HELIOS-A: 9-Month Results from the Randomized Treatment Extension Period of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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Conclusions

- **Non-inferiority of vutrisiran 50 mg Q6M versus 25 mg Q3M was established, based on mean TTR percent reduction through 9 months of the HELIOS-A RTE period**
  - **However, some TTR recovery was noted at the end of the Q6M dosing regimen**
  - **Efficacy endpoint results were comparable between the vutrisiran 25 mg Q3M and 50 mg Q6M arms through 9 months of the RTE period**
- **Overall, the safety profile of vutrisiran 50 mg Q6M was acceptable and comparable with vutrisiran 25 mg Q3M**
- **Through Month 9 of the RTE period, a consistent benefit in serum TTR reduction and clinical endpoints was observed following switch from patisiran to vutrisiran**
- **During the HELIOS-A RTE period through Month 9, vutrisiran demonstrated sustained efficacy and an acceptable safety profile, consistent with previous reports and irrespective of the dosing regimen**

Background and Rationale

ATTRv Amyloidosis, Also Known as hATTR Amyloidosis

- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease
- Caused by variants in the *TTR* gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues[1–4]
- The majority of individuals develop a mixed phenotype of polyneuropathy and cardiomyopathy[5,6]

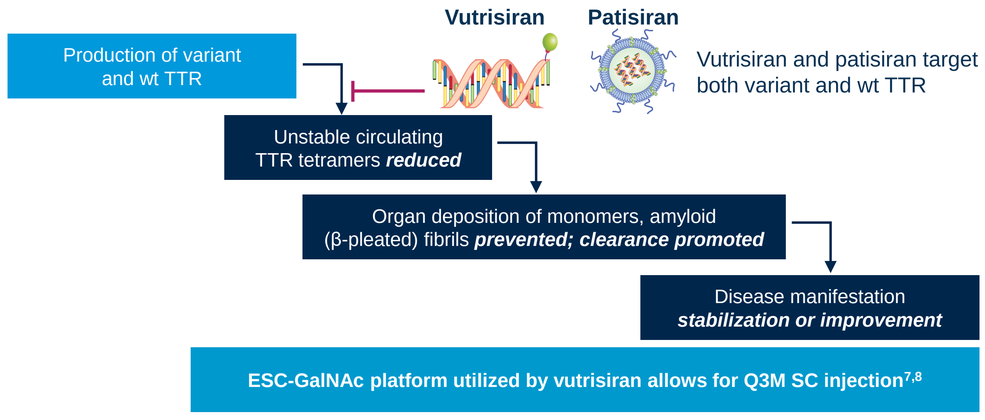
Patisiran

- IV infusion-administered RNAi therapeutic **(Figure 1)** approved for the treatment of ATTRv amyloidosis with polyneuropathy based on the Phase 3, placebo-controlled APOLLO study[7–9]

Vutrisiran

- SC-administered RNAi therapeutic **(Figure 1)** approved for the treatment of ATTRv amyloidosis with polyneuropathy based on the 18-month treatment period of the Phase 3, open-label HELIOS-A study[10,11]
- 18 months of vutrisiran treatment demonstrated significant benefit on several disease-relevant endpoints versus an external placebo group[12]
- Patients who completed the HELIOS-A 18-month timepoint entered into the RTE where they were re-randomized to vutrisiran 25 mg Q3M or 50 mg Q6M **(Figure 2)**

