Evaluation of Patisiran with Concomitant or Prior Use of Transthyretin Stabilizers

Hollis Lin, Madeline Merkel, Cecilia Hale, Jing L. Marantz

Alnylam Pharmaceuticals, Cambridge, MA, USA

Hollis Lin reports research support funded by Alnylam Pharmaceuticals, and employment and shareholdings for Alnylam Pharmaceuticals

June 27-30, 2020 | Peripheral Nerve Society (PNS) Annual Meeting | Miami, USA (held virtually)

Background

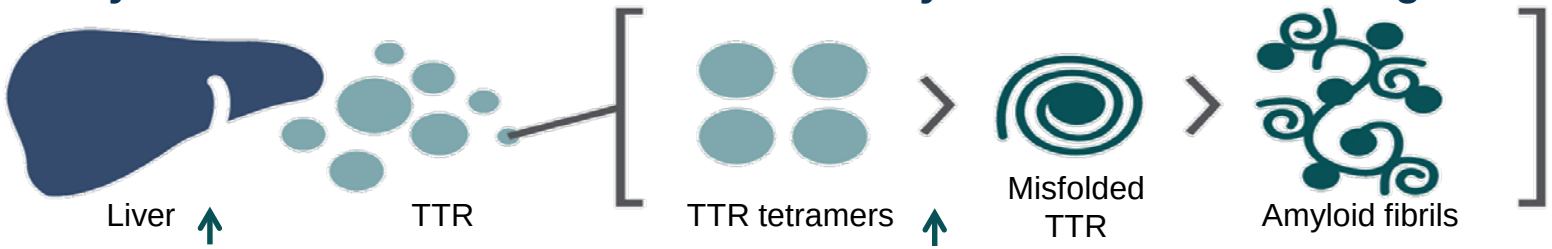
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis, Also Known As ATTRv Amyloidosis

- **Rare, inherited and progressively debilitating disease** caused by a **variant in the *TTR* gene**[1–5]
  - The majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[6–9]
- There is growing interest **to understand the potential position** of each therapy within the therapeutic landscape to optimize care for patients with hATTR amyloidosis

Analysis Objectives

- Evaluate safety and pharmacodynamics of patisiran alone or with a concomitant TTR stabilizer (diflunisal or tafamidis) from the Phase 2 OLE study
- Evaluate safety and efficacy of patisiran in patients with prior TTR stabilizer use from the Phase 3 APOLLO study

hATTR Amyloidosis Disease Cascade and Currently Available Pharmacologic Therapies[5]



TTR Silencing Therapies
- Patisiran
- Inotersen

TTR Stabilizers
- Tafamidis
- Diflunisal

ATTRv, hereditary transthyretin-mediated (v for variant); hATTR, hereditary transthyretin-mediated; OLE, open-label extension; TTR, transthyretin

1. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 3. Adams et al. *Neurology* 2015;85:675–82; 4. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 5. Hawkins et al. *Ann Med* 2015;47:625–38; 6. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 7. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 8. Adams et al. *N Engl J Med* 2018;379:11–21; 9. Benson et al. *N Engl J Med* 2018;379:22–31

Patisiran Phase 2 OLE Overview and Baseline Characteristics by Concomitant TTR Stabilizer Use

- **The Phase 2 OLE (NCT01961921)** was a 24-month multicenter, international OLE of the Phase 2 study of patisiran treatment
- **Primary objective** of the Phase 2 OLE study was to evaluate **safety and tolerability** of long-term patisiran dosing; **assessment of pharmacodynamics effect** (serum TTR reduction) was a secondary objective of the study
  - Patients were **permitted to receive concomitant tafamidis or diflunisal** during the study if the patient started either treatment prior to study entry

Baseline Characteristics	Patisiran Alone (n=7)	Patisiran and Tafamidis (n=13)	Patisiran and Diflunisal (n=7)
Median age, years (range)	55 (40–75)	45 (29–77)	69 (63–75)
Male, n (%)	4 (57.1)	9 (69.2)	5 (71.4)
Median years since hATTR amyloidosis diagnosis, (range)	2.0 (1–4)	3.1 (2–8)	2.1 (1–3)
V30M genotype, n (%)	4 (57.1)	9 (69.2)	7 (100.0)
FAP stage[a], n (%)			
1	6 (85.7)	11 (84.6)	7 (100.0)
2	1 (14.3)	2 (15.4)	0
Cardiac subpopulation[b], n (%)	1 (14.3)	5 (38.5)	5 (71.4)

