Efficacy and Safety of Vutrisiran in ATTR-CM Across the Spectrum of Age

Awais Sheikh[1], Zi Michael Miao[2], Brian Claggett[2], Pablo Garcia-Pavia[3], Francesco Cappelli[4], Emre Aldinc[5], Julian Gillmore[1], Scott D. Solomon[2], Marianna Fontana[1]

[1]National Amyloidosis Centre, University College London, Royal Free Campus, Rowland Hill Street, NW3 2PF, London, UK
[2]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[3]Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, CIBERCV, and Centro Nacional de Investigaciones Cardiovasculares (CNIC) Madrid, Spain
[4]Tuscan Regional Amyloid Center, Careggi University Hospital, Florence, Italy
[5]Alnylam Pharmaceuticals, Cambridge, MA

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Disclosures

- Study funded by Alnylam Pharmaceuticals
- No relevant personal disclosures

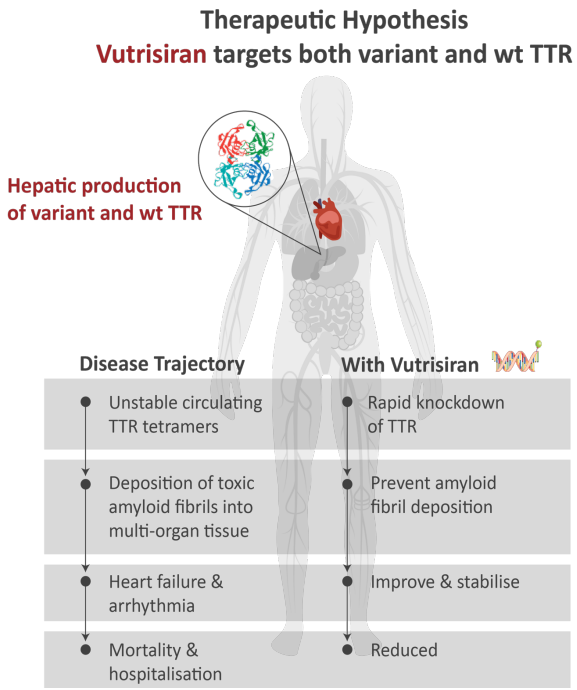
Background

ATTR cardiomyopathy

- Results from accumulation of wild-type or variant TTR amyloid fibrils in the heart[1-5]
- Leads to progressive heart failure, with significant morbidity and mortality

Heart failure treatment in elderly patients

- **Older adults face disproportionate burden of disease**
- Higher risk of death and hospitalisations[6]
- Concerns over frailty, polypharmacy leads to **lower use of guideline-directed medical therapy (GDMT)**

