Efficacy and Safety of Vutrisiran in South American Patients With Transthyretin Amyloidosis With Cardiomyopathy: Post Hoc Analysis of HELIOS-B

Juan Pablo Costabel[1], Alejandro Gabriel Quiroga[2], Shuaiqi Zhang[3], Raphael Sayegh[4], Amy Chan-Daniels[3], Fabio Fernandes[5]

[1]Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina; [2]Hospital Universitario Fundacion Favaloro, Buenos Aires, Argentina; [3]Alnylam Pharmaceuticals, Cambridge, MA, USA; [4]Alnylam Pharmaceuticals, São Paulo, Brazil; [5]Instituto do Coração–HCFMUSP, São Paulo, Brazil.

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HELIOS·B

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Conclusions

- This post-hoc analysis of HELIOS-B demonstrated consistent treatment effects of vutrisiran in the South American subpopulation and global study population
- In the South American subpopulation, vutrisiran monotherapy when compared with placebo resulted in:
  - A reduction in risk of the composite endpoint of ACM and recurrent CV events, and ACM alone
  - Attenuation of decline in functional capacity and QoL, and stabilization of cardiac biomarker levels
- Safety was consistent with the global study population and the established safety profile of vutrisiran

Key takeaway

The clinical benefits of vutrisiran in the South American subpopulation of patients with ATTR-CM were consistent with effects seen in the overall HELIOS-B population

Introduction

ATTR-CM

- ATTR-CM is a progressive and debilitating disease caused by the accumulation of misfolded TTR (variant or wild-type) protein as amyloid deposits in the heart,[1,2] and is associated with impaired functional capacity and QoL, frequent CV events, high morbidity, and mortality[2–4]
- Data on ATTR-CM in South America are limited
  - Approximately 30% of South American patients with ATTR in the THAOS registry were reported to have a predominantly cardiac or mixed phenotype (cardiomyopathy and polyneuropathy)[5,6]
  - There remains a clear need for increased awareness to avoid delays in diagnosis and to encourage initiation of newer disease-modifying therapies for ATTR-CM[6,7]

Vutrisiran

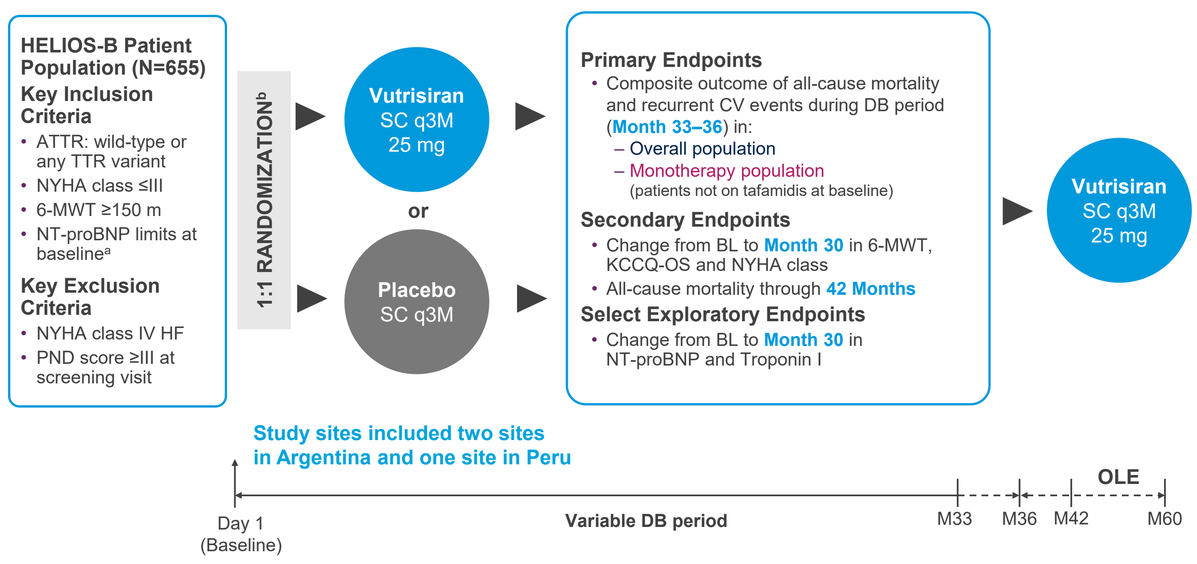
- Vutrisiran, an RNAi silencer that reduces the hepatic synthesis of both variant and wild-type TTR,[8] is approved for the treatment of both ATTR-CM and hATTR-PN[9]
- In the phase 3 HELIOS-B study (NCT04153149) of patients with ATTR-CM, vutrisiran significantly reduced the risk of the composite endpoint of ACM and recurrent CV events vs placebo, and met all 10 primary and secondary endpoints in the overall and monotherapy populations[10]
- Efficacy of the RNAi silencer patisiran has been demonstrated in the Brazilian subpopulation of the phase 3 APOLLO-B study (NCT03997383) in patients with ATTR-CM;[11] however, analysis of the South American subpopulation of HELIOS-B has not been conducted

