Evidence of Fewer Gastrointestinal Events in ATTR-CM Patients Treated with Vutrisiran Compared with Placebo: Analysis from HELIOS-B

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Introduction and Objectives

Introduction

- ATTR is a progressive, systemic disease caused by misfolded amyloidogenic TTR deposits (hereditary or wild-type) accumulating in multiple tissues, and is associated with high morbidity and mortality[1–3]
- In addition to cardiomyopathy, patients with ATTR-CM can experience extracardiac involvement, leading to neuropathy, and musculoskeletal, GI, and renal manifestations[4,5]
  - GI manifestations such as nausea, vomiting, diarrhea, and constipation have a large impact on QoL[6,7]
- Vutrisiran, an RNAi therapeutic that reduces the hepatic synthesis of hereditary and wild-type TTR, was evaluated in patients with ATTR-CM in the Phase 3 HELIOS–B study (NCT04153149)[8]
  - Vutrisiran significantly reduced ACM and recurrent CV events in patients with ATTR-CM in the overall population and the monotherapy populations versus placebo
  - In the overall population, 89% (289/326) of vutrisiran patients, and 88% (289/328) of placebo patients had wild-type ATTR

Objectives

- This analysis assessed whether vutrisiran treatment versus placebo was associated with fewer GI events among patients with ATTR-CM in the HELIOS-B study
  - All AEs classified under the GI disorders system organ class during the double-blind period of HELIOS-B, were compared between the vutrisiran and placebo arms of the overall population, as well as the monotherapy population and baseline tafamidis subgroup

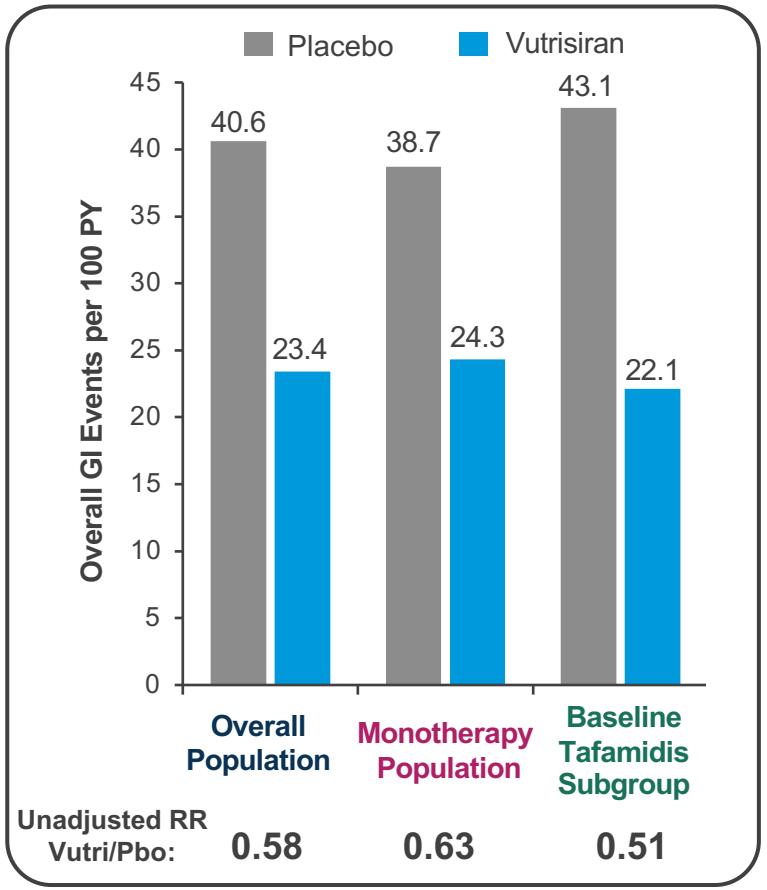
Abbreviations: AE, adverse event; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; CV, cardiovascular; GI, gastrointestinal; QoL, quality of life; TTR, transthyretin.