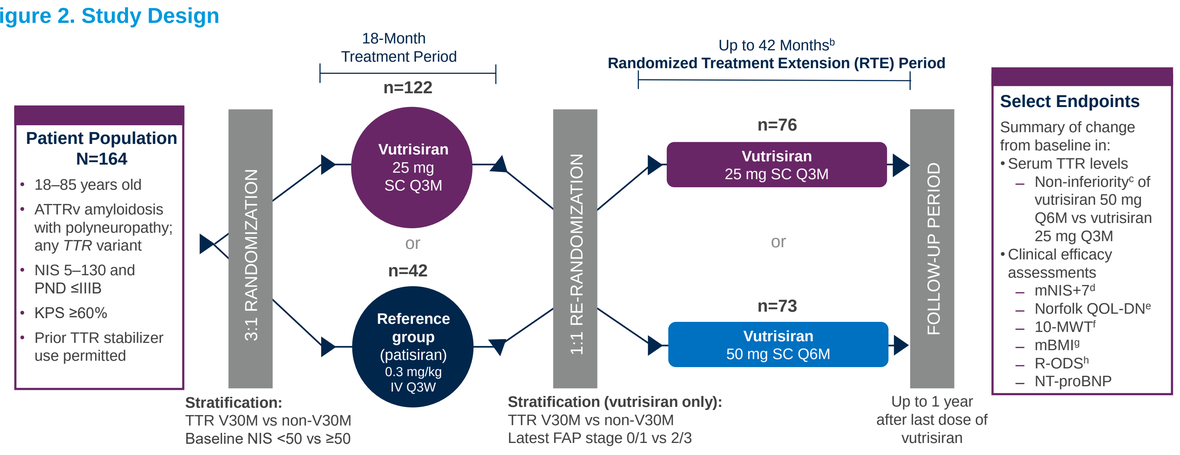
Figure 1. Therapeutic Hypothesis



HELIOS-A Randomized Treatment Extension

- Results from a 9-month interim analysis of the RTE period are presented[a]

Figure 2. Study Design



[a]Data cutoff October 7, 2022. [b]Patients completed the study following 18 months of the RTE period. [c]Non-inferiority analysis of serum mean TTR percent 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 HL median difference, the inferential statistic estimated based on this endpoint. [d]Higher scores of mNIS+7 indicate more neuropathy impairment (range, 0 to 304). [e]Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136). [f]10-MWT speed (m/s) = 10 meters/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. [g]Lower scores of mBMI (weight [in kg/m^2] × serum albumin [in g/L]) indicate worse nutritional status. [h]Lower scores of R-ODS indicate more disability (range, 0 to 48).

Results

Patient Demographics and Disease Characteristics at the RTE Baseline

- More vutrisiran Q3M patients had early-onset V30M and FAP stage ≥II, reflective of more significant polyneuropathy **(Table 1)**
- More vutrisiran Q6M patients had non-V30M genotype, NYHA class III or IV, and NT-proBNP >3000 ng/L, reflective of more significant cardiomyopathy

Table 1. Baseline Demographics and Disease Characteristics at the RTE Baseline

Parameter	Vutrisiran 25 mg Q3M (n=76)	Vutrisiran 50 mg Q6M (n=73)	Total (n=149)
Age at RTE randomization, median (range), years	61.5 (33–83)	63.0 (33–83)	62.0 (33–83)
Female, n (%)	26 (34.2)	30 (41.1)	56 (37.6)
Race, n (%)			
White/Caucasian	47 (61.8)	58 (79.5)	105 (70.5)
Asian	17 (22.4)	10 (13.7)	27 (18.1)
Other[a]	12 (15.8)	5 (6.8)	17 (11.4)
Non-V30M, n (%)	38 (50.0)	42 (57.5)	80 (53.7)
Early-onset V30M (<50 years), n (%)	19 (25.0)	11 (15.1)	30 (20.1)
NIS <50, n (%)	48 (63.2)	46 (63.0)	94 (63.1)
FAP stage ≥II, n (%)	24 (31.6)	19 (26.0)	43 (28.9)
PND score ≥III, n (%)	22 (28.9)	17 (23.3)	39 (26.2)
NYHA class III or IV, n (%)	4 (5.3)	9 (12.3)	13 (8.7)
NT-proBNP >3000 ng/L, n (%)	3 (3.9)	7 (9.6)	10 (6.7)
Randomized to vutrisiran during 18M treatment period	57 (75.0)	55 (75.3)	112 (75.2)
Randomized to patisiran during 18M treatment period	19 (25.0)	18 (24.7)	37 (24.8)

