Vutrisiran in Patients with Transthyretin Amyloidosis With Cardiomyopathy in HELIOS-B who had Progressed on Tafamidis

Dr José Gonzalez-Costello[1], Dr Michel Khouri[2], Dr Nitasha Sarswat[3], Dr Juan Pablo Costabel[4], Dr Chongshu Chen[5], Dr Colleen Moffitt[5],Dr Satish Eraly[5], Prof. Vincent Algalarrondo[6]

[1]Bellvitge University Hospital, IDIBELL, CIBER-CV, Barcelona, Spain; [2]Duke University Health System, Durham, NC, USA; [3]University of Chicago, Chicago, IL, USA; [4]Cardiovascular Institute of Buenos Aires, Buenos Aires, Argentina; [5]Alnylam Pharmaceuticals, Cambridge, MA, USA; [6]Bichat University Hospital, AP-HP, Paris, France

Introduction

HELIOS-B: A randomised, DB study in patients with ATTR-CM

Background

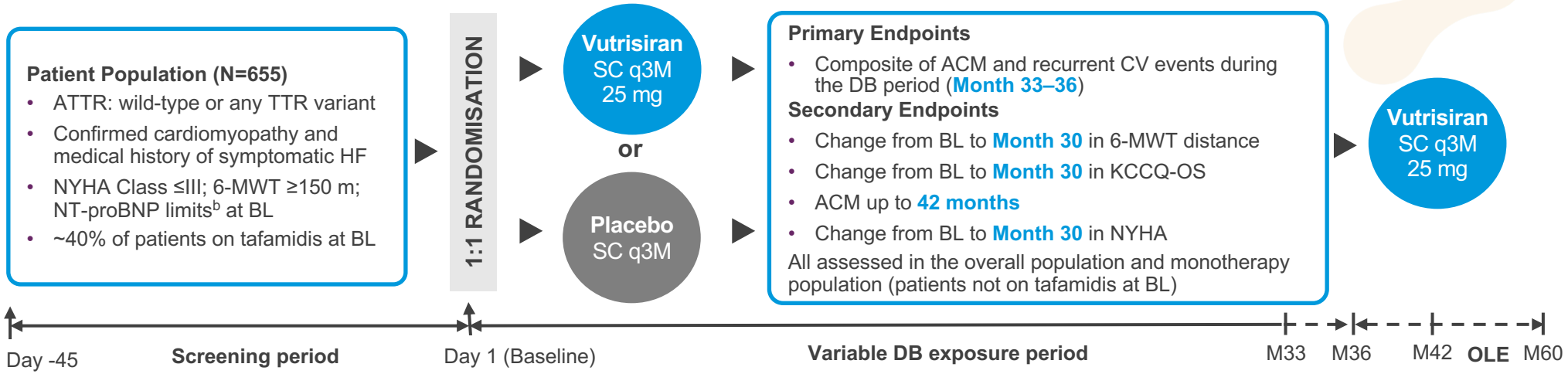
- In HELIOS-B (NCT04153149), vutrisiran, an RNAi therapeutic, reduced the risk of all-cause mortality (ACM) and recurrent cardiovascular (CV) events, and preserved functional capacity and QoL, in both the overall and monotherapy (no tafamidis use at baseline) populations when compared with placebo[1]

Objective

- To assess the impact of vutrisiran on ACM and recurrent CV events among patients identified by investigators at baseline as having manifested disease progression while on tafamidis (i.e., 'tafamidis progressors')

Patients

- Of 259 patients enrolled receiving tafamidis at baseline, 61 were enrolled due to disease progression[a] (vutrisiran n=28; placebo n=33)



[a]Determined by investigators. [b]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation).
Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; BL, baseline; CV, cardiovascular; DB, double blind; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; q3M, every 3 months; QoL, quality of life; RNAi, RNA interference; SC, subcutaneous; TTR, transthyretin. **Reference:** 1. Fontana M, et al. *N Engl J Med*. 2025 Jan 2;392(1):33–44.

Baseline Demographics and Disease Characteristics

Tafamidis progressors had similar baseline demographics to the overall population

