HELIOS-A: 18-month randomised treatment extension analysis of vutrisiran in patients with hereditary transthyretin amyloidosis with polyneuropathy

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Disclosures

- Cécile Cauquil reports consultancy for Alnylam Pharmaceuticals, AstraZeneca, and Pfizer
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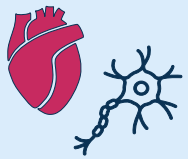
Background and Rationale



ATTRv

- A rare, underdiagnosed, inherited, rapidly progressive, debilitating and fatal disease[1,2]
- Caused by variants in the TTR gene that result in misfolded TTR protein accumulating as toxic amyloid fibrils in multiple organs and tissues, including the peripheral nerves and heart[1,3,4]
- Many individuals with ATTRv develop a mixed phenotype of polyneuropathy and cardiomyopathy[1,3,4]

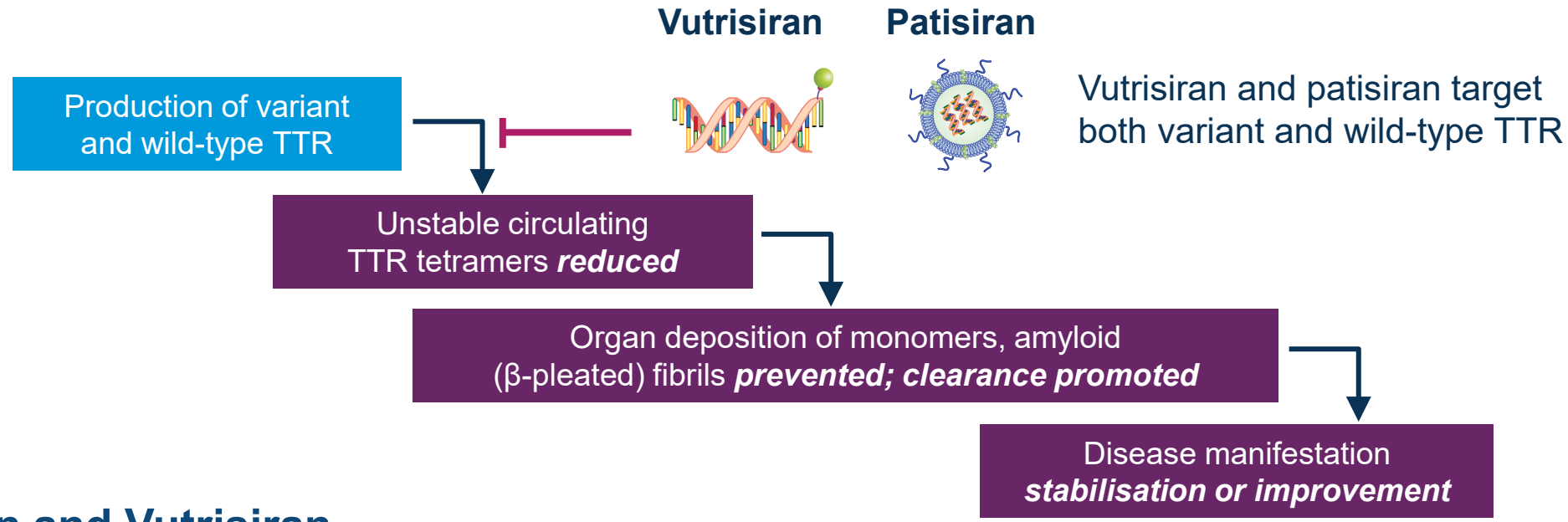
Patisiran and Vutrisiran

- Patisiran and vutrisiran are RNAi therapeutics that degrade wild-type and variant *TTR* mRNA, resulting in rapid knockdown of circulating toxic TTR[5–8]

Abbreviations: ATTRv, hereditary transthyretin amyloidosis (v for variant); mRNA, messenger RNA; RNAi, RNA interference; TTR, transthyretin.

References: 1. Adams et al. *Nat Rev Neurol*. 2019;15:387–404; 2. Ruberg et al. *J Am Coll Cardiol*. 2019;73:2872–92; 3. Maurer et al. *J Am Coll Cardiol*. 2016;68:161–72; 4. Gentile et al. *Orphanet J Rare Dis*. 2023;18:350–62; 5. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use (2020); 6. European Medicines Agency. Summary of product characteristics: ONPATTRO 2 mg/mL concentrate for solution for infusion. 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf (accessed September 2024); 7. Alnylam Pharmaceuticals Inc. US prescribing information: AMVUTTRA (vutrisiran) injection, for subcutaneous use. 2022; 8. European Medicines Agency. Summary of product characteristics: AMVUTTRA 25 mg solution for injection. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf (accessed September 2024).