References: 1. Maurer et al. *Circ Heart Fail* 2019;12:e006075; 2. Ruberg, Maurer. *JAMA*. 2024;331:778–91; 3. Nativi-Nicolau et al. *ESC Heart Fail* 2021;8:3875–84; 4. Nativi-Nicolau et al. *Heart Fail Rev*. 2022;27:785–793; 5. Brito et al. *Glob Heart*. 2023;18:59; 6. Wixner et al. *Orphanet J Rare Dis* 2014;9:61; 7. Obici, Suhr. *Clin Auton Res* 2019;29(Suppl 1):55–63; 8. Fontana M et al. *N Engl J Med*. 2025;392:33–44.

Reduction of 37– 49% in Rates of Overall GI Events vs Placebo was Observed in Patients Treated with Vutrisiran

HELIOS-B

Lower rates were observed with vutrisiran vs placebo for GI events commonly associated with a negative impact on QoL in patients with ATTR-CM



GI Event[a]	Overall Population[b,c]			Monotherapy Population[d]			Baseline Tafamidis Subgroup[e]		
	ER per 100 PY		RR	ER per 100 PY		RR	ER per 100 PY		RR
	Placebo	Vutrisiran		Placebo	Vutrisiran		Placebo	Vutrisiran	
Constipation	6.9	4.2	**0.61**	6.3	5.1	**0.80**	7.8	3.0	**0.39**
Diarrhea	4.1	1.9	**0.46**	4.8	2.3	**0.48**	3.2	1.4	**0.44**
Nausea	3.4	1.2	**0.35**	2.5	0.4	**0.17**	4.6	2.2	**0.48**
Abdominal Pain Grouping[f]	3.6	1.6	**0.43**	3.2	1.5	**0.47**	4.3	1.7	**0.38**
Vomiting	1.5	0.2	**0.16**	1.7	0.4	**0.25**	1.2	0	**0.00**

[a]GI events are coded using MedDRA v23.0 preferred terms (PT). Out of 103 PTs reported within the GI disorder SOC, all had event rate ratios that favored vutrisiran or had differences in frequencies that were balanced between arms (defined as a difference in frequency of <1%). [b]Out of 529 GI AEs reported, 10 were deemed by the PI to be related to treatment (8 placebo and 2 vutrisiran). [c]Placebo (n=328, PY=823.2), vutrisiran (n=326, PY=834.9). [d]Placebo (n=199, PY=475.6), vutrisiran (n=196, PY=473.5). [e]Placebo (n=129, PY=347.7), vutrisiran (n=130, PY=361.4). [f]Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain PTs.

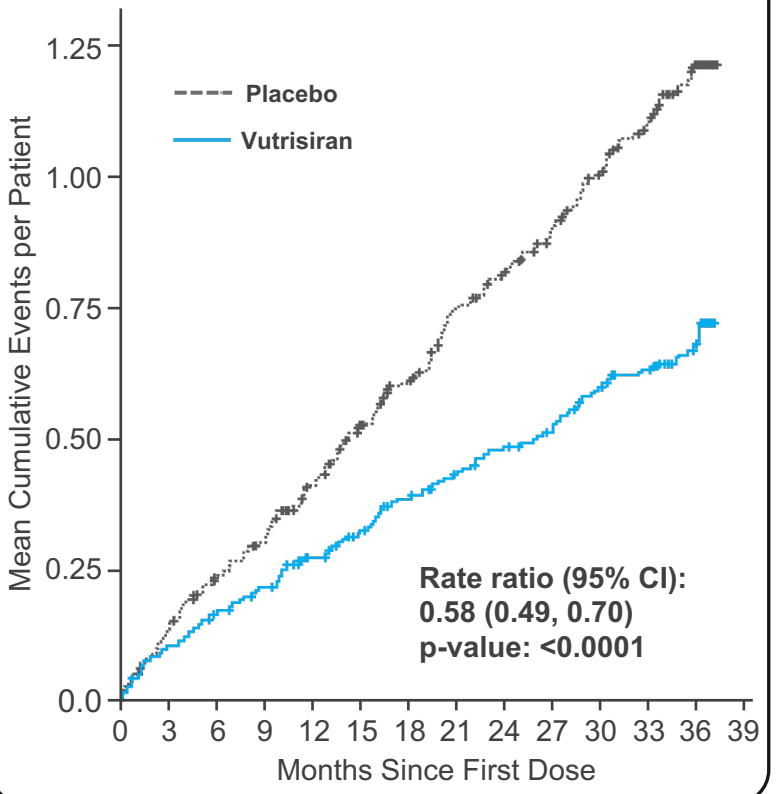
Abbreviations: ATTR-CM, ATTR with cardiomyopathy; ER, event rate; GI, gastrointestinal; MedRA, Medical Dictionary for Regulatory Activities; Pbo, placebo; PI, principal investigator; PY, patient-years; QoL, quality of life; RR, rate ratio; Vutri, vutrisiran.