	Tafamidis Progressors			HELIOS-B Overall Population[1]	Baseline Tafamidis Subgroup
	Total (n=61)	Vutrisiran (n=28)	Placebo (n=33)	Total (N=654)	Total (n=259)
Age, years, median (range)	**77.0 (64–85)**	77.0 (64–85)	77.0 (64–85)	77.0 (45–85)	76.0 (45–85)
Male sex, n (%)	**60 (98.4)**	28 (100.0)	32 (97.0)	605 (92.5)	244 (94.2)
wtATTR, n (%)	**56 (91.8)**	26 (92.9)	30 (90.9)	578 (88.4)	231 (89.2)
Time from start of tafamidis therapy, months, median (range)	**13.2 (1.1–65.5)**	12.2 (1.1–58.8)	13.6 (2.6–65.5)	10.8 (1.1–65.5)	10.8 (1.1–65.5)
Previous HF hospitalisation, n (%)	**24 (39.3)**	10 (35.7)	14 (42.4)	221 (33.8)	88 (34.0)
NYHA Class, n (%) **I** **II** **III**	 **19 (31.1)** **37 (60.7)** **5 (8.2)**	 11 (39.3) 13 (46.4) 4 (14.3)	 8 (24.2) 24 (72.7) 1 (3.0)	 84 (12.8) 508 (77.7) 62 (9.5)	 57 (22.0) 167 (64.5) 35 (13.5)
6MWT distance, m, mean (SD)	**393.0 (85.9)**	374.9 (90.4)	408.4 (80.0)	374.6 (100.0)	384.9 (98.7)
KCCQ-OS, points, mean (SD)	**75.6 (19.1)**	75.7 (19.4)	75.4 (19.2)	72.6 (19.7)	76.4 (17.7)
NT-proBNP >3000 ng/L, n (%)	**16 (26.2)**	9 (32.1)	7 (21.2)	185 (28.3)	58 (22.4)

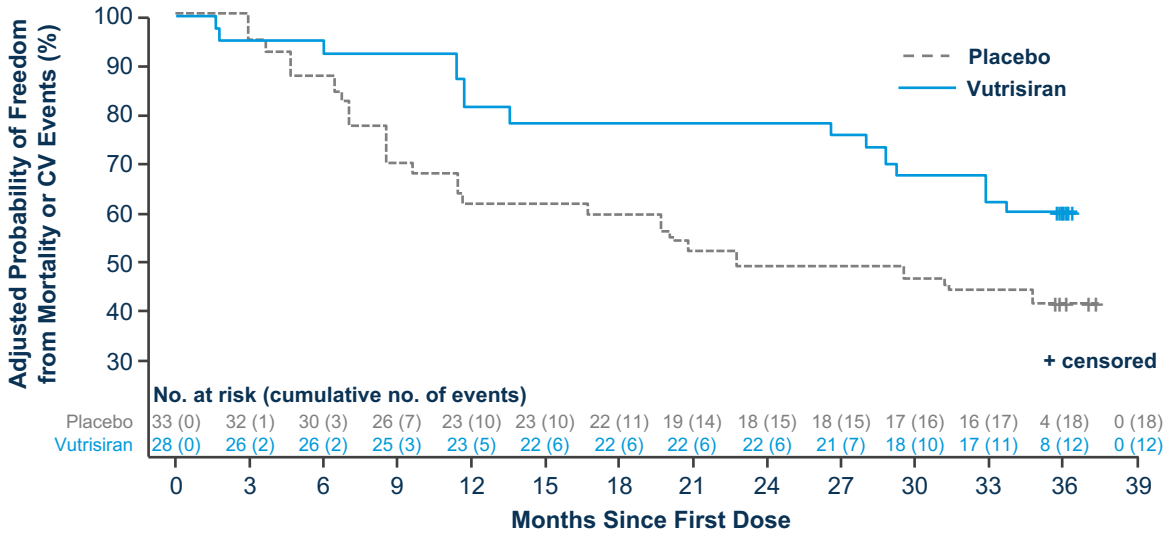
.**Abbreviations:** 6MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; wtATTR, wild-type transthyretin amyloidosis. **Reference:** 1. Fontana M, et al. *N Engl J Med*. 2025 Jan 2;392(1):33–44.

Favorable Trend for Reduced Rates of ACM and CV Events with Vutrisiran

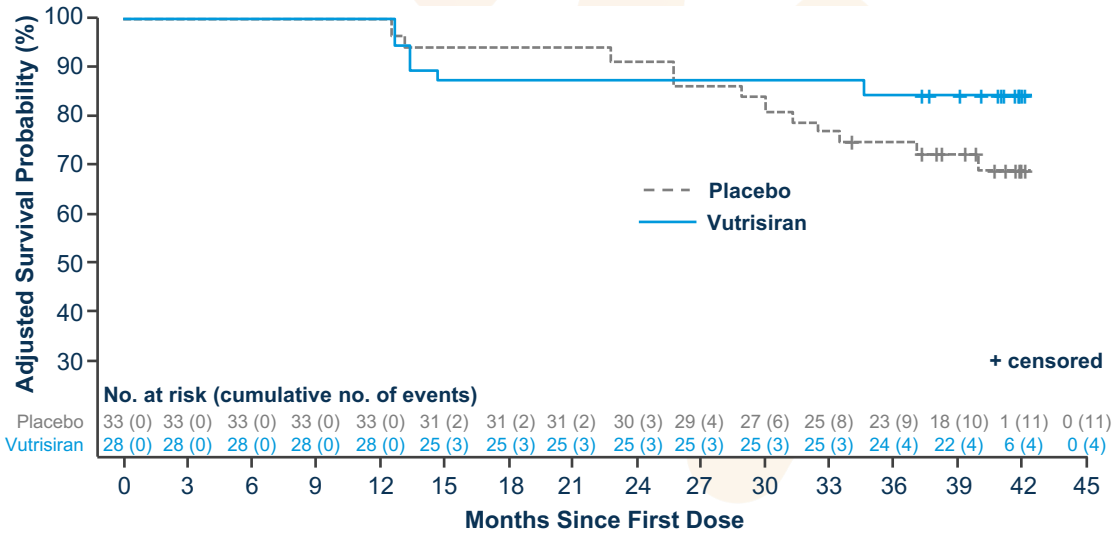
HELIOS-B

Tafamidis progressors achieved 41% reduction in ACM and CV events, and 56% reduction in ACM alone, consistent with results seen in the overall population and baseline tafamidis subgroup

