HELIOS-A: 9-Month Subgroup Analyses and Exploratory Efficacy Results From the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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Conclusions

- **As previously reported, vutrisiran met the primary and both secondary endpoints at 9 months in patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy, with statistically significant improvements in neuropathy impairment (modified Neuropathy Impairment Score [mNIS+7]), quality of life (QOL; Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QOL-DN] questionnaire score), and gait speed (10-meter walk test [10-MWT]), compared with the external placebo group**
- **A consistent improvement in neuropathy impairment (mNIS+7) and QOL (Norfolk QOL-DN), compared with the external placebo group, was seen across all components of the endpoints and patient subgroups**
- **Vutrisiran demonstrated improvements in the exploratory endpoints for nutritional status (modified body mass index [mBMI]), disability (Rasch-built Overall Disability Scale [R-ODS]), QOL (EuroQol Visual Analog Scale [EQ-VAS]), and neuropathy impairment (Neuropathy Impairment Score [NIS]) compared with the external placebo group at 9 months**
- **Vutrisiran demonstrated an improvement in the cardiac biomarker, *N*-terminal pro-brain natriuretic peptide (NT-proBNP), in both the modified intent-to-treat (mITT) population and in the cardiac subpopulation, compared with the external placebo group**
- **The positive effects of vutrisiran on multiple endpoints combined with an acceptable safety profile[1] indicates benefit across important areas of patient health and function**

Background and Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- A rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease[2–5]
- Caused by variants in the *TTR* gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues[2–5]
- Multisystem disease with a heterogeneous clinical presentation (sensory, motor, autonomic, and cardiac symptoms)[5–7]
- The majority of individuals develop a mixed phenotype of both polyneuropathy and cardiomyopathy[8,9]

Vutrisiran

- An investigational, subcutaneously administered, RNAi therapeutic targeting hepatic production of variant and wt TTR, in development for the treatment of ATTR amyloidosis[10,11]
- ESC-GalNAc platform utilized by vutrisiran allows for Q3M SC injection[10,11]

Patisiran

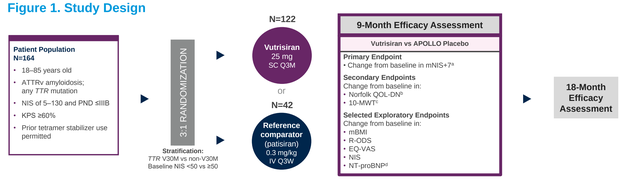
- RNAi therapeutic administered via intravenous infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO trial[12–14]

Methods

HELIOS-A Study

- HELIOS-A is a Phase 3, global, open-label study of vutrisiran 25 mg SC Q3M in patients with ATTRv amyloidosis with polyneuropathy (**Figure 1**)
- The 9-month subgroup analyses and exploratory efficacy analysis are presented; for each endpoint, vutrisiran is compared with the external placebo group (placebo arm of APOLLO[13]), selected on the basis of similar patient populations and endpoints
- The mITT population comprised all randomized patients who received ≥1 dose of vutrisiran or placebo

Figure 1. Study Design



[a]Higher scores of mNIS+7 indicate more neuropathy impairment (range 0 to 304). [b]Higher scores of Norfolk QOL-DN indicate worse QOL (range −4 to 136). [c]10-MWT speed (m/s) = 10 meter/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function. [d]A prespecified cardiac subpopulation was included (baseline left ventricular wall thickness ≥1.3 cm and no medical history of aortic valve disease or hypertension).