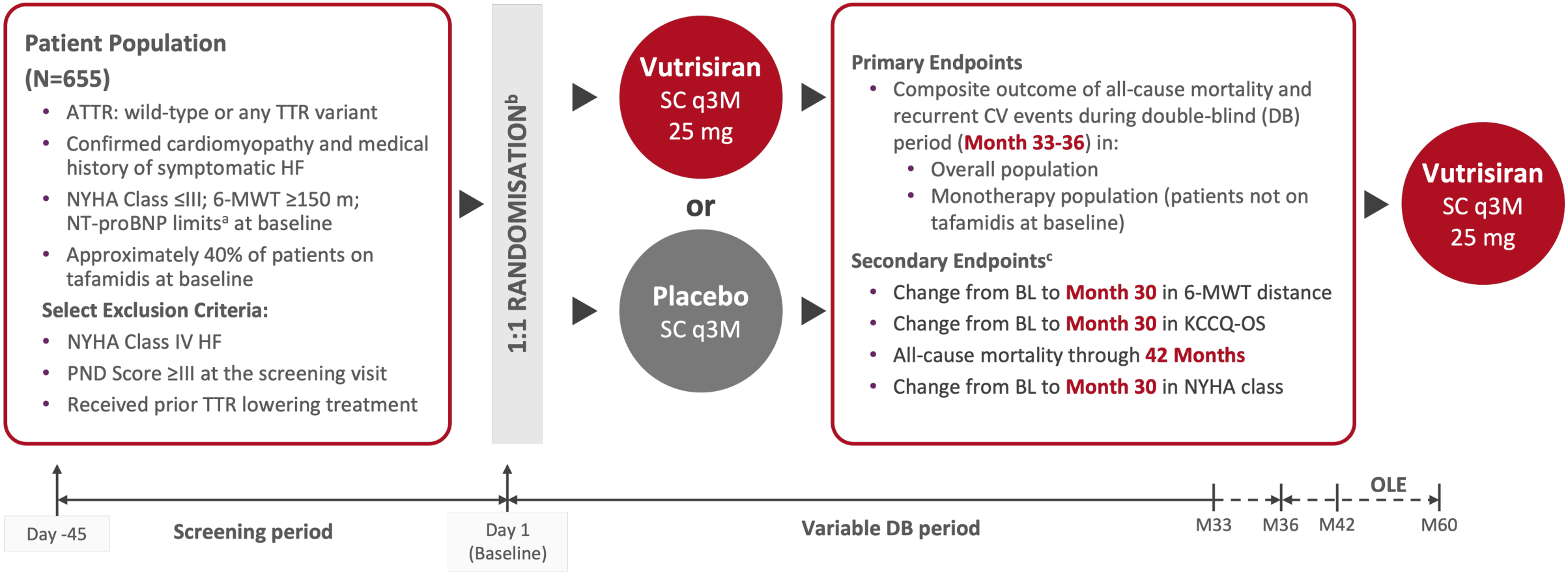


Aim of the study

- Vutrisiran, a recently approved RNAi therapeutic, was evaluated in patients with ATTR-CM in the HELIOS-B study (NCT04153149). It provided **significant benefits** in the **primary and all secondary endpoints**
- To determine whether the **benefits of vutrisiran extend consistently across all age groups including patients ≥80 years**

References: 1. Hawkins et al. *Ann Med* 2015;47:625–38; 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. Živković et al. *Amyloid* 2020;27:142–3; 5. Sipe et al. *Amyloid* 2014;21:221–4; 6. Tolfo D, Lund LH, Becher PM, et al. Eur J Heart Fail. 2022;24(6):1047–1062. doi:10.1002/ejhf.2483.
Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; GDMT, guideline-directed medical therapy; RNAi, RNA interference; TTR, transthyretin; wt TTR, wild-type transthyretin.

HELIOS-B study design



[a]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation).
[b]Randomisation was stratified according to the use of tafamidis at baseline (yes versus no), ATTR disease type (hATTR or wtATTR), and NYHA class and age at baseline (NYHA class I or II and age <75 years versus all others).
[c]Assessed in the overall population and monotherapy population as separate endpoints.

References: Clinicaltrials.gov identifier: NCT04153149.
Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; CV, cardiovascular; DB, double-blind; hATTR, hereditary ATTR; HF, heart failure; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NYHA, New York Heart Association; OLE, open label extension; PND, polyneuropathy disability; q3M, every 3 months; SC, subcutaneous; TTR, transthyretin; wtATTR, wild-type ATTR.

Methods

- Endpoints assessed using **age categories (<75, 75 to <80 and ≥80 years)** and **age as a continuous variable (using restricted cubic splines)**, in both overall and monotherapy populations (patients not receiving tafamidis at baseline)

Primary endpoint

- Composite endpoint of all-cause mortality and recurrent CV events during double-blind period (**Month 33-36**)

Components of the composite primary endpoint

- Recurrent CV events

Secondary endpoints

- All-cause mortality through **42 months**
- Change from BL to **Month 30** in 6-MWT distance
- Change from BL to **Month 30** in KCCQ-OS

Other endpoints

- Composite of all-cause mortality or first CV event
- Safety endpoints (SAEs, discontinuations)

Abbreviations: 6-MWT, 6-minute walk test; BL, baseline; CV, cardiovascular; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; SAE, serious adverse event.

