Efficacy of Patisiran in Patients with hATTR Amyloidosis and Prior Tafamidis Use: Analysis of APOLLO

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Introduction

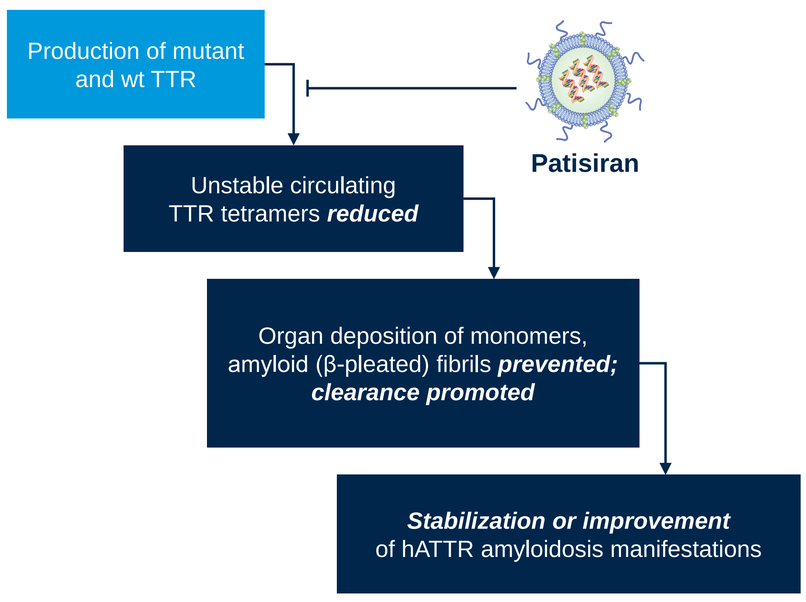
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, progressively debilitating, and fatal disease caused by a mutation in the transthyretin (*TTR*) gene that results in multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunction across these multiple organs[1–5]
- Affects ~50,000 people worldwide[4]; median survival of 4.7 years following diagnosis, with a reduced survival of 3.4 years for patients presenting with cardiomyopathy[6–9]
- Non-specific heterogeneous clinical presentation[5,10]; the majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[11–14]

Patisiran

- Patisiran, a lipid nanoparticle-delivered RNA interference (RNAi) therapeutic, reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing mutant and wt TTR proteins[15,16] (**Figure 1**)

Figure 1. Patisiran Therapeutic Hypothesis



- In the Phase 3 APOLLO study, patisiran improved multiple manifestations of polyneuropathy (including mNIS+7, quality of life [QOL], motor strength, disability, gait speed, and autonomic symptoms) compared with placebo at 18 months in patients with hATTR amyloidosis with polyneuropathy[11]
  - Patisiran also demonstrated an acceptable benefit:risk profile[11]
- Patisiran is 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[17,18]
  - Regulatory review of patisiran is ongoing in additional countries

Tafamidis

- TTR tetramer stabilizer shown to delay neurologic impairment in patients with early-stage V30M hATTR amyloidosis with polyneuropathy[19]
  - Disease progression has been observed with 40–65% of patients experiencing neurologic progression (NIS-LL: ≥2) at 12 months[20,21]
  - Effect of tafamidis on slowing disease progression has shown to be diminished among patients with later stages of disease[22,23]
- Tafamidis is approved in the EU and in select other countries outside the US for the treatment of stage 1 polyneuropathy in patients with hATTR amyloidosis; approved in the US for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis[24-26]

Objective

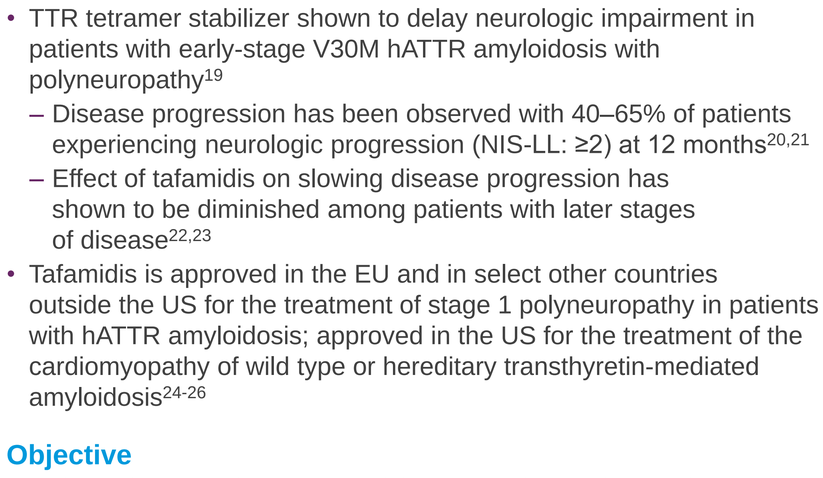
- To investigate the impact of patisiran on patients who received tafamidis treatment prior to enrolling in APOLLO

