Fewer Adverse Events Reported in ATTR-CM Patients Treated With Vutrisiran Versus Placebo: Post Hoc Safety Analysis From HELIOS-B

Stéphanie K. Schwarting[1], Kenichi Tsujita[2], Brett W. Sperry[3], Julian D. Gillmore[4], Marcus Anthony Urey[5], Juan Pablo Costabel[6], Tomas Ripoll[7], Hua Zheng[8], Satish Eraly[8], Patricia Reant[9]

[1]Department of Medicine I, LMU University Hospital, Ludwig Maximillian University of Munich, Germany; [2]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; [3]Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; [4]National Amyloidosis Centre, Division of Medicine, University College London, Royal Free Hospital, London, UK; [5]Department of Medicine, University of California San Diego Health, La Jolla, CA, USA; [6]Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina; [7]Hospital Son Llàtzer & IdISBa, Palma de Mallorca, Spain; [8]Alnylam Pharmaceuticals, Cambridge, MA, USA; [9]University and University Hospital Center of Bordeaux, Bordeaux, France.

Conclusions

- In HELIOS-B, while patients with ATTR-CM experienced AEs across a range of system organ classes (SOC), vutrisiran-treated patients had fewer AEs overall
  - Among the most frequent SOCs, the lowest AE rate ratios were observed in GI disorders and nervous system disorders (42% and 41% lower AE rates with vutrisiran vs placebo, respectively)
  - The SOC of eye disorders also showed a 46% lower AE rate with vutrisiran vs placebo
  - Lower AE rates were observed early in the trial for all populations assessed
- While these data are limited by the post hoc nature of the analysis, the results suggest that vutrisiran may provide a treatment benefit extending beyond the primary cardiac manifestations of ATTR-CM

Key takeaway

Vutrisiran-treated patients had fewer AEs across multiple systems, suggesting that vutrisiran's benefit in ATTR-CM may extend beyond cardiac manifestations

Introduction

ATTR-CM

- ATTR-CM is a progressive, debilitating, and fatal disease caused by the deposition of misfolded TTR protein in cardiac tissue and other organ systems[1–3]
  - Patients with ATTR-CM (hereditary [ATTRv] or wild-type [ATTRwt]) commonly have multisystemic manifestations beyond the heart (e.g., polyneuropathy, GI, renal, or musculoskeletal manifestations), which can negatively impact their QoL[4–8]
- These systemic manifestations likely contribute to the high burden of AEs, across multiple SOCs, observed in clinical trials and in routine practice in patients with ATTR-CM[9,10]

Vutrisiran

- Vutrisiran, an RNAi therapeutic that reduces the hepatic synthesis of TTR,[11] was evaluated in patients with ATTR-CM in the phase 3 HELIOS–B study (NCT04153149)[12]
  - Vutrisiran significantly reduced ACM and recurrent CV events and met all secondary endpoints vs placebo in patients with ATTR-CM in the overall and monotherapy populations of patients in HELIOS-B[12]
- Vutrisiran has demonstrated an acceptable and well-tolerated safety profile across both phase 3 studies, HELIOS-A and HELIOS-B, and their respective extension studies[12–16]

Objective

- To compare event rates for overall and SOC-specific AEs in vutrisiran- and placebo-treated patients with ATTR-CM from HELIOS-B

Methods

Figure 1. HELIOS-B Study Design: Safety Analysis

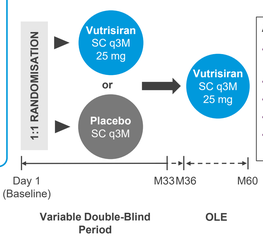
HELIOS-B: A Randomised, Double-Blind Phase 3 Outcomes Study in Patients With ATTR-CM[12]

Key Inclusion Criteria

- ATTR: wild-type or any TTR variant
- NYHA class ≤III
- 6-MWT ≥150 m
- NT-proBNP levels >300 pg/mL and <8500 pg/mL[a]

Key Exclusion Criteria

- NYHA class IV HF
- PND score ≥III at screening visit



Post hoc analyses of patients in the HELIOS-B overall population (n=654), monotherapy population (n=395; not on baseline tafamidis) and baseline tafamidis subgroup (n=259):

Assessments conducted for all AEs:

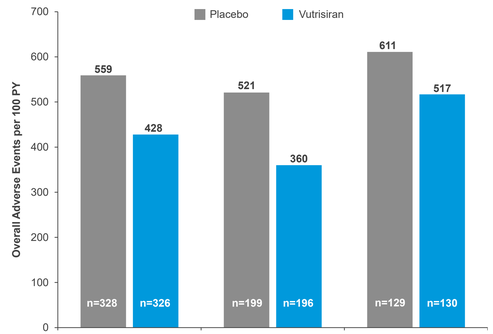
- Exposure-adjusted event rate per 100 patient-years (ER)
- Unadjusted rate ratio (RR; vutrisiran/placebo)
- Adjusted rate ratio (ARR; vutrisiran/placebo)
- Mean cumulative function plots
- Subgroup analysis in patients with ATTR-CM (ATTRv or ATTRwt)

[a]NT-proBNP >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation.

