Patisiran, an investigational RNAi therapeutic for patients with hereditary transthyretin-mediated (hATTR) amyloidosis: Phase 3 APOLLO study sub-analysis of Japanese patients

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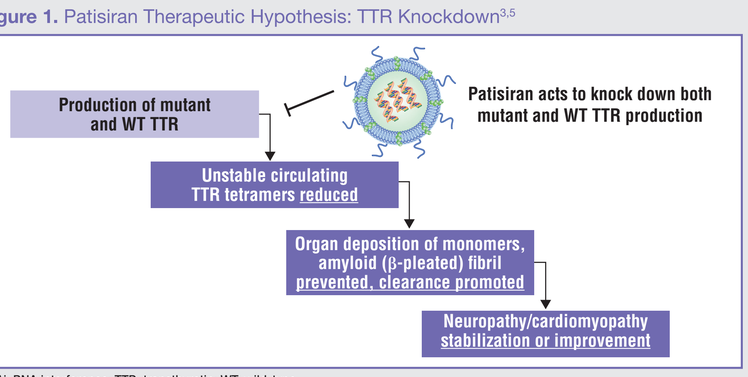
BACKGROUND

- Hereditary ATTR (hATTR) amyloidosis (also referred to as transthyretin-related mutant-form amyloidosis [ATTRm]) is a rapidly progressive, life-threatening disease caused by a mutation in the transthyretin (*TTR*) gene that results in misfolded TTR protein accumulating as amyloid fibrils in multiple tissues including the nerves, heart, and gastrointestinal tract[1,2]
- Patisiran is an investigational RNA interference (RNAi) agent that utilizes an endogenous cellular mechanism for regulating protein synthesis to target TTR mRNA in the liver, where TTR is predominantly produced (**Figure 1**)[3]
- In APOLLO, the largest Phase 3, international, multicenter, randomized, double-blind, placebo-controlled clinical study in hATTR amyloidosis with polyneuropathy, 225 patients were enrolled from 19 countries. Patisiran treatment resulted in clinically significant improvements in sensory, motor, and autonomic neuropathy symptoms and quality of life. Patisiran was generally well tolerated[4]
- This poster presents the findings of an analysis of the efficacy and safety of patisiran in the subpopulation of patients from Japan, which is one of several endemic foci of hATTR amyloidosis in which the V30M mutation is the most common mutation and patients present predominantly with polyneuropathy[5]

Figure 1. Patisiran Therapeutic Hypothesis: TTR Knockdown[3,5]



RNAi, RNA interference; TTR, transthyretin; WT, wild-type.

OBJECTIVE

- This analysis evaluates the safety and efficacy of patisiran in the subpopulation of patients from Japan in the Phase 3 APOLLO study

METHODS

Study Design

- APOLLO was a randomized, multicenter, international, double-blind, placebo-controlled Phase 3 study designed to evaluate the efficacy of patisiran and establish the safety of chronic dosing over 18 months in adult patients with symptomatic hATTR amyloidosis with polyneuropathy (**Figure 2**).[6] Patients were randomized to patisiran 0.3 mg/kg or placebo intravenously (IV) once every 3 weeks

Patient Population[6]

Key inclusion criteria

- Diagnosis of hATTR amyloidosis with documented mutation
- Anticipated survival ≥2 years
- 18–85 years of age
- Neurologic Impairment Score (NIS) of 5–130
- Polyneuropathy disability (PND) score ≤IIIb
- Nerve conduction study (NCS) sum of the sural sensory nerve action potential (SNAP), tibial compound muscle action potential (CMAP), ulnar SNAP, ulnar CMAP, and peroneal CMAP of ≥2 points
- Karnofsky performance status ≥60%
- Adequate biochemical liver function (aspartate transaminase and alanine transaminase levels ≤2.5 x upper limit of normal (ULN); total bilirubin levels within normal limits; international normalized ratio ≤2.0)
- Serum creatinine ≤2 x ULN