Objective

- To assess treatment outcomes with vutrisiran vs placebo in patients with ATTR-CM from South America who were enrolled in the HELIOS-B study

Methods

Figure 1. HELIOS-B Study Design: A Randomized, Double-Blind Phase 3 Outcomes Study in Patients With ATTR-CM[10]



[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]Randomization was stratified according to the use of tafamidis at BL (yes vs no), ATTR disease type (hATTR vs wtATTR), and NYHA class and age at BL (NYHA class I vs II and age <75 years vs all others).

Results

Table 1. No Patients in the HELIOS-B South American Subpopulation Were Receiving Baseline Tafamidis and Baseline Characteristics Were Generally Consistent With the Overall Population

Baseline Characteristic	South American Subpopulation		Monotherapy Population[10]		Overall Population[10]	
	Placebo (n=8)	Vutrisiran (n=9)	Placebo (n=199)	Vutrisiran (n=196)	Placebo (n=328)	Vutrisiran (n=326)
Age at randomization, years, median (IQR)	75 (71–81)	80 (78–81)	76 (72–80)	78 (73–82)	76 (72–80)	77 (72–81)
Male sex, n (%)	8 (100)	8 (89)	183 (92)	178 (91)	306 (93)	299 (92)
wtATTR, n (%)	7 (88)	7 (78)	174 (87)	173 (88)	289 (88)	289 (89)
Time since ATTR diagnosis, years, median (range)	0.9 (0.1–1.5)	1.6 (0.1–2.4)	0.63 (0–6.2)	0.5 (0–8.3)	1.03 (0–10.8)	0.86 (0–11.1)
NAC ATTR stage, n (%)						
1	7 (88)	5 (56)	138 (69)	113 (58)	229 (70)	208 (64)
2	1 (13)	3 (33)	55 (28)	68 (35)	87 (27)	100 (31)
3	0	1 (11)	6 (3)	15 (8)	12 (4)	18 (6)
6-MWT, m, mean (SD)	334.9 (54.0)	345.5 (75.4)	372.8 (98.1)	362.7 (102.7)	377.1 (96.3)	372.0 (103.7)
KCCQ-OS, mean (SD)	62.7 (34.2)	68.1 (24.8)	69.9 (20.8)	70.3 (20.2)	72.3 (19.9)	73.0 (19.4)
NT-proBNP, ng/L, median (IQR)	2023 (1369–2549)	2704 (1552–7090)	1865 (1067–3099)	2402 (1322–3868)	1801 (1042–3082)	2021 (1138–3312)
Troponin I, ng/L, median (IQR)	71.8 (41.8–137.4)	102.7 (36.6–172.0)	62.2 (39.2–105.6)	76.3 (48.4–138.8)	65.2 (41.1–105.5)	71.9 (44.9–115.9)
Baseline tafamidis, n (%)	0	0	0	0	130 (40)	129 (39)

Table 2. Vutrisiran vs Placebo Reduced the Risk of the Primary Composite Endpoint, Consistent With the Overall Population

