

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

Marcus A. Urey¹, Quan M. Bui¹, Laura Obici², Shaun Bender³, Satish Eraly³, Emre Aldinc³, Caroline Morbach⁴

¹Division of Cardiovascular Medicine, University of California San Diego Health, La Jolla, CA, USA;

²Amyloidosis Research and Treatment Centre, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy;

³Alnylam Pharmaceuticals, Cambridge, MA, USA;

⁴Department of Clinical Research and Epidemiology, Comprehensive Heart Failure Center, and Department of Medicine I, University Hospital Würzburg, Würzburg, Germany.



Introduction and Objectives

Introduction

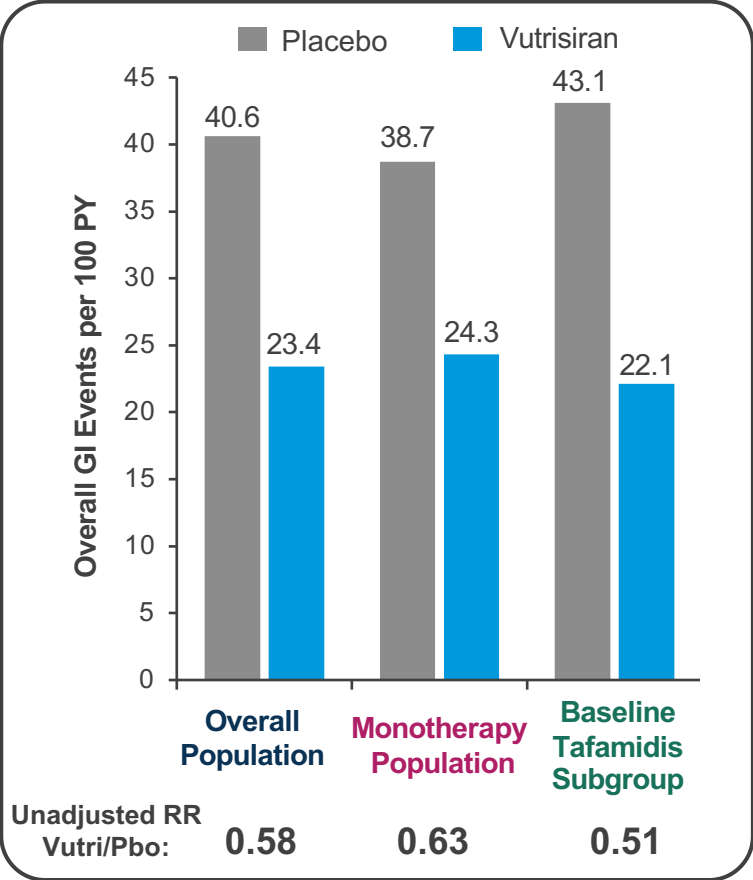
- ATTR is a progressive, systemic disease caused by misfolded amyloidogenic TTR deposits (hereditary or wild-type) accumulating in multiple tissues, and is associated with high morbidity and mortality^{1–3}
- In addition to cardiomyopathy, patients with ATTR-CM can experience extracardiac involvement, 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