Key exclusion criteria

- Previous liver transplantation, or liver transplantation planned during the study period
- Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis
- Primary or leptomeningeal amyloidosis
- Type 1 diabetes or a history of type 2 diabetes (≥5 years)
- Active hepatitis B or C, or human immunodeficiency virus (HIV) infection
- Uncontrolled cardiac arrhythmia or unstable angina
- Acute coronary syndrome within the past 3 months

Outcomes[6]

- All endpoints compared baseline (42-day pre-treatment period) and the 18-month period after the first dose of study. Unless stated, parameters are assessed at screening/baseline, baseline, 9, and 18 months

Primary endpoint[6]

- Change from baseline in the modified Neurologic Impairment Score (mNIS+7) relative to placebo at 18 months

Key secondary endpoints[6]

- Change from baseline to 18 months in:
  - Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire, which has been shown to be sensitive to small fiber, large fiber, and autonomic nerve function and an indicator of disease severity of patients with hATTR amyloidosis (higher scores indicate worsening quality of life)
  - Neurologic Impairment Score (NIS)-weakness score (NIS-W), which assesses motor function and strength (higher scores indicate worsening strength)
  - Rasch-built Overall Disability Scale (R-ODS), a 24-item scale that captures limitations on everyday activity (a decrease in score indicates worsening disability)
  - Timed 10-meter walk test (10-MWT), which assesses ambulation based on the measurement of gait speed (a decrease in distance traveled per unit time indicates worsening symptoms)
  - Modified body mass index (mBMI) (kg/m^2 x albumin [g/L]), to gauge nutritional status (a negative change indicates worsening nutritional status)
  - Composite Autonomic Symptom Score (COMPASS-31), questionnaire to evaluate patient-reported autonomic symptoms across six autonomic domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor; an increase in score indicates worsening symptoms)

Other[6]

- Safety and Tolerability: adverse events (AEs), vital signs, clinical lab tests, thyroid function parameters, urinalysis, anti-drug antibodies, electrocardiograms, and ophthalmology examinations were assessed throughout the study

Statistics[6]

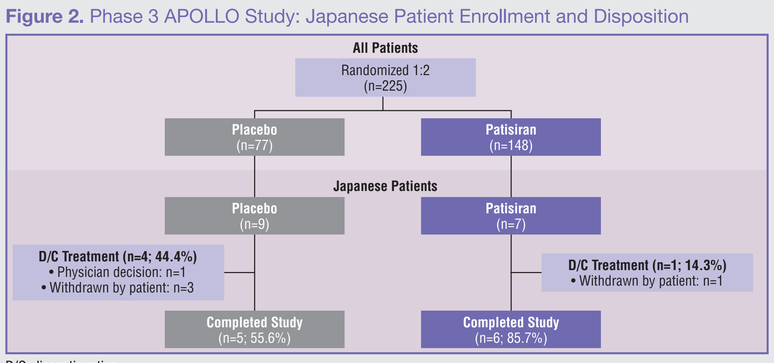
- Efficacy analyses were conducted for the modified intent-to-treat (mITT) population: randomized patients who received ≥1 dose of study drug. Patients were analyzed according to the treatment to which they were randomized
- Safety population: randomized patients who received ≥1 dose of study drug. Patients were analyzed according to the treatment received

RESULTS

Patients

- From December 2013 to January 2016, a total of 225 patients were enrolled at 44 sites in 19 countries, including 16 patients from Japan (**Figure 2**)

Figure 2. Phase 3 APOLLO Study: Japanese Patient Enrollment and Disposition



D/C, discontinuation.

