Long-Term use of Patisiran, an Investigational RNAi Therapeutic, in Patients with Hereditary Transthyretin-Mediated Amyloidosis:12 Month Efficacy and Safety Data from Global Open Label Extension (OLE) Study

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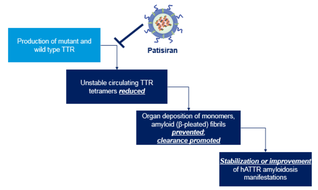
Background and Rationale

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 gastrointestinal 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]
  - Risk factors for poor prognosis include increasing age, non-V30M genotype with late onset disease (>50 years), and presence of cardiac involvement (such as increased NT-proBNP levels, increased IVS thickness, and poor diastolic function, among others)[6-8]
- Among published studies in patients with hATTR amyloidosis, the mortality rate ranges from 7 to 18 deaths per 100 patient-years, demonstrating the severity of this disease[7,9-12]

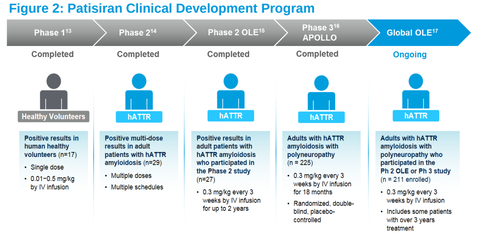
Figure 1: Patisiran Therapeutic Hypothesis



Patisiran (Figure 1, 2)

- Lipid nanoparticle formulation of RNAi (RNA interference) targeting hepatic production of WT and mutant TTR
- Patisiran clinical development program shown in Figure 2[13-17]
- Patisiran is now approved in the US for the treatment of the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy[18,19]

Figure 2: Patisiran Clinical Development Program



Objective

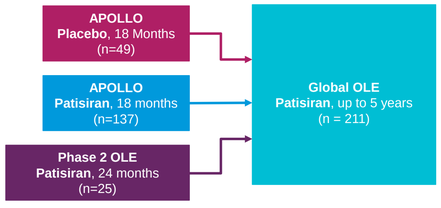
- To describe the interim 12 month efficacy and safety data for patients in the ongoing Global Open Label Extension (OLE) study

Methods

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
- Patients with hATTR amyloidosis who completed the Phase 2 OLE and Phase 3 APOLLO studies and met eligibility criteria were able to roll over and receive patisiran 0.3 mg/kg IV q3W for up to 5 years
- Patients who enrolled into the Global OLE are presented in one of three unique groups based on the parent study (Figure 3):
  - **APOLLO placebo**: received placebo in APOLLO and started patisiran for first time in Global OLE
  - **APOLLO patisiran**: received patisiran for 18 months in APOLLO and continued in Global OLE
  - **Phase 2 OLE patisiran**: received patisiran for 24 months in Phase 2 OLE and continued in Global OLE

Figure 3: Transition of Eligible Patients to Global OLE



Results

Global OLE Baseline Demographics

- 186 of 187 (99%) of patients who completed APOLLO and were eligible for the Global OLE, and 25 patients from the Phase 2 OLE enrolled in the Global OLE
- The patisiran clinical program enrolled a broad patient population with a wide spectrum of disease severity
  - Phase 2 OLE enrolled more patients with V30M and had a milder neuropathy at baseline than in APOLLO
  - At baseline for APOLLO, the placebo and patisiran groups were balanced in terms of disease characteristics
  - At entry into the Global OLE, the APOLLO placebo patients had greater disease burden due to longer time from diagnosis to starting patisiran
- This spectrum of disease is reflected in the characteristics among the groups at baseline in the Global OLE (Table 1, 2)
  - 67% APOLLO placebo patients had a PND ≥IIIA compared to 8% of Phase 2 OLE patisiran patients
  - Median NT-proBNP at Global OLE baseline in the APOLLO placebo patients was 868 ng/L while it was 166 ng/L in the Phase 2 OLE patisiran patients