Methods

APOLLO Phase 3 Study Design

- APOLLO (NCT01960348) was a Phase 3, randomized, placebo-controlled study of patisiran 0.3 mg/kg intravenous (IV) every 3 weeks (q3w) in patients with hATTR amyloidosis with polyneuropathy[11] (**Figure 2**)

Figure 2. APOLLO Study Design



[a]Stratification factors of randomization include NIS: <50 vs ≥50, early-onset V30M (<50 years of age at onset) vs all other mutations (including late-onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs no previous use

[b]To reduce likelihood of infusion-related reactions, patients receive the following premedication or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol: H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine)

*Evaluated change from baseline to 18 months for each endpoint

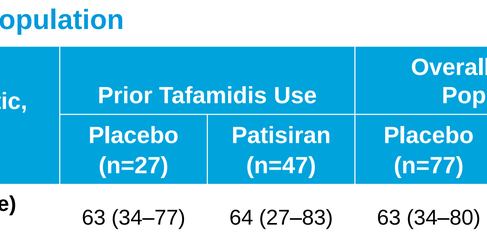
- The primary endpoint was the change from baseline in mNIS+7 at 18 months
  - mNIS+7 is a composite measure of polyneuropathy; higher score indicates worsening of neuropathy (range: 0 to 304)
- The key secondary endpoint was the change from baseline in the Norfolk Quality of Life Diabetic Neuropathy questionnaire (Norfolk QOL-DN) score at 18 months
  - Norfolk QOL-DN is a 35-item QOL questionnaire sensitive to small-fiber, large-fiber, and autonomic nerve function; higher score indicates worsening in QOL (range: −4 to 136)
- Previous TTR tetramer stabilizer use (diflunisal or tafamidis) vs no previous stabilizer use was a stratification factor at randomization
- Patients with prior tafamidis use were required to discontinue ≥14 days before study entry; the reason for discontinuation, as specified by the investigator, was recorded
- Post hoc analyses evaluated changes in mNIS+7 and Norfolk QOL-DN among patients in APOLLO who had received prior tafamidis treatment

Results

Patient Demographics

- APOLLO enrolled 225 patients, of whom 74 (32.9%) reported prior tafamidis use
- Most patients with prior tafamidis use (n=46, 62.2%) discontinued tafamidis to enroll in APOLLO and 25 patients (33.8%) discontinued tafamidis due to disease progression (**Figure 3**)

Figure 3. Reasons for Tafamidis Discontinuation



- Baseline demographics and the disease characteristics of patients with prior tafamidis use and of the overall APOLLO population are shown in **Table 1**
- Overall, the median (range) time on prior tafamidis was 13.5 (1.0–108.0) months and the median (range) time from discontinuation of tafamidis to the start of study-drug administration was 25.5 (15.0–318.0) days

Table 1. Baseline Demographics and Characteristics of Patients with Prior Tafamidis Use and of the Overall APOLLO Population

Characteristic, n (%)[a]	Prior Tafamidis Use		Overall APOLLO Population	
	Placebo (n=27)	Patisiran (n=47)	Placebo (n=77)	Patisiran (n=148)
Median (range) age, years	63 (34–77)	64 (27–83)	63 (34–80)	62 (24–83)
Sex, male	22 (81)	33 (70)	58 (75)	109 (74)
Region[b]				
North America	0 (0)	0 (0)	10 (13)	37 (25)
Western Europe	17 (63)	34 (72)	36 (47)	62 (42)
Rest of World	10 (37)	13 (28)	31 (40)	49 (33)
Median (range) time since hATTR amyloidosis diagnosis, years	2.1 (0.0–7.7)	1.9 (0.2–17.5)	1.4 (0.0–16.5)	1.3 (0.0–21.0)
Median (range) time on prior tafamidis, months	13.8 (1.0–43.0)	12.4 (1.3–108.0)	NA	NA
***TTR* genotype**				
V30M	18 (67)	22 (47)	40 (52)	56 (38)
Early-onset V30M (<50 years)	3 (11)	6 (13)	10 (13)	13 (9)
Non-V30M	9 (33)	25 (53)	37 (48)	92 (62)
FAP stage				
1: Unimpaired ambulation	15 (56)	19 (40)	37 (48)	67 (45)
2: Assistance with ambulation required	12 (44)	28 (60)	39 (51)	81 (55)
3: Wheelchair bound or bedridden	0 (0)	0 (0)	1 (1)	0 (0)
Cardiac subpopulation[c]	9 (33)	28 (60)	36 (47)	90 (61)
mNIS+7, mean (SD)	69.1 (32.7)	84.7 (37.0)	74.6 (37.0)	80.9 (41.5)
Norfolk QOL-DN, mean (SD)	51.4 (21.5)	60.0 (26.8)	55.5 (24.3)	59.6 (28.2)