- For the 16 patients from Japan, baseline demographics are reported in **Table 1**:

Table 1. Baseline Demographics and Disease Characteristics in Japanese Patients and in All Patients

	Japanese Patients		All Patients	
	Placebo n=9	Patisiran (0.3 mg/kg) n=7	Placebo n=77	Patisiran (0.3 mg/kg) n=148
Age, median (range)	62.0 (38, 77)	67.0 (52, 72)	63 (34, 80)	62 (24, 83)
Male, n (%)	8 (88.9%)	5 (71.4%)	58 (75.3%)	109 (73.6%)
Years since hATTR diagnosis, mean (min, max)	1.26 (0.1, 3.0)	1.38 (0.2, 5.0)	2.60 (0.0, 16.5)	2.39 (0.0, 21.0)
TTR genotype, n (%)				
V30M	7 (77.8%)	3 (42.9%)	40 (51.9)	56 (37.8)
Non-V30M	2 (22.2%)	4 (57.1%)	37 (48.1)	92 (62.2)
Genotype class, n (%)				
Early onset V30M (<50 years of age at onset)	2 (22.2%)	1 (14.3%)	10 (13.0%)	13 (8.8%)
All other mutations (including late-onset V30M)	7 (77.8%)	6 (85.7%)	67 (87.0%)	135 (91.2%)
Previous tetramer stabilizer use, n (%)	7 (77.8%)	7 (100.0%)	41 (53.2%)	78 (52.7%)
NIS, mean (Japanese: SD; All: range)	44.38 (21.38)	65.36 (30.92)	57.0 (7.0, 125.5)	60.5 (6.0, 141.6)
FAP stage, n (%)				
0	0	0	0	0
I	7 (77.8%)	2 (28.6%)	37 (48.1%)	67 (45.3%)
II	2 (22.2%)	5 (71.4%)	39 (50.6%)	81 (54.7%)
III	0	0	1 (1.3%)	0
PND score, n (%)				
I	1 (11.1%)	0	20 (26.0%)	36 (24.3%)
II	6 (66.7%)	4 (57.1%)	23 (29.9%)	43 (29.1%)
IIIA	2 (22.2%)	1 (14.3%)	22 (28.6%)	41 (27.7%)
IIIB	0	2 (28.6%)	11 (14.3%)	28 (18.9%)
IV	0	0	1 (1.3%)	0
Cardiac subpopulation[a], n (%)	4 (44.4%)	5 (71.4%)	36 (46.8%)	90 (60.8%)

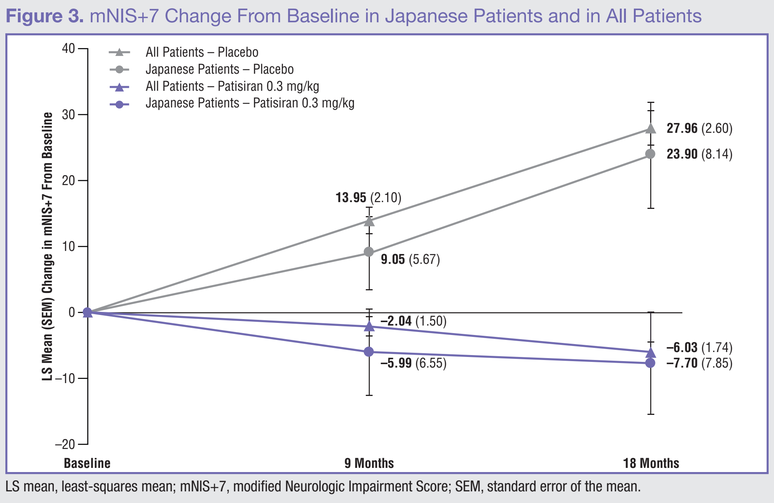
FAP, familial amyloidotic polyneuropathy; hATTR, hereditary ATTR; NIS, Neurologic Impairment Score; PND, polyneuropathy disability; SD, standard deviation.

[a]Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement and without confounding medical conditions; i.e., patients with baseline left ventricular wall thickness greater than or equal to 1.3 cm and no aortic valve disease or hypertension in medical history.