Therapeutic Hypothesis



Patisiran and Vutrisiran

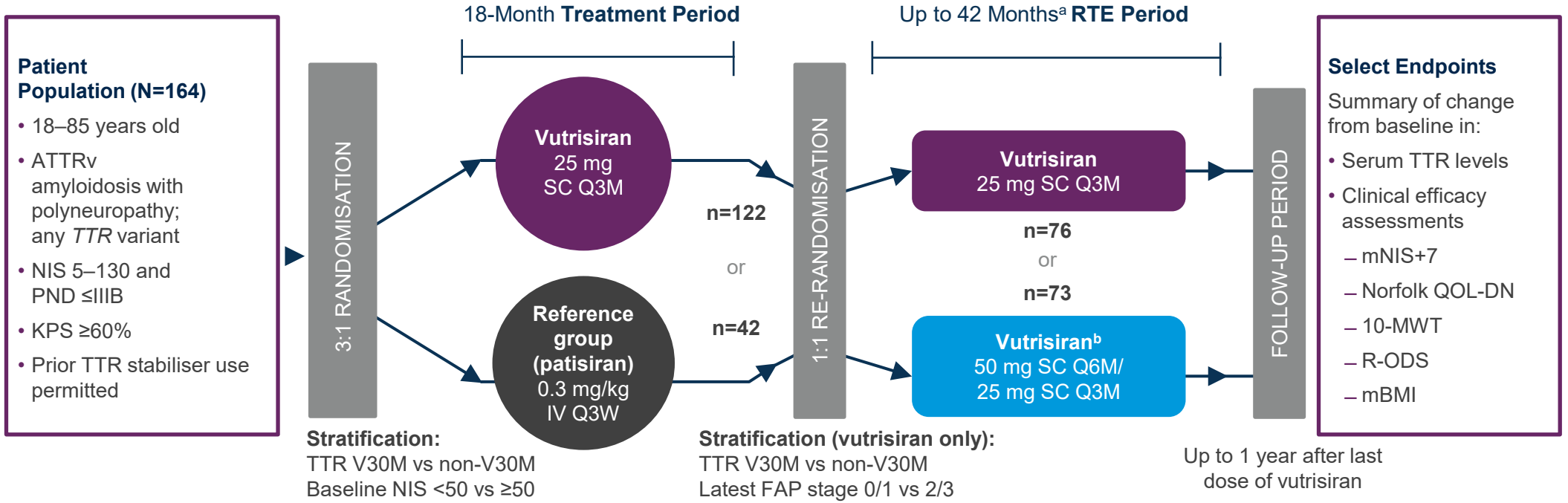
- Patisiran is administered intravenously and approved for the treatment of ATTRv-PN based on the Phase 3, placebo-controlled APOLLO study[1–3]
- Vutrisiran is administered subcutaneously and approved for the treatment of ATTRv-PN in adults based on the Phase 3, open-label HELIOS-A study[4–6]
  - In HELIOS-A (NCT03759379), 18 months of vutrisiran treatment demonstrated significant benefit on multiple disease-relevant endpoints versus an external placebo[6]

Abbreviations: ATTRv, hereditary transthyretin amyloidosis; PN, polyneuropathy; TTR, transthyretin.

References: 1. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use (2020); 2. European Medicines Agency. Summary of product characteristics: ONPATTRO 2 mg/mL concentrate for solution for infusion. 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf (accessed September 2024); 3. Adams et al. *N Engl J Med*. 2018;379:11–21; 4. Alnylam Pharmaceuticals Inc. US prescribing information: AMVUTTRA (vutrisiran) injection, for subcutaneous use (2022); 5. European Medicines Agency. Summary of product characteristics: AMVUTTRA 25 mg solution for injection. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf (accessed September 2024); 6. Adams et al. *Amyloid*. 2023;90:30–6.