[a]All values are n (%) unless otherwise stated

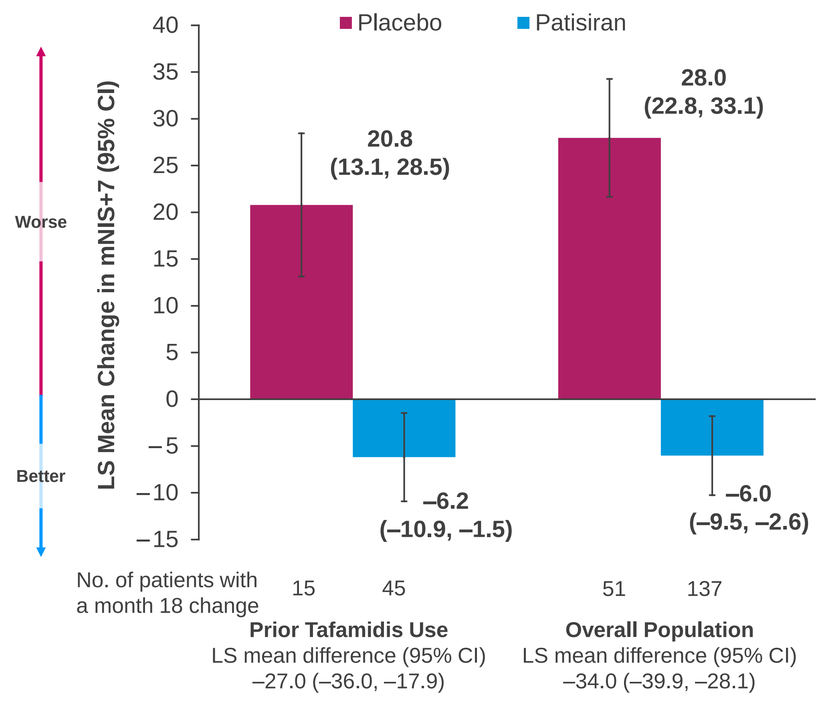
[b]North America: USA, Canada; Western Europe: France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom; Rest of World: Argentina, Brazil, Bulgaria, Cyprus, Japan, Mexico, South Korea, Taiwan, and Turkey

[c]Patients with a baseline left ventricular wall thickness of ≥1.3 cm and no medical history of aortic valve disease or hypertension were included in the pre-specified cardiac subpopulation

Primary Endpoint: mNIS+7 (Figure 4)

- In the prior tafamidis subgroup, improvement in mNIS+7 observed at 18 months with patisiran compared with placebo was seen as an least squares (LS) mean difference (95% confidence interval [CI]) of −27.0 (−36.0, −17.9)
  - Improvement was seen as early as 9 months with an LS mean difference (95% CI) of −10.2 (-17.5, -2.8)
  - In the overall APOLLO population, the improvement in mNIS+7 observed at 18 months with patisiran compared with placebo was seen as an LS mean difference (95% CI) of −34.0 (−39.9, −28.1)