Primary Endpoint: Change From Baseline in mNIS+7 at 18 Months

- Patients treated with patisiran in the Japanese subpopulation ('Japanese patients') showed improvement in the primary endpoint as compared with placebo, consistent with that seen in the overall study population ('All patients') (**Figure 3**)
  - In Japanese patients, the least-squares (LS) mean difference between treatment groups for change in the mNIS+7 at 18 months was –31.6 points (standard error of the mean [SEM]: 11.23), representing an improvement in neuropathy in the patisiran group relative to the placebo group
    - In the overall study population, the LS mean difference between treatment groups for change in the mNIS+7 at 18 months was –33.99 points
  - The LS mean change from baseline at Month 18 for Japanese patients treated with patisiran was –7.70 (SEM: 7.85) compared with 23.90 (SEM: 8.14) for patients given placebo

Figure 3. mNIS+7 Change From Baseline in Japanese Patients and in All Patients

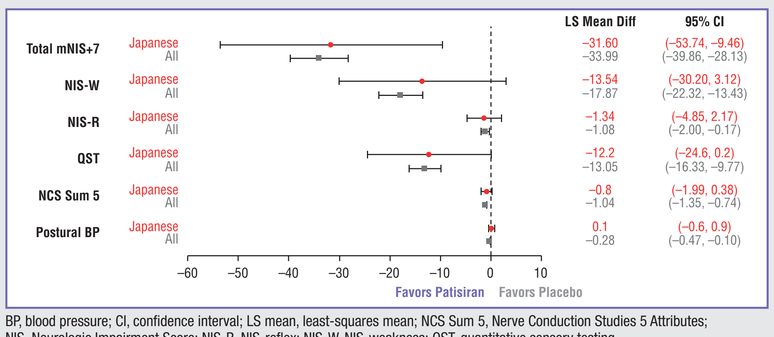


LS mean, least-squares mean; mNIS+7, modified Neurologic Impairment Score; SEM, standard error of the mean.

mNIS+7 Component Analyses in Japanese Patients and All Patients

- Component analyses demonstrated that Japanese patients treated with patisiran showed improvement in NIS-Weakness (LS mean difference: –13.54; 95% confidence interval [CI]: –30.20, 3.12), NIS-Reflex (LS mean difference: –1.34; 95% CI: –4.85, 2.17), and quantitative sensory testing (LS mean difference: –12.2; 95% CI: –24.6, 0.2) component scores compared with Japanese patients given placebo (**Figure 4**)
  - These results are consistent with results from the overall APOLLO patient population

Figure 4. Component Analyses of Change From Baseline to Month 18 in Japanese Patients and All Patients