HELIOS-A Study Design and Analysis Objective

- Patients who completed the HELIOS-A 18-month treatment period entered the RTE where they were re-randomised 1:1 to receive vutrisiran at 25 mg Q3M or 50 mg Q6M
  - During the RTE period, the protocol was amended to transition patients on vutrisiran 50 mg Q6M to vutrisiran 25 mg Q3M



- **Objective:** Present serum TTR levels, clinical efficacy and safety data from the 18-month analysis of the HELIOS-A RTE period

During the 18-month treatment period, patients were randomised (3:1) to vutrisiran (25 mg SC Q3M) or patisiran (0.3 mg/kg IV Q3W). Patients treated with patisiran received premedication with a corticosteroid, paracetamol and antihistamines at least 60 minutes prior to the infusion. In the RTE, patients were re-randomised to vutrisiran SC 25 mg Q3M or 50 mg Q6M. [a]Results from an 18-month analysis of the RTE period are presented; data cutoff 23 February 2024. [b]Upon implementation of Protocol Amendment 6, patients in the vutrisiran 50 mg Q6M arm were transitioned to vutrisiran 25 mg Q3M for the remainder of their dosing visits in the study.

Abbreviations: 10-MWT, 10-metre walk test; ATTRv, hereditary transthyretin amyloidosis (v for variant); FAP, familial amyloid polyneuropathy; IV, intravenous; KPS, Karnofsky Performance Status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PND, polyneuropathy disability; Q3/6M, every 3/6 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; RTE, randomised treatment extension; SC, subcutaneous; TTR, transthyretin.

Demographics and Disease Characteristics at RTE Baseline

- At data cutoff (23 February 2024), 64 patients (43%) were continuing treatment, 67 patients (45%) had completed treatment, and 18 patients (12%) had discontinued treatment
  - Reasons for discontinuation were 12 deaths, 1 AE, 2 lost to follow-up, and 3 physician decisions

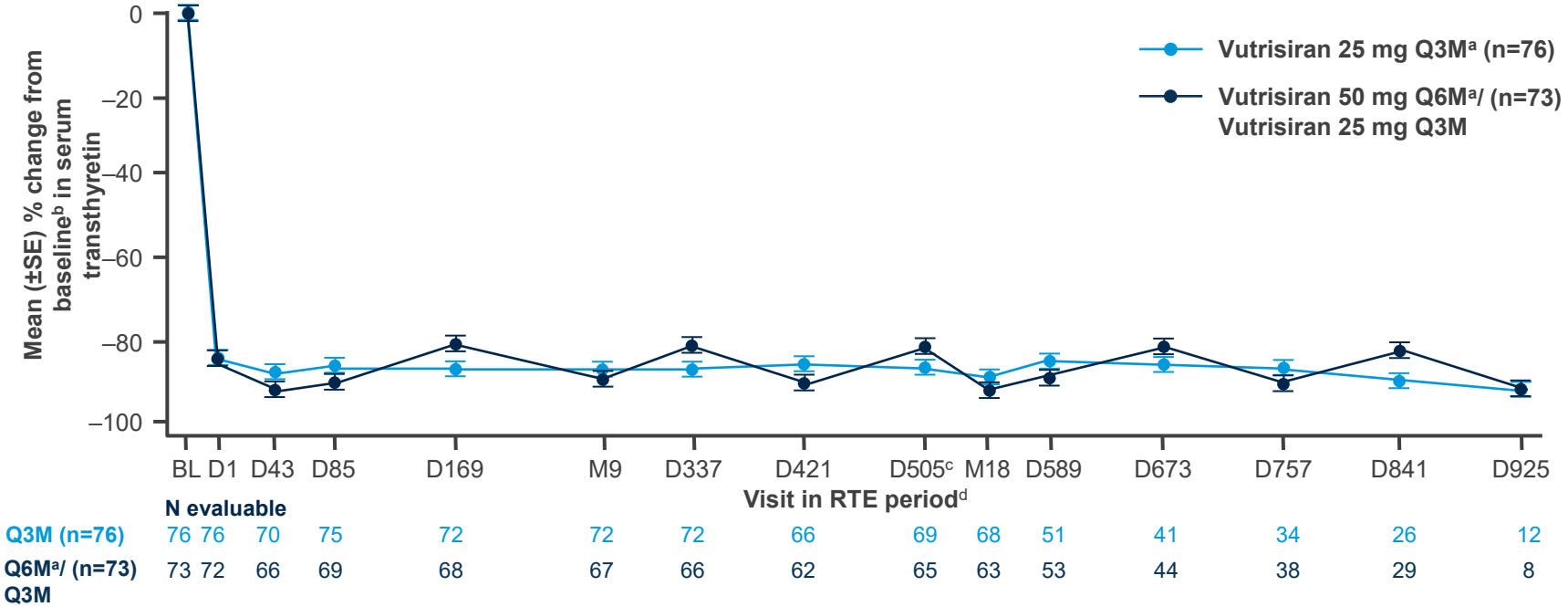
Baseline Demographic and Disease Characteristics	Total Vutrisiran (n=149)
Male, n (%)	93 (62.4)
Age, years, median (range)	62.0 (33.0–83.0)
Age at ATTRv symptom onset <50 years, n (%)	54 (36.2)
***TTR* genotype: V30M, n (%)**	69 (46.3)
***TTR* genotype: Non-V30M, n (%)**	80 (53.7)
Early-onset V30M (<50 years), n (%)	30 (20.1)
Previous tetramer stabiliser use, n (%)	98 (65.8)