Table 1: Baseline Demographics at Entry into the Global OLE

	APOLLO Placebo N=49	APOLLO Patisiran N=137	Phase 2 OLE Patisiran N=25	Global OLE Total N=211
Median age (years)	66	63	65	64
Male, n (%)	37 (76)	102 (75)	17 (68)	156 (74)
Mean time since hATTR amyloidosis diagnosis to first patisiran dose† (range), years	**4.5 (2-18)**	**2.4 (0-21)**	**2.7 (1-8)**	2.9 (0-21)
Genotype, n (%)				
V30M	**24 (49)**	**56 (41)**	**18 (72)**	98 (46)
Non-V30M	**25 (51)**	**81 (59)**	**7 (28)**	113 (54)
Region*, n (%)				
North America	5 (10)	34 (25)	1 (4)	40 (19)
Western Europe	26 (53)	61 (45)	23 (92)	110 (52)
Rest of World	18 (37)	42 (31)	1 (4)	61 (29)

Bolded text highlights specific baseline difference between groups
†First patisiran dose could have been in Phase 2 OLE, APOLLO, or Global OLE; integrated data across all patisiran treated patients (APOLLO placebo n=49; APOLLO patisiran n=148; Phase 2 OLE n=27; total patisiran n=224)
*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

Results Continued

Table 2: Disease Characteristics at Entry into the Global OLE

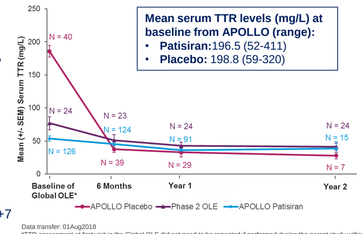
	APOLLO Placebo N=49	APOLLO Patisiran N=137	Phase 2 OLE Patisiran N=25	Global OLE Total N=211
PND Score, n (%)				
0: no symptoms	0	1 (1)	0	1 (<1)
I: preserved walking, sensory disturbances	7 (14)	32 (23)	10 (40)	49 (23)
II: impaired walking but can walk without stick/crutch	9 (18)	36 (26)	13 (52)	58 (27)
IIIA/B: walk with 1 or 2 sticks/crutches	**25 (51)**	**60 (44)**	**2 (8)**	87 (41)
IV: confined to wheelchair or bedridden	**8 (16)**	**8 (6)**	**0**	16 (8)
Modified Neuropathy Impairment Score (mNIS+7), mean (min, max)	**101 (22,190)**	**75 (8,199)**	**46 (3,128)**	77 (3,199)
New York Heart Association (NYHA) Classification				
I: no symptoms	**22 (45)**	**67 (49)**	**19 (76)**	108 (51)
II: symptoms with ordinary physical activity	**21 (43)**	**59 (43)**	**4 (16)**	84 (40)
III: symptoms with less than ordinary physical activity	4 (8)	9 (7)	2 (8)	15 (7)
IV: symptoms at rest	2 (4)	2 (1)	0	4 (2)
Median NT-proBNP (range), ng/L	**868 (56-15101)**	**375 (21-10282)**	**166 (5-1897)**	376 (5-15101)
Mean LV wall thickness (SD), cm	1.5 (0.3)	1.5 (0.3)	1.3 (0.3)	1.5 (0.3)

Bolded text highlights specific baseline difference between groups

Serum TTR Levels in Global OLE Patients (Figure 4)

- Robust TTR reduction was observed in the APOLLO placebo group, with a 79% mean TTR reduction at week 26 (6 months), which is sustained over time
- TTR reduction was maintained in the APOLLO patisiran patients and Phase 2 OLE patients with continued dosing, with some patients having >4 years of exposure

Figure 4: TTR Serum Levels (mg/L) up to 2 Years in Global OLE

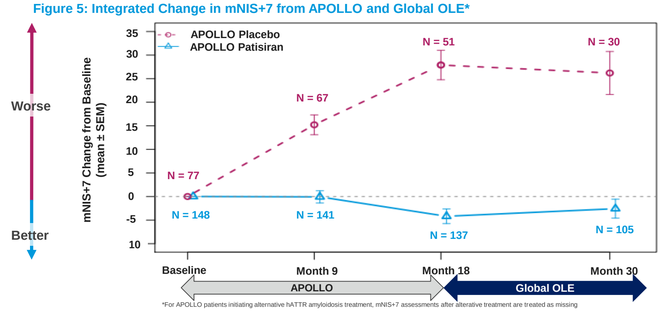


Data transfer: 01Aug2018
*TTR assessment at first visit in the Global OLE did not need to be repeated if performed during the parent study within 45 days of the first dose in the Global OLE
Note: Pharmacodynamics (PD) analysis set includes all patients who received at least 1 dose of patisiran in this study and have both baseline and at least 1 post-baseline PD assessment; for a patient who received patisiran in the parent study, if more than 45 days elapsed between the last dose of patisiran in the parent study and the first dose of patisiran in this study, patient was excluded from the PD analysis set