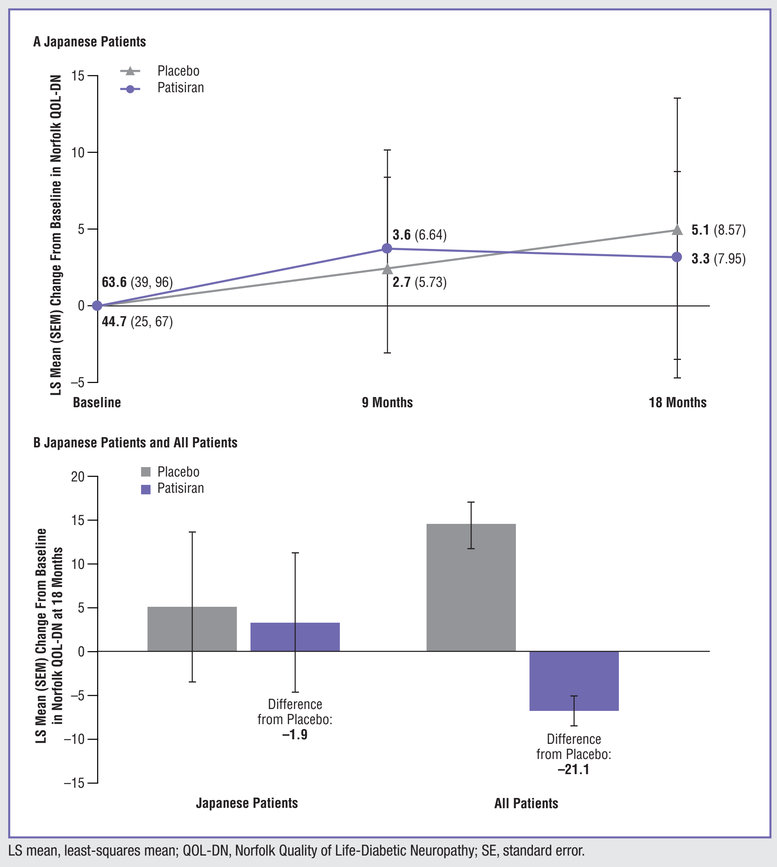


BP, blood pressure; CI, confidence interval; LS mean, least-squares mean; NCS Sum 5, Nerve Conduction Studies 5 Attributes; NIS, Neurologic Impairment Score; NIS-R, NIS-reflex; NIS-W, NIS-weakness; QST, quantitative sensory testing.

Change From Baseline in Quality of Life in Japanese Patients and All Patients

- Compared with placebo (LS mean change from baseline: 5.1; SEM: 8.57), Japanese patients treated with patisiran showed improvement in Norfolk QOL-DN score at 18 months (LS mean change from baseline: 3.3; SEM: 7.95) (**Figure 5A**)
  - The LS mean difference between Japanese patients treated with patisiran and those treated with placebo was –1.9 (SEM: 11.62) (**Figure 5B**)
  - The LS mean difference between patients treated with patisiran and those treated with placebo in the overall population was –21.1 (**Figure 5B**)

Figure 5. Change From Baseline in Norfolk QOL-DN at 18 Months in Japanese Patients and All Patients



LS mean, least-squares mean; QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SE, standard error.

Additional Secondary Endpoints in Japanese Patients and All Patients

- Japanese patients treated with patisiran demonstrated improvement in motor strength (NIS-W), autonomic symptoms (COMPASS-31), and nutritional status (mBMI) (**Table 2**)
- Patisiran treatment improved disability (R-ODS) and ambulation (10-MWT) parameters in Japanese patients (**Table 2**)
- These data are consistent with what is observed in the overall patient population (**Table 2**)

Table 2. Additional Secondary Endpoints in Japanese Patients and in All Patients

LS Mean (95% CI)	Japanese Patients		All Patients	
	Placebo n=9	Patisiran (0.3 mg/kg) n=7	Placebo n=77	Patisiran (0.3 mg/kg) n=148
NIS-W change from baseline at Month 18	13.24 (1.19, 25.30)	–0.30 (–11.95, 11.36)	17.93 (14.07, 21.79)	0.05 (–2.52, 2.63)
R-ODS change from baseline at Month 18	–7.7 (–13.4, –1.9)	–3.9 (–9.1, 1.4)	–8.9 (–10.7, –7.2)	0.0 (–1.1, 1.2)
10-MWT change from baseline at Month 18	–0.13 (–0.36, 0.11)	–0.06 (–0.28, 0.16)	–0.24 (–0.31, –0.16)	0.08 (–0.03, 0.12)
mBMI change from baseline at Month 18	–119.3 (–209.8, –28.9)	26.5 (–60.5, 113.6)	–119.4 (–148.0, –90.8)	–3.7 (–22.6, 15.1)
COMPASS-31 change from baseline at Month 18	–0.88 (–13.75, 11.98)	–5.45 (–16.81, 5.92)	2.24 (–1.59, 6.06)	–5.29 (–7.85, –2.72)

10-MWT, 10-meter walk test; CI, confidence interval; COMPASS-31, Composite Autonomic Symptom Score questionnaire; LS mean, least-squares mean; mBMI, modified body mass index; NIS, Neurologic Impairment Score; NIS-W, NIS-weakness; R-ODS, Rasch-Built Overall Disability Scale.

