the Phase 2 OLE
- Interim data analysis shows neuropathy stabilization (as measured by mNIS+7) in all groups receiving patisiran, including those patients who had previously received placebo
- Patisiran continues to show a positive benefit:risk profile in clinical studies; safety was similar to that seen in APOLLO study
- This study continues to evaluate the long-term efficacy and safety profile of patisiran in a globally-diverse patient population with respect to the type of TTR mutation, stage and disease severity

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; Neuropathy Impairment Score; 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. Coelho T et al. N Engl J Med. 2013;369:819-29. Disclosures: Pritesch J Gandhi, Marianne Sweetser, Jihong Chen, Sunita Goyal and Jared Gollob are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.

Alnylam PHARMACEUTICALS