Evaluation of Patisiran with Concomitant or Prior Use of Transthyretin Stabilizers in Patients with Hereditary Transthyretin-Mediated Amyloidosis

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Conclusions

- With the recent approvals of new therapies for hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, there is growing interest to understand the position of these therapies in the therapeutic landscape
- Data from the Phase 2 open-label extension (OLE) study suggested the safety of, and transthyretin (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*. 2020;10:289–300

Background

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

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

Methods

Patisiran Phase 2 OLE Overview

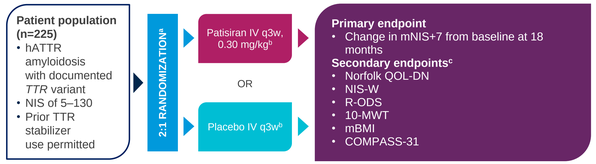
- The Phase 2 OLE (NCT01961921) was a 24-month, multicenter, international OLE of the Phase 2 study of patisiran treatment
- Primary objective of the Phase 2 OLE study was to evaluate safety and tolerability of long-term patisiran dosing; assessment of pharmacodynamics effect (serum TTR reduction) was 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

Phase 3 APOLLO Study Overview

- Randomized, placebo-controlled study of patisiran over 18 months[10] (NCT01960348)
  - Primary and key secondary endpoints were change in mNIS+7 and Norfolk QOL-DN, respectively, from baseline at 18 months[8]
  - 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[10]

Methods continued

Figure 1. Phase 3 APOLLO Study Overview and Prior Use of TTR Stabilizers



[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

Results

Table 1. Patisiran Phase 2 OLE Baseline Characteristics by Concomitant TTR Stabilizer Use

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

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

- Overall, safety in each group appeared to be consistent with the reported safety profiles of each monotherapy as reported in their respective pivotal clinical studies[11–14]

	Patisiran Alone (n=7)	Patisiran and Tafamidis (n=13)	Patisiran and Diflunisal (n=7)
Safety event, n (%)			
Any 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)

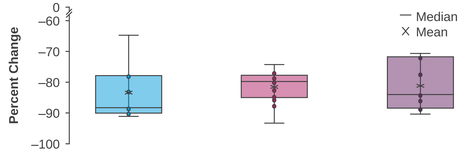
[a]Causes of death were myocardial infarction and gastro-esophageal cancer, respectively, and both were deemed not drug-related by investigators

Results continued

Patisiran Phase 2 OLE Pharmacodynamics

- 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

Figure 2. TTR Percent Change from Baseline Averaged over 24 Months



Median TTR Change (%) From Baseline Averaged Over 24 months (range)	Patisiran Alone (n=7)	Patisiran and Tafamidis (n=13)	Patisiran and Diflunisal (n=7)
	–88.4 (–91.1 to –65.0)	–79.9 (–93.3 to –74.4)	–84.1 (–90.4 to –70.7)

Table 3. Patisiran Phase 3 APOLLO Baseline Characteristics by Prior TTR Stabilizer Use

- 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
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

Patisiran Phase 3 APOLLO Efficacy

- 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

Figure 3. Change in (A) mNIS+7 and (B) Norfolk QOL-DN from Baseline to 18 Months

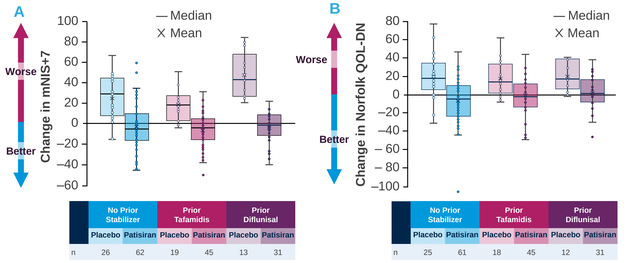


Table 4. Patisiran Phase 3 APOLLO Safety Summary According to Prior TTR Stabilizer Use

- Safety and tolerability were consistent regardless of any prior TTR stabilizer history and were comparable across the overall APOLLO population[8]

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

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

Acknowledgments: Editorial assistance in the development of the poster provided by Adelphi Communications Ltd, UK, was funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice (GPP3) guidelines. **Funding:** This study was funded by Alnylam Pharmaceuticals.

Disclosures: HL, MM, CH, and JLM have received personal compensation for serving as employees of Alnylam Pharmaceuticals and received stock or an ownership interest from Alnylam Pharmaceuticals. JLM is now an employee at Acceleron Pharma Inc. **Abbreviations:** 10-MWT, 10-meter walk test; AE, adverse event; ATTRv, hereditary transthyretin-mediated; COMPASS-31, Composite Autonomic Symptom Score: 31-item questionnaire; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated; IV, intravenous; mBMI, modified BMI; mNIS+7, modified NIS+7; n/a, not applicable; NIS, Neuropathy Impairment Score; NIS-W, NIS-Weakness; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; OLE, open-label extension; q3w, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin. **References:** 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; 10. Adams et al. *BMC Neurol* 2017;17:181; 11. Berk et al. *JAMA* 2013;310:2658–67; 12. Coelho et al. *Neurology* 2012;79:785–92; 13. 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 9 March 2021); 14. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO. 2019. Available from: http://www.alnylam.com/wp-content/uploads/2018/08/ONPATTRO-Prescribing-Information.pdf (accessed 9 March 2021).

First presented at the Peripheral Nerve Society (PNS) Virtual Event, 27–30 June 2020