Results

Baseline Demographic and Disease Characteristics

- Patients in HELIOS-A had characteristics that were widely overlapping with patients in the external placebo group, and the two populations were clinically comparable (**Table 1**)

Prespecified Patient Subgroup Analysis and Individual Component Analysis

- Vutrisiran achieved statistically significant improvement in **mNIS+7 (neuropathy impairment)** at 9 months, compared with the external placebo group
- A consistent improvement in neuropathy impairment was seen across all prespecified patient subgroups (**Figure 2**) and components of mNIS+7 (**Figure 4**)
- Vutrisiran achieved statistically significant improvement in **Norfolk QOL-DN** at 9 months, compared with the external placebo group
- A consistent improvement in QOL was seen across all prespecified patient subgroups (**Figure 3**) and domains of Norfolk QOL-DN (**Figure 5**)

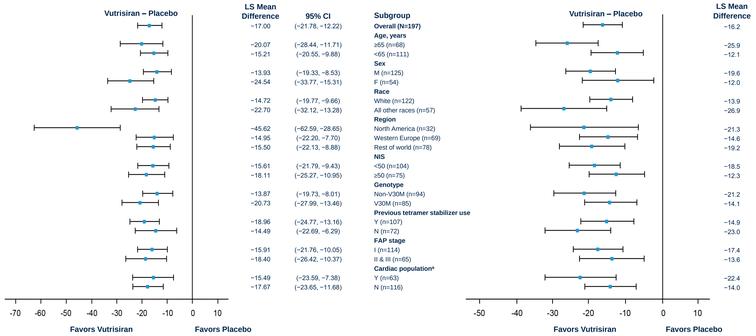
Results

Table 1. Baseline Characteristics

Characteristic	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Age, median (range), years	63 (34–80)	60 (26–85)	60 (31–81)
Males, n (%)	58 (75)	79 (65)	27 (64)
TTR genotype, n (%)			
V30M	40 (52)	54 (44)	20 (48)
Non-V30M[a]	37 (48)	68 (56)	22 (52)
NIS, mean (range)	57 (7–126)	43 (5–127)	43 (6–116)
Previous tetramer stabilizer use, n (%)	41 (53)	75 (61)	33 (79)
PND score[b], n (%)			
I/II/ IIIA/IIIB	20 (26)/23 (30)/ 22 (29)/11 (14)	44 (36)/50 (41)/ 16 (13)/12 (10)	15 (36)/17 (40)/ 7 (17)/3 (7)
NT-proBNP[c], median (range)	563 (25–16498)	287 (5–18755)	388 (5–14324)
Cardiac subpopulation, n (%)[d]	36 (47)	35 (29)	13 (31)

[a]The non-V30M TTR genotype represents 18 different variants in the APOLLO placebo group, and 21 non-V30M variant in the HELIOS-A vutrisiran group. [b]PND score: I, preserved walking, sensory disturbances; II, impaired walking, but can walk without stick or crutch; IIIA, walk with 1 stick or crutch; IIIB, walk with 2 sticks or crutches. One patient (1.3%) in external placebo group had a PND score of IV defined as confined to wheelchair or bedridden (not shown in Table 1). [c]NT-proBNP missing for 2 patients in APOLLO placebo group. [d]Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history).

Figure 2. mNIS+7 LS Mean Change from Baseline in Prespecified Subgroups (mITT Population)



[a]Cardiac subpopulation (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history).

Figure 3. Norfolk QOL-DN LS Mean Change from Baseline in Prespecified Subgroups (mITT Population)

Figure 4. mNIS+7 Total and Component Scores LS Mean Change from Baseline (mITT Population)

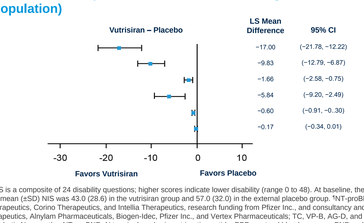
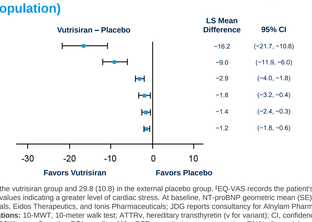


