Treatment Effect of Vutrisiran on Measures of Polyneuropathy in HELIOS-B

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HELIOS·B

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Conclusions

- A substantial proportion of patients in the overall HELIOS-B population had at least one elevated PN-related parameter at baseline, indicating PN burden in these patients
- In HELIOS-B patients with elevated baseline Norfolk QoL-DN scores (>16 and >21 at baseline), vutrisiran demonstrated significant reductions in Norfolk QoL-DN versus placebo
- In the relatively small number of patients with abnormally elevated baseline NfL levels (per Mayo Clinic reference values), treatment with vutrisiran also demonstrated substantial reductions in NfL levels versus placebo

Key takeaway

These findings highlight the potential burden of PN in patients with ATTR-CM and the benefit of vutrisiran

Introduction

Vutrisiran in Patients With ATTR

- ATTR, classified as wtATTR or hATTR, is a rapidly progressive, debilitating, and fatal disease caused by pathogenic TTR accumulating as amyloid deposits in the heart, nerves, and other systems[1]
  - wtATTR predominantly manifests as CM, while hATTR can manifest as PN, CM, or in most cases a mixed phenotype. The prevalence and extent of PN in patients with wtATTR is not well understood
- Vutrisiran, an RNAi silencer that rapidly inhibits hepatic synthesis of TTR protein, demonstrated significant clinical benefit in HELIOS-B, an international, randomized, multicenter, double-blind, placebo-controlled, phase 3 study in patients with ATTR-CM[2]
  - Patients with a PND score of III or higher were excluded from HELIOS-B[2]

Objective

- To assess the impact of vutrisiran on PN-related parameters in a post-hoc analysis of patients with ATTR-CM from the HELIOS-B study

Methods

- In HELIOS-B, patients with ATTR-CM were randomized to receive up to 33–36 months of treatment with vutrisiran (25 mg SC q3M) or placebo (SC q3M) during the double-blind period
- Change from baseline at Month 30 in Norfolk QoL-DN and NfL levels was assessed for patients treated with vutrisiran versus placebo in the overall and monotherapy populations (no tafamidis use at baseline) with evidence of PN based on either Norfolk QoL-DN or NfL (according to Mayo Clinic reference values) levels at baseline

Norfolk QoL-DN

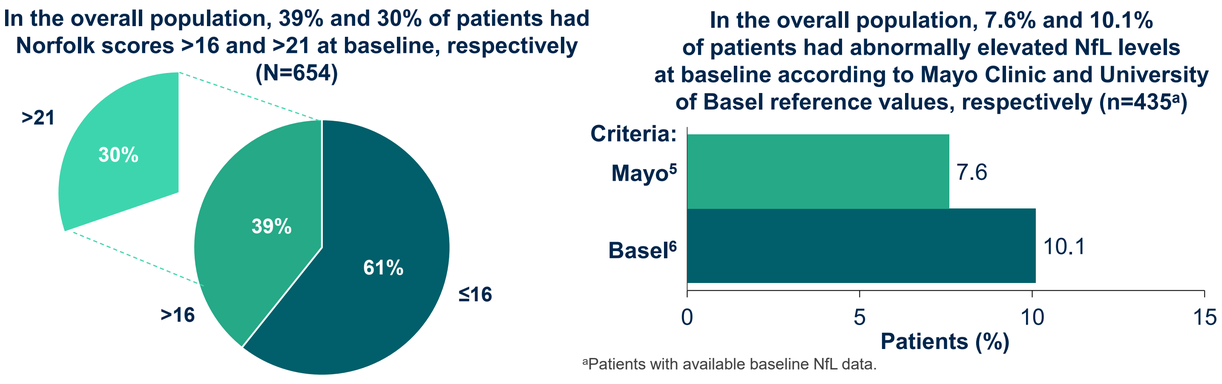
Patients with baseline Norfolk QoL-DN scores
- >16 (upper limit of normal)[3]
- >21 (mean value reported in hATTR-PN patients with FAP 1)[4]

NfL Levels

Patients with abnormally elevated baseline NfL levels per Mayo Clinic reference values[5]

Results

Figure 1. A Substantial Proportion of Patients Had at Least One Elevated PN-Related Parameter at Baseline



[a]Patients with available baseline NfL data.