Composite Primary Endpoint and Components	South American Subpopulation		Monotherapy Population[10]		Overall Population[10]	
	Placebo (n=8)	Vutrisiran (n=9)	Placebo (n=199)	Vutrisiran (n=196)	Placebo (n=328)	Vutrisiran (n=326)
Composite of ACM and recurrent CV events, HR (95% CI)	0.33 (0.11, 0.99)		0.67 (0.49, 0.93)		0.72 (0.56, 0.93)	
Total composite events, n	15	7	211	155	332	251
ACM	3	2	46	36	69	51
CV events	12	5	165	119	263	200
Patients with ≥1 composite event, n (%)	4 (50)	6 (67)	105 (53)	76 (39)	159 (48)	125 (38)
ACM	3 (38)	2 (22)	46 (23)	36 (18)	69 (21)	51 (16)
CV events	3 (38)	5 (56)	87 (44)	66 (34)	133 (41)	112 (34)
Total follow-up time, years	16.8	23.8	489.4	495.6	841.7	864.3

Figure 2. The Effect of Vutrisiran on All-Cause Mortality Was Consistent With the Overall Population

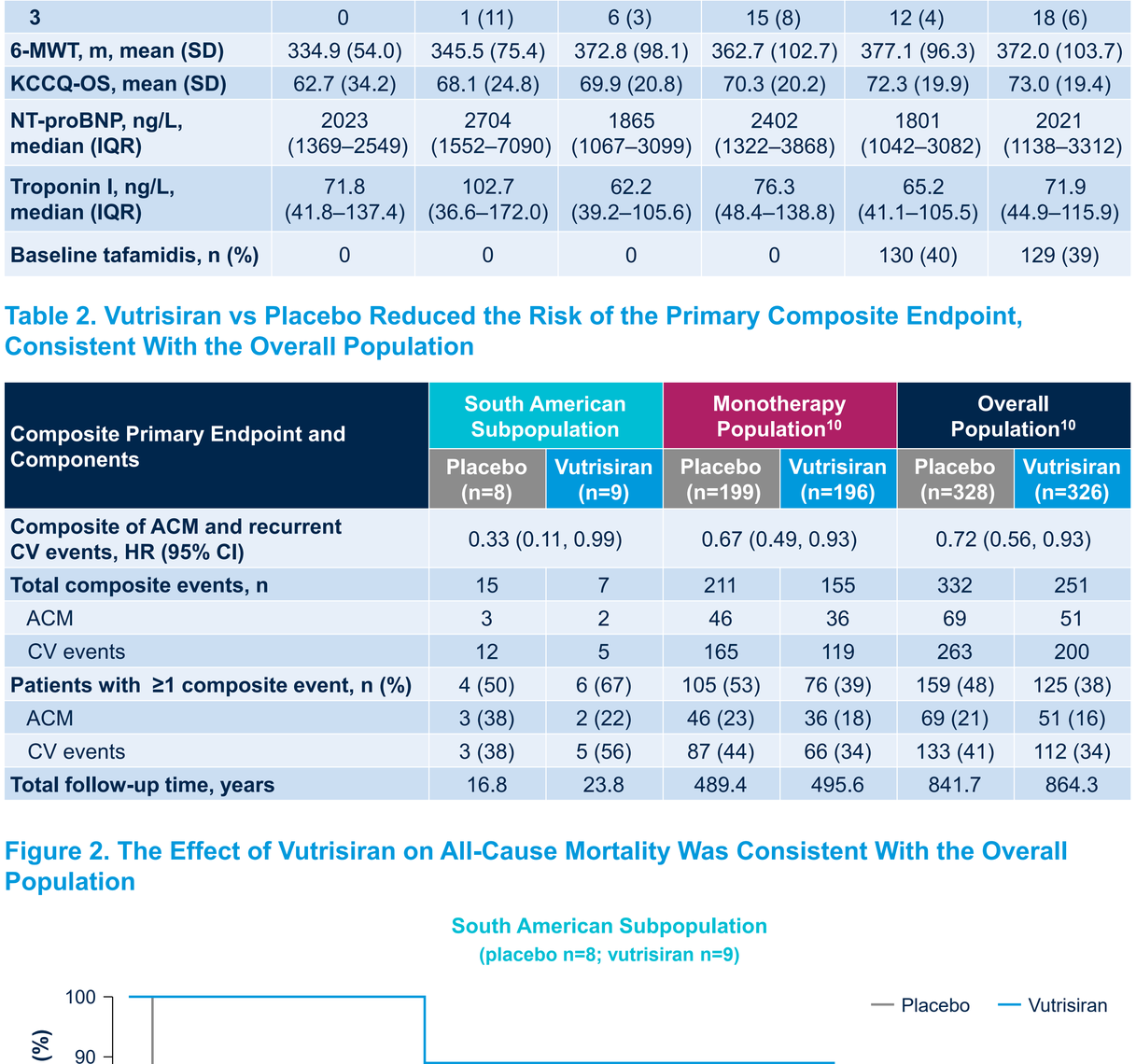
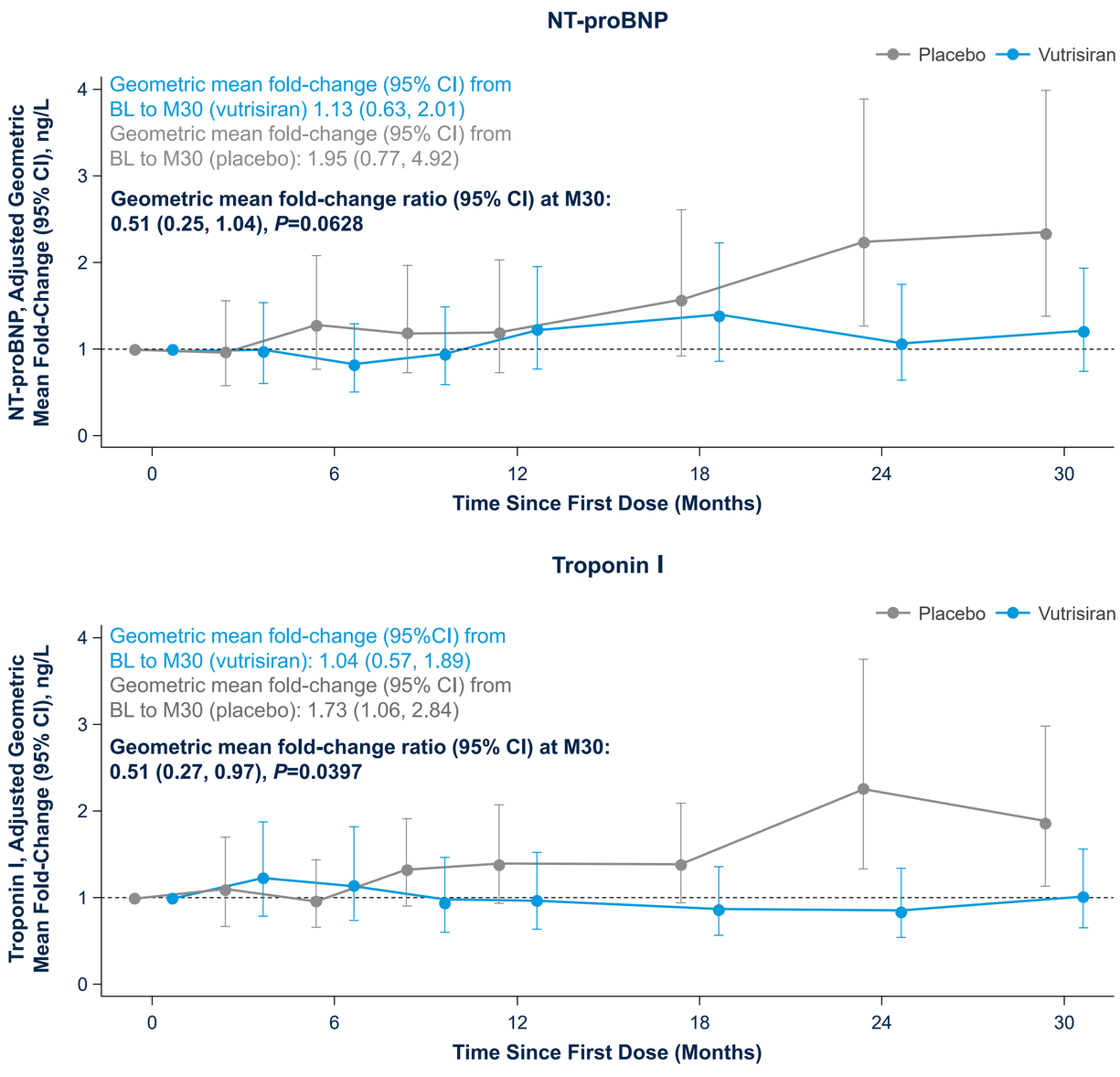


Table 3. Vutrisiran Attenuated Worsening of Secondary Endpoints, Consistent With the Overall Population