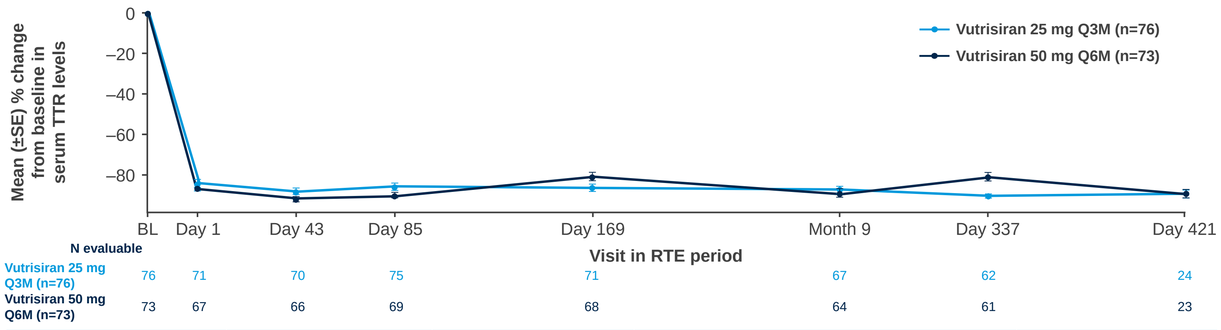
[a]Includes Black/African American, ≥2 races, and other races.

Efficacy of Vutrisiran 25 mg Q3M vs 50 mg Q6M at RTE Month 9

Non-inferiority of vutrisiran 50 mg Q6M compared with 25 mg Q3M

- Non-inferiority was established based on serum mean TTR percent reduction (vutrisiran 50 mg vs vutrisiran 25 mg), HL median difference (95% CI): 0.50 (–1.40, 2.75), in which the lower 95% CI limit was >–10%, the prespecified non-inferiority margin **(Figure 3)**
- At Day 169 of the RTE, 80.3% of patients on vutrisiran 25 mg Q3M achieved >80% reduction in trough TTR levels compared with 63.2% of patients on vutrisiran 50 mg Q6M

Figure 3. Mean (±SE) Percent Change from Baseline in Serum TTR during the RTE



N evaluable	BL	Day 1	Day 43	Day 85	Day 169	Month 9	Day 337	Day 421
Vutrisiran 25 mg Q3M (n=76)	76	71	70	75	71	67	62	24
Vutrisiran 50 mg Q6M (n=73)	73	67	66	69	68	64	61	23

Endpoint (non-inferiority)	Vutrisiran 25 mg Q3M (n=76) HL Median[b]	Vutrisiran 50 mg Q6M (n=73) HL Median[b]	Vutrisiran 50 mg Q6M – Vutrisiran 25 mg Q3M HL Median Difference[a] (95% CI)	Non-inferiority (95% Lower CI >–10%)
TTR percent reduction	89.87	90.38	0.50 (–1.40, 2.75)	Yes

Baseline is defined as the same as the 18-month treatment period, which is the mean of all non-missing measurements before first dose of 18-month treatment period. Data >5 patients per treatment arm presented at given study visit. [a]Hodges–Lehmann 2-sample median difference. [b]Hodges–Lehmann 1-sample medians.

Clinical Efficacy of Vutrisiran 50 mg Q6M and 25 mg Q3M

- Vutrisiran showed sustained efficacy during long term treatment in the study
- Clinical efficacy endpoint results were generally comparable between vutrisiran 25 mg Q3M and 50 mg Q6M at RTE Month 9 **(Table 2)**

Table 2. Change from RTE Baseline at RTE Month 9 for Selected Clinical Efficacy Endpoints