- A slightly higher proportion of patients in the monotherapy population had elevated baseline Norfolk scores (44% and 35% with scores >16 and >21, respectively) versus the overall population, whilst the proportion of patients with abnormally elevated baseline NfL levels was similar across populations
- The proportion of patients with elevated Norfolk scores and abnormally elevated NfL levels at baseline was similar between treatment groups
- Importantly, since patients with a PND score of III or higher were excluded from HELIOS-B, these results may underestimate PN burden in the general ATTR-CM population

Table 1. In Patients With a Baseline Norfolk Score >16, Baseline Characteristics Were Generally Similar Across Treatment Groups

		Overall Population		Monotherapy Population	
		Placebo (n=125)	Vutrisiran (n=132)	Placebo (n=87)	Vutrisiran (n=87)
Time since diagnosis, years, median (IQR)		1.0 (0.4–2.1)	0.8 (0.3–1.7)	0.9 (0.2–1.7)	0.7 (0.2–1.6)
hATTR, n (%)		18 (14.4)	11 (8.3)	15 (17.2)	7 (8.0)
wtATTR, n (%)		107 (85.6)	121 (91.7)	72 (82.8)	80 (92.0)
NYHA class, n (%)	I	5 (4.0)	7 (5.3)	4 (4.6)	3 (3.4)
	II	98 (78.4)	108 (81.8)	70 (80.5)	77 (88.5)
	III	22 (17.6)	17 (12.9)	13 (14.9)	7 (8.0)
PND score at screening, n (%)	0	67 (53.6)	77 (58.3)	53 (60.9)	49 (56.3)
	I	41 (32.8)	46 (34.8)	25 (28.7)	33 (37.9)
	II	17 (13.6)	9 (6.8)	9 (10.3)	5 (5.7)
Norfolk QoL-DN total score, mean (SD)		35.1 (17.4)	33.8 (16.2)	36.3 (18.2)	34.8 (17.7)
Previous HF hospitalization, n (%)		46 (36.8)	42 (31.8)	34 (39.1)	28 (32.2)
6-MWT, m, mean (SD)		331.6 (93.2)	331.2 (90.9)[a]	335.2 (93.7)	330.9 (83.5)
KCCQ-OS, points, mean (SD)		55.8 (17.9)	58.6 (18.1)	54.1 (18.1)	56.7 (18.7)

[a]n=131.

Table 2. In Patients With a Baseline Norfolk Score >21, Baseline Characteristics Were Generally Similar Across Treatment Groups

		Overall Population		Monotherapy Population	
		Placebo (n=95)	Vutrisiran (n=103)	Placebo (n=71)	Vutrisiran (n=68)
Time since diagnosis, years, median (IQR)		1.0 (0.3–2.1)	0.7 (0.3–1.6)	0.9 (0.2–1.8)	0.5 (0.2–1.4)
hATTR, n (%)		14 (14.7)	9 (8.7)	13 (18.3)	7 (10.3)
wtATTR, n (%)		81 (85.3)	94 (91.3)	58 (81.7)	61 (89.7)
NYHA class, n (%)	I	5 (5.3)	4 (3.9)	4 (5.6)	2 (2.9)
	II	71 (74.7)	84 (81.6)	55 (77.5)	59 (86.8)
	III	19 (20.0)	15 (14.6)	12 (16.9)	7 (10.3)
PND score at screening, n (%)	0	50 (52.6)	56 (54.4)	41 (57.7)	35 (51.5)
	I	30 (31.6)	38 (36.9)	21 (29.6)	28 (41.2)
	II	15 (15.8)	9 (8.7)	9 (12.7)	5 (7.4)
Norfolk QoL-DN total score, mean (SD)		40.2 (17.0)	38.0 (16.0)	40.2 (17.9)	39.1 (17.8)
Previous HF hospitalization, n (%)		36 (37.9)	35 (34.0)	27 (38.0)	24 (35.3)
6-MWT, m, mean (SD)		323.4 (95.5)	323.4 (88.6)[a]	325.9 (95.8)	326.0 (83.2)
KCCQ-OS, points, mean (SD)		51.0 (16.6)	56.0 (18.4)	50.9 (17.8)	54.5 (19.8)

[a]n=102.