Results

Overall Rates of AEs in All Populations

Figure 2. Rates of Overall AEs Were 15–31% Lower in Vutrisiran-Treated Patients Across All Populations



	Overall Population	Monotherapy Population	Baseline Tafamidis Subgroup
RR Vutrisiran/Placebo:	0.77	0.69	0.85
ARR Vutrisiran/Placebo:	0.75	0.67	0.84

Rates of AEs by SOC in All Populations

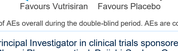
- The top 10 SOCs displayed were identified as those with the highest number of AEs overall during the double-blind period
- Among these top 10 SOCs, the lowest rates of AEs observed in the vutrisiran vs placebo groups were related to:
  - GI and nervous system disorders (42% and 41% lower AE rates, respectively) for the overall population (**Figure 3**)
  - Nervous system disorders (57% lower AE rates) for the monotherapy population
  - GI disorders (49% lower AE rates) for the baseline tafamidis subgroup
- In the overall population, an additional SOC of interest, eye disorders, also had a lower event rate with vutrisiran vs placebo: 7.8 vs 13.5 per 100 PY, respectively; ARR: 0.54

Figure 3. AE Rates by SOC Were Consistently Lower With Vutrisiran vs Placebo Across the Top 10 SOCs in All Populations

System Organ Class	Overall Population[a] Adjusted Rate Ratio (95% CI) (Vutrisiran/Placebo)	Overall Population[a] ER per 100 PY Placebo (n=328, PY=823.2)	Overall Population[a] ER per 100 PY Vutrisiran (n=326, PY=834.9)
All AEs	0.75 (0.71, 0.78)	558.6	427.6
Cardiac disorders	0.74 (0.66, 0.83)	83.9	64.3
Infections and infestations	0.79 (0.69, 0.90)	64.3	50.8
Musculoskeletal and connective tissue disorders	0.96 (0.82, 1.12)	45.2	43.4
Nervous system disorders	0.59 (0.49, 0.70)	44.0	28.1
Injury, poisoning and procedural complications	0.68 (0.57, 0.81)	39.4	28.0
GI disorders	0.58 (0.49, 0.70)	40.6	23.4
General disorders and administration site conditions	0.70 (0.58, 0.84)	35.3	26.5
Metabolism and nutrition disorders	0.73 (0.61, 0.87)	36.0	26.2
Respiratory, thoracic and mediastinal disorders	0.82 (0.68, 0.99)	30.6	25.4
Renal and urinary disorders	0.81 (0.66, 1.01)	22.7	18.8

System Organ Class	Monotherapy Population[a] Adjusted Rate Ratio (95% CI) (Vutrisiran/Placebo)	Monotherapy Population[a] ER per 100 PY Placebo (n=199, PY=475.6)	Monotherapy Population[a] ER per 100 PY Vutrisiran (n=196, PY=473.5)
All AEs	0.67 (0.63, 0.72)	520.7	359.7
Cardiac disorders	0.60 (0.52, 0.71)	87.5	55.1
Infections and infestations	0.73 (0.62, 0.87)	68.8	51.3
Musculoskeletal and connective tissue disorders	0.90 (0.72, 1.13)	33.4	30.2
Nervous system disorders	0.43 (0.33, 0.55)	43.9	19.0
Injury, poisoning and procedural complications	0.61 (0.47, 0.80)	30.3	19.2
GI disorders	0.62 (0.49, 0.79)	38.7	24.3
General disorders and administration site conditions	0.62 (0.47, 0.81)	27.1	17.1
Metabolism and nutrition disorders	0.69 (0.54, 0.89)	31.5	22.8
Respiratory, thoracic and mediastinal disorders	0.75 (0.58, 0.98)	28.4	21.8
Renal and urinary disorders	0.81 (0.61, 1.08)	22.1	18.4