Change From Baseline at Month 30	South American Subpopulation		Monotherapy Population[10]		Overall Population[10]	
	Placebo (n=8)	Vutrisiran (n=9)	Placebo (n=199)	Vutrisiran (n=196)	Placebo (n=328)	Vutrisiran (n=326)
6-MWT, n	7	7	166	170	285	294
Mean (SEM), m	−97.60 (55.40)	−19.91 (27.86)	−86.56 (6.63)	−60.59 (6.90)	−68.00 (5.03)	−46.10 (4.82)
LS mean difference (95% CI)	77.79 (−19.00, 174.58)		32.09 (14.03, 50.15)		26.46 (13.38, 39.55)	
KCCQ-OS, n	7	9	175	180	298	306
Mean (SEM)	−10.44 (9.73)	−8.30 (7.60)	−19.50 (1.77)	−10.25 (1.75)	−15.39 (1.28)	−9.34 (1.23)
LS mean difference (95% CI)	7.77 (−15.46, 31.00)		8.69 (3.98, 13.40)		5.80 (2.40, 9.20)	

Figure 3. Vutrisiran Stabilized Cardiac Biomarkers Levels, Consistent With the Overall Population



- Geometric mean fold-change ratios (95% CI) at M30 in the HELIOS-B overall and monotherapy populations were 0.68 (0.61, 0.76) and 0.57 (0.49, 0.66) for NT-proBNP and 0.68 (0.62, 0.75) and 0.55 (0.48, 0.63) for troponin I, respectively

Table 4. The Rate of Adverse Events Was Lower With Vutrisiran vs Placebo and Was Generally Consistent With the Overall Population

EAER per 100 PY	South American Subpopulation		Overall Population	
	Placebo (n=8, PY=16.6)	Vutrisiran (n=9, PY=23.8)	Placebo (n=328, PY=822.4)	Vutrisiran (n=326, PY=833.9)
≥1 AE	366.9	273.2	553.1	424.7
≥1 serious AE	108.3	54.6	76.5	63.3
≥1 severe AE	66.2	42.0	62.6	43.9
≥1 AE leading to study drug discontinuation	0	0	2.2	1.2
Death, n (%)	3 (37.5)	2 (22.2)	63 (19.2)	49 (15.0)

Adverse events are coded using MedDRA version 23.0.

Limitations

- Limitations include the post hoc nature of this analysis as well as limited sample size and number of events in the South American subpopulation

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

Acknowledgments: Medical writing support, under the guidance of the authors, was provided by Kristen Brown, PhD, an employee from the Publications and Medical Affairs Division of Omnicom Health Medical Communications and was funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice, GPP 2022 (*Ann Intern Med* 2022;175:1298–1304).

Funding: This study was funded by Alnylam Pharmaceuticals.

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.

Presented at: The XX International Symposium of Amyloidosis - ISA 2026, Nov 15–18, 2026, Montevideo, Uruguay.

Disclosures: JPC received speaker honoraria from AstraZeneca, Medison, and Pfizer, and research funding from Alnylam Pharmaceuticals, AstraZeneca, Intellia Therapeutics, and Pfizer; **AGQ** received speaker honoraria from Bagó, Medison, Pfizer, PTC Therapeutics, and Tuteur, and research funding from Alnylam Pharmaceuticals, AstraZeneca, and Intellia Therapeutics; **SZ, RS, and AC-D** are employees of Alnylam Pharmaceuticals, and report ownership of equity in Alnylam Pharmaceuticals; **FF** received speaker honoraria from Alnylam Pharmaceuticals and Pfizer, and research funding from Pfizer.

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Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; AE, adverse event; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; BL, baseline; CI, confidence interval; CV, cardiovascular; DB, double-blind; EAER, exposure-adjusted event rate; hATTR-PN, hereditary ATTR with polyneuropathy; HF, heart failure; HR, hazard ratio; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least squares; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open label extension; PND, polyneuropathy disability; PY, patient years; q3M, once every 3 months; QoL, quality of life; RNAi, RNA interference; SC, subcutaneous; SD, standard deviation; SEM, standard error of the mean; THAOS, Transthyretin Amyloidosis Outcomes Survey; TTR, transthyretin; wtATTR, wild-type ATTR.