A Reduction in Rates of GI Events with Vutrisiran vs Placebo Was Observed by Month 3 of the Double-Blind Period in All Populations

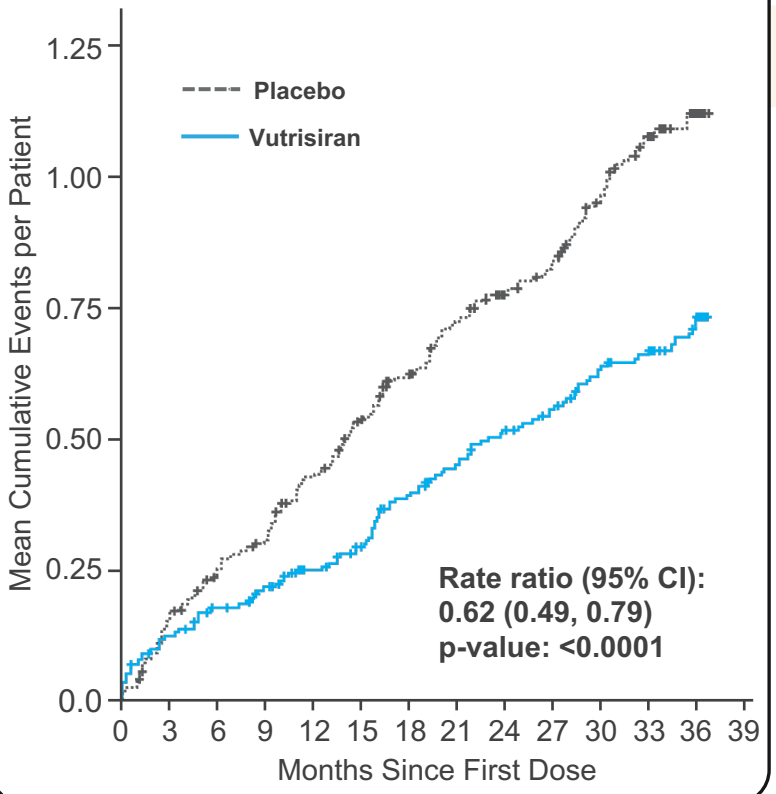
HELIOS-B

Mean Cumulative GI Events Per Patient

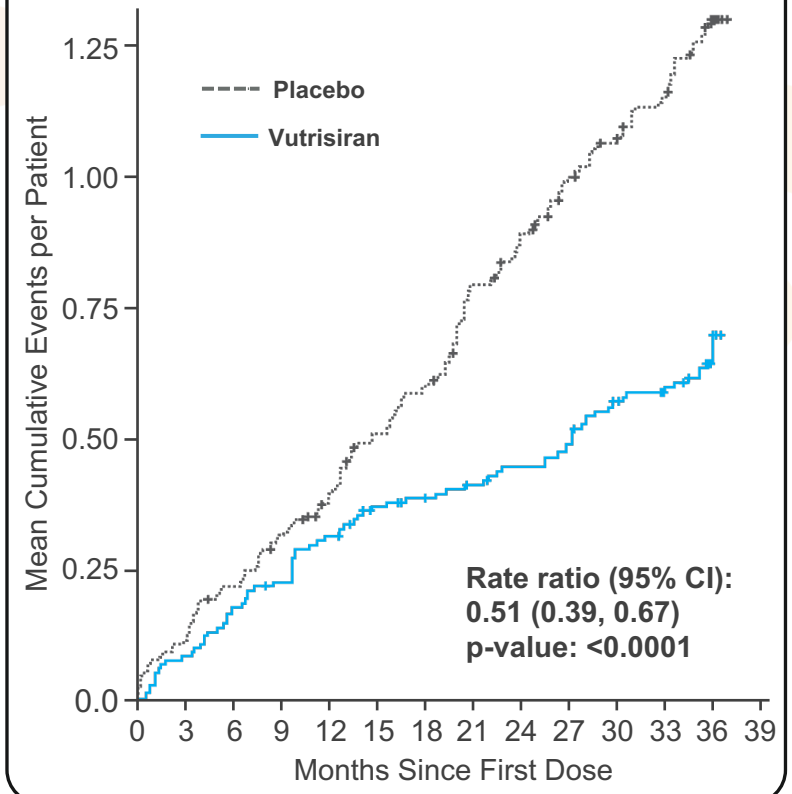
Overall Population



Monotherapy Population



Baseline Tafamidis Subgroup



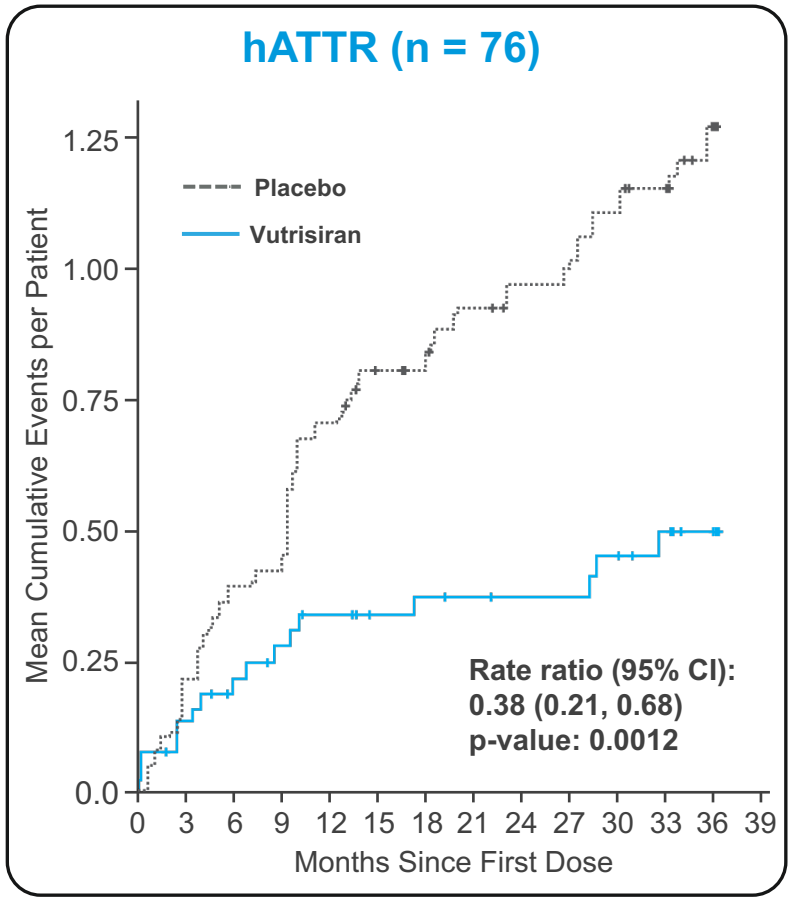
Rate ratio, 95% CI, and p-values are from a Poisson regression model including treatment group, log-transformed NT-proBNP, ATTR type, NYHA class, and age group as covariates, and the logarithm of the follow-up time as an offset variable. The overall population also included baseline tafamidis use and treatment-by-baseline tafamidis use interaction as covariates. Lines are truncated after reaching less than 5 patients at risk.