Safety and Tolerability

- Similar proportions of patients in each treatment arm reported at least one AE in both the Japanese patient subpopulation and in the overall patient population (**Table 3**)
- Severe AEs were infrequent in both the patisiran and placebo arms of the Japanese patient subpopulation and the overall patient population (**Table 3**)
- Similar proportions of serious AEs were reported in each treatment arm in both Japanese patients and in the overall patient population (**Table 3**)
- AEs leading to study withdrawal were lower in the patisiran arm compared with the placebo arm (**Table 3**)
  - There were no treatment discontinuations due to an AE or deaths reported in the Japanese patient subpopulation
- In the patisiran treatment group, the proportion of Japanese patients experiencing treatment-related AEs (28.6%) was lower than in the overall patient population (49.3%)

Table 3. Additional Safety and Tolerability in Japanese Patients and in All Patients

Type of AE Number of Patients (%)	Japanese Patients		All Patients	
	Placebo n=9	Patisiran (0.3 mg/kg) n=7	Placebo n=77	Patisiran (0.3 mg/kg) n=148
Adverse events (≥1 AE)	9 (100.0%)	6 (85.7%)	75 (97.4%)	143 (96.6%)
Severe AEs	1 (11.1%)	0	28 (36.4%)	42 (28.4%)
Serious AEs (SAEs)	4 (44.4%)	2 (28.6%)	31 (40.3%)	54 (36.5%)
AEs leading to treatment discontinuation	0	0	11 (14.3%)	7 (4.7%)
AEs leading to study withdrawal	1 (11.1%)	0	9 (11.7%)	7 (4.7%)
Deaths	0	0	6 (7.8%)	7 (4.7%)

AE, adverse event.

CONCLUSIONS

- In this sub-analysis of Japanese patients with hATTR amyloidosis from the APOLLO study, patisiran treatment resulted in clinically meaningful improvements in motor, sensory and autonomic neuropathy, nutritional status, and quality of life
- In general, the efficacy and safety profile of patisiran in Japanese patients was consistent with the overall APOLLO study population

Disclosures

- Taro Yamashita: Investigator in the APOLLO trial and received research funding from Alnylam.
- Yoshiki Sekijima: Investigator in the APOLLO trial and received research funding from Alnylam.
- Haruki Koike: Investigator in the APOLLO trial and received research funding from Alnylam.
- Mitsuharu Ueda: Investigator in the APOLLO trial and received research funding from Alnylam.
- Tsuneaki Yoshinaga: Investigator in the APOLLO trial and received research funding from Alnylam.
- Minori Kodaira: Investigator in the APOLLO trial and received research funding from Alnylam.
- Gen Sobue: Investigator in the APOLLO trial and received research funding from Alnylam. Received funding for travel and speaker honoraria from several entities.
- Masahisa Katsuno: Investigator in the APOLLO trial and received research funding from Alnylam. Received a research grant and personal compensation for activities (speaker fees) from Sanofi Genzyme.
- Teji Singh: Employee of Sanofi Genzyme.
- Yasuhiro Hashimoto: Employee of Sanofi.
- Ketaki Kadam: Employee of Sanofi Genzyme.
- Audrey W. Hou: Employee of Sanofi Genzyme.
- Yukio Ando: Investigator in the APOLLO trial and received research funding from Alnylam.

REFERENCES

1. Ando Y, Coelho T, Berk JL, *et al*. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis* 2013;8:31.
2. Sekijima Y, Ueda M, Koike H, *et al*. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: red-flag symptom clusters and treatment algorithm. *Orphanet J Rare Dis* 2018;13:6.
3. Coelho T, Adams D, Silva A, *et al*. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *N Engl J Med* 2013;369:819–829.
4. Adams D, Gonzalez-Duarte A, O'Riordan W, *et al*. Patisiran, an investigational RNAi therapeutic for patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy: results from the Phase 3 APOLLO study [EU-ATTR abstract 57]. *Orphanet J Rare Dis* 2017;12(suppl1):165.
5. Kato-Motozaki Y, Ono K, Shima K, *et al*. Epidemiology of familial amyloid polyneuropathy in Japan: Identification of a novel endemic focus. *J Neurol Sci* 2008;270:133–140.
6. Adams D, Suhr OB, Dyck PJ, *et al*. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. *BMC Neurology* 2017;17:181.

Presented at **The XVIth International Symposium on Amyloidosis**, Kumamoto, Japan. March 26–29, 2018

This study was co-sponsored by Alnylam and Sanofi Genzyme