Baseline characteristics

	Baseline characteristics by age categories – Overall (trend-p)				Baseline characteristics by age categories – Monotherapy (trend-p)			
	< 75 (n=257)	75 to < 80 (n=201)	≥ 80 (n=196)	P value	< 75 (n=153)	75 to < 80 (n=105)	≥ 80 (n=137)	P value
Baseline Characteristics								
Age	68.7 ± 5.4	77.2 ± 1.4	82.2 ± 1.8	p<0.001	69.2 ± 5.2	77.2 ± 1.3	82.2 ± 1.8	p<0.001
Sex	233 (90.7%)	191 (95.0%)	181 (92.3%)	p=0.43	137 (89.5%)	100 (95.2%)	124 (90.5%)	p=0.73
Wild-Type ATTR	208 (80.9%)	183 (91.0%)	187 (95.4%)	p<0.001	121 (79.1%)	97 (92.4%)	129 (94.2%)	p<0.001
Baseline Tafamidis Use	104 (40.5%)	96 (47.8%)	59 (30.1%)	p=0.044				
NYHA Class I	34 (13.2%)	26 (12.9%)	24 (12.2%)	p=0.84	7 (4.6%)	9 (8.6%)	11 (8.0%)	p=0.75
NYHA Class II	199 (77.4%)	155 (77.1%)	154 (78.6%)		137 (89.5%)	89 (84.8%)	115 (83.9%)	
NYHA Class III	24 (9.3 %)	20 (10.0%)	18 (9.2 %)		9 (5.9%)	7 (6.7%)	11 (8.0%)	
NAC Stage 1	183 (71.2%)	134 (66.7%)	120 (61.2%)		105 (68.6%)	65 (61.9%)	81 (59.1%)	p=0.08
NAC Stage 2	66 (25.7%)	58 (28.9%)	63 (32.1%)	p=0.018	42 (27.5%)	34 (32.4%)	47 (34.3%)	
NAC Stage 3	8 (3.1 %)	9 (4.5 %)	13 (6.6 %)		6 (3.9%)	6 (5.7%)	9 (6.6%)	
Biomarkers								
NT-proBNP at Baseline (ng/L)	1649 [903-2990]	2062 [1138-3083]	2330 [1340-3742]	p<0.001	1763 [1029, 3194]	2199 [1258, 3455]	2481 [1325, 4056]	p=0.018
Troponin I (ng/L), Serum	63.1 [39.3-93.2]	68.6 [41.1-120.7]	73.8 [47.3-121.6]	p=0.013	63.9 [43.3, 104.8]	74.6 [39.0, 133.7]	71.8 [43.3, 126.3]	p=0.17
6MWT	409.9 ± 99.9	369.2 ± 94.0	333.9 ± 89.5	P<0.001	404.3 ± 100.7	369.7 ± 96.5	325.6 ± 86.4	P<0.001

Contemporary population with baseline characteristics balanced across arms

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association.