Endpoint, Mean (SE)	Change from RTE Baseline at RTE Month 9	
	Vutrisiran 25 mg Q3M (n=66)	Vutrisiran 50 mg Q6M (n=64)
mNIS+7	–0.21 (1.82)	0.88 (1.64)
Norfolk QOL-DN	1.1 (2.0)	4.5 (1.8)
10-MWT, m/s	–0.061 (0.023)	–0.069 (0.022)
mBMI[a]	8.5 (10.9)[b]	–4.1 (9.7)
R-ODS	–1.1 (0.5)	–1.7 (0.6)[c]
Endpoint, Median (Range)	**Change from RTE Baseline at RTE Month 9**	
	Vutrisiran 25 mg Q3M (n=66)	**Vutrisiran 50 mg Q6M (n=64)**
NT-proBNP, ng/L[d]	1.95 (–6606.27, 3653.42)[e]	–1.95 (–1322.25, 3986.71)[c]

RTE baseline is defined as the last non-missing derived value before the first dose in the RTE period. [a]mBMI is defined as [weight in kilograms divided by square of height in meters] x albumin level in grams per liter. [b]n=64. [c]n=65. [d]Medians presented due to large variations. [e]n=67.

Overall Safety of Vutrisiran 25 mg Q3M and 50 mg Q6M during the RTE Period

- The safety profiles of vutrisiran 25 mg Q3M and 50 mg Q6M were acceptable and comparable **(Table 3)**
- Median (range) treatment duration[a] was 13.2 (2.4–16.9) months in the vutrisiran 25 mg Q3M group and 13.0 (0.7–16.5) months in the vutrisiran 50 mg Q6M group
- The majority of AEs were mild or moderate in severity
- AEs reported in ≥10% of patients (in any arm) were COVID-19, Fall, and UTI
- One SAE (vutrisiran 50 mg Q6M) was considered related to treatment: elevated AST and ALT (with normal bilirubin) in a patient with non-alcoholic fatty liver disease and gallstones; resolved without treatment or disruption of vutrisiran
- 6 deaths reported; none considered treatment related
  - All patients had multiple risk factors for poor prognosis
- No new safety concerns identified, including no cardiac, hepatic, or renal issues

[a](Last dose date - first dose date + window)/30.4375; window = 84 if last dose was vutrisiran 25 mg Q3M; window = 168 if last dose was vutrisiran 50 mg Q6M.

Table 3. Safety Profile of Vutrisiran 25 mg Q3M and 50 mg Q6M

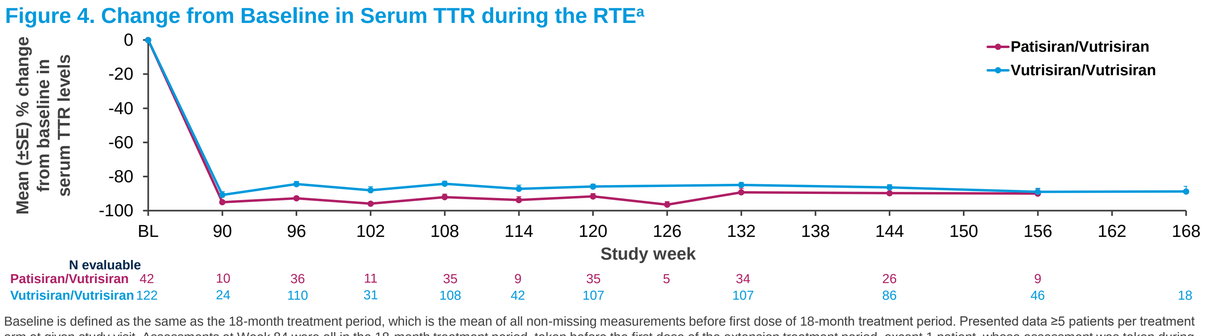
At Least 1 Event, n (%)	Vutrisiran 25 mg Q3M (n=76)	Vutrisiran 50 mg Q6M (n=73)	Total (n=149)
AEs	58 (76.3)	63 (86.3)	121 (81.2)
SAEs	18 (23.7)	18 (24.7)	36 (24.2)
Severe AEs	12 (15.8)	17 (23.3)	29 (19.5)
AEs leading to treatment discontinuation[a]	1 (1.3)	5 (6.8)	6 (4.0)
Death[b]	0	5 (6.8)	5 (3.4)
Death after stopping study participation	1 (1.3)	0	1 (0.7)