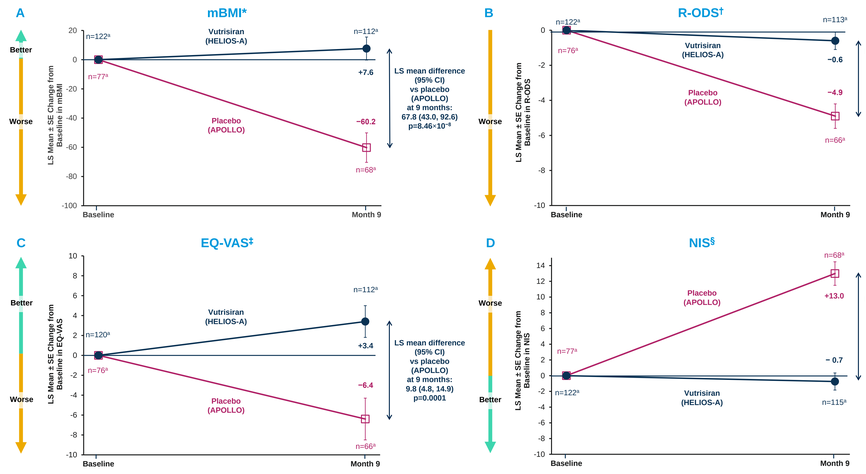
Figure 5. Norfolk QOL-DN Total and Domain Scores LS Mean Change from Baseline (mITT Population)



Exploratory Endpoints

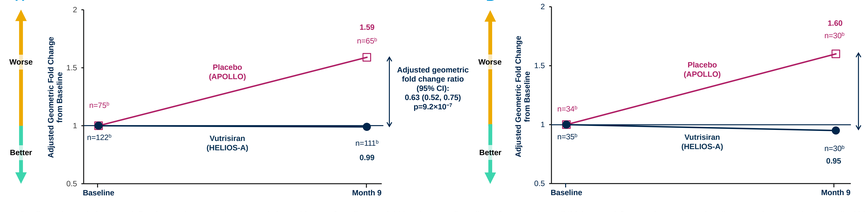
- Vutrisiran achieved improvement in the exploratory endpoints of mBMI (**Figure 6A**), R-ODS (**Figure 6B**), EQ-VAS (**Figure 6C**), and NIS (**Figure 6D**) compared with the external placebo group at 9 months
  - mBMI (**Figure 6A**), EQ-VAS (**Figure 6C**), and NIS (**Figure 6D**) were also improved compared with baseline
- NT-proBNP levels (**Figure 7**) were reduced compared with external placebo group in both the mITT population and the cardiac subpopulation

Figure 6. LS Mean Change from Baseline in A) mBMI*, B) R-ODS†, C) EQ-VAS‡, and D) NIS§ (mITT Population)



[a]Number of evaluable patients.

Figure 7. Change From Baseline in NT-proBNP¶ in A) mITT Population and B) Cardiac Subpopulation[a,#]



[a]Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history). [b]Number of evaluable patients