[a]No patients were recorded to have FAP stage 3. [b]Defined as baseline left ventricular wall thickness ≥13 mm, normotensive or with hypertension that is well controlled, and no aortic valve disease history

FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated; OLE, open-label extension; TTR, transthyretin

Patisiran Phase 2 OLE Safety Summary and Exposure by Concomitant TTR Stabilizer Use Status

Overall, safety in each group **appears to be consistent with the reported safety profiles** of each monotherapy as reported **in their respective pivotal clinical studies**[1–4]

	Patisiran Alone (n=7)	Patisiran and Tafamidis (n=13)	Patisiran and Diflunisal (n=7)
Safety Event, n (%)			
Any adverse event (AE)	6 (85.7)	13 (100.0)	7 (100.0)
Any severe AE	2 (28.6)	2 (15.4)	1 (14.3)
Any serious AE	2 (28.6)	4 (30.8)	1 (14.3)
AE leading to discontinuation	1 (14.3)	0	1 (14.3)
Death	1 (14.3)[a]	0	1 (14.3)[a]
Exposure			
Median days of exposure, (range)	736 (735–737)	736 (19–747)	421 (139–736)

[a]Causes of death were myocardial infarction and gastro-oesophageal cancer, respectively, and both were deemed not drug-related by investigators

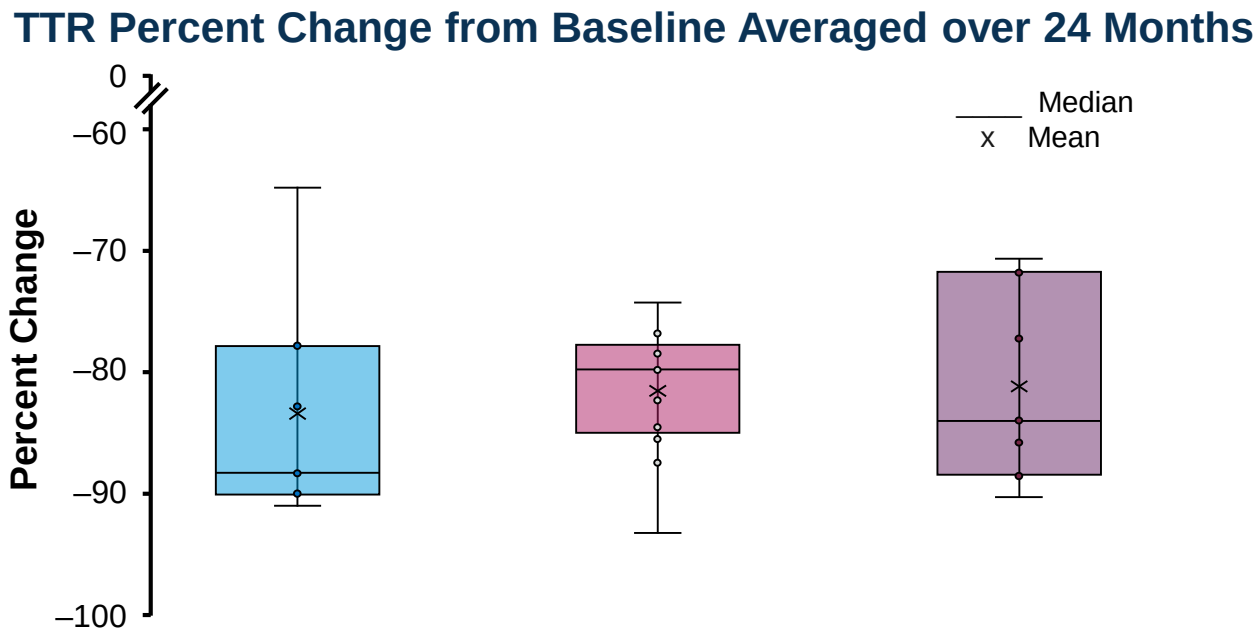
AE, adverse event; OLE, open-label extension; TTR, transthyretin