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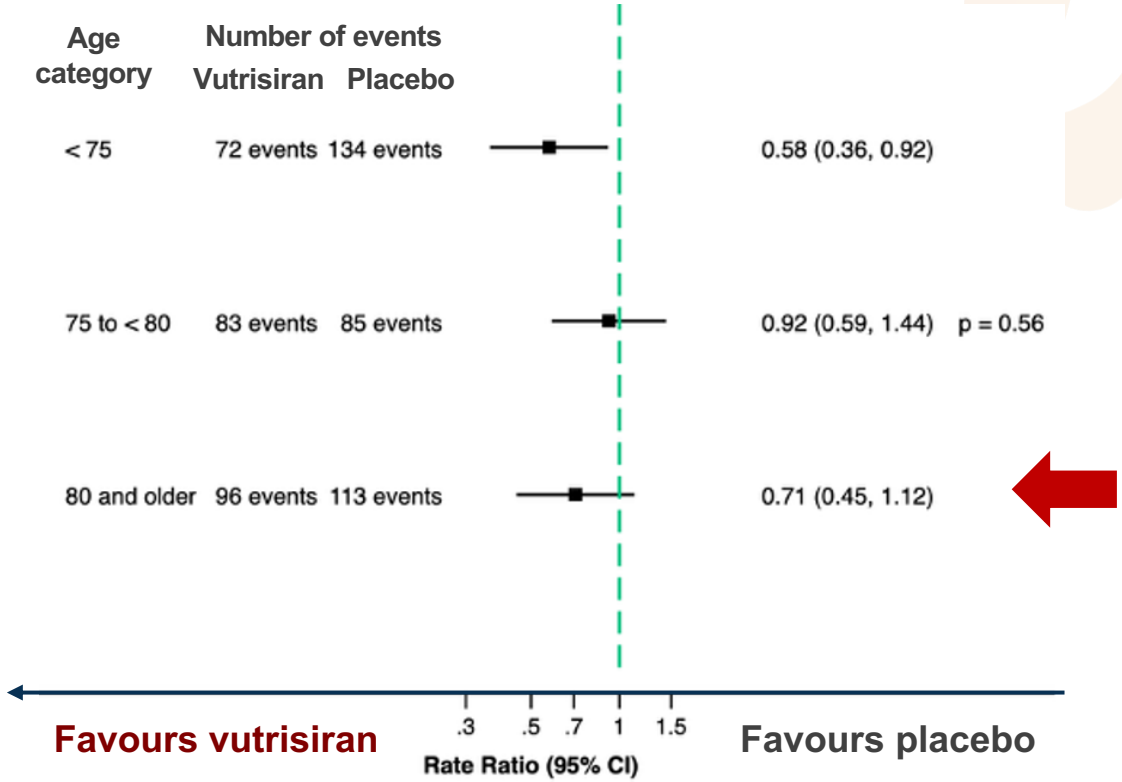
Primary endpoint
All cause mortality and recurrent CV events

Primary Composite (LWYY): Overall Population



P for interaction 0.56

Consistent benefit across all age groups

Primary analysis based on the modified Anderson-Gill model, also known as LWYY.
Abbreviations: LWYY, Lin, Wei, Yang , and Ying

Secondary endpoints in the overall population

	<75			75 to <80			≥80 years			
Endpoint	**Vutrisiran (n=123)**	**Placebo (n=134)**	**Hazard ratio or rate ratio (95% CI)**	**Vutrisiran (n=98)**	**Placebo (n=103)**	**Hazard ratio or rate ratio (95% CI)**	**Vutrisiran (n=105)**	**Placebo (n=91)**	**Hazard ratio or rate ratio (95% CI)**	**Interaction P**
Components of the composite primary endpoint	Events (/100py)			Events (/100py)			Events (/100py)			
Recurrent cardiovascular events	59 events [17.6/100py]	111 events [32.1/100py]	RR 0.57 (0.34-0.93),	67 events [25.1/100py]	69 events [25.5/100py]	RR 0.93 (0.59-1.47)	74 events [28.3/100py]	83 events [36.8/100py]	RR 0.74 (0.43-1.27)	0.50
Secondary endpoints	n (%) [events/100py]			n (%) [events/100py]			n (%) [events/100py]			
All-cause mortality (up to 42 months)	16 (13%) [4.1/100py]	29 (22%) [7.1/100py]	HR 0.59 (0.32-1.09),	19 (19%) [6.1/100py]	24 (23%) [7.5/100py]	HR 0.73 (0.39-1.34)	28 (27%) [9.2/100py]	37 (41%) [14.0/100py]	HR 0.62 (0.38-1.02)	0.87
	Difference in score (95% CI)			Difference in score (95% CI)			Difference in score (95% CI)			
KCCQ-OSS change from baseline to month 30	+5 (-0, +10)			+2 (-4, +8)			+9 (+3, +16)			0.35
6MWT distance change from baseline to month 30	+22 (+4, +41)			+23 (+1, +46)			+23 (0, +46)			1.00