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

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

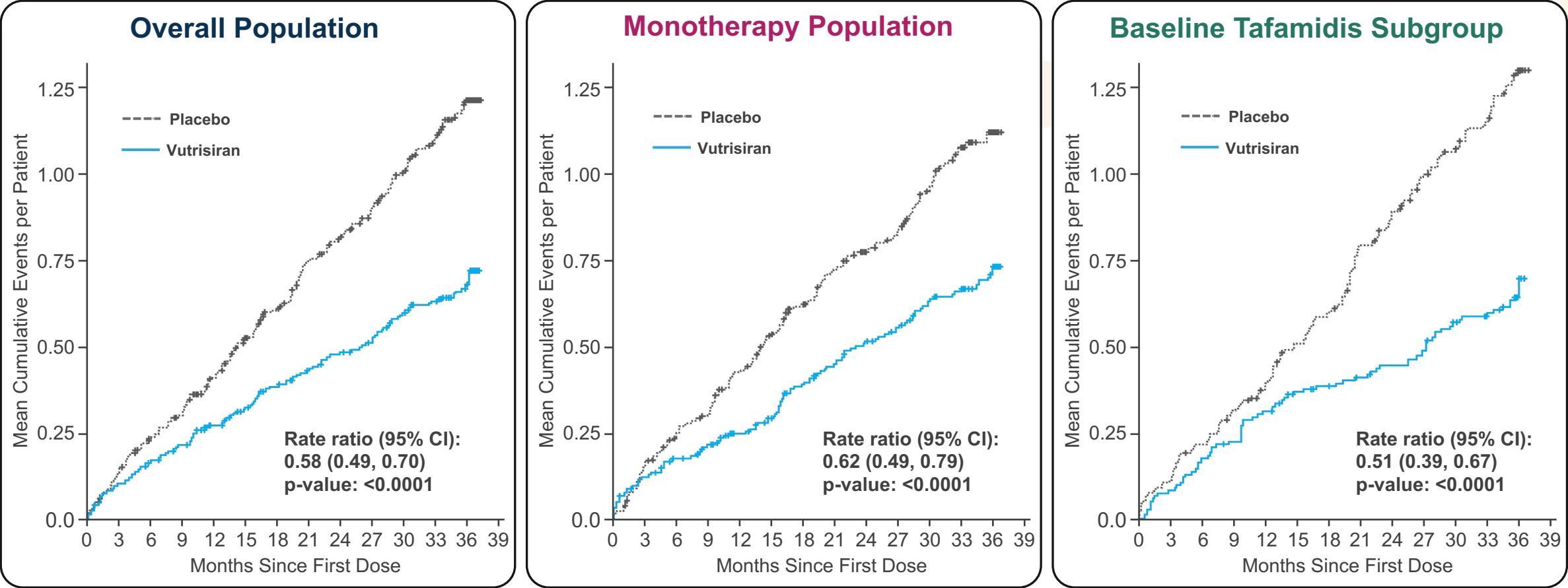


GI Event ^a	Overall Population ^{b,c}			Monotherapy Population ^d			Baseline Tafamidis Subgroup ^e		
	ER per 100 PY		RR	ER per 100 PY		RR	ER per 100 PY		RR
	Placebo	Vutrisiran		Placebo	Vutrisiran		Placebo	Vutrisiran	
Constipation	6.9	4.2	0.61	6.3	5.1	0.80	7.8	3.0	0.39
Diarrhea	4.1	1.9	0.46	4.8	2.3	0.48	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

^aGI 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%). ^bOut of 529 GI AEs reported, 10 were deemed by the PI to be related to treatment (8 placebo and 2 vutrisiran). ^cPlacebo (n=328, PY=823.2), vutrisiran (n=326, PY=834.9). ^dPlacebo (n=199, PY=475.6), vutrisiran (n=196, PY=473.5). ^ePlacebo (n=129, PY=347.7), vutrisiran (n=130, PY=361.4). ^fIncludes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain PTs.