Baseline Disease Characteristics	Total Vutrisiran (n=149)
NIS <50, n (%)	94 (63.1)
FAP stage ≥II, n (%)	42 (28.2)
PND score ≥IIIa, n (%)	39 (26.2)
NYHA Class III or IV, n (%)	13 (8.7)
NT-proBNP >3000 ng/L, n (%)	10 (6.7)
mBMI[a], median (range)	1057.7 (615, 1843)

Percentages may not add up to 100 due to rounding. [a]The vutrisiran 25 mg Q3M and the vutrisiran 50 mg Q6M represent the randomization treatment assignment at the beginning of the RTE period. [a]mBMI is defined as [weight in kilogrammes divided by square of height in metres] × albumin level in grammes per litre.

Abbreviations: AE, adverse event; ATTRv, hereditary transthyretin amyloidosis (v for variant); FAP, familial amyloid polyneuropathy; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; NT-proBNP, *N*-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; Q3/6M, every 3/6 months; RTE, randomised treatment extension; TTR, transthyretin.

Serum TTR Reduction from Baseline During the RTE



N evaluable	BL	D1	D43	D85	D169	M9	D337	D421	D505[c]	M18	D589	D673	D757	D841	D925
Vutrisiran 25 mg Q3M (n=76)	76	76	70	75	72	72	72	66	69	68	51	41	34	26	12
Vutrisiran 50 mg Q6M[a]/ (n=73) Vutrisiran 25 mg Q3M	73	72	66	69	68	67	66	62	65	63	53	44	38	29	8

Endpoint (Non-inferiority[e]) at RTE M9	Vutrisiran 25 mg Q3M (n=76) H–L Median[f]	Vutrisiran 50 mg Q6M (n=73) H–L Median[f]	Vutrisiran 50 mg – Vutrisiran 25 mg H–L Median Difference[g] (95% CI)	Non-inferiority (95% Lower CI >–10%)
TTR % reduction	89.73	90.37	0.58 (–1.28, 2.92)	Yes

- Non-inferiority of vutrisiran 50 mg Q6M versus 25 mg Q3M was established based on mean percent serum TTR reduction at Month 9; however, serum TTR recovery was noted at the end of the Q6M dosing interval
  - Thus, a protocol amendment was initiated to transition all patients in the vutrisiran 50 mg Q6M arm to the vutrisiran 25 mg Q3M arm[c].

Data for ≥5 patients per treatment arm are presented at a given study visit. [a]The vutrisiran 25 mg Q3M and the vutrisiran 50 mg Q6M represent the randomization treatment assignment at the beginning of the RTE period. [b]Baseline is defined as the same as the 18-month treatment period, which is the mean of all non-missing measurements before the first dose of the 18-month treatment period; [c]The first patient transitioned from vutrisiran 50 mg Q6M to 25 mg Q3M at this timepoint. [d]As of a data cut of 23 February 2024. [e]Non-inferiority analysis of serum mean TTR % reduction through RTE Month 9, which is defined as patient mean percentage reductions derived from all non-missing, post-baseline TTR assessments through RTE Month 9 during the RTE period, including non-trough assessments and regardless of missed doses. Data reported as H–L median difference, the inferential statistic estimated based on this endpoint. [f]H–L 1-sample medians. [g]H–L 2-sample median difference.

Abbreviations: BL, baseline; CI, confidence interval; D, day; H–L, Hodges–Lehmann; M, month; Q3/6M, every 3/6 months; RTE, randomised treatment extension; SE, standard error; TTR, transthyretin.