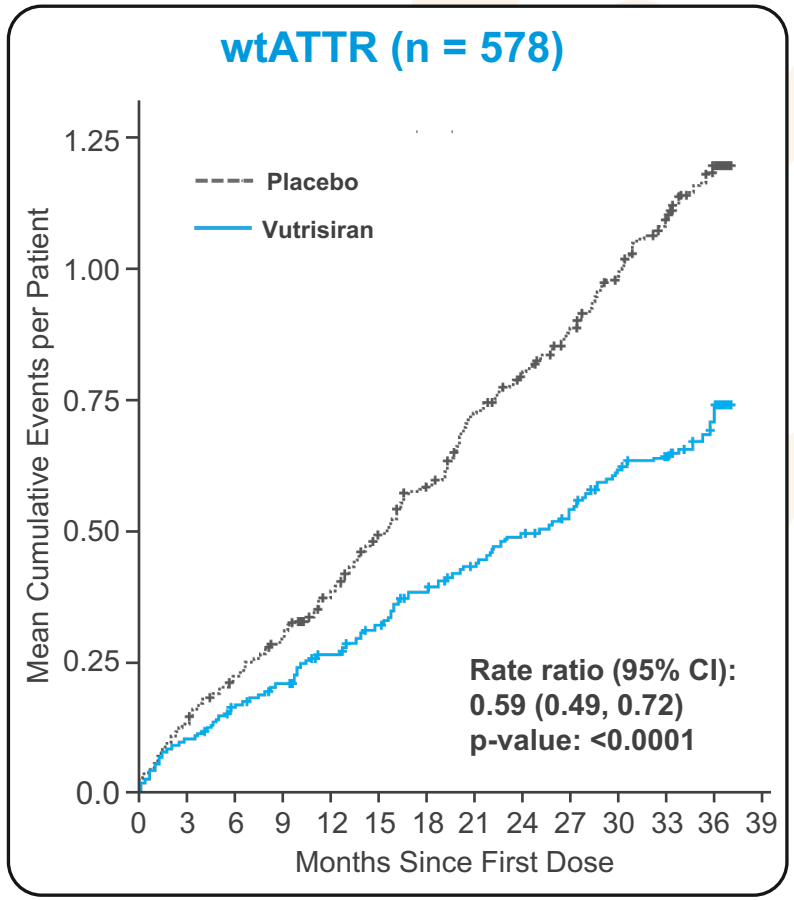
Abbreviations: ATTR, transthyretin amyloidosis; CI, confidence interval; GI, gastrointestinal; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.

A Consistent Trend Emerged in Patients with Either hATTR-CM or wtATTR-CM

HELIOS-B

Mean Cumulative GI Events Per Patient





Rate ratio, 95% CI, and p-values are from a Poisson regression model including treatment group and log-transformed NT-proBNP as covariates, and the logarithm of the follow-up time as an offset variable. The overall population also included baseline tafamidis use as a covariate. Lines are truncated after reaching less than five patients at risk.

Abbreviations: ATTR, transthyretin amyloidosis; CI, confidence interval; CM, cardiomyopathy; GI, gastrointestinal; hATTR, hereditary transthyretin amyloidosis; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; wtATTR, wild-type transthyretin amyloidosis.

Treatment with Vutrisiran was Associated with Fewer GI Events Compared with Placebo

US HCPs Only

HELIOS-B

- In HELIOS-B, patients with ATTR-CM experienced a considerable number of GI events suggesting possible GI involvement in this patient population
- The reduction in rates of GI events with vutrisiran vs placebo was large in magnitude, statistically significant, and observed early in the trial for all populations assessed
  - Consistent results were observed across the overall and monotherapy populations and the baseline tafamidis subgroup, and in patients with either hATTR or wtATTR
- >50% rate reductions were observed on certain GI events that are known to have significant impact on patient's QoL, including diarrhea, nausea, and vomiting
- These results suggest that vutrisiran may provide a treatment benefit on GI manifestations potentially caused by ATTR
  - AEs were self-reported and not adjudicated, which may limit interpretation
- Future trials should consider assessment of extracardiac variables to better understand the impact of treatment options outside of traditional cardiac parameters

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

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Abbreviations: AE, adverse event; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; GI, gastrointestinal; hATTR, hereditary transthyretin amyloidosis; HCP, healthcare professional; HF, heart failure; QoL, quality of life; TTR, transthyretin; wtATTR, wild-type transthyretin amyloidosis.