Data cutoff October 7, 2022. AEs during the RTE period included AE with onset or worsening in severity after first dose of the RTE through last dose + 84 days (vutrisiran 25 mg Q3M) or + 168 days (vutrisiran 50 mg Q6M), or AE considered treatment related at any time after first dose of the RTE. [a]Includes 1 patient in the vutrisiran 25 mg Q3M arm with end-stage endometrial neoplasm and the 5 deaths in the vutrisiran 50 mg Q6M arm. [b]In the vutrisiran 50 mg Q6M arm, 3 deaths were adjudicated as CV deaths (2 sudden deaths; 1 presumed CV death) in patients with cardiac amyloidosis, chronic heart failure, and advanced cardiac disease (NYHA class III; elevated NT-proBNP levels [>2000 ng/L]). 2 deaths were adjudicated as non-CV deaths (1 patient with advanced ATTRv amyloidosis [PND score IIIB] and fatal pneumonia, and 1 patient with a fatal reaction to chemotherapy for acute myeloid leukemia). Excludes 1 death due to endometrial neoplasm in the vutrisiran 25 mg Q3M arm that occurred after the patient stopped study participation.

Observed Benefit following Switch from Patisiran to Vutrisiran

- As previously reported,[12] serum TTR reduction with vutrisiran was non-inferior to the within-study patisiran reference group over 18 months
- Serum TTR reduction in patients on patisiran during the 18-month treatment period who switched to vutrisiran during the RTE period (patisiran/vutrisiran) was comparable to patients who had been on vutrisiran for the entire study (vutrisiran/vutrisiran) **(Figure 4)**

Figure 4. Change from Baseline in Serum TTR during the RTE[a]



N evaluable	BL	90	96	102	108	114	120	126	132	138	144	150	156	162	168
Patisiran/Vutrisiran	42	10	36	11	35	9	35	5	34		26		9		
Vutrisiran/Vutrisiran	122	24	110	31	108	42	107		107		86		46		18

Baseline is defined as the same as the 18-month treatment period, which is the mean of all non-missing measurements before first dose of 18-month treatment period. Presented data ≥5 patients per treatment arm at given study visit. Assessments at Week 84 were all in the 18-month treatment period, taken before the first dose of the extension treatment period, except 1 patient, whose assessment was taken during the legacy treatment period. Figure includes patients who switched to vutrisiran after Week 84 (legacy or randomized treatment extension period). [a]Vutrisiran data shown during the RTE is pooled 25 mg Q3M and 50 mg Q6M.

- Through Month 9 of the RTE, a consistent clinical benefit was observed compared with study baseline across key endpoints following switch from patisiran to vutrisiran during the RTE **(Table 4)**

Table 4. Change from Baseline in mNIS+7, Norfolk QOL-DN, 10-MWT, mBMI, R-ODS, and NT-proBNP: Patisiran → Vutrisiran (25 mg Q3M and 50 mg Q6M Results Pooled)

Endpoint, Median (Range)	Change from Baseline at:					
	n	Month 9 (Patisiran)	n	Month 18[a] (Patisiran)	n	RTE Month 9 (Vutrisiran)
mNIS+7	40	**–1.25** (–47.0, 62.9)	36	**1.00** (–30.4, 106.1)	30	**–1.06** (–44.9, 28.6)
Norfolk QOL-DN	40	**–4.5** (–26, 54)	38	**–2.0** (–49, 58)	30	**–2.0** (–29, 59)
10-MWT, m/s	40	**–0.039** (–0.50, 0.38)	38	**–0.034** (–0.95, 0.45)	30	**–0.076** (–0.46, 0.25)
mBMI[b]	38	**–2.7** (–369, 169)	38	**–3.0** (–284, 179)	29	**27.1** (–335, 222)
R-ODS	40	**–0.5** (–21, 10)	38	**0.0** (–18, 8)	30	**–1.0** (–15, 16)
NT-proBNP, ng/L	38	**3.98** (–1180, 8723)	38	**–6.47** (–1911, 4741)	29	**7.95** (–2057, 1823)