Change in mNIS+7 Following 52 Weeks of Patisiran Treatment on Global OLE (Figure 5,6)

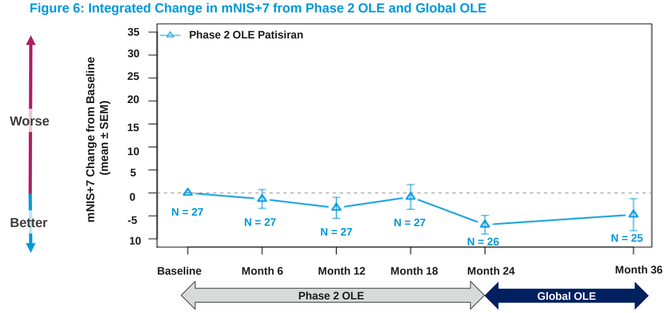
- 77% of patients completed the week 52 (year 1) mNIS+7 assessment in the Global OLE as of 01 August 2018
- Patients in the APOLLO patisiran and Phase 2 OLE patisiran group demonstrated an improvement in neuropathy (defined as a mean negative change in mNIS+7 from parent study baseline)
- Notably, the APOLLO placebo patients had halting of their rapid disease progression trajectory once beginning patisiran treatment in the Global OLE

Figure 5: Integrated Change in mNIS+7 from APOLLO and Global OLE*



*For APOLLO patients initiating alternative hATTR amyloidosis treatment, mNIS+7 assessments after alterative treatment are treated as missing

Figure 6: Integrated Change in mNIS+7 from Phase 2 OLE and Global OLE



Overall Exposure in Global OLE

- As of 01 August 2018, 211 patients were treated with patisiran for an overall mean of 18 months with 5,484 doses given
  - APOLLO placebo: received patisiran for mean 16 months
  - APOLLO patisiran: received an additional mean 18 months (overall mean ~34 months)
  - Phase 2 OLE patisiran: received an additional mean 25 months (overall mean ~51 months)

Summary of Safety in Global OLE (Table 3)

- Majority of AEs were mild or moderate
- Most commonly related AEs were mild or moderate infusion-related reactions (IRRs) (12%)
  - IRRs were higher in patients newly treated with patisiran (APOLLO placebo) and decreased over time
  - There were no serious IRRs or discontinuations due to IRRs
- Deaths were reported in 18 patients; none were considered related to patisiran by the investigators
  - Deaths were higher in the APOLLO placebo group who had progression of disease prior to starting patisiran
    - 7 of these 10 deaths occurred within the first 6 months of starting the Global OLE

Table 3: Overall Safety in the Global OLE Study

Patients with at Least 1 Event, n (%)	APOLLO Placebo N=49	APOLLO Patisiran N=137	Phase 2 OLE Patisiran N=25	Global OLE Total N=211
AE	48 (98)	129 (94)	25 (100)	202 (96)
Severe AE	22 (45)	31 (23)	4 (16)	57 (27)
SAE	25 (51)	44 (32)	6 (24)	75 (36)
IRRs	13 (27)	10 (7)	2 (8)	25 (12)
AE Leading to Study Withdrawal	12 (24)	10 (7)	0	22 (10)
Death*	10 (20)	8 (6)	0	18 (9)

*Includes all deaths reported within 3 months after the last dose of patisiran. Data transfer: 01Aug2018

Integrated Data: Exposure Adjusted Mortality Rates Across the Patisiran Clinical Program

- Overall mortality rate (as of 01 August 2018) in patients who received ≥1 dose of patisiran: 4.3 per 100 patient-years (CI: 2.9-6.2) with over 600 patient-years of exposure (Table 4)

Table 4: Exposure Adjusted Mortality Rates Across all Patisiran Treated Patients (Integrated Data)*

	APOLLO Placebo N=49	APOLLO Patisiran N=148	Phase 2 OLE Patisiran N=27	All Treated Patients N=224
Deaths, n (%)	10 (20)	14 (9)	2 (7)	26 (12)
Exposure Adjusted Mortality Rate (CI), deaths per 100 patient-years	15.7 (7.9-27.6)	3.3 (1.9-5.3)	1.7 (0.3-5.4)	4.3 (2.9-6.2)