*mBMI = albumin (g/L) x weight (kg)/height (m)^2; higher values indicate higher nutritional status. At baseline, the mean (±SD) mBMI was 1057.5 (234.0) in the vutrisiran group and 989.9 (214.2) in the external placebo group. †R-ODS is a composite of 24 disability questions; higher scores indicate lower disability (range 0 to 48). At baseline, the mean (±SD) R-ODS score was 34.1 (11.0) in the vutrisiran group and 29.8 (10.8) in the external placebo group. ‡EQ-VAS records the patient's self-rated health on a vertical visual analog scale; higher scores indicate higher quality of life (range=0 to 100). At baseline, the mean (±SD) EQ-VAS was 0.708 64.5 (18.5) in the vutrisiran group and 54.6 (18.0) in the external placebo group. §NIS is a composite score of clinical impairments (weakness, reflex loss, and sensory loss); higher scores indicate greater impairment (range=0 to 244). A 2-point change is considered the least degree of change a physician could recognize. At baseline, the mean (±SD) NIS was 43.0 (28.6) in the vutrisiran group and 57.0 (32.0) in the external placebo group. ¶NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. At baseline, NT-proBNP geometric mean (SE) was 273.0 (42.2) ng/mL in the vutrisiran group (n=122) and 531.3 (86.7) ng/L in APOLLO placebo (n=75) group. #At baseline, NT-proBNP geometric mean (SE) was 772.8 (195.0) ng/L in the vutrisiran cardiac subpopulation group (n=35) and 771.1 (151.1) ng/L in APOLLO placebo cardiac subpopulation (n=34) group. **Disclosures:** DA reports consultancy for Alnylam Pharmaceuticals and Pfizer Inc.; MST reports Speakers Bureau fees from Pfizer Inc.; JLB reports consultancy for Akcea Therapeutics, Corino Therapeutics, and Intellia Therapeutics, research funding from Pfizer Inc., and consultancy and research funding from Alnylam Pharmaceuticals, Eidos Therapeutics, and Ionis Pharmaceuticals; JDG reports consultancy for Alnylam Pharmaceuticals; YS reports honoraria and research funding from Alnylam Pharmaceuticals and Pfizer Inc.; LO reports Speakers Bureau fees from Akcea Therapeutics, Alnylam Pharmaceuticals, and Pfizer Inc.; RB, RS, and JV are all employees of Alnylam Pharmaceuticals, and report ownership of equity in Alnylam Pharmaceuticals; SA is an employee of Alnylam Pharmaceuticals and has received personal fees for editing from Wolters Kluwer; MP reports consultancy for Akcea Therapeutics, Alnylam Pharmaceuticals, Biogen-Idec, Pfizer Inc., and Vertex Pharmaceuticals; TC, VP-D, AG-D, and S-CL report no financial disclosures. **Abbreviations:** 10-MWT, 10-meter walk test; ATTRv, hereditary transthyretin (v for variant); CI, confidence interval; EQ-VAS, EuroQol Visual Analog Scale; ESC-GalNAc, Enhanced Stabilization Chemistry-GalNAc; FAP, familial amyloidotic polyneuropathy; hATTR, hereditary transthyretin-mediated; IV, intravenous; KPS, Karnofsky performance status; LS, least squares; mBMI, modified body mass index; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; NCS, nerve conduction studies; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; PBP, postural blood pressure; PND, polyneuropathy disability; Q3M, *every* 3 months; Q3W, every 3 weeks; QOL, quality of life; QST, quantitative sensory testing; RNAi, ribonucleic acid interference; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; SD, standard deviation; SE, standard error; TTR, transthyretin; wt, wild-type. **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. **References:** 1. Adams et al. *Poster PNS Congress* 2021; 2. Hanna M. *Curr Heart Fail Rep* 2014;11:50–57; 3. Hawkins PN et al. *Ann Med* 2015;47:625–38; 4. Damy T et al. *J Cardiovasc Transl Res* 2015;8:117–27; 5. Mohty D et al. *Arch Cardiovasc Dis* 2013;106:528–40; 6. Conceição I et al. *J Peripher Nerv Syst* 2016;21:5–9; 7. Shin & Robinson-Papp. *Mt Sinai J Med* 2012;79:733–48; 8. Rapezzi C et al. *Eur Heart J* 2013;34:520–28 9. Coelho T et al. *Curr Med Res Opin* 2013;29:63–76; 10. Habtemariam BA et al. *Clin Pharmacol Ther* 2021;109:372–82; 11. Nair JK et al. *J Am Chem Soc* 2014;136:16958–61; 12. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. February 2020; 13. Adams D et al. *N Engl J Med* 2018;379:11–21; 14. Adams D et al. *Lancet Neurology* 2021;20:49–59.

Presented at the 3rd European ATTR Amyloidosis meeting for Patients and Doctors (EU-ATTR) September 6–8, 2021

Thank you to the patients, their families, Investigators, study staff, and collaborators for their participation in the HELIOS-A study

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