ACM and CV Events (DB Period)



ACM (DB Period + 6 Months OLE)



Composite ACM & CV Events	Tafamidis Progressors	
	Vutrisiran (n=28)	Placebo (n=33)
Total events, n	29	45
Patients with ≥1 event, n (%)	12 (42.9)	18 (54.5)

Composite ACM & CV Events	HR (95% CI)	
	Composite Events	Time to First Event
Tafamidis progressors (n=61)	**0.59 (0.22, 1.58)**	**0.56 (0.25, 1.29)**
Baseline tafamidis subgroup (n=259)	0.79 (0.51, 1.21)	0.83 (0.57, 1.23)
Overall population[1] (n=654)	0.72 (0.56, 0.93)	0.72 (0.57, 0.91)

ACM (DB + 6 Months OLE)	Tafamidis Progressors	
	Vutrisiran (n=28)	Placebo (n=33)
Deaths, n (%)	4 (14.3)	11 (33.3)

ACM (DB + 6 Months OLE)	HR (95% CI)
Tafamidis progressors (n=61)	**0.44 (0.13, 1.48)**
Baseline tafamidis subgroup (n=259)	0.59 (0.32, 1.08)
Overall population[1] (n=654)	0.65 (0.46, 0.90)

Adjusted probabilities were estimated using the Kaplan-Meier method with the Inverse Probability of Treatment Weighting applied. HRs derived from Cox proportional hazards model.

Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; DB, double-blind; HF, heart failure; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; OLE, open-label extension; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; ATTR, transthyretin amyloidosis. **Reference:** 1. Fontana M et al. *N Engl J Med*. 2025 Jan 2;392(1):33–44.

Safety Profile in Tafamidis Progressors

Safety events with vutrisiran in tafamidis progressors were generally similar to the overall population

AE Category, n (%)	Tafamidis Progressors		Total HELIOS-B Overall Population[1]	
	Vutrisiran (n=28)	Placebo (n=33)	Vutrisiran (n=326)	Placebo (n=328)
Any AE	28 (100)	33 (100)	322 (99)	323 (98)
Any SAE	21 (75)	23 (70)	201 (62)	220 (67)
Any AE leading to discontinuation	0	1 (3)	10 (3)	13 (4)
Any AE leading to death	4 (14)	9 (27)	49 (15)	63 (19)
Most common AEs occurring in ≥20% in either tafamidis progressors treatment group				
COVID-19	16 (57)	12 (36)	87 (27)	99 (30)
Atrial fibrillation	8 (29)	9 (27)	69 (21)	68 (21)
Acute kidney injury	6 (21)	7 (21)	32 (10)	27 (8)
Atrial flutter	6 (21)	1 (3)	30 (9)	23 (7)
Dizziness	6 (21)	3 (9)	32 (10)	43 (13)
Hypervolemia	6 (21)	6 (18)	17 (5)	21 (6)
Cardiac failure	5 (18)	8 (24)	101 (31)	128 (39)
Dyspnoea	4 (14)	10 (30)	43 (13)	51 (16)
Fatigue	4 (14)	11 (33)	28 (9)	45 (14)
Fall	2 (7)	9 (27)	42 (13)	69 (21)

Abbreviations: AE, adverse event; COVID-19, coronavirus-19; SAE, serious AE.

Reference: 1. Fontana M, et al. *N Engl J Med*. 2025 Jan 2;392(1):33–44.

Conclusions

- Vutrisiran vs placebo demonstrated favourable trends for reduced risk of ACM and recurrent CV events in the subgroup of patients identified by investigators as having manifested disease progression while on tafamidis at baseline (tafamidis progressors)
- Vutrisiran also demonstrated a favourable trend for reduced rates of ACM vs placebo through Month 42 (DB period + 6 months OLE)
- The safety profile in tafamidis progressors was similar to that observed in the overall population of HELIOS-B
- Limitations: These data represent post hoc analyses with limited patient numbers; further research into this patient population is warranted
- These data suggest that vutrisiran may provide potential benefits to patients with ATTR-CM who have progressed on tafamidis

We thank the patients, their families, investigators, staff, and collaborators for their participation in HELIOS-B

This study was funded by Alnylam Pharmaceuticals. Medical writing assistance was provided by Elizabeth Drysdale, MBChB, of Adelphi Communications Ltd, UK, and funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice guidelines. 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: ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; DB, double-blind; HCP, healthcare provider; OLE, open-label extension.