N=42 at baseline for all assessments. Baseline is defined as the last non-missing measurement before the first dose in the 18-month treatment period. Scores indicate the mean of 2 non-missing assessments planned to be performed ≥24 hours to ≤7 days apart at baseline, Month 9, and Month 18 visits during the 18-month treatment period; and a single assessment performed at RTE Month 9 visit after component imputation. [a]Patients switched from patisiran to vutrisiran after the 18-month timepoint. [b]mBMI is defined as [weight in kilograms divided by square of height in meters] x albumin level in grams per liter.

Disclosures: L.O. reports consultancy fees from Alnylam Pharmaceuticals, AstraZeneca, Pfizer, and SOBI, and honoraria or speaker's bureau fees for presentations, manuscripts, or educational events from Alnylam Pharmaceuticals, AstraZeneca, Novartis, Pfizer, and SOBI. M.P. reports participation in clinical trials sponsored by Akcea, Alnylam Pharmaceuticals, and Pfizer, and consultancy fees from Akcea, Alnylam Pharmaceuticals, Biogen-Idec, Pfizer, and Vertex Pharmaceuticals. A.G.-D. reports honoraria from Alnylam Pharmaceuticals. M.W.-C. reports consultancy fees and support to attend meetings from Alnylam Pharmaceuticals. Y.S. reports consultancy fees, honoraria for lectures, and research grants from Alnylam Pharmaceuticals. J.D.G. reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, Bridgebio, and Pfizer, consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, ATTRalus, Bridgebio, NovoNordisk, and Pfizer, and research/educational support to his institution from Alnylam Pharmaceuticals. E.Y., P.B., C.C., M.S., and J.V. are employed by Alnylam Pharmaceuticals and report ownership of Alnylam Pharmaceuticals shares. D.A. reports participation in clinical trials sponsored by Akcea and Alnylam Pharmaceuticals, and consultancy fees from Alnylam Pharmaceuticals, Eidos, and Pfizer. **Abbreviations:** 10-MWT, 10-meter walk test; AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; ATTRv, hereditary transthyretin (v for variant); BL, baseline; CI, confidence interval; CV, cardiovascular; ESC, enhanced stabilization chemistry; FAP, familial amyloid polyneuropathy; GalNAc, *N*-acetylgalactosamine; hATTR, hereditary transthyretin-mediated; HL, Hodges–Lehmann; 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; NT-proBNP, *N*-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; Q3M, every 3 months; Q6M, every 6 months; RNAi, ribonucleic acid interference; R-ODS, Rasch-built Overall Disability Scale; RTE, randomized treatment extension; SAE, serious AE; SC, subcutaneous; SD, standard deviation; SE, standard error; TTR, transthyretin; UTI, urinary tract infection; wt, wild-type.
References: 1. Hanna. *Curr Heart Fail Rep* 2014;11:50–57; 2. Hawkins et al. *Ann Med* 2015;47:625–38; 3. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 4. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 5. Rapezzi et al. *Eur Heart J* 2013;34:520–28; 6. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 7. Adams et al. *N Engl J Med* 2018;379:11–21; 8. 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 March 2023); 9. Food and Drug Administration. Prescribing information: Onpattro lipid complex injection. 2023. https://www.alnylam.com/sites/default/files/pdfs/ONPATTRO-Prescribing-Information.pdf (accessed March 2023); 10. Food and Drug Administration. Prescribing information: Amvuttra injection. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215515s000lbl.pdf (accessed March 2023); 11. European Medicines Agency. Summary of product characteristics: Amvuttra 25 mg solution for injection. 2022. https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf (accessed March 2023); 12. Adams et al. *Amyloid* 2023;30:19–26.
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