Sustained Clinical Efficacy of Vutrisiran During the RTE

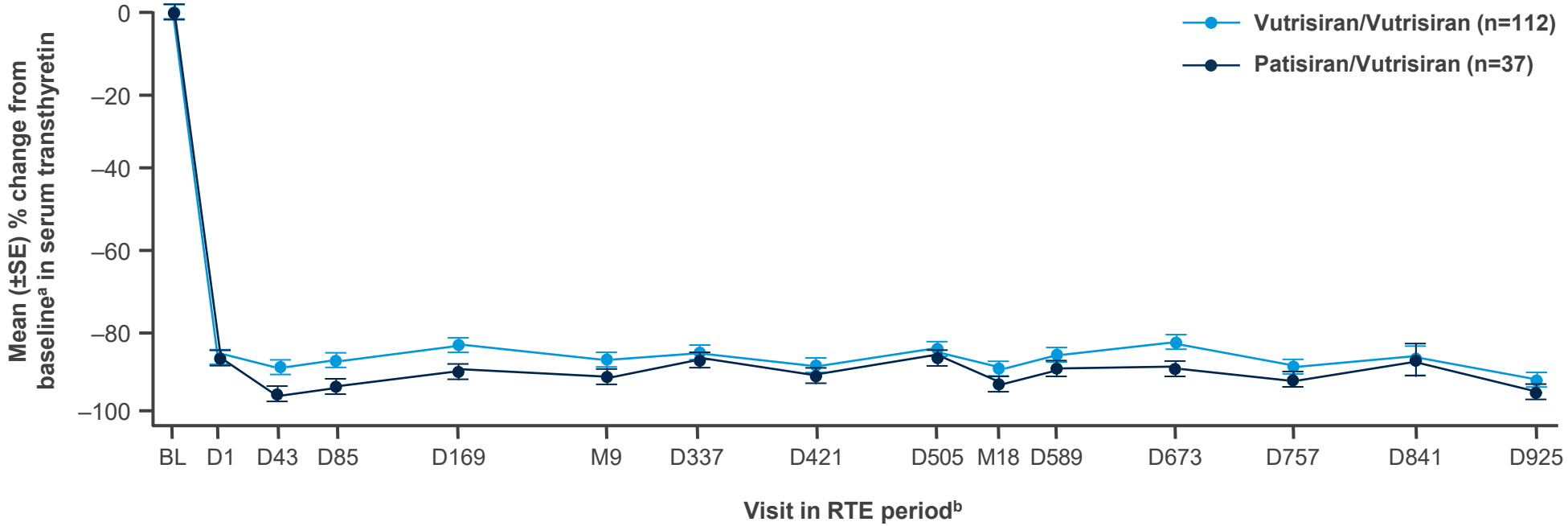
Endpoint, Mean (SE), n	Mean Change from RTE Baseline[a]	
	Month 9 RTE Total Vutrisiran Group (n=149)	Month 18 RTE Total Vutrisiran Group (n=149)
mNIS+7	0.34 (1.19), n=137	5.44 (1.39), n=130
Norfolk QOL-DN	2.4 (1.3), n=137	5.2 (1.5), n=131
10-MWT,	-0.063 (0.016), n=137	–0.087 (0.018), n=131
R-ODS	-1.3 (0.4), n=137	–2.3 (0.4), n=132
mBMI[b]	0.2 (7.2), n=135	–10.3 (8.4), n=128

- Vutrisiran demonstrated sustained clinical efficacy at M18 of the RTE period.

Assessments after initiation of local standard treatment for ATTRv amyloidosis and assessments on or after onset of a serious COVID-19 AE were excluded from the analysis. [a]RTE baseline is defined as the last non-missing derived value before the first dose in the RTE period. [b]mBMI is defined as [weight in kilogrammes divided by square of height in metres] × albumin level in grammes per litre.

Abbreviations: 10-MWT, 10-metre walk test; AE, adverse event; ATTRv, hereditary transthyretin amyloidosis (v for variant); COVID-19, coronavirus disease 2019; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; Q3/6M, every 3/6 months; R-ODS, Rasch-built Overall Disability Scale; RTE, randomised treatment extension; SE, standard error.

Serum TTR Reduction Following Switch from Patisiran to Vutrisiran During the RTE



N evaluable														
Vutrisiran/Vutrisiran (n=112)	112	111	101	108	107	106	105	97	102	100	80	68	56	41	14
Patisiran/Vutrisiran (n=37)	37	37	35	36	33	33	33	31	32	31	24	17	16	14	6

- Sustained TTR reduction was observed in patients who received patisiran during the 18M treatment period and transitioned to vutrisiran during the RTE (patisiran/vutrisiran)
  - Comparable TTR reduction was seen between those in the patisiran/vutrisiran group, and those that received vutrisiran during both the 18M treatment period and the RTE (vutrisiran/vutrisiran).