1. Berk et al. *JAMA* 2013;310:2658–67; 2. Coelho et al. *Neurology* 2012;79:785–92; 3. EMA. Summary of product characteristics: Onpattro. 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf(accessed January 21, 2020); 4. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO. 2019. Available from: http://www.alnylam.com/wp-content/uploads/2018/08/ONPATTRO-Prescribing-Information.pdf (accessed January 21, 2020)

Patisiran Phase 2 OLE Pharmacodynamics

TTR Percent Change from Baseline Averaged over 24 Months

Median (range) **serum TTR percent change from baseline averaged over 24 months was similar** regardless of whether a patient received patisiran alone or with a concomitant TTR stabilizer

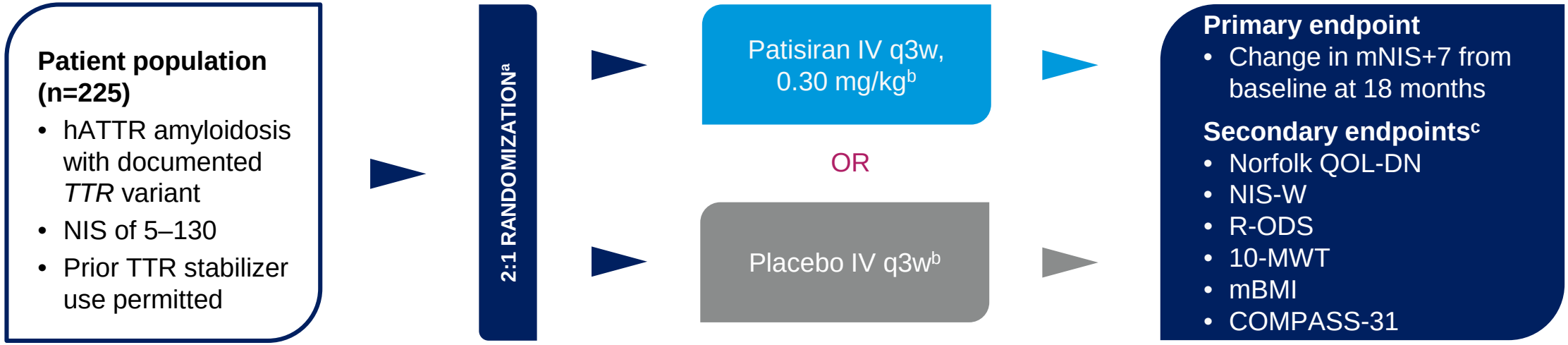


	Patisiran Alone (n=7)	Patisiran and Tafamidis (n=13)	Patisiran and Diflunisal (n=7)
Median TTR change (%) from baseline averaged over 24 months, (range)	–88.4 (–91.1 to –65.0)	–79.9 (–93.3 to –74.4)	–84.1 (–90.4 to –70.7)

OLE, open-label extension; TTR, transthyretin

Phase 3 APOLLO Study Overview and Prior Use of TTR Stabilizers

- Randomized, placebo-controlled study of patisiran over 18 months[1]
  - **Primary and key secondary endpoints** were change in **mNIS+7** and **Norfolk QOL-DN**, respectively, from baseline at 18 months[2]
  - Patients with prior tafamidis or diflunisal use were permitted to enroll and required to complete a wash-out period before starting study drug
    - Prior TTR stabilizer use (tafamidis or diflunisal) was a **stratification factor** at randomization[1]



[a]Stratification factors for 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 TTR stabilizer use (tafamidis or diflunisal) vs no previous TTR stabilizer use. [b]To reduce likelihood of infusion-related reactions, patients receive the following premedication or equivalent ≥60 minutes before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine). [c]Evaluated change from baseline to 18 months for each endpoint

10-MWT, 10-meter walk test; COMPASS-31, Composite Autonomic Symptom Score: 31-item questionnaire; IV, intravenous; hATTR, hereditary transthyretin-mediated; mBMI, modified body mass index; mNIS+7, modified NIS+7; NIS, Neuropathy Impairment Score; NIS-W, Neuropathy Impairment Score-Weakness; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; q3w, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin

1. Adams et al. *BMC Neurol* 2017;17:181; 2. Adams et al. *N Engl J Med* 2018;379:11–21

Patisiran Phase 3 APOLLO Baseline

Characteristics by Prior TTR Stabilizer Use Status

119 (52.9%) patients received a TTR stabilizer prior to study drug treatment in APOLLO