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

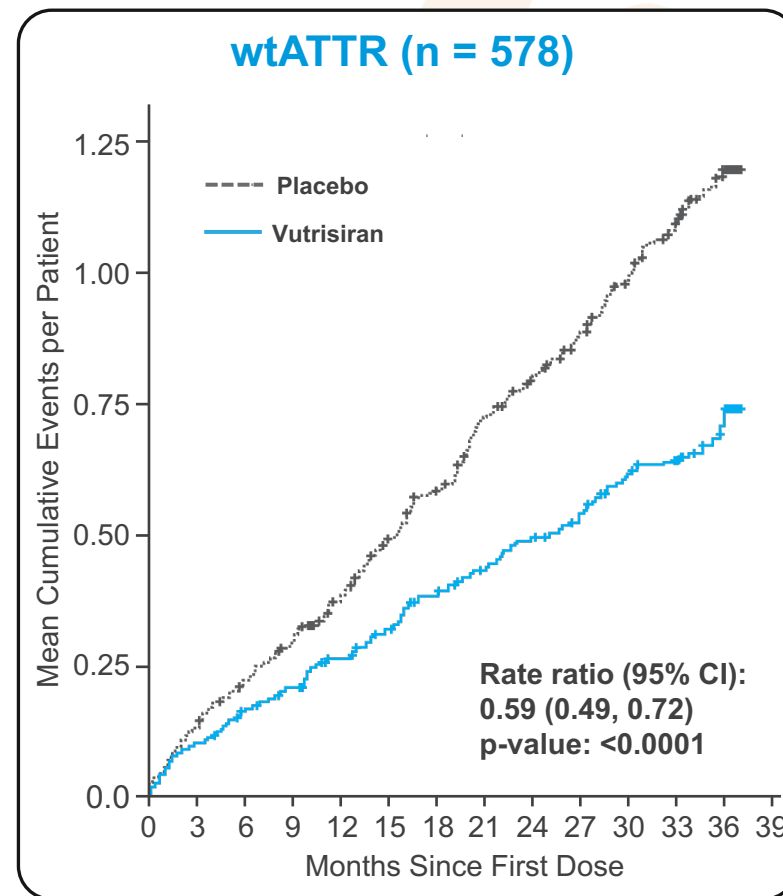
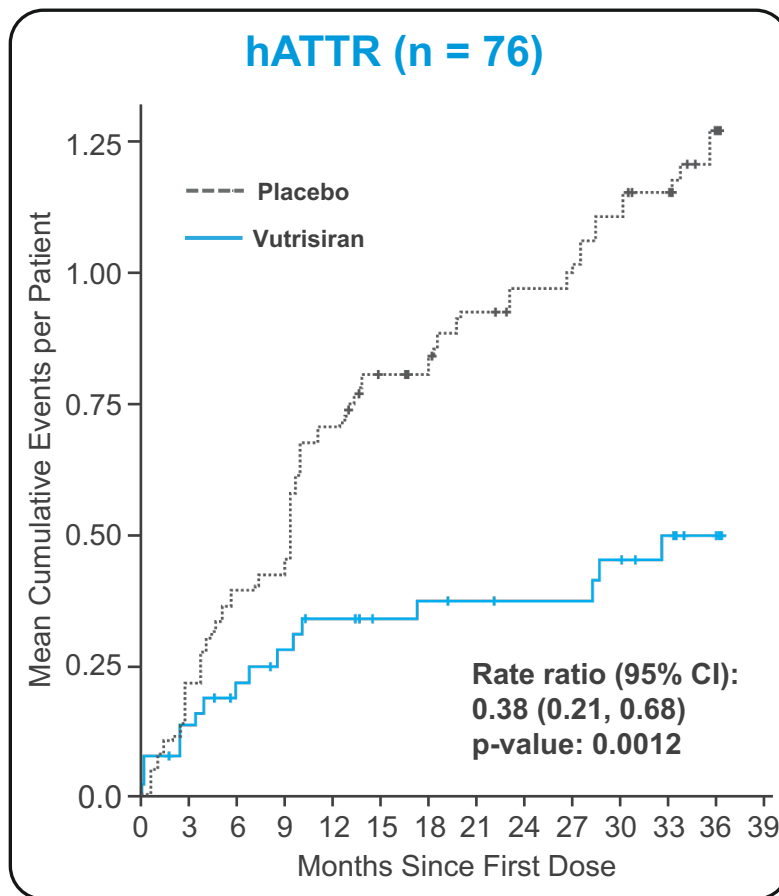
Mean Cumulative GI Events Per Patient



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.

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

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.

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



- 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