*Integrated data includes Phase 2 OLE, APOLLO, and Global OLE

- Causes of death consistent with natural history; none were considered related to patisiran by the investigators
  - Majority of patients had known risk factors for poor prognosis, such as non-V30M, advanced age, advanced disease status, long duration of disease, and cardiac involvement
  - Deaths were consistent with complications of hATTR amyloidosis:
    - 17 deaths were cardiovascular in nature (including presumed cardiovascular etiology, sudden death, myocardial infarction, and heart failure)
    - 9 deaths were non-cardiovascular or unknown (including infection, worsening disease, and post-operative complication)

Estimated Mortality Rates in ATTR Amyloidosis (Table 5)

- Based on a review of the literature using studies that had sufficient information to estimate a mortality rate, the mortality rate in patients who received patisiran appears lower than the expected range for patients with hATTR amyloidosis

Table 5: Natural History Estimated Mortality Rates in the Literature on ATTR Amyloidosis*

Reference	Patient Population	Observational Period	Estimated Mortality Rate* (deaths per 100 patient-years)
Berk et al. JAMA 2013	66 placebo hATTR patients (47% non-V30M)	Up to 2 years	6.8
Sattianayagam et al. Eur Heart J 2012	Prospective study in 60 Thr60Ala patients	Median 2.6 years	13
Ruberg et al. Am Heart J 2012	Observational study in 29 ATTR patients (62% wtATTR, 38% V122I)	Mean 1.3 years	16
Arruda-Olsen et al. Amyloid 2013	Observational study in 116 hATTR patients (68% non-V30M)	Mean 3.0 years	18
Maurer et al. NEJM 2018	177 placebo ATTR patients (24% hATTR, mostly non-V30M)	Up to 2.5 years	19
Patisiran Clinical Program	224 hATTR patients in Phase 2 OLE, APOLLO, Global OLE (55% non-V30M)	Mean 2.7 years Cumulative 603 patient-years	4.3

*Estimated based on the data in the publication; rates may be underestimated

Summary

- Patients on Global OLE represent the longest treatment with a RNAi therapeutic, with some patients receiving >4 years of patisiran
- Patients treated with patisiran early in their disease demonstrated continued improvement in neuropathy (as defined by negative change in mNIS+7 from baseline of parent study) up through one additional year on the Global OLE
- Placebo-treated patients from APOLLO exhibited rapid halting of neurologic disease progression after initiation of patisiran treatment and subsequent improvement of neurologic function, despite more advanced disease at Global OLE baseline
- Patisiran continues to show a positive benefit:risk profile
- This study continues to evaluate the long-term efficacy and safety profile of patisiran across varying disease severities

AE, adverse event; CI, confidence interval; IRR, infusion-related reaction; IV, intravenous; IVS, interventricular septum; LV, left ventricular; mNIS+7, modified neuropathy impairment score + 7; NYHA, New York Heart Association; PND, polyneuropathy disability; OLE, open label extension; Q3W, every 3 weeks; RNAi, RNA interference; SAE, serious adverse event; TTR, transthyretin; WT, wild type. 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. Sweeckb PL et al. Amyloid. 2015;22(2):123-31; 7. Sattianayagam AJ et al. Eur Heart J. 2012;33:1120–7; 8. Geltz MA et al. Mayo Clin Proc. 1992;67(5):428-40; 9. Maurer M et al. N Engl J Med. 2018; 379:1007-10016. 10. Ruberg FL et al. Am Heart J. 2012; 164(2): 222-228. 11. Berk JL et al. JAMA. 2013; 310: 2658-67; 12. Arruda-Olson AM et al. Amyloid. 2013; 20:263-8; 13. Coelho T et al. N Engl J Med. 2013; 369 (9):819-29. 14. Suhr O et al. Orphanet J Rare Dis. 2015;10:109; 15. Adams D et al. Neurology. 2017;88:16 Supplement S27.004 (NCT01961921); 16. Adams D et al. N Engl J Med. 2018; 379:11–21; 17. Clinicaltrials.gov: NCT02510261; 18. Alnylam Pharmaceuticals. ONPATTRO Highlights of Prescribing Information; 19. Alnylam Pharmaceuticals. ONPATTRO Summary of Product Characteristics. Disclosures: Pritesh J Gandhi, Marianne Sweetser, and Matthew T White are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam Pharmaceuticals.