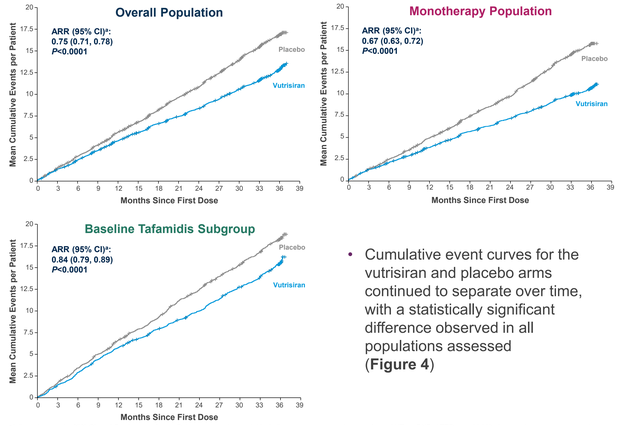
System Organ Class	Baseline Tafamidis Subgroup[a] Adjusted Rate Ratio (95% CI) (Vutrisiran/Placebo)	Baseline Tafamidis Subgroup[a] ER per 100 PY Placebo (n=129, PY=347.7)	Baseline Tafamidis Subgroup[a] ER per 100 PY Vutrisiran (n=130, PY=361.4)
All AEs	0.84 (0.79, 0.89)	610.6	516.6
Cardiac disorders	0.97 (0.82, 1.14)	79.1	76.4
Infections and infestations	0.86 (0.71, 1.05)	58.1	50.1
Musculoskeletal and connective tissue disorders	0.98 (0.81, 1.18)	61.3	60.6
Nervous system disorders	0.90 (0.72, 1.13)	44.0	40.1
Injury, poisoning and procedural complications	0.76 (0.61, 0.95)	51.8	39.6
GI disorders	0.51 (0.39, 0.67)	43.1	22.1
General disorders and administration site conditions	0.82 (0.66, 1.03)	46.6	38.7
Metabolism and nutrition disorders	0.73 (0.57, 0.94)	42.0	30.7
Respiratory, thoracic and mediastinal disorders	0.89 (0.69, 1.16)	33.7	30.2
Renal and urinary disorders	0.83 (0.60, 1.14)	23.6	19.4



[a]Top ten SOCs displayed as those with the highest number of AEs overall during the double-blind period. AEs are coded using MedDRA v23.0 preferred terms.

Mean Cumulative AE Events per Patient

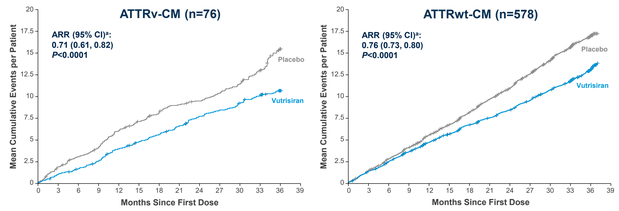
Figure 4. Lower Overall Rates of AEs Were First Observed Between Month 3 and 6 of the Double-Blind Period in All Populations



- Cumulative event curves for the vutrisiran and placebo arms continued to separate over time, with a statistically significant difference observed in all populations assessed (**Figure 4**)

[a]Adjusted rate ratio, 95% CI, and *P*-values are from a Poisson regression model including treatment group, log-transformed NT-proBNP, ATTR type, NYHA class, and age group as covariates, and the logarithm of the follow-up time as an offset variable. The overall population also included baseline tafamidis use and treatment-by-baseline tafamidis use interaction as covariates.

Figure 5. A Consistent Trend With Early and Continued Separation of Vutrisiran and Placebo Cumulative Event Curves Was Observed With Either ATTRv-CM or ATTRwt-CM



[a]Adjusted rate ratio, 95% CI, and *P*-values are from a Poisson regression model including treatment group, log-transformed NT-proBNP, ATTR type, NYHA class, and age group as covariates, and the logarithm of the follow-up time as an offset variable. The overall population also included baseline tafamidis use and treatment-by-baseline tafamidis use interaction as covariates.

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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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Abbreviations: 6-MWT, 6-minute walk test; AE, adverse event; ARR, adjusted rate ratio; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv, hereditary ATTR; ATTRwt, wild-type ATTR; CV, cardiovascular; CI, confidence interval; ER, exposure-adjusted event rate per 100 patient-years; GI, gastrointestinal; HF, heart failure; IV, intravenous; MedDRA, medical dictionary for regulatory activities; 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, every 3 months; QoL, quality of life; RR, unadjusted rate ratio; RNAi, RNA interference; SC, subcutaneous; SOC, system organ class; TTR, transthyretin.