Table 3. Baseline Characteristics of Patients With Abnormally Elevated Baseline NfL Levels (Mayo Clinic Reference Values)

		Overall Population		Monotherapy Population	
		Placebo (n=17)	Vutrisiran (n=16)	Placebo (n=11)	Vutrisiran (n=12)
Time since diagnosis, years, median (IQR)		1.0 (0.3–1.7)	0.4 (0.2–2.6)	0.6 (0.1–1.0)	0.4 (0.2–0.8)
hATTR, n (%)		6 (35.3)	4 (25.0)	6 (54.5)	4 (33.3)
wtATTR, n (%)		11 (64.7)	12 (75.0)	5 (45.5)	8 (66.7)
NYHA class, n (%)	I	4 (23.5)	1 (6.3)	2 (18.2)	1 (8.3)
	II	13 (76.5)	13 (81.3)	9 (81.8)	10 (83.3)
	III	0	2 (12.5)	0	1 (8.3)
PND score at screening, n (%)	0	11 (64.7)	10 (62.5)	8 (72.7)	6 (50.0)
	I	5 (29.4)	4 (25.0)	2 (18.2)	4 (33.3)
	II	1 (5.9)	2 (12.5)	1 (9.1)	2 (16.7)
Previous HF hospitalization, n (%)		5 (29.4)	8 (50.0)	4 (36.4)	6 (50.0)
6-MWT, m, mean (SD)		377.4 (104.0)	357.7 (132.7)	354.0 (93.3)	359.6 (134.6)
KCCQ-OS, points, mean (SD)		71.4 (20.1)	70.0 (24.3)	64.6 (20.1)	59.7 (25.4)
NfL, pg/mL, mean (SD)		58.3 (18.2)	61.8 (24.7)	54.8 (12.5)	66.0 (27.2)

Figure 2. In Patients With Elevated Baseline Norfolk Scores, Significant Differences Were Observed Between Vutrisiran and Placebo Arms in Change From Baseline in Norfolk QoL-DN Scores at Month 30