Baseline Characteristics	No Prior TTR Stabilizer Use		Prior Tafamidis Use		Prior Diflunisal Use	
	Placebo (n=36)	Patisiran (n=70)	Placebo (n=27)	Patisiran (n=47)	Placebo (n=14)	Patisiran (n=31)
Median age, years (range)	62.5 (36–80)	61 (24–77)	63 (34–77)	64 (27–83)	66 (46–75)	62 (35–75)
Male, n (%)	25 (69.4)	51 (72.9)	22 (81.5)	33 (70.2)	11 (78.6)	25 (80.6)
Median years since hATTR amyloidosis diagnosis, (range)	0.7 (0.1–16.5)	1.1 (0.0–21.0)	2.1 (0.0–7.7)	1.9 (0.2–17.5)	2.9 (0.4–13.0)	1.9 (0.0–11.9)
Median months on prior TTR stabilizer, (range)	n/a	n/a	13.8 (1.0–43.0)	12.4 (1.3–108.0)	10.6 (0.1–133.6)	9.9 (0.5–85.9)
V30M genotype, n (%)	17 (47.2)	25 (35.7)	18 (66.7)	22 (46.8)	5 (35.7)	9 (29.0)
FAP stage, n (%)						
1	17 (47.2)	31 (44.3)	15 (55.6)	19 (40.4)	5 (35.7)	17 (54.8)
2	18 (50.0)	39 (55.7)	12 (44.4)	28 (59.6)	9 (64.3)	14 (45.2)
3	1 (2.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac subpopulation[a], n (%)	19 (52.8)	44 (62.9)	9 (33.3)	28 (59.6)	8 (57.1)	18 (58.1)
Median baseline mNIS+7, (range)	72 (11–154)	81 (9–165)	71 (17–132)	87 (14–152)	76 (17–137)	66 (8–163)
Median baseline Norfolk QOL-DN, (range)	50 (14–111)	68 (5–119)	54 (17–91)	62 (10–113)	61 (8–83)	49 (7–95)

[a]Defined as left ventricular wall thickness ≥13 mm, and no history of uncontrolled hypertension or aortic valve disease

FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated; mNIS+7, modified Neuropathy Impairment Score +7; n/a, not applicable; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; TTR, transthyretin

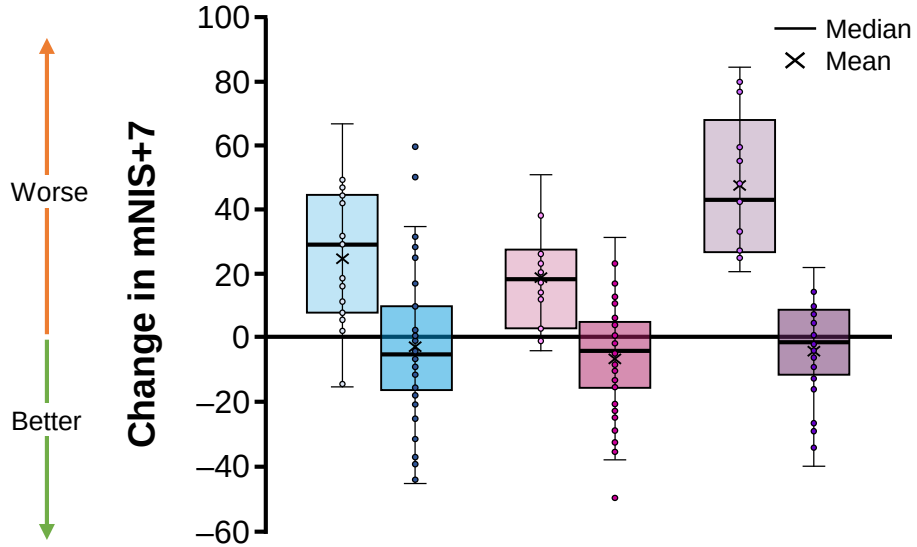
Patisiran Phase 3 APOLLO Efficacy

Change in mNIS+7 and Norfolk QOL-DN from Baseline to 18 Months

Mean change from baseline in mNIS+7 and Norfolk QOL-DN at 18 months trended consistently, regardless of prior TTR stabilizer use