Data for ≥5 patients per treatment arm are presented at a given study visit. [a]Baseline is defined as the same as the 18-month treatment period, which is the mean of all non-missing measurements before the first dose in the 18-month treatment period. [b]As of a data cut of 23 February 2024.

Abbreviations: BL, baseline; D, day; M, month; RTE, randomised treatment extension; SE, standard error; TTR, transthyretin.

Change from Baseline for Selected Clinical Efficacy Endpoints in Patients Who Switched from Patisiran to Vutrisiran During the RTE

Endpoint, Mean (SD)	Change from Baseline[a] at:			
	n	Treatment Period Month 18 Patisiran (n=42)	n	RTE Month 18 Patisiran/Vutrisiran (n=37)
mNIS+7	36	1.59 (21.50)	32	3.73 (20.79)
Norfolk QOL-DN	38	–0.6 (19.3)	32	1.8 (19.3)
10-MWT	38	–0.043 (0.276)	32	–0.092 (0.250)
R-ODS	38	–1.2 (5.9)	32	–3.0 (6.2)
mBMI[b]	38	6.9 (91.8)	29	26.8 (113.2)

- Patients switching from patisiran to vutrisiran demonstrated consistent clinical benefit across key endpoints

Assessments after initiation of local standard treatment for ATTRv amyloidosis and assessments on or after onset of a serious COVID-19 AE were excluded from the analysis. [a]Baseline is defined as the last non-missing measurement before the first dose in the 18-month treatment period. [b]mBMI is defined as [weight in kilogrammes divided by square of height in metres] × albumin level in grammes per litre.

Abbreviations: 10-MWT, 10-metre walk test; AE, adverse event; ATTRv, hereditary transthyretin amyloidosis (v for variant); COVID-19, coronavirus disease 2019; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Scale; RTE, randomised treatment extension; SD, standard deviation.

Safety of Vutrisiran During the RTE

n (%)	Total Vutrisiran (n=149; PY 308.3)
Any AE	137 (91.9)
SAEs[a]	54 (36.2)
Severe AEs	46 (30.9)
AEs leading to treatment discontinuation	11 (7.4)
AEs leading to stopping study participation	11 (7.4)
Death	13 (8.7)

- The safety profile of vutrisiran was acceptable with the majority of AEs being mild or moderate in severity.
- AEs reported in ≥10% in the total vutrisiran group were COVID-19 (28.9%), urinary tract infection (15.4%) and fall (12.8%)
- None of the deaths were considered related to study drug by the investigators
- No new risks or safety concerns were identified, including no cardiac, hepatic or renal issues

All safety data during the RTE period as of the database cutoff date (23 February 2024) are included. For the vutrisiran total group, mean treatment duration was 24.4 months (range: 0.7–33.0 months). [a]SAEs reported in ≥2 patients were cellulitis (5 patients); pneumonia (4 patients); cardiac failure and osteoarthritis (3 patients each); atrial fibrillation, cardiac arrest, cardiac failure acute, cardiac failure congestive, sudden cardiac death, sudden death, abdominal pain, COVID-19, septic shock, urinary tract infection, cerebrovascular accident, syncope, dyspnoea, respiratory failure and orthostatic hypotension (2 patients each).

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; PY, patient-years; Q3/6M, every 3/6 months; RTE, randomised treatment extension; SAE, serious adverse event.

Conclusions

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- Vutrisiran led to rapid and sustained TTR knockdown
- Vutrisiran demonstrated relative stability in neuropathy in ATTRv-PN patients through 18M of the HELIOS-A RTE, with only modest changes observed, confirming the established clinical efficacy of vutrisiran
- Patients transitioning from patisiran to vutrisiran showed comparable TTR knockdown and consistent clinical benefits as those who received vutrisiran throughout
- The safety profile of vutrisiran during the RTE period was acceptable and consistent with that observed previously
- These findings reinforce the established clinical efficacy and long-term safety profile of vutrisiran in patients with ATTRv-PN

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

Abbreviations: ATTRv, hereditary transthyretin amyloidosis (v for variant); HCPs, healthcare professionals; PN, polyneuropathy; RTE, randomised treatment extension; TTR, transthyretin.

Thank you