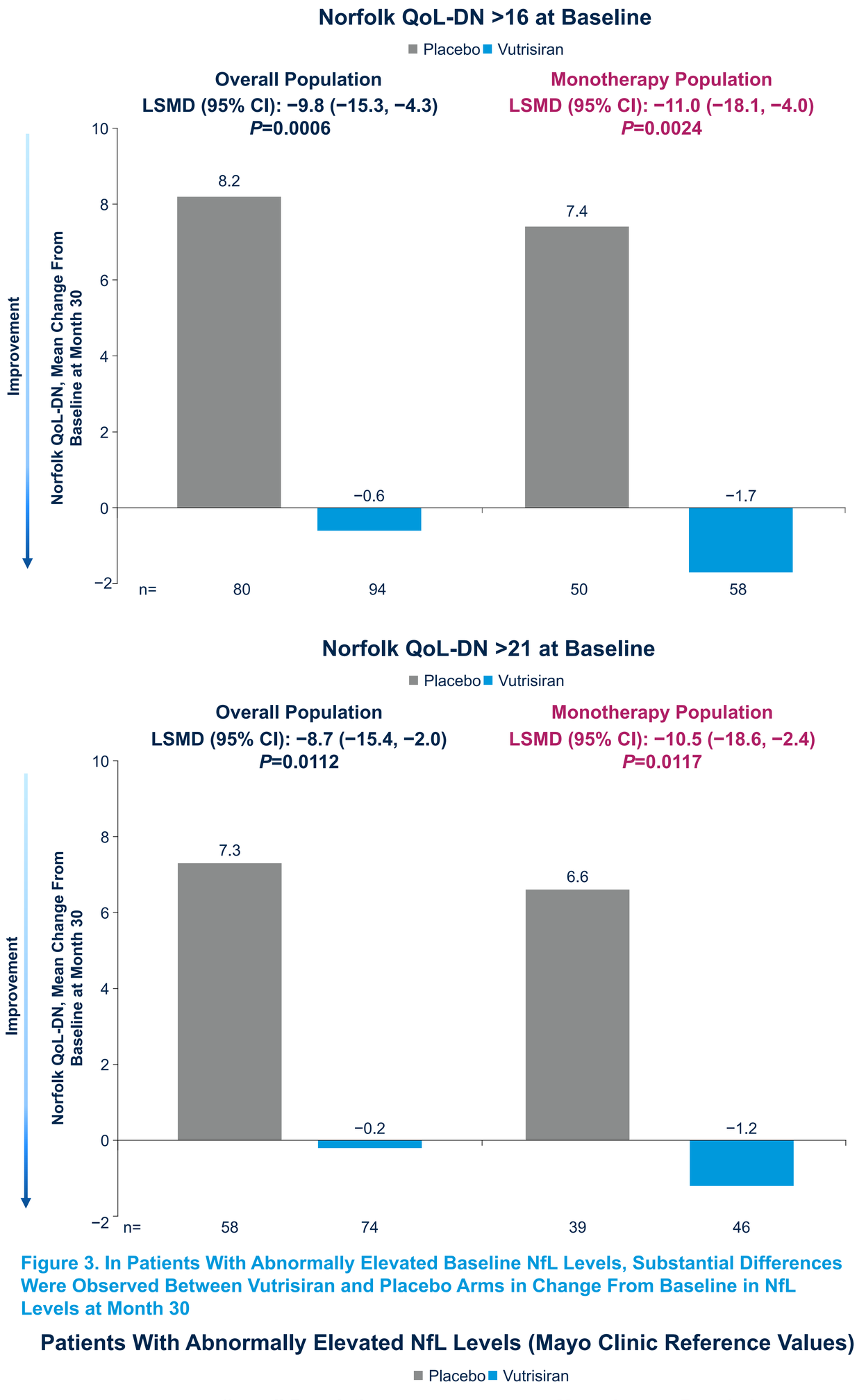


Figure 3. In Patients With Abnormally Elevated Baseline NfL Levels, Substantial Differences Were Observed Between Vutrisiran and Placebo Arms in Change From Baseline in NfL Levels at Month 30

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If you are seeking additional scientific information related to Alnylam therapeutics, non-US HCPs should contact medinfo@alnylam.com. US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com.

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References: 1. Ruberg & Maurer. *JAMA* 2024;331:778–91; 2. Fontana et al. *N Engl J Med* 2025;392:33–44; 3. Vinik et al. *Diabetes Technol Ther* 2005;7:497–508; 4. Vinik et al. *J Peripher Nerv Syst* 2014;19:104–14;
5. Mayo Clinic Laboratories. Test ID: Neurofilament Light Chain, Plasma. Accessed August 18, 2026. https://www.mayocliniclabs.com/test-catalog/overview/622765/neurofilament-light-chain-plasma#clinical-and-interpretive; 6. Benkert et al. *Lancet Neurol* 2022;21:246–57.

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; CI, confidence interval; CM, cardiomyopathy; FAP, familial amyloid polyneuropathy; hATTR, hereditary ATTR; HF, heart failure; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LSMD, least squares mean difference; NfL, neurofilament light chain; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NYHA, New York Heart Association; PN, polyneuropathy; PND, polyneuropathy disability; q3M, once every 3 months; RNAi, RNA interference; SC, subcutaneous; SD, standard deviation; TTR, transthyretin; wtATTR, wild-type ATTR.