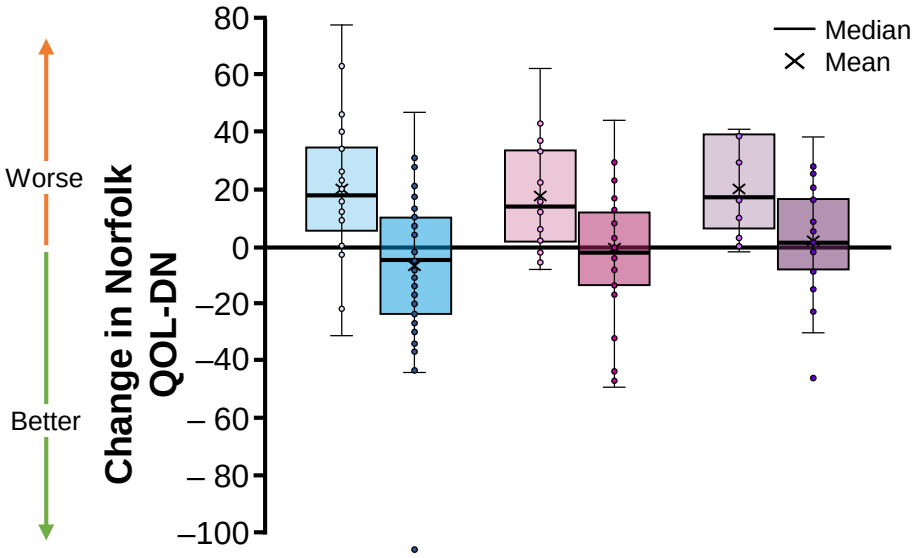
A **mean improvement or stabilization was observed for patisiran-treated patients**, whereas **placebo-treated patients progressed** on average

mNIS+7 Change from Baseline to Month 18



	No Prior Stabilizer		Prior Tafamidis		Prior Diflunisal	
	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran
n	26	62	19	45	13	31

Norfolk QOL-DN Change from Baseline to Month 18



	No Prior Stabilizer		Prior Tafamidis		Prior Diflunisal	
	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran
n	25	61	18	45	12	31

mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; TTR, transthyretin

Patisiran Phase 3 APOLLO Safety

Safety Summary According to Prior TTR Stabilizer Use

Safety and tolerability were consistent regardless of any prior TTR stabilizer history
and were comparable across the overall APOLLO population[1]

Event, n (%)	No Prior TTR Stabilizer Use		Prior Tafamidis Use		Prior Diflunisal Use	
	Placebo (n=36)	Patisiran (n=70)	Placebo (n=27)	Patisiran (n=47)	Placebo (n=14)	Patisiran (n=31)
Any AE	35 (97.2)	68 (97.1)	26 (96.3)	45 (95.7)	14 (100.0)	30 (96.8)
Any severe AE	14 (38.9)	30 (42.9)	8 (29.6)	8 (17.0)	6 (42.9)	4 (12.9)
Any serious AE	14 (38.9)	29 (41.4)	12 (44.4)	20 (42.6)	5 (35.7)	5 (16.1)
AE leading to study withdrawal	5 (13.9)	6 (8.6)	3 (11.1)	1 (2.1)	1 (7.1)	0
Death	4 (11.1)[a]	5 (7.1)[a]	2 (7.4)[a]	2 (4.3)[a]	0	0

[a]Deemed not to be drug-related by investigators

AE, adverse event; TTR, transthyretin

1. Adams et al. N Engl J Med 2018;379:11–21

Conclusions

- With the recent approvals of new therapies for hATTR amyloidosis, there is growing interest to understand the position of these therapies in the therapeutic landscape
- Data from the Phase 2 OLE study suggested the **safety** of, and **TTR reduction** with, patisiran **were unaffected by concomitant TTR stabilizer** use
- Data from APOLLO demonstrated that the **efficacy and safety profiles of patisiran** were **unaffected** by prior TTR stabilizer use
- These data indicate that patients with hATTR amyloidosis with polyneuropathy benefit from patisiran treatment **regardless of concomitant or prior use of a TTR stabilizer**
- **Full data published as:** Lin et al. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 10 Jun 2020, doi.org/10.2217/nmt-2020-0020

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the Phase 2 OLE and APOLLO studies

Editorial assistance was provided by Adelphi Communications (Bollington, UK) and funded by Alnylam Pharmaceuticals (Cambridge, MA, US)

hATTR, hereditary transthyretin-mediated; OLE, open-label extension; TTR, transthyretin