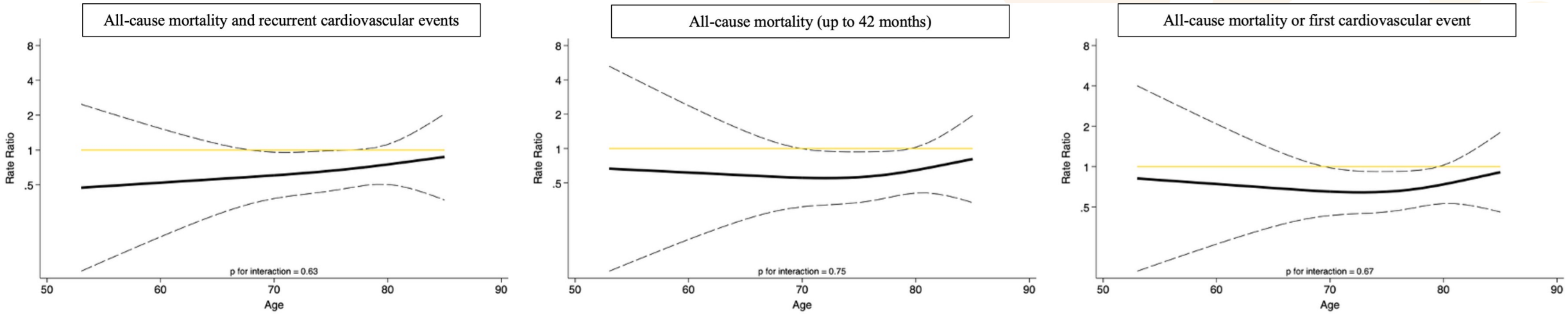
Vutrisiran reduced ACM and improved functional status and QoL across all age categories

Abbreviations: ACM, all-cause mortality; CI, confidence interval; py, person years, 6-MWT, 6-minute walk test; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; QoL, quality of life.

Analysis using age as a continuous variable

Restricted cubic spline evaluating vutrisiran's efficacy as a **continuous function of age in overall population**

- Primary endpoint up to 36 months (left), ACM up to 42 months (middle), time to first event (ACM or first cardiovascular event; right).
- The solid black line represents the estimated HR for treatment effect at each age, and dashed lines indicate the 95% CI.
- The horizontal yellow line denotes the line of no effect (HR = 1.0).



Benefits across the spectrum of age

- Estimated treatment effect **consistent** across spectrum of age for primary and secondary endpoints
- **No attenuation of benefit** with increasing age

ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio.

Safety endpoints
AEs, SAEs and rates discontinuations in the overall population

	Age < 75		Age 75 to < 80		Age 80 and older		
	Placebo n=134	Vutrisiran n=123	Placebo n=103	Vutrisiran n=98	Placebo n=91	Vutrisiran n=105	Interaction p-value
Any treatment-emergent adverse event	131 (97.8%)	121 (98.4%)	102 (99.0%)	97 (99.0%)	90 (98.9%)	104 (99.0%)	p=0.86
Any treatment-emergent serious adverse event	87 (64.9%)	72 (58.5%)	67 (65.0%)	66 (67.3%)	66 (72.5%)	63 (60.0%)	p=0.53
Any treatment-emergent AE leading to trt disc	3 (2.2 %)	5 (4.1 %)	6 (5.8 %)	3 (3.1 %)	4 (4.4 %)	2 (1.9 %)	p=0.19
Any treatment-emergent SAE leading to trt disc	3 (2.2 %)	3 (2.4 %)	3 (2.9 %)	1 (1.0 %)	4 (4.4 %)	1 (1.0 %)	p=0.21

No increase in SAEs or discontinuations in older patients

- Safety profile remained favourable across age categories

Abbreviations: AE, adverse event; SAE, serious adverse event; trt, treatment; disc, discontinuation

Conclusions

Vutrisiran demonstrates consistent benefit across the spectrum of age – therefore, age should not be a barrier to offering an effective, disease modifying treatment

- **Contemporary population** with less advanced disease at baseline
- Vutrisiran associated with **consistent clinical benefit across age categories**
- In patients ≥80 years, vutrisiran reduced the incidence of the primary composite endpoint by 29%
- Similar findings across other key endpoints including **functional capacity** and **quality of life**
- **Discontinuation rates were low**, with no evidence of increased SAE across age categories

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Acknowledgements

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

This study was funded by Alnylam Pharmaceuticals. 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

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