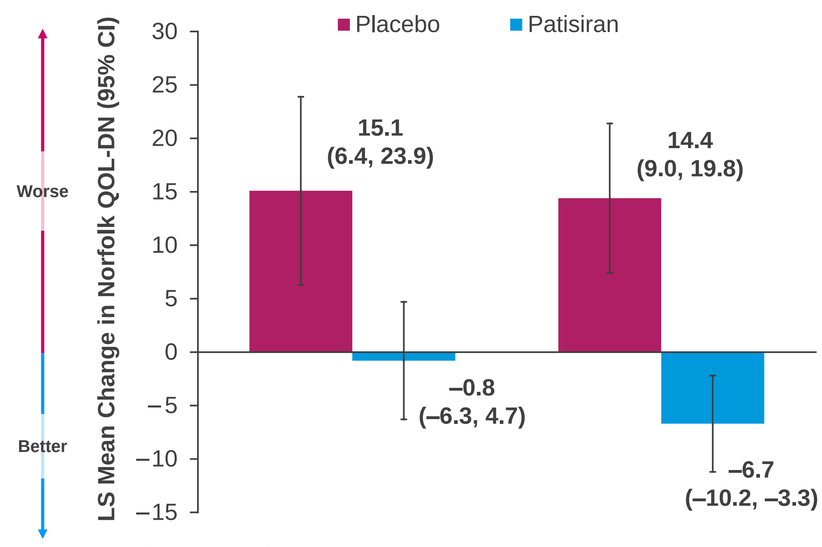
Figure 4. Change in mNIS+7 from Baseline to 18 Months



Secondary Endpoint: Norfolk QOL-DN (Figure 5)

- In the prior tafamidis subgroup, improvement in Norfolk QOL-DN observed at 18 months with patisiran compared with placebo was seen as an LS mean difference (95% CI) of −15.9 (−26.4, −5.5)
  - Improvement was seen as early as 9 months with an LS mean difference (95% CI) of −11.5 (−19.7, −3.4)
  - In the overall APOLLO population, the improvement in Norfolk QOL-DN observed at 18 months with patisiran compared with placebo was seen as an LS mean difference (95% CI) of −21.1 (−27.2, −15.0)

Figure 5. Change in Norfolk QOL-DN from Baseline to 18 Months



Safety and Tolerability in APOLLO (Table 2)

- Safety and tolerability in the prior tafamidis group was consistent with that seen in the overall APOLLO population
- Majority of adverse events (AEs) were mild or moderate in severity
- Common AEs that occurred more frequently with patisiran than placebo in the overall APOLLO population were peripheral edema (30% vs 22%) and infusion-related reactions (19% vs 9%)
- No safety concerns with regard to hematology laboratory parameters (including platelets), hepatic dysfunction, or renal dysfunction
- Causes of deaths were consistent with natural history of hATTR amyloidosis

Table 2. Safety Summary for the Overall APOLLO Population

Event, n (%)	Prior Tafamidis Use		Overall APOLLO Population	
	Placebo (n=27)	Patisiran (n=47)	Placebo (n=77)	Patisiran (n=148)
Any AE	26 (96)	45 (96)	75 (97)	143 (97)
Any severe AE	8 (30)	8 (17)	28 (36)	42 (28)
Any serious AE	12 (44)	20 (43)	31 (40)	54 (36)
AE leading to treatment discontinuation	4 (15)	1 (2)	11 (14)	7 (5)
AE leading to study withdrawal	3 (11)	1 (2)	9 (12)	7 (5)
Death[a]	2 (7)	2 (4)	6 (8)	7 (5)

[a]All deaths deemed not related or unlikely related to study drug by investigators

Conclusions

- Approximately one-third of patients enrolled in the randomized, placebo-controlled patisiran Phase 3 APOLLO study were previously treated with tafamidis
  - 34% of the patients with prior tafamidis use discontinued tafamidis due to disease progression; majority of other patients discontinued tafamidis to participate in the APOLLO study, although reason for discontinuation not specified
- Patients with prior tafamidis use who received patisiran treatment for 18 months experienced a significant improvement from baseline in polyneuropathy and QOL compared with placebo, similar to that experienced by the overall APOLLO population
- These data suggest that patients who discontinue tafamidis treatment due to disease progression or for other reasons may benefit from treatment with patisiran
- Patisiran demonstrated an acceptable benefit:risk profile

Abbreviations: AE, adverse event; CI, confidence interval; COMPASS-31, Composite Autonomic Symptom Score-31 item questionnaire; EQ-5D, EuroQoL 5-Dimensions questionnaire; hATTR, hereditary transthyretin-mediated; IV, intravenous; LS, least squares; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; NIS-LL, NIS-Lower Limb; NIS-W, NIS-Weakness; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; q3w, every 3 weeks; QOL, quality of life; R-ODS, Rasch-built Overall Disability Scale; RNAi, RNA interference; SD, standard deviation; *TTR*, transthyretin gene; TTR, transthyretin protein; wt, wild-type.

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